Sedation of Adult Ventilated Patients in the Intensive Care Unit.
Department of Clinical Nursing
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I certify that this doctoral portfolio entitled “The Sedation of Adult Ventilated Patients in the Intensive Care Unit” and submitted for the degree of Doctor of Nursing, is the result of my own research and contains no material which has been accepted for the award of any other degree or diploma, in any university or tertiary institution. To the best of my knowledge and belief it contains no material previously published or written by another person, except where due reference is made in the text.

Signed:  

Date:  15 July 2002
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PORTFOLIO OVERVIEW

This research portfolio is comprised of the following sections:

Introduction to the topic

The research reports:

- The Effectiveness of Propofol versus Midazolam for the Sedation of Adult Ventilated Patients in Intensive care Units (ICUs) A Systematic Review. (completed 2000)

- The Efficacy of an Alternative Sedation Regimen Compared to the Existing Regimen for the Sedation of Adult Ventilated Patients in Intensive Care, (study not completed).

- A Descriptive Study To Explore Patients’ Memories of Their Stay In An Intensive Care Unit (ICU) And To Investigate The Association of Their Memories with the Sedation Regimens Used. Completed 2001.


Portfolio Conclusion

Publications
INTRODUCTION TO THE TOPIC

The topic of this doctoral portfolio is sedation of adult ventilated patients in the Intensive Care Unit (ICU). The three completed components of the portfolio consider three very different aspects of this topic. The systematic review evaluates the literature relating to the effectiveness of two of the most common agents used to sedate patients in the ICU, while the second study investigates memories of sedated patients. The final study investigates the relationship between the Bispectral Index of the EEG monitoring compared to a clinical assessment scale for the assessment of the level of sedation in ICU patients.
The Sedation of Adult Ventilated Patients in the ICU

The area of practice, which was investigated in this study, is the sedation of adult patients in the intensive care unit. The word sedation comes from the Latin “sedo” which means to “soothe, still calm and allay, to assuage physical or mental disturbance”. Sedating drugs have been used in intensive care since its development as a discipline in the 1950s. At this time, in order to reduce the high number of fatalities associated with anaesthesia, hospitals began to establish specialised units where patients could be recovered. These areas were the first intensive care units (ICUs). Some of the first patients nurses in an ICU were those with tetanus and sedatives were used to prevent muscle spasms and convulsions. Another important influence in the development of intensive care was the “Copenhagen experience”. In 1952, Denmark experienced a catastrophic poliomyelitis epidemic in which 866 patients were admitted with paralysis over a 19-week period. Nearly a half of these patients suffered from paralysis of the muscles of the muscles of the mouth, tongue and pharynx (bulbar palsy). An anaesthetist, Bjorn Ibsen, recommended that patients be tracheostomised and manually ventilated. This practice reduced the mortality from 80% at the beginning of the epidemic to 23% at its end.

Since that time, with the introduction of mechanical ventilation, intensive care has developed rapidly into a separate specialty. Now the intensive care unit is where the sickest patients in hospitals are cared for and life supporting treatment such as artificial ventilation is employed. The unit in which the research was conducted developed from a theatre recovery area and was established in 1969. It now has 21 beds and in 2001 –2002 had 1188 admissions.

In the early 1980s in the unit in which the research was conducted, it was common practice for all ventilated patients to be heavily sedated and paralysed unless they were being weaned from artificial ventilation or were deeply unconscious (personal experience of the researcher). The ventilators in use at the time only delivered controlled breaths and
although patients were able to trigger breaths, there was no synchronisation with effort. Intermittent mandatory ventilation was possible through a one-way valve situated in the ventilation circuit, but the ventilator was unable to detect inspiration through this valve and stacking of breaths could occur. This meant that it was possible for a controlled breath to be delivered on top of a spontaneous breath and this could result in increased inspiratory pressure and discomfort to the patient. Patients with severe respiratory failure usually had to be paralysed and sedated so this controlled ventilation could be tolerated and oxygenation maintained.

The drugs used at that time for sedation and analgesia were phenoperidine, a synthetic narcotic analgesic with a sedative action, diazepam, a benzodiazepine sedative and pancuronium a paralysing drug. The agents were administered by bolus injection on an hourly basis by the team-leader, an intensive care qualified registered nurse who had the overall responsibility for a group of patients. From a study of the literature it appears that this type of sedation regimen was common in the 1980s. In 1981, Merriman surveyed 34 ICUs in Great Britain and Northern Ireland. He found that the majority of units (67%) chose to heavily sedate patients and that 91% of units frequently used the paralysing agent pancuronium. However, there was a wide variation of the drugs used for sedation; a total of 21 different drugs were used including analgesics, benzodiazepines and other agents such as althesin.

In the late 1980s, practice in the unit in which the research was conducted changed; infusion pumps were introduced allowing sedation to be administered continuously. The narcotic morphine and the benzodiazepine midazolam were used almost exclusively for sedation and continuous infusions were titrated by the nurse caring for the patient. This meant a more constant level of sedation could be achieved. As a result paralysing agents were not required as frequently to control patient movement. In addition new generation ventilators were developed with modes such as synchronised intermittent mandatory ventilation (SIMV) that allowed patients to breathe spontaneously between controlled breaths and synchronised the breaths to patient effort. This helped to prevent the patient fighting ventilation, one of the main reasons for usage of sedation and paralysing agents.
Moreover, there was an increasing recognition of problems relating to the use of paralysing agents such as patient awareness. There were also concerning reports of a correlation between the use of these drugs and the occurrence of a polyneuropathy. This complication appears to occur most commonly in patients with sepsis, particularly if they are treated with steroids. Similar to Guillain Barré syndrome, Critical Illness Polyneuropathy may result in severe weakness, prolonging weaning from ventilation and even influencing mortality.

In the 1980s two commonly used drugs were withdrawn from usage. Althesin due to the potential for anaphylaxis related to its solvent and etomidate after a retrospective study by Ledingham and Watt in 1983, serendipitously found there was an increased mortality related to its use. This was subsequently found to be related to adrenocortical suppression. These findings further limited the number of different agents used for sedation.

A survey of 348 ICUs in the United Kingdom, performed by Bion and Ledingham in 1987 found most units used exclusively opiates and benzodiazepines and that use of paralysing agents was rare. In most units sedation was administered by continuous infusion. Likewise a survey by Hansen-Flachen and colleagues of 265 hospitals (1991) in the USA, also found opiates and benzodiazepines were commonly used and that use of paralysing agents was rare. A survey of 72 units in Australia performed in 1996, showed that the majority of units used a combination of narcotics and benzodiazepines for sedation, specifically morphine and midazolam, that paralysing agents were rarely used and sedation was administered by infusions which were titrated by the nurse caring for the patient. Most units occasionally used paralysing agents.

With the increased acuity in hospitals over the last decade, it appears virtually every patient in the ICU where the research was conducted now requires ventilation and most are sedated. Nevertheless, ensuring the appropriate level of sedation for each individual may be problematic. No perfect sedation agent exists and over-sedation may increase
length of stay, cost and morbidity.\textsuperscript{16,17} However, under-sedation is also undesirable resulting in increased oxygen consumption, poor ventilation, pain, distress and catheter removal\textsuperscript{18} and even injuries such as fractures.\textsuperscript{19} The level of sedation required also varies according to the patient’s diagnosis and the treatment required. Some patients, such as those with raised intracranial pressure or severe lung disease require heavy sedation, others such as post-operative patients may be comfortably maintained in a lightly sedated state.\textsuperscript{16,20,21}

The doses of sedation agents required to produce the desired level of sedation vary greatly between individuals and critical illness complicates the situation by interfering with the distribution, metabolism and elimination of agents.\textsuperscript{21,22} For these reasons it is essential that sedation be titrated according to individual response and that the most appropriate level of sedation is maintained.

Sedation is one of the most common therapies patients receive in the ICU and there are many problems related to over- or under-sedation. Evidence is required regarding the effectiveness of particular agents, on what memories patients have of the ICU and how these are influenced by the sedation regimen chosen and on how the level of sedation can be more accurately assessed. These are some of the topics that the research studies in this portfolio aimed to address.

**PORTFOLIO STRUCTURE**

Each study of the portfolio is presented in a separate section. These are numbered individually, each with its own contents page and references. The first study is a systematic review and this is followed by the reports of studies investigating, an alternative sedation regimen, the memories of patients who have been in the ICU and the Bispectral Index of the EEG. At the end of the portfolio is a brief conclusion. Publications from the doctoral studies are attached.
REFERENCES


A SYSTEMATIC REVIEW

THE EFFECTIVENESS OF PROPOFOL VERSUS MIDAZOLAM FOR THE SEDATION OF ADULT VENTILATED PATIENTS IN INTENSIVE CARE UNITS (ICUS)

Systematic Review Completed 2000
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INTRODUCTION
The Rationale for Use of Sedation

Intensive care developed as a distinct specialty in the 1950s and since this time, sedation has played an integral role in treatment of the critically ill. The most seriously ill patients in hospital are cared for in the intensive care unit (ICU) and it can be a highly distressing place. The therapy that is required to maintain life can itself be painful and frightening. Tubes placed into the patient’s trachea to facilitate artificial ventilation prevent speaking or swallowing and may cause a choking sensation. Being unable to control your own breathing is one of the most distressing experiences possible and patients in intensive care have only limited control over the gas pushed into the lungs by the ventilators. Lines are inserted into arteries and veins to provide nourishment and to monitor the patient’s haemodynamic status. In addition to these stressors the patient has often suffered trauma or undergone surgery resulting in pain from incisions and injuries. There may be fear of death or disfigurement. Thirst is common and can cause extreme discomfort. Constant treatment prevents sleep, resulting in sleep deprivation and sometimes disorientation. For all these reasons the experience of intensive care has been likened to torture. Nevertheless, such treatment is necessary to sustain life. Thus sedating drugs are used to relieve anxiety and distress and to enable patients to tolerate therapy such as artificial ventilation. In some cases sedation itself may be part of the treatment, for example for patients with intracranial hypertension.

Definition of Sedation

The word sedation means a “calm and restful state”. Many drugs have been used to produce sedation or anxiolysis, including opiates, benzodiazepines, anaesthetics and neuroleptic agents, but no agent produces sedation alone. Each may have a range of actions, including hypnosis (producing sleep), analgesia (relieving pain) and amnesia (loss of memory). They also have various side effects. Therefore, the drug chosen will depend on the action required and the anticipated side effects. However, recent surveys of ICUs in the United Kingdom, North America and Australia have shown that the
drugs most commonly used to sedate intensive care patients are benzodiazepines and these are usually administered in combination with narcotics. In Australia midazolam and morphine were found to be the most common drugs used for the sedation of patients in ICUs.5

Shelly and Snyde state that the ideal agent “should have rapid onset of action, be easily titratable and have no adverse side effects or accumulation problem”.6 Accumulation can result in over-sedation causing respiratory depression and prolonged weaning times, hypotension, ileus, immunosupression, renal dysfunction and may actually increase morbidity.79 Both morphine and midazolam have the potential for accumulation, particularly in the critically ill.

**Midazolam**

Midazolam is a relatively short acting benzodiazepine which is rapidly distributed into peripheral tissues.10 In common with other benzodiazepines, the actions of midazolam include anxiolysis, hypnosis and antegrade amnesia. These drugs act on the inhibitory gamma-aminobutyric acid (GABA) receptors in the central nervous system resulting in decreased neurotransmission.11 GABA is an inhibitory neurotransmittor found in the central nervous system that acts on specific neuronal membrane receptors. Low doses of benzodiazepines result in relief of anxiety, higher doses cause muscle relaxation and hypnosis.11 Although midazolam has been considered short acting, this is not the case when infusions are administered continuously to the critically ill. The main problem with predicting the action of drugs in these patients is that the pharmokinetics (pK) of drugs are usually calculated using studies performed on young, healthy individuals given single doses.12 Critically ill patients commonly have impaired renal and hepatic function and many are elderly. The half-life of midazolam is normally from thirty minutes to two hours. However, its action is extended in renal failure, as the active metabolite α-hydroxymidazolam will accumulate. Shock and reduced hepatic perfusion can also interfere with metabolism prolonging its action.13 If it is administered in
continuous infusions the peripheral tissues become saturated and the action may be extended to days.\textsuperscript{10} Elderly patients are also at greater risk of accumulation due to reduced metabolism.\textsuperscript{14,15} Thus midazolam may easily accumulate in the critically ill causing over-sedation and associated complications.

**Propofol**

Around 1995 (personal communication Zeneca Pharmaceuticals) propofol, was introduced to intensive care practice for sedation of ventilated patients in Australia. Propofol is an aquiphenol agent that has sedative and hypnotic actions, but has little amnesic and no analgesia action.\textsuperscript{16} But propofol has one major advantage over other sedative agents, even in the critically ill and elderly patient as it has a very short redistribution half-life of 1.3 - 2.2 minutes.\textsuperscript{17-19} Propofol is comprised of soybean oil, egg lecithin, sodium hydroxide and glycerol.\textsuperscript{16} Its mode of action is unclear, but it may work by exerting a non-specific effect on lipid membranes.\textsuperscript{20} Nevertheless, propofol does have some side effects. It may cause hypotension, and allergy and convulsions have been reported in susceptible individuals.\textsuperscript{16} Currently it is not recommended for the long term sedation of children, due to reports of lactic acidosis and even death in paediatric patients on long term propofol sedation\textsuperscript{21,22}, though the link is not proven and remains subject to some controversy. Recent surveys of the practice of sedation in ICUs demonstrate that benzodiazepines are most commonly used, but also indicate that propofol is being used in some units.\textsuperscript{4,5,23,24} The main impediment to its use appears to be the cost. Propofol is expensive and a twenty-four hour infusion may cost up to six times as much as an infusion of midazolam. In addition tachyphylaxis may occur with administration of propofol necessitating ever increasing doses for long term sedation, thereby further increasing cost.\textsuperscript{25} Despite this fact propofol may provide safer sedation for intensive care patients, particularly those with renal or hepatic impairment. The plasma clearance time for patients with end stage renal disease and moderate hepatic cirrhosis are comparable to normal.\textsuperscript{12} The terminal elimination half-life in ICU patients
receiving long-term infusions is reported to be from 24 – 48 hrs. However, rapid clearance from the plasma renders this clinically irrelevant.¹²
OBJECTIVE OF THE REVIEW

The objective of this review, was to present the best available evidence relating to the sedation of adult ventilated patients in (ICUs). The specific questions proposed were:

What is the most effective sedation regime for adult ventilated patients in ICU?
Which agent is the most effective sedative midazolam or propofol?
How should it be administered by bolus or continuous infusion?

The variables evaluated to assess the effectiveness of the regimes were the:

- ability to achieve a chosen sedation level; (as evaluated by use of a recognised sedation scale)
- time from cessation of sedation until extubation;
- duration of admission in ICU;
- incidence of haemodynamic complications during sedation (ie changes in heart rate and blood pressure).

Patients in ICUs are commonly administered narcotics with sedation and this factor may complicate the question because narcotics such as morphine also act as sedatives.\textsuperscript{4, 5, 21, 22}

This review did not specifically target the issue of narcotics. However, studies included in the review were examined to establish what narcotics were administered so the possible influence on sedation could be evaluated.

Quality of sedation

The aim of sedation in ICU is to provide anxiolysis and promote sleep. The level of sedation most commonly chosen in the United Kingdom, North America and Australia is light sedation. Described by Reeve and Wallace as “lightly sedated, periods of sleep, easily roused”.\textsuperscript{23} Both midazolam and propofol can produce various levels of sedation, from light, to hypnosis, to deep sleep. Therefore, the first question considered by this review was: Which drug provides the best quality of sedation, midazolam or propofol?
The outcome measure used to evaluate quality of sedation was: the ability to achieve a chosen sedation level, as evaluated by use of a recognised sedation scale, or expert observation.

Many different objective methods of assessing sedation levels have been investigated, such as lower oesophageal contractility. Bispectral Index of the EEG (electroencephlogram)\textsuperscript{26} has shown some promise, but at this time cost and technical problems preclude its widespread use. Currently, the recommended method to assess the sedation level is clinical observation using a recognised scale. Shelly states that a sedation scale should have the following characteristics, it should be “accurate, reproducible, simple, minimal work required, easy to chart, minimally invasive, no discomfort to the individual, not time consuming”.\textsuperscript{7} Many different sedation scales are currently used to assess sedation. The Glasgow Coma Scale (GCS) which was developed in 1970s\textsuperscript{27} is sometimes used\textsuperscript{3}, despite the fact that it was not designed for monitoring of therapeutic sedation, but for the assessment of patients with a recent head injury and to predict prognosis. It is not suitable to assess sedation in the critically ill.\textsuperscript{7,28} However, it was modified in 1989 to make it more suitable to assess sedation levels.\textsuperscript{29}

Other published scales include those developed by Cohen and Kelly, Ralley, Addenbrooke, and Riker.\textsuperscript{7,30} Current scales are ordinal rather than interval or ratio scales, as they are not evenly spaced and have no true zero points.\textsuperscript{31} The scale most commonly used in research appears to be the Ramsay scale, which was first published in 1974.\textsuperscript{32} The scale has the following levels:

**Awake Levels**

1. Patient anxious and agitated or restless or both.
2. Patient cooperative, orientated and tranquil.
3. Patient responds to commands only.

**Asleep levels (Dependent on response to a glabella tap or loud auditory stimulus)**

5. Sluggish response.
6. No response.
Another problem with most sedation scales is that their reliability and validity has not been established. Reliability is the ability of a tool to reproduce results on repeated measurement. Validity is its capacity to measure what it is designed to measure. Until recently there were no published studies which investigated the reliability or validity of the Ramsay scale. In 1996 Shah, Clack, Chea, Tayong and Anderson compared a modified Ramsay scale with Bispectral index of the EEG (BIS) and demonstrated good correlation (r = 0.71). The BIS is a “multivariate discriminate analysis of the EEG”. In 1998 Magarey compared three sedation scales, the Ramsay, a visual analogue scale (VAS) and scale developed for a specific unit. Forty three independent simultaneous ratings were performed by the investigator, an intensivist and the bedside nurses, on a total of twenty two patients. The results were compared for correlation and total percentage agreement. For all scales there was good correlation between raters. The lowest total percentage agreements occurred with the VAS and for the Ramsay scale these ranged from 51% to 67%. Despite the fact that it has not been extensively tested for reliability and validity, the Ramsay scale is still considered to be the gold standard for assessing sedation in ICU.

As the observations of experts may also be subject to bias and their reliability is questionable, the opinion of the patients themselves would be the best measure of quality of sedation produced. However, midazolam is an excellent amnesic agent and the dose required to produce amnesia in 90% of individuals is 0.045mg/kg or 2.7mg in a 60kg person. This is a small dose for intensive care patients. Propofol is not an effective amnesic agent and therefore memories of the sedation time cannot be considered to be a reliable guide to the effectiveness of midazolam compared to propofol.
Problems Relating to Sedation

Over-sedation

One of the main complications of sedation is over-sedation, which may prolong weaning times and increase morbidity. The outcome measures that were considered in order to assess the probability of over-sedation were:

- time from cessation of sedation until extubation; and
- duration of admission in ICU.

Haemodynamic complications

Cardiovascular system (CVS) depression, in particular hypotension, may limit the usefulness of some sedating drugs. In order to compare the propensity of propofol or midazolam to cause CVS depression the incidence of haemodynamic complications was evaluated, in particular changes in heart rate and blood pressure. Thus the outcome measure considered was:

- the incidence of haemodynamic complications during sedation (changes in heart rate and blood pressure).

METHODS

Criteria for considering studies

Types of Participants

This review considered all studies that included adult ventilated patients in intensive care units. The data were analysed for each specific subgroup such as, critically ill patients, and post-cardiac surgery and combined when appropriate. For example, when the duration of sedation is similar the data may be combined. Studies conducted on paediatric patients or during anaesthesia were excluded. Propofol is not currently recommended for use in paediatric ICUs, due to reports of complications such as lactic acidosis and even deaths relating to its use. Nevertheless, this issue remains controversial as the link between propofol and these complications has not been proven.

The ideal level of sedation in ICU has been described as “lightly sedated, periods of
sleep easily aroused”. During anaesthesia these drugs are administered with different aims, not just to provide sedation “a calm and restful state”, but to induce anaesthesia, “complete loss of sensation”. Studies done on patients in recovery units or cardiac units and who were not artificially ventilated, were excluded as sedation in this population must be managed in an entirely different manner to avoid the possibility of respiratory depression.

Interventions of interest are those relating to the sedation of adult ventilated patients in intensive care and included:
- use of midazolam versus propofol with or without concurrent administration of narcotics; and
- continuous infusions versus intermittent bolus administration of sedation.

Types of Outcome Measures
The effectiveness of sedation was evaluated by the following outcome measures:
- The ability to achieve desired sedation level as measured by a sedation scale or expert observation;
- length of time from cessation of sedation till extubation and recovery time;
- Duration of admission in ICU; and
- Incidence of haemodynamic complications during sedation.

Types of Studies
The review considered randomised controlled trials that evaluated the effectiveness of midazolam and propofol to sedate adult ventilated patients in ICUs. The search was conducted to locate studies that compared midazolam and propofol for the sedation of adult ventilated patients in intensive care. It is ideal to use randomised controlled trials (RCTs) as these are considered to be the best form of evidence, and to be less susceptible to bias.
**Search strategy**

The search sought all published and unpublished studies relating to the research question. The initial search was performed using the databases MEDLINE and CINAHL. It is essential that the search is not limited to MEDLINE, as this database only represents 23% of medical type journals.\(^{39}\) It is recommended that the databases CINAHL and EMBASE also be searched.\(^ {40}\) The Cochrane Collaboration maintains a database of current and anticipated reviews and EMBASE lists journals relevant to this review that are not indexed on the other bases, such as The Journal of Drug Development. Finally, the reference lists and bibliographies of the relevant articles were also examined to identify any new articles. The initial search terms were:

- sedation
- intensive care
- therapy
- ventilation
- mechanical ventilation
- propofol
- midazolam
- propofol and midazolam

The databases searched included:

- CINAHL
- MEDLINE
- Current contents
- The Cochrane Library
- Expanded Academic Index
- EMBASE
- Australian and New Zealand Scientific meeting on intensive care, conference proceedings from 1994.
- Papers First
- Proceedings First
The search for unpublished studies included the Dissertation Abstracts International, Papers First and Proceedings First, which located unpublished conference papers and posters on the subject. McManus and colleagues state that it is predicted that, only about half of the relevant articles will be identified by electronic searching and it is recommended that relevant journals are also hand searched. A hand search of Intensive Care Medicine and Critical Care Medicine from 1989 was conducted. The Australian and New Zealand meeting on intensive care proceedings were also hand searched from 1994 in order to locate unpublished research. In addition several experts were contacted to identify any unpublished research. Due to resource and time limitations, non-English articles were excluded from the search. When a relevant poster or conference presentation abstract was located, the author was contacted in writing to request details of the paper to establish if the article had been published. The studies identified by this search were assessed for their relevance to the review question based on the information provided in the title, abstract and descriptor/MeSH terms. If studies met the inclusion criteria the full text was obtained. The studies that were identified from the search of reference lists were assessed for relevance, by evaluation of the title.

Two hundred and twelve papers that appeared to meet the inclusion criteria were retrieved. One hundred and sixty eight papers were found to be general discussion papers, or did not compare propofol with midazolam. These were not included in the study. Of the remaining forty-four, eight were found to be duplicates. A total of thirty-six studies were included in the review. After evaluation of the methodological quality using the developed appraisal form, sixteen studies fulfilled the conditions and were considered in the initial analysis. The studies that were excluded after appraisal were included in the narrative review; this is because with many papers inadequate reporting of the method caused them to be excluded. Evans indicates that while it is important not to include the research that does not meet appraisal guidelines in meta-analyses, these may still be included in the narrative review.
Assessment of methodological quality

The methodological quality of the identified articles was assessed using a checklist based on the work of the Cochrane Collaboration and the Centre for Reviews and Dissemination (Appendices 1 & 2). Randomised controlled trials (RCTS) were considered in this review as on the hierarchy of evidence, these are considered to be the least susceptible to bias. As this study is being conducted as part of a doctorate program, the articles were only assessed by the reviewer. However, several articles were also appraised by an expert in the performance of systematic reviews to assess for concordance. Studies that fulfilled the first four criteria on the appraisal form, were included in the initial analysis. Excluded articles were also considered in the narrative analysis.

Data collection

Data were extracted using a form developed for the review (Appendix 3).

Data synthesis

Data from studies which compared propofol with midazolam were combined for meta-analysis where appropriate. Where possible, standardised mean differences and their 95% confidence intervals were calculated for each study included in the review. Studies were evaluated for homogeneity, which was also evaluated by assessing if the confidence interval lines overlap and the chi-square test. If there was little or no overlap, possible reasons for heterogeneity were further investigated. In particular the studies were evaluated to see if they had the same types of participants, interventions and outcome measures. Meta-analysis was used to estimate the effectiveness and relative value of the different interventions. For all meta-analyses, propofol was on the left side of the graph and midazolam on the right. The outcome data in the meta-analysis is all negative data. For example, increased extubation time and recovery time is a negative outcome. Thus if the standardised mean difference and 95% confidence intervals are less than zero this indicates a significant effect favouring propofol, whereas if they are
greater than zero the result favours midazolam. Raw data were requested from authors where standard deviations or mean scores were not published. Where statistical pooling was not appropriate or the data were not suitable, the findings of studies were considered in a narrative summary.

RESULTS
All studies were evaluated for their relevance to the question and their methodological rigour. Any study in which patients received paralysing agents was excluded. This is because evaluation of the quality of sedation, extubation time, recovery time, haemodynamic responses and length of admission may all be complicated by the use of paralysing agents. It is not possible to use a sedation scale to assess consciousness if the patient is paralysed and many factors variably influence the metabolism and excretion of these drugs. These include renal and hepatic function, temperature, use of other drugs and pH. In addition, critical illness neuropathy may occur when these drugs are used in the critically ill, particularly in association with sepsis and the use of steroids. This condition results in prolonged weakness and will therefore influence weaning times and the length of admission. In addition some paralysing agents such as pancuronium may also cause haemodynamic variations such as tachycardia and hypertension.

The subgroups considered were;

- propofol infusions versus midazolam infusions for critically ill ventilated patients;
- propofol infusions versus midazolam infusions for patients ventilated following cardiac surgery;
- propofol infusions versus midazolam boluses for patients ventilated following cardiac surgery;
- propofol infusions versus midazolam infusions for patients ventilated following general surgery;
- propofol infusions versus midazolam infusions for patients ventilated for medical conditions & following general surgery;
• propofol infusions versus midazolam infusions for patients ventilated post head injury or neurological surgery; and
• propofol infusions versus midazolam infusions for patients who required ventilation for chronic obstructive pulmonary disease.

STUDIES LOCATED

Propofol Infusions versus Midazolam Infusions for Critically Ill Ventilated Patients

Fourteen studies were located which compared propofol with midazolam for the sedation of critically ill, ventilated patients. But after evaluation of the methodological quality using the appraisal form developed for the study, only five of the studies were considered in the analysis (see Table 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Inclusion</th>
<th>Rationale for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitkenhead, A. R.</td>
<td>Comparison of propofol and midazolam for sedation in critically ill patients</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Pepperman, M.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Willatts, S. M et al 1989</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrasco, G.</td>
<td>Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients. A cost-benefit analysis</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Molina, R.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costa, J. et al 1993</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrientos Vega, R.</td>
<td>Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Mar Sanchez Soria, M.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales Garcia, C. et al 1997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chamorro, C.</td>
<td>Comparative study of propofol versus midazolam in the sedation of critically ill patients: results of a prospective, randomized, multicenter trial</td>
<td>Excluded</td>
<td>Paralysing agents stated exclusion but given to patients in both groups. Groups not comparable.</td>
</tr>
<tr>
<td>de Latorre, F. J.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montero, A. et al 1996</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costa, J.</td>
<td>Cost of ICU sedation: comparison of empirical and controlled methods</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Cabre, I.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molina, R.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrasco, G.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruh, B. 1989</td>
<td>A comparison of propofol and midazolam for long-term sedation of ventilated patients: A cross over study.</td>
<td>Excluded</td>
<td>Not clear if groups comparable at entry</td>
</tr>
<tr>
<td>Glew, R. 1989</td>
<td>A comparison of propofol and midazolam</td>
<td>Excluded</td>
<td>Not clear if groups comparable at entry or how the outcomes were measured</td>
</tr>
<tr>
<td>Harris, C. E.</td>
<td>Propofol for long-term sedation in the intensive care unit. A comparison with papaveretum and midazolam</td>
<td>Excluded</td>
<td>Compares propofol with papaveretum and midazolam.</td>
</tr>
<tr>
<td>Grounds, R. M.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray, A. M. et al 1990</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>Included/Excluded</td>
<td>Reason</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kox, W.</td>
<td>Effect of sedation with alfentanil, Midazolam or propofol on oxygen transport variables in the critically ill</td>
<td>Excluded</td>
<td>Not clear if groups comparable at entry or if they were treated identically.</td>
</tr>
<tr>
<td>Brydon, C. 1990</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kress, J. P.</td>
<td>Sedation of critically ill patients during mechanical ventilation. A comparison of propofol and midazolam</td>
<td>Excluded</td>
<td>Groups not comparable patients with hepatic and renal failure not excluded.</td>
</tr>
<tr>
<td>O'Connor, M. F.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pohlman, A. S. et al 1996</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehmkuhl, P.</td>
<td>Intensive care sedation with propofol or midazolam infusions</td>
<td>Excluded</td>
<td>Not clear if groups comparable at entry or if they were treated identically.</td>
</tr>
<tr>
<td>Pichlmair, l. 1991</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manley, N.</td>
<td>A Cost Analysis of Alfentanil + Propofol vs Morphine + Midazolam for sedation of Critically Ill Patients</td>
<td>Excluded</td>
<td>Compares propofol and alfentanil with morphine &amp; midazolam</td>
</tr>
<tr>
<td>Fitzpatrick, R.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long, T. et al 1997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanchez Izquierdo Riera, J. A.</td>
<td>Propofol versus midazolam: safety and efficacy for sedating the severe trauma patient</td>
<td>Excluded</td>
<td>Paralysing agents used</td>
</tr>
<tr>
<td>Caballero Cubedo, R. E.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez Vela, J. L. et al 1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinbroum, A. A.</td>
<td>Midazolam versus propofol for long-term sedation in the ICU: a randomized prospective comparison</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Halpern, P.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rudick, V. et al 1997</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Propofol Infusions versus Midazolam Infusions for Patients Ventilated Post-cardiac Surgery

Nine studies were located which compared propofol infusions with midazolam infusions for the sedation of patients who were ventilated post-cardiac surgery. Six of the studies were considered in the analysis after evaluation of the methodological quality using the appraisal form developed for the study (see Table 2).

Table 2 Propofol Infusions versus Midazolam Infusions for Patients Ventilated Post-cardiac Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Inclusion</th>
<th>Rationale for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriansen, H. Van Overberge, L. Vermeyen, K. et al 1991</td>
<td>A comparison of midazolam and propofol to supplement sufentanil for coronary artery surgery and postoperative sedation.</td>
<td>Excluded</td>
<td>Not clear if groups comparable at entry</td>
</tr>
<tr>
<td>Carrasco, G. Cabre, L. Sobrepere, G. et al 1998</td>
<td>Synergistic sedation with propofol and midazolam in intensive care patients after coronary artery bypass grafting</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Chaudhri, S. Kenny, G. N. 1992</td>
<td>Sedation after cardiac bypass surgery: comparison of propofol and midazolam in the presence of a computerized closed loop arterial pressure controller</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Higgins, T. L. Yared, J. P. Estafanous, F. G. et al 1994</td>
<td>Propofol versus midazolam for intensive care unit sedation after coronary artery bypass grafting</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Roekaerts, P. M. Huygen, F. J. de Lange, S. 1993</td>
<td>Infusion of propofol versus midazolam for sedation in the intensive care unit following coronary artery surgery</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Searle, N. R. Cote, S. Tailliefer, J. et al 1997</td>
<td>Propofol or midazolam for sedation and early extubation following cardiac surgery</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>Snellen, F. Lauwers, P. Demeyere, R.</td>
<td>The use of midazolam versus propofol for short-term sedation following coronary artery bypass grafting</td>
<td>Included</td>
<td></td>
</tr>
</tbody>
</table>
Propofol Infusions versus Midazolam Boluses for Patients Ventilated Post-cardiac Surgery

Three studies were located which compared propofol infusions with midazolam bolii for the sedation of patients ventilated post-cardiac surgery. After evaluation of the methodological quality using the appraisal form developed for the study, all were included in the review (see Table 3).

Table 3 Propofol Infusions versus Midazolam Boluses for Patients Ventilated Post-cardiac Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
</tr>
</thead>
</table>
Propofol Infusions versus Midazolam Infusions for Patients Ventilated Following General Surgery

Six studies were located which compared propofol infusions with infusions of midazolam for the sedation of patients ventilated following general surgery. After evaluation of the methodological quality using the appraisal form developed for the study, two were included in the review (see Table 4).

Table 4 Propofol Infusions versus Midazolam Infusions for Patients Ventilated Following General Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Inclusion</th>
<th>Rationale for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyd, O. Mackay, C. J. Rushmer, F. et al 1993 77</td>
<td>Propofol or midazolam for short-term alterations in sedation</td>
<td>Excluded</td>
<td>Heavy sedation induced for physio</td>
</tr>
<tr>
<td>Hecht, U. Lehmkuhl, P. Pichlmayr, I. 78</td>
<td>Propofol for Maintenance of Sedation with EEG Monitoring</td>
<td>Excluded</td>
<td>Methodology unclear: randomisation, treatment, groups etc</td>
</tr>
<tr>
<td>Ronan, K. P. Gallagher, T. J. George, B. et al 1995 79</td>
<td>Comparison of propofol and midazolam for sedation in intensive care unit patients</td>
<td>Included</td>
<td></td>
</tr>
</tbody>
</table>
Propofol Infusions Versus Midazolam Infusions for Patients Ventilated for Medical Conditions and Following General Surgery

One study compared propofol with midazolam for the sedation of patients ventilated post surgery or in those with medical conditions. This study was included in the review.

Table 5 Propofol Infusions Versus Midazolam Infusions For Patients Ventilated For Medical Conditions & Following General Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyle, W. Shear, J. White, P. et al 1991</td>
<td>Long-term sedation in the intensive care unit propofol versus midazolam</td>
</tr>
</tbody>
</table>

Propofol Infusions versus Midazolam Infusions for Patients Ventilated Post Head Injury or Neurological Surgery

Three studies were located which compared propofol with midazolam for the sedation of patients ventilated post head injury or neurological surgery. After evaluation of the methodological quality using the appraisal form developed for the study, all were excluded (see Table 6).

Table 6 Propofol Infusions versus Midazolam Infusions for Patients Ventilated Post Head Injury or Neurological Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farling,P. Johnston, J. Coppel, D. 1989</td>
<td>Propofol infusion compared with morphine and midazolam bolus doses for sedation of patients with severe head injuries in the intensive care unit.</td>
</tr>
<tr>
<td>Excluded</td>
<td>Propofol compared with morphine and midazolam. Not clear if groups comparable at entry or if they were treated identically.</td>
</tr>
</tbody>
</table>

| Clarke, T. 1991 | Propofol compared with midazolam for sedation following prolonged neurosurgery. |
| Excluded         | Paralysing agents given |

| Plainer, B. Weinstabl, Ch. Spiss, CK. et al 1989 | Propofol vs midazolam in combination with sufentanil for continuous sedation in the neurosurgical ICU |
| Excluded         | Does not state whether the patients were ventilated. Not clear if groups comparable at entry. |
Propofol Infusions versus Midazolam Infusions for Patients who Required Ventilation for Chronic Obstructive Pulmonary Disease

One study compared propofol infusions versus midazolam infusions for patients who required ventilation for chronic obstructive pulmonary disease. After evaluation of the methodological quality using the appraisal form developed for the study, it was excluded (see Table 7).

Table 7 Propofol Infusions versus Midazolam Infusions for Patients who Required Ventilation for Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Rationale for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degauque, C.</td>
<td>A study to compare the use of propofol and midazolam for the sedation of patients with acute respiratory failure.</td>
<td>The groups were not treated identically, supplementary sedation administered.</td>
</tr>
</tbody>
</table>
Quality of Sedation

The first variable considered by this study was: The ability of the sedation regime to achieve a chosen sedation level as evaluated by a recognised scale. Most studies reported data relating to the quality of sedation as the mean percentage of time at ideal sedation, as evaluated by the Ramsay scale. Typically levels 2-4 or 2-5 were considered ideal. Most of the data were not suitable for meta-analysis as few studies reported standard deviations. For this reason the results are also presented in tables.

Quality of Sedation, Critically Ill Patients (General ICU Patients)

Of the five studies includes in the analysis four published data on the quality of sedation. There was no agreement in the results of the studies with several reporting that infusions of propofol produced significantly better quality sedation, another that midazolam produced better sedation and the third finding no difference (see Table 8).
<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M)</th>
<th>Measurement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitkenhead, A. R.</td>
<td>94% (1 - 100%)</td>
<td>93% (0-100%)</td>
<td>% time at Ramsay 2-5</td>
<td>Similar quality. Assessed continuously by the nurse caring for the patient.</td>
</tr>
<tr>
<td>Pepperman, M. L.</td>
<td>(n= 53)</td>
<td>(n= 47)</td>
<td>Most lightly sedated</td>
<td></td>
</tr>
<tr>
<td>Willatts, S. M. et al. 198948</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrasco, G. Molina, R.</td>
<td>93% (74 - 100%)</td>
<td>82% (73-100%)</td>
<td>% time at Ramsay 2-4</td>
<td>Propofol better statistically significant. Assessed continuously by the nurse caring for the patient.</td>
</tr>
<tr>
<td>Costa, J. et al. 199349</td>
<td>(n= 46)</td>
<td>(n= 42)</td>
<td>Patients lightly sedated</td>
<td></td>
</tr>
<tr>
<td>Costa, J. Cabre, I. Molina, r.</td>
<td>94% p&lt; 0.05</td>
<td>85% p&lt; 0.05</td>
<td>% time at required Ramsay</td>
<td>Always rated good or optimal.</td>
</tr>
<tr>
<td>Carrasco, G. 199432</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinbraum A. Halpern, P.</td>
<td>7.3± 0.1</td>
<td>8.2±0.1</td>
<td>VAS 1 totally unsatisfactory</td>
<td>Midazolam significantly better scores. Assessed at the end of the shift by the nurse caring for the patient.</td>
</tr>
<tr>
<td>Rudick, V. et al. 199761</td>
<td>(7.1 - 7.5)</td>
<td>(8.7-8.4)</td>
<td>10 optimal rating by nurses</td>
<td>Propofol patients more agitated during &amp; post sedation.</td>
</tr>
<tr>
<td></td>
<td>p&lt; 0.001</td>
<td>p&lt; 0.001</td>
<td>Agitation Hrs/Day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6±0.3</td>
<td>1.7±0.2</td>
<td>5 point sedation scale Awake – deeply asleep</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt; 0.01</td>
<td>p&lt; 0.01</td>
<td>Aim 2-3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n= 31)</td>
<td>(n= 36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.3±0.1</td>
<td>2.2±0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt; 0.05</td>
<td>p&lt; 0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There are several possible reasons for the differences between the studies. Firstly in the studies by Aitkinhead, Costa and Carrasco the Ramsay scale was used to assess quality of sedation and for the study by Weinbraum a visual analogue and a five point scale were used. Secondly, the ideal sedation level was considered to be Ramsay 2-5 in the study by Aitkinhead, varied in the study by Costa and 2-4 in Carrasco’s. Other studies not included in the initial analysis also produced conflicting results, with the study by Sanchez Izquierdo Riera, Caballero Cubedo and Perez Vela et al finding both regimes were equally effective, Glew reporting that “patients on propofol were more often and more easily sedated to Ramsay 2 - 3” and Lehmkuhl and Pichlmar stating that midazolam infusions provided “deep even sedation” and propofol “smooth
sedation”. Thus, no conclusions could be drawn on which regime provides the best quality of sedation in critically ill, general ICU patients. However, several studies reported a higher incidence of agitation in patients during and following maintenance infusions with propofol.\textsuperscript{54,61}

Only one study in this group by Lehmkuhl and Pichlmar considered the use of boli of midazolam as compared to infusions of midazolam or propofol.\textsuperscript{58} The authors found that the patients on boli of midazolam had “marked changes in depth of sedation” and “unwanted phases of wakefulness and agitation”.
Quality of Sedation, Propofol Infusions versus Midazolam infusion
Post-cardiac Surgery

Six studies were included in the analysis that compared infusions of midazolam with propofol for post-cardiac surgery patients. Of these, five considered the quality of sedation (see Table 9).

Table 9 Quality of Sedation Post-cardiac Surgery Patients Propofol versus Midazolam infusions

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam(M)</th>
<th>Measurement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco, G. Cabre, L. Sobrepere, G. et al 1998</td>
<td>93% Hrs adequate n=25 14.4± 1.5 hrs</td>
<td>88% Hrs adequate n=25 14.1±1.1 hrs</td>
<td>Modified GCS Cook Palma ≥12 insufficient 4-7 insufficient</td>
<td>Assessed on continuous basis by nurse. Similar efficacy</td>
</tr>
<tr>
<td>Chaudhri, S. Kenny, G. N. 1992</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higgins, T. L. Yared, J. P. Estafanous, F. G. et al 1994</td>
<td>2-4 70% n=42 55% level 3 Completely comfortable or no recall 78%</td>
<td>2-4 80% n=38 65% level 3 Completely comfortable or no recall 80%</td>
<td>% time Ramsay level 2 - 4 % time Ramsay 3</td>
<td>No significant difference.</td>
</tr>
<tr>
<td>Searle, N. Cote, S. Taillefer, J et al 1997</td>
<td>67% n=21 sedation time 4hrs</td>
<td>65.4% n=20 sedation time 4hrs</td>
<td>Ramsay 2 - 4</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Snellen, F. Lauwers, P. Demeyere, R. et al 1990</td>
<td>59.6% n=20 sedation time 632± 15 mins</td>
<td>53% n= 20 sedation time 635± 15 mins</td>
<td>Ramsay 2 - 4</td>
<td>No significant difference</td>
</tr>
</tbody>
</table>

None of the studies reported a significant difference in the quality of sedation provided by the different regimes. The reasons for the agreement in results may be due to the homogenous patient groups and the same aim of sedation (Ramsay 2 – 4) in the majority of studies. One study not included in the initial analysis also reported that both regimes provided adequate sedation. It is noteworthy that patients sedated with propofol had more hours of sedation assessed as a satisfactory level. But these assessments were only made every three hours. Therefore from these studies it can be concluded that infusions of midazolam or propofol provide similar quality sedation.
Post-cardiac Surgery Patients Propofol infusion versus Midazolam bolus Quality of Sedation

Two of the studies which compared propofol infusions with boli of midazolam for post-cardiac surgery patients reported on the quality of sedation (see Table 10).

Table 10 Post-cardiac Surgery Patients Propofol infusion versus Midazolam bolus Quality of Sedation

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M) bolus</th>
<th>Measurement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grounds, R. M. Lalor, J. M. Lumley, J. 1987&lt;sup&gt;1&lt;/sup&gt;</td>
<td>44.6%</td>
<td>28.1%</td>
<td>% time Ramsay level 3</td>
<td>Preliminary report. Exclusion: none given, groups comparable Midazolam group required significantly more analgesia.</td>
</tr>
<tr>
<td>McMurray, T. J. Collier, P. S. Carson, I. W. 1990&lt;sup&gt;2&lt;/sup&gt;</td>
<td>91%</td>
<td>81%</td>
<td>% time satisfactory sedation</td>
<td>Midazolam group required significantly more analgesia. Exclusion: hepatic dysfunction, current benzodiazepine therapy, allergy to P or M.</td>
</tr>
</tbody>
</table>

Both studies demonstrated that propofol infusions provided better quality sedation than boli of midazolam.

Quality of Sedation Surgical Patients

Two of the studies which compared propofol infusions with midazolam infusions in post-operative patients reported data on quality of sedation (see Table 11).

Table 11 Quality of Sedation Surgical Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M)</th>
<th>Measurement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronan, K. P. Gallagher, T. J. George, B. et al 1995&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2.5±0.7 p 0.05 2.2±0.62 p 0.05 n=30</td>
<td>3.3±1.1 p 0.05 2.48±0.63 p 0.05 n=30</td>
<td>Average Ramsay Nurses’ rating of patient tolerance of ICU 1 excellent 5 poor Ratings at 5 – 90 mins</td>
<td>Post op IPPV surgical, orthopaedic, intra abdo patients. Target Ramsay 3 Drugs titrated to score 12 – 24 hrs sedation Nurse’s rating of tolerance significantly better for propofol.</td>
</tr>
<tr>
<td>Wolfs, C. Kimbimbi, P Colin, L. et al 1991&lt;sup&gt;8&lt;/sup&gt;</td>
<td>2.94 n=17</td>
<td>3.16 n=17</td>
<td>Average Ramsay</td>
<td>Abdo surgery patients IPPV without NMBAs Sedation equally satisfactory. Target Ramsay 3 –4 6 hrs sedation</td>
</tr>
</tbody>
</table>
The results of these studies are conflicting. One possible reason for the different results may be that the patients were post-operative and in the study by Wolfs and colleagues they received a standard infusion of analgesia and in the study by Ronan, Gallager and George et al. patients were given boli of analgesia to control pain. Neither study reported the percentage of time of adequate sedation.

Quality of Sedation Surgical and Medical Patients
The single study that compared the efficacy of propofol infusions with midazolam infusions in surgical and medical patients found both regimes were equally effective. These reported that ideal sedation (evaluated by Ramsay scale) was achieved 71.1% of the time for patients sedated with propofol and 71.4% of the time for patients sedated with midazolam.

Other studies reporting on quality of sedation
The study which investigated sedation in patients ventilated for chronic obstructive airways disease reported that the quality of sedation was better in patients treated with propofol, though the number of patients was very small (five & six). In addition, the evaluation was performed by nurses, who did not use the Ramsay scale to evaluate sedation. This study was eliminated from the initial analysis as patients were given supplementary sedation. A pilot study of post neurosurgery patients by Plainer, Weinstable, Spiss et al. was also excluded from the initial analysis. Nevertheless, this study reported similar quality of sedation as assessed by EEG and somato-sensory evoked potentials (SSEP).

Quality of Sedation Conclusion
The conclusions which can be drawn from the results for the various groups are that:
- there are conflicting results on which regime provides better quality sedation in critically ill, general ICU patients;
• both propofol infusions and midazolam infusions provide similar quality of sedation in patients post-cardiac surgery and in medical and surgical patients;
• propofol infusions provide better quality sedation than boli of midazolam in post-cardiac surgery patients; and
• reports on which regime provides better quality sedation in surgical patients are conflicting.

Thus the only group in which the results are conclusive is post-cardiac surgery patients. This may be because this group of patients are more homogenous with less variation in diagnosis and other treatments. Though most studies used the Ramsay scale for assessment of quality of sedation, this scale has not been extensively tested for its reliability and validity. There appears to be only one study published that tests the reliability of the Ramsay as compared to Bispectral index of the EEG. From searches of the literature it appears other scales, such as the modified Glasgow Coma Scale by Cook and Palma, do not appear to have been tested for reliability and validity.

**Time from Cessation of Sedation until Extubation**

**Time From Cessation of Sedation until Extubation and in General ICU Patients**

Three studies which compared infusions of propofol with midazolam in general ICU, critically ill, patients reported extubation times (time from cessation of sedation until extubation).
One study reported the times separately for short, medium and long-term sedation.\(^{49}\)

Extubation times from three studies in which patients were sedated from 24 hrs to 7 days were combined in meta-analysis.\(^{49,50,52}\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Extubation time for propofol (P)</th>
<th>Extubation time for midazolam (M)</th>
<th>Length of time sedated</th>
<th>Sedation level</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitkenhead, A. R. Pepperman, M. L. Willatts, S. M. et al. 1989 (^{48})</td>
<td>0.83 hrs (0-0.22) 5 mins (range 0-13) n= 21</td>
<td>2.47hrs (0.28 – 9.25) 148 mins (range 17-555) n= 18</td>
<td>At least 12hrs</td>
<td>Ramsay 2-4</td>
<td>Critically ill pts. Exclusions: allergy to P/M, pregnancy, coma, head injury, muscle relaxants, sedation &amp; etomidate during previous 24 hrs.</td>
</tr>
<tr>
<td>Barrientos Vega, R. Mar Sanchez Soria, M. Morales Garcia, C. et al. 1997 (^{50})</td>
<td>34.8± 29.4 hrs p 0.0001 n= 25</td>
<td>97.9 ± 54.6 hrs p 0.0001 n=27</td>
<td>P 141± 76.8hrs</td>
<td>M 136.8± 74.4hrs Ramsay 4 - 5</td>
<td>Medical &amp; Surgical Pts Apache P 21.2 / M 21.3 Exclusions: age &lt;14, Cranial trauma, coma, Liver disease, history of alcohol abuse, muscle relaxants, pregnancy.</td>
</tr>
<tr>
<td>Carrasco, G. Molina, R. Costa, J. et al. 1993 (^{49})</td>
<td>0.3± 0 hrs 18± 0 mins p&lt;0.05 n=20 0.4± 0.1 hrs 24± 6 mins p&lt;0.05 n=16 0.8± 0.3 hrs 48± 18 mins p&lt;0.05 n=10</td>
<td>2.5 ± 0.9 hrs 150± 54 mins p&lt;0.05 n=20 13.5± 4 hrs 810± 240 mins p&lt;0.05 n=12 36.6± 6.8 hrs 2196± 408 mins p&lt;0.05 n=10</td>
<td>Short term</td>
<td>&lt; 24 hrs</td>
<td>Critically ill pts SAPS P 12.5 M 13.1 Exclusions: allergy to P/M, pregnancy, coma, Cranial trauma, neuro surgery, muscle relaxants, gross obesity.</td>
</tr>
<tr>
<td>Costa, J. Cabre, I. Molina, r. Carrasco, G.1994(^{52})</td>
<td>2.0 ± 0.4 hrs p&lt;0.05</td>
<td>7.2± 1.6hrs p&lt;0.05</td>
<td>P 35.4±7.5</td>
<td>M 35.1±8.1</td>
<td>Critically ill Ventilation at least 72hrs Exclusions: Coma Neurosurgery Cranial trauma Hepatic or renal disease Muscle relaxants</td>
</tr>
</tbody>
</table>
### Figure 1

**Review:** Propofol versus midazolam  
**Comparison:** Extubation Time  
**Outcome:** Extubation Time Critically ill

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol</th>
<th>Midazolam</th>
<th>WMD (95%CI) Fixed</th>
<th>Weight</th>
<th>Year</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimido &amp; Vega</td>
<td>25</td>
<td>14.00 (20.41)</td>
<td>27</td>
<td>97.90 (54.00)</td>
<td>&lt;</td>
<td>0.0</td>
</tr>
<tr>
<td>Canino</td>
<td>18</td>
<td>0.40 (0.70)</td>
<td>12</td>
<td>13.50 (4.00)</td>
<td>&lt;</td>
<td>0.0</td>
</tr>
<tr>
<td>Deu</td>
<td>53</td>
<td>2.00 (2.40)</td>
<td>51</td>
<td>7.20 (1.00)</td>
<td>□</td>
<td>100.0</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>54</td>
<td>99</td>
<td>□</td>
<td>100.0</td>
<td>-1.025 (0.0070, 0.007)</td>
<td>1994</td>
</tr>
</tbody>
</table>

The meta-analysis revealed non-homogeneity between the studies. Though all patients were considered to be critically ill, there was considerable variation in the diagnoses of patients, even within studies. Patients with renal failure (which greatly influences the excretion of midazolam) were excluded in one study and patients with hepatic failure were excluded from two. In addition, variation in the procedures used to wean patients from ventilation would have a considerable influence on the result. Nevertheless, in all studies patients took less time to wean from ventilation when propofol was used for sedation.

Two of the three studies not considered in the analysis reached the same conclusions, Glew reported that there was no significant difference in weaning times between groups, but this study has no information regarding inclusion and exclusion criteria and was an extremely small study with 15 in one group and 14 in the other.
Time From Cessation of Sedation Till Extubation and Post-cardiac Surgery Patients

Five studies which compared infusions of propofol with midazolam for post-cardiac surgery patients reported extubation times (time from cessation of sedation till extubation) (see Table 13).

Table 13 Post-cardiac Surgery Propofol versus Midazolam Infusions Extubation Time

<table>
<thead>
<tr>
<th>Study</th>
<th>Extubation time for propofol (P)</th>
<th>Extubation time for midazolam (M)</th>
<th>Length of time sedated</th>
<th>Sedation level</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco, G. Cabre, L. Sobrepere, G. et al 1998^63</td>
<td>0.9 hrs ± 0.3 hrs 54 ± 18 mins p = 0.01 n=25</td>
<td>2.3 ± 0.8 hrs 138 ± 48 mins p = 0.01 n=25</td>
<td>Modified GCS Cook &amp; Palma 8 – 11 points</td>
<td>Sedation time P = 14.4 ± 1.5 hrs M = 14.1 ± 1.1 hrs</td>
<td>Exubation significantly less time.</td>
</tr>
<tr>
<td>Chaudhri, S. Kenny, G. N. 1992^64</td>
<td>3.28 hrs (0-1) 197 mins (30-720) n=20 3 pts required ventilation,</td>
<td>4.08 hrs (0-9.33) 245 mins (0 – 560) n=20 1 pt required ventilation,</td>
<td>Sedation time not clear &gt; 4hrs 6 point sedation score aim 3 – 4 (light)</td>
<td></td>
<td>Propofol less time but not significant.</td>
</tr>
<tr>
<td>Rockaerts, P. Huygen, F. deLange, S. 1993^68</td>
<td>4.17 ± 2.25 hr 250 ± 135 min p&lt;0.014 n=15</td>
<td>6.57 ± 2.13 hr 391 ± 128 min p&lt;0.014 n=15</td>
<td>Ramsay 5 Deep sedation Sedation time: P 9.5 ± 2 hrs M 9.8 ± 2.6 hrs</td>
<td></td>
<td>Propofol shorter extubation time</td>
</tr>
<tr>
<td>Searle, N. Cote, S. Taillefer, J et al 1997^69</td>
<td>1.46 ± 1.09 hr 87.5 ± 65.4 min p NS n= 21</td>
<td>1.53 ± 0.99 hr 91.5 ± 59.4 min p NS n= 20</td>
<td>Ramsay 2 - 4 Sedation time:4hrs both groups</td>
<td></td>
<td>No significant difference</td>
</tr>
<tr>
<td>Snellen, F. Lauwers, P. Demeyere, R. et al 1990^70</td>
<td>2.57 ± 0.55 hrs 154 ± 33 mins p 0.059 n=20</td>
<td>4.05 ± 0.73 hrs 243 ± 44 mins p 0.059 n=20</td>
<td>Ramsay 2 - 4 sedation time P 10.5 ± 0.25 hrs M 10.6 ± 0.25 hrs</td>
<td></td>
<td>Significantly shorter in propofol</td>
</tr>
</tbody>
</table>

Meta-analysis of the results revealed heterogeneity (see Figure 2 & 3). This may be due to the short sedation time in the study by Searle et al.^69 In addition, all other studies
excluded patients with renal and hepatic disease. When this study was excluded from the meta-analysis the results revealed homogeneity.

**Figure 2**

**Review:** Propofol versus midazolam  
**Comparison:** Extubation time  
**Outcome:** Post Cardiac Surgery Infusion A

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol mean(sd)</th>
<th>Midazolam mean(sd)</th>
<th>WMD (95%CI Fixed)</th>
<th>Weight</th>
<th>WMD (95%CI Fixed)</th>
<th>Year</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco &amp; Cabre</td>
<td>25.00 (0.00) 25</td>
<td>2.30 (0.19) 25</td>
<td>48.6</td>
<td>-1.400 (1.735, -1.010)</td>
<td>1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rockearts</td>
<td>15.00 (0.20) 15</td>
<td>6.37 (2.16) 15</td>
<td>2.3</td>
<td>-2.400 (3.968, -0.832)</td>
<td>1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seale</td>
<td>21.00 (0.36) 20</td>
<td>1.55 (0.49) 20</td>
<td>13.7</td>
<td>-0.070 (0.707, 0.607)</td>
<td>1997</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiellsen</td>
<td>20.00 (0.36) 20</td>
<td>4.28 (0.76) 20</td>
<td>34.8</td>
<td>-1.480 (1.981, -1.074)</td>
<td>1990</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>61.00 60</td>
<td></td>
<td></td>
<td>100.0</td>
<td>-1.200 (1.564, -1.032)</td>
<td>1990</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3**

**Review:** Propofol versus midazolam  
**Comparison:** Extubation time  
**Outcome:** Post Cardiac Surgery Infusion B

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol mean(sd)</th>
<th>Midazolam mean(sd)</th>
<th>WMD (95%CI Fixed)</th>
<th>Weight</th>
<th>WMD (95%CI Fixed)</th>
<th>Year</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco &amp; Cabre</td>
<td>28.00 (0.90) 28</td>
<td>2.30 (0.19) 28</td>
<td>57.3</td>
<td>-1.400 (1.735, -1.085)</td>
<td>1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rockearts</td>
<td>15.00 (1.25) 15</td>
<td>0.57 (2.13) 15</td>
<td>2.6</td>
<td>-2.400 (3.968, -0.832)</td>
<td>1993</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiellsen</td>
<td>20.00 (0.36) 20</td>
<td>4.08 (0.73) 20</td>
<td>40.4</td>
<td>-1.480 (1.981, -1.074)</td>
<td>1990</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>60.00 60</td>
<td></td>
<td></td>
<td>100.0</td>
<td>-1.450 (1.712, -1.205)</td>
<td>1990</td>
<td></td>
</tr>
</tbody>
</table>

These results were supported in other studies not included in the initial analysis. Both reported shorter extubation times for patients sedated with propofol infusions.62,66
Time From Cessation of Sedation Till Extubation Post-cardiac Surgery Patients Propofol infusion versus midazolam bolus

Two studies that compared propofol infusions with midazolam bolus for post-cardiac surgery patients reported extubation times (time from cessation of sedation till extubation) (see Table 14).

Table 14 Post-cardiac Surgery Patients Propofol Infusion versus Midazolam Bolus, Extubation Time

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M) bolus</th>
<th>Sedation level &amp; Time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grounds, R. M.</td>
<td>0.42± 0.5 hrs 24.9± 2.97 mins p &lt; 0.001 n=30</td>
<td>3.77± 0.38 hrs 226.1± 22.8 mins p &lt; 0.001 n=30</td>
<td>Sedation time not clear Ramsay 3 2-5 suitable</td>
<td>Preliminary report. propofol significantly less time</td>
</tr>
<tr>
<td>Lumley, J. 1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McMurray, T. J.</td>
<td>0.2 ± 0.42 hrs 11.9± 2.5 mins p &lt; 0.001 n=50</td>
<td>2.13± 0.17 hrs 127.9± 9.9 mins p &lt; 0.001 n=50</td>
<td>P 16.7 (0.4) Mc 16.2 (0.3) Ramsay 2-5</td>
<td>propofol significantly less time</td>
</tr>
<tr>
<td>Collier, P. S. Carson, I. W. 1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meta-analysis (see Figure 4) showed a significant difference in the extubation times, with patients sedated with propofol taking less time to extubate.

Figure 4

The meta-analysis revealed non-homogeneity between the studies. Reasons for this may include, different inclusion criteria for the participants, as one study included patients following valve surgery and AV canal repair, while the other was performed exclusively on post-cardiac surgery patients. The dosage of the sedative agents also differed.
Other Studies Reporting Time Till Extubation

Several other studies reported extubation times but all were excluded from the initial analysis. Nevertheless, all showed shorter extubation times for patients sedated with propofol compared to those sedated with infusions of midazolam.\(^74,78,83\)

**Extubation Time Conclusion**

When the extubation times of all studies (where mean and standard deviation were reported) were combined in meta-analysis considerable heterogeneity was demonstrated. However, all studies reported shorter extubation time for patients treated with propofol infusions (see Figure 5):

**Figure 5**

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol mean[SD]</th>
<th>Midazolam mean[SD]</th>
<th>WMD [95% CI Fixed]</th>
<th>Weight %</th>
<th>WMD [95% CI Fixed]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrientes Vega</td>
<td>25 0.40 [0.45]</td>
<td>27 0.42 [0.45]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00 [0.21, 0.56]</td>
</tr>
<tr>
<td>Carmazco</td>
<td>20 0.20 [0.03]</td>
<td>20 0.50 [0.30]</td>
<td>0.0</td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Carmazco &amp; Ciele</td>
<td>25 0.30 [0.50]</td>
<td>25 0.20 [0.30]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00 [0.00, 0.20]</td>
</tr>
<tr>
<td>Costa</td>
<td>53 0.70 [0.10]</td>
<td>51 0.40 [0.10]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00 [0.00, 0.20]</td>
</tr>
<tr>
<td>Gracia</td>
<td>30 0.45 [0.50]</td>
<td>30 0.75 [0.45]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00 [0.00, 0.20]</td>
</tr>
<tr>
<td>McDonald</td>
<td>60 0.20 [0.45]</td>
<td>60 0.30 [0.20]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00 [0.00, 0.20]</td>
</tr>
<tr>
<td>Rokkevold</td>
<td>10 0.10 [0.20]</td>
<td>10 0.20 [0.20]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00 [0.00, 0.20]</td>
</tr>
<tr>
<td>Sealee</td>
<td>21 0.30 [0.50]</td>
<td>21 0.50 [0.30]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00 [0.00, 0.20]</td>
</tr>
<tr>
<td>Snelten</td>
<td>10 0.50 [0.50]</td>
<td>10 0.70 [0.50]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00 [0.00, 0.20]</td>
</tr>
<tr>
<td>Total (99%)</td>
<td>259</td>
<td>259</td>
<td>100.0</td>
<td>2.238</td>
<td>2.238 [2.332, 2.130]</td>
</tr>
<tr>
<td>Chi-square 3.68 [df=7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A further meta-analysis combining the critically ill, general ICU patients and post-cardiac surgery patients treated with infusions and sedated short term < 24hrs demonstrated homogeneity and significantly shorter extubation times in patients treated with propofol infusions. The study by Searle was excluded from this analysis due to the extremely short sedation time (four hours).\(^89\)
Figure 6

Review: Propofol versus midazolam
Comparison: Extubation Time
Outcome: Extubation Time Post Cardiac Surgery Infusion & Critically Ill

The conclusion that can be drawn from this result, is that patients sedated with propofol infusions take less time to extubate from the cessation of sedation, than those sedated with infusions or boli of midazolam.
Time From Cessation of Sedation Until Recovery

Recovery Time Critically Ill, General ICU Patients

Four studies that compared propofol infusions with midazolam infusions in critically ill, general ICU patients reported recovery times (see Table 15).

Table 15 Critically Ill, General ICU Patients Recovery Times

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M)</th>
<th>Measurement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitkenhead, A. R. Pepperman, M. L. Willatts, S. M. et al. 1989</td>
<td>29 (73%) Immed</td>
<td>23 (61%) Immed</td>
<td>Minutes from cessation of sedation till patient could obey specific command</td>
<td>Ramsay 2-5 Sedation time at least 12hrs</td>
</tr>
<tr>
<td></td>
<td>10 within 20 mins</td>
<td>6 within 20 mins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 pt 105 mins n=53</td>
<td>405 longest n=47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrasco, G. Molina, Costa, J. R. et al. 1993</td>
<td>(short term)</td>
<td>(short term)</td>
<td>Response to simple orders minutes</td>
<td>Ramsay 2-5 Sedation time: Short term &lt; 24 hrs Medium term 24 hrs – 7 days (P 4.85±0.74, M 4.70±0.71 days, P 116.4± 17.9, M 113±17.2 hrs) Long term &gt; 7 days</td>
</tr>
<tr>
<td></td>
<td>1.0±0 hrs 60±0 mins p&lt;0.05 n=20</td>
<td>3.6±0.8 hrs 216±48 mins p&lt;0.05 n=20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4±0.5 hrs 84±30mins p&lt;0.05 n=16</td>
<td>(Med term) 21.0±5.8 hrs 1260±348mins p&lt;0.05 n=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.8±0.7 hrs 108±42 mins p&lt;0.05 n=10</td>
<td>(Long term) 54±12.3 hrs 3240±738mins p&lt;0.05 n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costa, J. Cabre, I. Molina, r. Carrasco, G.1994</td>
<td>3.2±0.4 hrs p&lt;0.05</td>
<td>10.6±2.1 hrs p&lt;0.05</td>
<td>Assessment method not reported</td>
<td>Ramsay, varying levels of sedation Sedation time &lt; 72hrs P 35.4 ± 7.5 M 35.1 ± 8.1</td>
</tr>
<tr>
<td>Weinbroum A. Halpern, P. Rudick, V. et al. 1997</td>
<td>1.8±0.4 hours 108±24 mins p&lt;0.02 n=31</td>
<td>2.8±0.4 hr 168±24 mins p&lt;0.02 n=36</td>
<td>How measured? Till fully awake.</td>
<td>Sedation titrated to 5 point scale More patients agitated after propofol ceased Sedation time: P 99±15 M 141±27 hrs P 4.12±0.62 days M 5.87±1.12 days</td>
</tr>
</tbody>
</table>

Although all studies reported shorter recovery times for patients sedated with propofol, meta-analysis did not demonstrate homogeneity (Figure 7). As with the extubation
times, this may be explained by the variation in the diagnoses of patients, different sedation times and varying practices between units. There may also have been differences in how recovery time was measured. In the studies by Weibraum, Halpern, Rudick, et al and Costa et al the means by which recovery time was measured was not described. Other studies not included in the initial analysis also reported significantly shorter recovery times for patients sedated with propofol.

Figure 7
Recovery Times Post-cardiac Surgery Patients Propofol versus Midazolam Infusions

Three studies which compared propofol infusions with midazolam infusions for post-cardiac surgery patients reported recovery times. All reported shorter recovery times for patients sedated with propofol infusions (see Table 16).

Table 16 Post-cardiac Surgery Patients Propofol versus Midazolam Infusions Recovery Times

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M)</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco, G. Cabre, L. Sobrepere, G. et al 63</td>
<td>1.3±0.5 hrs 78±30 mins p 0.01 n=25 sedation time 14.4±1.5 hrs</td>
<td>3.8±1.8 hrs 228±108 mins p 0.01 n=25 sedation time 14.1±1.1 hrs</td>
<td>Time to reach Modified GCS Cook Palma &gt;16</td>
</tr>
<tr>
<td>Rockaerts, P. Huygen, F. de Lange, S. 1993 68</td>
<td>0.18± 0.13 hrs 11±8 min p &lt; 0.001 n=15 Sedation time 568±120 mins</td>
<td>1.2±1.17 hrs 72± 70 min p &lt; 0.001 n=15 Sedation time 585±158 mins</td>
<td>Raise arm</td>
</tr>
<tr>
<td>Searle, N. Cote, S. Taillefer, J et al 1997 69</td>
<td>1.48±0.85 hrs 88,6±51 mins p NS n=21 Sedation time 4hrs</td>
<td>1.56±1.02 hrs 93,8±61.4 mins p NS n=21 Sedation time 4hrs</td>
<td>Time till awakening How measured?</td>
</tr>
</tbody>
</table>

Meta-analysis did not demonstrate homogeneity (see Figure 8).

Figure 8

Review: Propofol versus midazolam
Comparison: Recovery Time
Outcome: Recovery Time Post Cardiac Surgery Infusion

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol mean(sd)</th>
<th>Midazolam mean(sd)</th>
<th>WMD (95%CI Fixed)</th>
<th>Weight %</th>
<th>WMD (95%CI Fixed)</th>
<th>Year</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco &amp; Cabre</td>
<td>1.30 (0.50)</td>
<td>3.60 (1.80)</td>
<td>-2.500 [-3.232,-1.768]</td>
<td>24.0</td>
<td>-2.500 [-3.232,-1.768]</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>Rockaerts</td>
<td>0.18 (0.13)</td>
<td>1.30 (1.17)</td>
<td>-1.020 [-1.616,-0.424]</td>
<td>39.2</td>
<td>-1.020 [-1.616,-0.424]</td>
<td>1993</td>
<td></td>
</tr>
<tr>
<td>Searle</td>
<td>1.49 (0.38)</td>
<td>1.56 (1.02)</td>
<td>-0.080 [-0.648,0.488]</td>
<td>39.8</td>
<td>-0.080 [-0.648,0.488]</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>61</td>
<td>61</td>
<td></td>
<td>100.0</td>
<td>-1.000 [-1.356,-0.642]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chi-square 26.20 (df=2) 2.16,67

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The short sedation time in the study by Searle may help explain the non-homogeneity. Nevertheless, when this study was not included in the meta-analysis the Chi-square still indicates non-homogeneity.

Figure 9

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol mean(sd)</th>
<th>Midazolam mean(sd)</th>
<th>WMD</th>
<th>Weight</th>
<th>WMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol vs Midazolam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrasco &amp; Cabre</td>
<td>1.30 (0.50)</td>
<td>3.60 (1.80)</td>
<td>0.80</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Roekaerts</td>
<td>0.16 (0.13)</td>
<td>1.22 (1.17)</td>
<td>1.72</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>0.44</td>
<td>1.95</td>
<td>1.72</td>
<td>0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

This heterogeneity may be due to the different manner in which recovery time was measured. In the study by Roekaerts, Huygen, and deLange, et al., it was measured as the time till the patient could raise their arm in response to command and in the study by Carrasco, Cabre, and Sobrepere et al. it was measured at the time taken to reach a Modified Glasgow Coma Score of greater than sixteen (sic).

Two other studies which were not included in the initial analysis supported this result, as both reported significantly shorter recovery times in those patients sedated with propofol.

Recovery Time in Surgical Patients

None of the studies included in the initial analysis reported recovery times. Two other studies reported recovery times which were shorter for patients sedated with propofol.
Recovery Time Conclusion

When studies done on critically ill, general ICU patients of patients and patients post-cardiac surgery sedated short term (<24 hrs > 4hrs) with infusions, were combined for meta-analysis, there was non-homogeneity in the results.

Figure 10

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol</th>
<th>Midazolam</th>
<th>WMD (95%CI Fixed)</th>
<th>Weight</th>
<th>Year</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco</td>
<td>20</td>
<td>20</td>
<td>3.50 (0.80)</td>
<td>0.0</td>
<td></td>
<td>Not estimable 1993</td>
</tr>
<tr>
<td>Carrasco &amp; Czebe</td>
<td>25</td>
<td>25</td>
<td>3.80 (1.80)</td>
<td>39.8</td>
<td>1998</td>
<td>[-3.232,-1.768]</td>
</tr>
<tr>
<td>Roekaerts</td>
<td>15</td>
<td>15</td>
<td>1.22 (1.17)</td>
<td>60.2</td>
<td>1993</td>
<td>[-1.616,-0.424]</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>50</td>
<td>50</td>
<td></td>
<td>100.0</td>
<td></td>
<td>-1.600 [2.072,-1.147]</td>
</tr>
</tbody>
</table>

Nevertheless, it can be concluded that post-cardiac surgery patients and general ICU patients sedated short term with propofol have recovery times which are significantly shorter than those who are sedated with infusions or boli of midazolam.
**Duration of Admission**

Only one study that was included in the initial analysis reported duration of admission. This study, by Weinbraum, Halpern and Rudick et al reported a shorter length of stay for patients sedated with propofol.\(^6\) It is difficult to interpret the significance of this result given the varying diagnoses and lack of results from similar studies. The study by Sanchez Izquierdo Riera and colleagues that was not included in the initial analysis, also reported a shorter ICU admission in patients sedated with propofol.\(^6\) In this study patients were not excluded if they were administered paralysing agents.

**Haemodynamic Complications**

The final outcome measure evaluated was the incidence of haemodynamic complications. The data reported was extensive and included changes in:

- mean arterial pressure (MAP);
- diastolic blood pressure (DBP);
- systolic blood pressure (SBP); and
- heart rate (HR).

Some studies also reported the incidence of adverse events such as hypertension and hypotension and requirements for treatment with inotropes and vasodilators and volume expanders. The extensive data results are presented in tables.

**Haemodynamic Complications, Critically Ill, General ICU Patients**

Haemodynamic complications in critically ill, general ICU patients are presented below.
From this table it can be seen that several studies reported that propofol was more likely to cause a decrease in HR. Nevertheless, cardiovascular depression was not significant, and the researchers reported that it limited the usefulness of the drug for similar numbers of patients in both regimens. However, the results are contradictory. Weinbroum Halpern, and Rudick et al. Reported that propofol caused a greater decrease in MAP and SBP, which necessitated fluid loading in significantly more patients sedated with propofol. The authors stated that since fluid and vasoactive requirements were similar prior to induction of sedation, the effect cannot be attributed solely to hypovolaemia. Another reason for variation in the results may be the different doses of the sedating agents administered, although the initial loading doses are similar (see Table 18).
Table 18 Critically Ill, General ICU Patients Sedation Doses

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol Protocol</th>
<th>Midazolam Protocol</th>
<th>Outcome Total dose propofol</th>
<th>Outcome Total dose midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitkenhead, A. R. Pepperman, M. L. Willatts, S. M. et al. 1989</td>
<td>Bolus if clinically indicated 1mg/kg Infusion 1-3mg/kg/hr then adjusted to sedation level</td>
<td>Bolus if clinically indicated 0.1mg/kg. Infusion 0.1-0.2mg/kg/hr then adjusted to sedation level</td>
<td>Mean 1.77mg/kg/hr (range 0.40-0.5)</td>
<td>0.10mg/kg/hr (range 0.01-0.26)</td>
</tr>
<tr>
<td>Barrientos Vega, R. Mar Sanchez Soria, M. Morales Garcia, C. et al. 1997</td>
<td>Bolus 100-200mg Infusion 1-6mg/kg/hr then adjusted to sedation level</td>
<td>Bolus15-30mg Infusion 0.1-0.5mg/kg/hr then adjusted to sedation level</td>
<td>Mean 2.36mg/kg/hr (range 1-4mg/kg/hr)</td>
<td>Mean 0.17mg/kg/hr (range 0.05-0.3mg/kg/hr)</td>
</tr>
<tr>
<td>Carrasco, G. Molina, R. Costa, J. et al. 1993</td>
<td>Bolus 1mg/kg if clinically indicated. Infusion 1-3mg/kg/hr then adjusted to sedation level</td>
<td>Bolus 0.1mg/kg if clinically indicated. Infusion 0.1-0.2mg/g/hr then adjusted to sedation level</td>
<td>Mean 1.8±0.08mg/kg/hr</td>
<td>Mean 0.07±0.03mg/kg/hr</td>
</tr>
<tr>
<td>Weinbroum, A. Halpern, P. Rudick, V. Sorkine, P. Freeman, M. 1997</td>
<td>Bolus 1.3±0.2mg/kg/hr Initial infusion dose the same</td>
<td>Bolus 0.11±0.02mg/kg/hr Initial infusion dose the same</td>
<td>Mean 1.8±0.08mg/kg/hr</td>
<td>Mean 0.07±0.03mg/kg/hr</td>
</tr>
</tbody>
</table>

Other studies not included in the initial analysis also reported contradictory results with, Chammorro, deLatorre and Montero et al. Reporting no significant differences between the groups. Fruh reported a small decrease in HR in patients sedated with propofol, but a increase in SBP and the opposite effect in patients sedated with midazolam. Sanchez Izquierdo Riera and colleagues found no differences between the groups.

Patients in these studies were commonly critically ill and many factors complicate their haemodynamic responses, including the use of drugs such as inotropes and
physiological condition. Many critically ill patients are already very unstable prior to the induction of sedation. This may explain the considerable differences in the results.

Haemodynamic Complications, Post-cardiac Surgery

Post-cardiac surgery patients can be considered to be a more homogenous group (see Table 19).

Table 19 Post-cardiac Surgery Patients Propofol versus Midazolam infusions

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco, G. Cabre, L. Sobrepere, G. et al\textsuperscript{63}</td>
<td>HD impairment recovered 30 mins HR decrease persisted ↓ MAP &gt;20% 7 pts n= 25</td>
<td>15 mins all HD variables back to normal ↓ MAP &gt;20% 5 pts n= 25</td>
<td>Induction both groups significant decrease in SBP &amp; HR</td>
</tr>
<tr>
<td>Chaudhri, S. Kenny, G. N. 1992\textsuperscript{64}</td>
<td>More time spent &lt; target BP minus 10mmHg &amp; minus 20mmHg Less Nitro but not significant n= 20</td>
<td>n=20</td>
<td>Closed loop arterial pressure controller No significant difference between groups in time BP &gt; target.</td>
</tr>
<tr>
<td>Higgins, T. L. Yared, J. P. Estafanous, F. G. et al 1994\textsuperscript{67}</td>
<td>5 and 10 mins Significantly lower MAP significant for 1st 2 hrs Significantly lower HR first 2 hrs Less nitroprusside required n=42</td>
<td>n=38</td>
<td>Propofol protocol changed after initial 4 boluses decrease due to MAP decrease Closed loop arterial pressure controller 1 pt each group required phenylephrine. No significant difference between groups in volume expansion requirements.</td>
</tr>
<tr>
<td>Roekaerts, P. Huygen, F. deLange, S. 1993\textsuperscript{68}</td>
<td>SBP DBP &amp; MAP decreased after loading dose remained &lt; base level n=15</td>
<td>HR &gt; propofol group increased with time. HR increased after 300 – 360 mins from base n=15</td>
<td>Inotropes not required Nitroprusside 2 each group, no difference in fluid requirements.</td>
</tr>
<tr>
<td>Searle, N. Cote, S. Taillefer, J et al 1997\textsuperscript{69}</td>
<td>n=21</td>
<td>n=20</td>
<td>No differences 4hrs only of sedation</td>
</tr>
<tr>
<td>Snellen, F. Lauwers, P. Demeyere, R. et al 1990\textsuperscript{70}</td>
<td>n=20</td>
<td>n=20</td>
<td>MAP decreased significantly in both P &amp; M after bol. No significant difference between groups other HD data or inotropes or vasodilators</td>
</tr>
</tbody>
</table>
Several studies reported a significant decrease in the SBP and MAP following induction of sedation with propofol.63,67,68,70 This was only reported to persist for the first 30 minutes in one study 63 and for the 1st two hours in another.67 Midazolam was also reported to cause a significant decrease in the MAP and or the SBP in several studies 63,70, but was reported by Carrasco and colleagues to return to normal more rapidly (within 15 minutes).63 One study reported that patients on propofol spent more time with their BP less than the target when compared to patients receiving midazolam. Two studies reported that patients on propofol required less nitroprusside6a,67, while several others reported no differences between the groups.68,70 In several studies the heart rate was reported to decrease in patients receiving propofol,63,67 this change persisted in one, but only lasted for 2hrs in the other. The HR of patients receiving midazolam increased more from the base measurement and was higher than those receiving propofol in the study by Roekarts.68 This effect occurred after 300 – 360 minutes.

From this discussion it can be concluded that propofol is perhaps more likely to cause hypotension accompanied by a decreased heart rate. Midazolam can also cause hypotension on induction of sedation and an increase in heart rate during maintenance. These haemodynamic responses did not appear to necessitate ceasing the sedation, but doses were decreased in some studies.63,67 Haemodynamic changes in most cases did not influence the overall inotrope or fluid requirements.63,67,68,70 Carrasco reported that cardiovascular depression was treated with fluids and inotropes with more patients in the propofol group requiring the latter. Nevertheless, the overall inotrope requirements did not differ between the groups. In several studies less vasodilators were required in patients sedated with propofol.64,67 One possible cause of the variation in results of the studies may be the different doses administered (Table 20). The numbers included in the studies were all small, varying from 15 to 42 in each group. Two studies used a closed loop arterial pressure controller, which may also have influenced the results.64,67
One study not included in the initial analysis found that both midazolam and propofol caused a reduction in the systolic BP during the first hour of sedation. This reduction required cessation of sedation in one patient on midazolam.

Table 20 Post-cardiac Surgery Patients Propofol versus Midazolam infusions sedimentation doses

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol protocol</th>
<th>Midazolam protocol</th>
<th>Outcome Total dose propofol</th>
<th>Outcome Total dose midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco, G. Cabre, L. Sobrepera, G. et al 63</td>
<td>Initial dose 0.5mg/kg Maintenance: 1mg/kg/hr</td>
<td>Initial dose 0.05mg/kg Maintenance: 0.05mg/kg/hr</td>
<td>Mean induction 0.55 ±0.05mg/kg Infusion 1.20±0.03mg/kg/hr</td>
<td>Mean induction 0.05±0.01 mg/kg Infusion 0.08±0.01mg/kg/hr</td>
</tr>
<tr>
<td>Chaudhri, S. Kenny, G. N. 1992 64</td>
<td>Initial dose 10 – 40mg Maintenance: 0.5 – 0.2mg/kg/hr</td>
<td>Initial dose Table 14mg Maintenance: 0.1 – 0.2mg/kg/hr</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Higgins, T. L. Yared, J. P. Estafanous, F. G. et al 1994 67</td>
<td>Initial dose 0.24 mg/kg Maintenance: 0.76 mg/kg/hr</td>
<td>Initial dose 0.012mg/kg Maintenance: 0.018mg/kg/hr</td>
<td>Induction 0.24 ± 0.021 mg/kg Infusion rate 0.7±0.09 mg/kg/hr</td>
<td>Induction 0.012±0.001 mg/kg Infusion rate 0.018±0.0001 mg/kg/hr</td>
</tr>
<tr>
<td>Roekaerts, P. Huygen, F. deLange, S. 1993 68</td>
<td>Initial dose 1 mg / kg Maintenance: 4mg/kg/hr</td>
<td>Initial dose 0.7 mg /kg Maintenance: 0.075 mg/kg/hr</td>
<td>Mean infusion rate 2.71±1.13 mg/kg/min</td>
<td>Mean infusion rate 0.092±0.02 mg/kg/min</td>
</tr>
<tr>
<td>Searle, N. Cote, S. Taillefer, J et al 1997 69</td>
<td>Initial dose 10mcg/kg/1 min</td>
<td>Initial dose 0.25 mcg /kg /1 min</td>
<td>Mean 10.6±2.9 mcg/kg/min</td>
<td>Mean 0.25±0.02 mcg/kg/min</td>
</tr>
<tr>
<td>Snellen, F. Lauwers, P. Demeyere, R. et al 1990 70</td>
<td>Initial dose 0.5mg/kg Maintenance: 1mg/kg/hr</td>
<td>Initial dose 0.05mg/kg Maintenance: 0.05mg/kg/hr</td>
<td>Bolus 59±12mg Infusion Mean 0.90±0.1mg/kg/hr</td>
<td>Bolus 4.4±0.4mg Infusion Mean 0.038±0.002 mg/kg/hr</td>
</tr>
</tbody>
</table>
Haemodynamic Complications, Post-cardiac Surgery Propofol Infusion Versus Midazolam Bolus

Two studies reported that there was no significant difference in the BP and HR in both patients receiving propofol or bolus of midazolam.\textsuperscript{71,72} But in the study by McMurray and colleagues, the MAP was lower than awake values, in both groups.\textsuperscript{72} Nevertheless, this was not thought to be clinically significant. A large study by Wahr, Plunkett, and Ramsay et al recorded haemodynamic episodes, these were tachycardia, bradycardia, hypotension and hypertension.\textsuperscript{73} In this study patients on propofol had a decreased incidence of tachycardia and hypertension, but there was no difference in the hypotensive episodes between the groups.

Other Studies Reporting Haemodynamic Complications

For post operative patients the only one study included in the initial analysis reported haemodynamic complications, the researchers found no statistical difference between the groups in the SBP, but reported that patients receiving propofol had a significant decrease from their baseline SBPs.\textsuperscript{79} There was also a decrease in the MAP evident in the first five minutes. Patients receiving propofol also had a decreased heart rate. This study supports the results reported in other studies.

Two other studies not included in the initial analysis similarly reported a decrease in BP on induction of sedation with propofol. Bayer and Syde, reported that this was evident in hypovolaemic patients.\textsuperscript{76} A small study by Hecht, Lemkuhl and Pichlmayr reported that there were minimal changes to HR and BP in either group.\textsuperscript{78}

In a study by Boyle, Shear, White and Schuller with medical and surgical patients, adjustments to infusion rates due to hypotension were required in more patients receiving propofol than those receiving midazolam.\textsuperscript{81} This again supports the indication that propofol is more likely to cause hypotension.
In neurological patients or neurosurgical patients, all studies were excluded from the initial analysis. Two of these reported slight changes in the BP in both groups of patients\textsuperscript{52,54} while the third reported a transient fall in the SBP, MAP and HR for patients receiving propofol.\textsuperscript{53}

**Administration of Narcotics**

One potential confounding factor that may influence the results of this review, is the administration of narcotics. It is common practice for patients in ICU to be administered narcotics to ensure analgesia. These narcotics also act as sedatives. The studies included in the review were examined to establish which narcotics were administered and in particular to detect differences in dosages and patterns of administration between the study groups.

For critically ill, general intensive care patients no significant differences were detected between the study groups (see Table 21).
Table 21 Propofol Infusions Versus Midazolam Infusions For Critically Ill Ventilated Patients Administration of Analgesia

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M)</th>
<th>Drug &amp; Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitkenhead, A. R. Pepperman, M. L. Willatts, S. M. et al. 1989</td>
<td>Total dose 47.5 ± 17.1 n= 53</td>
<td>Total dose 44.4 ± 14.7 n= 47</td>
<td>Morphine infusion commenced at 2mg/hr adjusted PRN</td>
<td>Increase dose in 12 of propofol group and 10 of midazolam group</td>
</tr>
<tr>
<td>Barrientos Vega, R. Mar Sanchez Soria, M. Morales Garcia, C. et al 1997</td>
<td>All patients received morphine 0.5mg/kg/24hrs</td>
<td>All patients received morphine 0.2mg/kg – 0.5mg/kg/24hrs</td>
<td>No differences between groups</td>
<td></td>
</tr>
<tr>
<td>Carrasco, G. Molina, R. Costa, J. et al. 1993</td>
<td>Mean dose per day 11.1 ± 3 (5.12-16.88) n= 22</td>
<td>Mean dose per day 8 ± 1 (6.04-9.96) n= 30</td>
<td>Morphine IV Boli 2mg PRN</td>
<td>No differences between groups</td>
</tr>
<tr>
<td>Weibraum A. Halpern, P. Rudick, V. et al. 1997</td>
<td>Similar daily doses</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most studies that compared propofol infusions with midazolam infusions in post-cardiac surgery patients reported no differences between the groups in the administration of analgesia. Only one study by Higgins and colleagues reported a significant difference in the morphine requested, although the mean dose administered was similar. In this study patients were administered analgesia if they acknowledged pain when questioned by nurses. There was no indication as to whether there was control over the questioning technique or timing. Fifty three percent of patients sedated with midazolam requested analgesia while only 33% of patients sedated with propofol requested analgesia. In the other studies analgesia was administered routinely, which is common practice when caring for post-operative patients (see Table 22).
In studies that compared propofol infusions with boli of midazolam the patients sedated with midazolam boli required more analgesia (see Table 23). This is not a surprising finding as the studies demonstrated that boli of midazolam provided poorer quality sedation and sedation may mask the need for analgesia.

### Table 22: Propofol Infusions Versus Midazolam Infusions For Patients Ventilated Post-cardiac Surgery, Administration of Analgesia

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P)</th>
<th>Midazolam (M)</th>
<th>Drug &amp; Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrasco, G. Cabre, L. Sobrepere, G. et al 1998&lt;sup&gt;63&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Morphine 0.015mg/kg/hr &amp; boli of 0.015mg/kg during painful procedures</td>
<td>Doses similar</td>
</tr>
<tr>
<td>Chaudhri, S. Kenny, G. N. 1992&lt;sup&gt;64&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Bolus dose of morphine 2mg followed by Infusion 2mg/hr Additional boli PRN</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Higgins, T. L. Yared, J. P. Estafanous, F. G. et al 1994&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Morphine requested by 14 (33%) Mean dose 11.36mg</td>
<td>Morphine requested by 20 (53%) Mean dose 12.35mg</td>
<td>Morphine administered for acknowledged pain.</td>
<td>Difference significant IV morphine boli PRN Dose similar</td>
</tr>
<tr>
<td>Roekaerts, P. Huygen, F. deLange, S. 1993&lt;sup&gt;68&lt;/sup&gt;</td>
<td></td>
<td>Sufentanil 0.625mcg/kg/hr Stopped after 4hrs</td>
<td>Identical dose in both groups.</td>
<td></td>
</tr>
<tr>
<td>Searle, N. Cote, S. Taillefer, J et al 1997&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Mean Post-operative morphine 3.94±2.6 p NS (0.6-9.2)</td>
<td>Mean Post-operative morphine 4.93±3.2 p NS (1.14)</td>
<td>Morphine Infusion 0.02mg/kg/hr Boli 2mg PRN</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Snellen, F. Lauwers, P. Demeyere, R. et al 1990&lt;sup&gt;70&lt;/sup&gt;</td>
<td></td>
<td>Narcotic piritramide infusion 50mcg/kg/hr</td>
<td>No difference between groups</td>
<td></td>
</tr>
</tbody>
</table>
Table 23 Propofol Infusions Versus Midazolam Bolus For Patients Ventilated Post-cardiac Surgery Administration of Analgesia

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P) Mean total dose</th>
<th>Midazolam (M) Mean total dose</th>
<th>Drug &amp; Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grounds, R. M. Lalor, J. M. Lumley, J. 1987</td>
<td>5.7 ± 1.36 mg (0 -35) Mean 0.153±0.03 mcg/kg/min</td>
<td>15.9 ± 2.10 mg (2.5-50.0) Mean 0.357 ± 0.50 mcg/kg/min</td>
<td>Papaveretum IV bolus PRN</td>
<td>Midazolam significantly greater analgesia requirements</td>
</tr>
<tr>
<td>McMurray, T. J. Collier, P. S. Carson, I. W. 1990</td>
<td>Morphine requirements 0.57±0.03mg /kg p&lt;0.001 0.55 ± 0.03mcg/kg/min p&lt;0.001</td>
<td>Morphine requirements 0.72 ±0.04mg /kg p&lt;0.001 0.75 ± 0.03mcg/kg/min p&lt;0.001</td>
<td>Morphine bolus 2mg PRN</td>
<td>Midazolam significantly greater analgesia requirements</td>
</tr>
<tr>
<td>Wahr, J. A. Plunkett, J. J. Ramsay, J. G. et al 1996</td>
<td>Morphine 1-4mg every 15mins until level 5 sedation reached</td>
<td>Morphine bolus required less opioids</td>
<td>Propofol group required less opioids</td>
<td></td>
</tr>
</tbody>
</table>

In the studies that investigated sedation in surgical patients no difference was found between patients sedated with propofol or midazolam regarding the administration of analgesia (see Table 24).

Table 24 Sedation Surgical Patients, Administration of Analgesia

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol (P) Mean dosage</th>
<th>Midazolam (M) Mean dosage</th>
<th>Drug &amp; Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronan, K. P. Gallagher, T. J. George, B. et al 1995</td>
<td>Mean dosage 17.4mg n=17</td>
<td>Mean dosage 31.6mg n=17</td>
<td>17 patients in each group received morphine</td>
<td>Surgical and &amp; orthopaedic patients Difference not statistically significant</td>
</tr>
<tr>
<td>Wolf's, C. Kimbimbi, P Colin, L. et al 1991</td>
<td></td>
<td>Fentanyl 1mcg/kg/hour for first 5 hours Abdominal surgery</td>
<td>No difference between groups</td>
<td></td>
</tr>
</tbody>
</table>

From this summary it can be concluded that it is unlikely the administration of analgesia influenced the results of the review, as for most studies there was no difference between the groups in the patterns of administration or doses administered.
CONCLUSION AND IMPLICATIONS FOR PRACTICE

The objective of this review was to present the best available evidence relating to the sedation of adult ventilated patients in intensive care units (ICUs). The specific questions addressed were:

What is the most effective sedation regime for adult ventilated patients in ICU? Which agent is the most effective midazolam or propofol? How should it be administered, by bolus or continuous infusion?

The first variable assessed in order to evaluate these questions was; the ability to achieve a chosen sedation level (as evaluated by use of a recognised sedation scale). For this variable the evidence supports the view that infusions of both propofol and midazolam provide similar quality sedation. However, for some groups for example the critically ill the results are conflicting. Many researchers reported no significant difference between the quality of sedation provided by infusions of either midazolam or propofol. One possible reason for this is that sedating drugs vary in their actions. Midazolam is an effective amnesic agent, while propofol has little amnesic action. They also vary in onset of action in producing hypnosis and the duration of action. The Ramsay sedation scale measures the patients’ clinical response to the agents but does not separately score calmness, orientation, alertness, and the incidence of complications such as agitation. Future research into the quality of sedation provided by either propofol or midazolam should be directed towards clarifying these variables. In addition, it would be useful to document patients’ memories of the time sedated. Only one of the studies in this review collected data on this factor and the data collected were limited as only a few of the patients were interviewed.

Another possible cause of the varying results may be that few of the studies were double blinded, which can lead to possible bias in those assessing the patient’s response. Nevertheless, it may not be practical to double blind in studies comparing infusions of
midazolam with propofol. This would mean either covering lines (which is potentially hazardous, as air cannot be seen), or running infusions at set rates with placebo infusions, which would mean the sedation could not be easily titrated to effect. Another possible action to reduce this bias would be to have the assessor unaware of the drug being infused. However, in most studies the nurse caring for the patient continually assessed the quality of sedation, so again this may not be practical.

In relation to the mode of administration, studies agreed that bolus of midazolam do not provide as good quality sedation as infusions of propofol.

For the next two variables assessed, time from cessation of sedation till extubation and recovery time, the results were more conclusive, with most studies reporting a shorter time till extubation and recovery for patients sedated with infusions of propofol. This was demonstrated best in studies conducted in post-cardiac surgery units, where participants had a greater degree of homogeneity.

There was not enough data on duration of admission to draw any conclusions regarding this outcome. Nevertheless, it may be that a shorter recovery and extubation time may lead to a reduced duration of admission in the ICU.

Regarding the incidence of haemodynamic complications, although many of the studies produced conflicting results, reports of hypotension related to induction of sedation were quite common. It appears that propofol is more likely to cause hypotension and bradycardia. Nevertheless, this may not be significant in the ICU environment where staff commonly manage hypotension with fluid loading and inotropes. The influence of propofol or midazolam on haemodynamic variables appears to be less significant as the infusion progresses. Few studies reported having to cease sedation due to haemodynamic responses. Propofol may have some advantages in the post-cardiac surgery patient where hypertension must be avoided.
The data were analysed using the following subgroups:

- propofol infusions versus midazolam infusions for critically ill ventilated patients;
- propofol infusions versus midazolam infusions for patients ventilated following cardiac surgery;
- propofol infusions versus midazolam boluses for patients ventilated following cardiac surgery;
- propofol infusions versus midazolam infusions for patients ventilated following general surgery;
- propofol infusions versus midazolam infusions for patients ventilated for medical conditions and following general surgery;
- propofol infusions versus midazolam infusions for patients ventilated post head injury or neurological surgery; and
- propofol infusions versus midazolam infusions for patients who required ventilation for chronic obstructive pulmonary disease.

Other possible stratifications such as a severity of illness score or dosages of drugs administered were considered. The use of severity of illness scores would be extremely problematic. Some studies did not record severity of illness using a scale, while the remainder used a range of different scales. For example, some reported scores using the APACHE scale\textsuperscript{48,50}, while others used the APACHE II\textsuperscript{61,61}, the Simplified Acute Physiologic Score (SAPS)\textsuperscript{49}, or the American Society of Anesthesiologists Physical Status (ASA).\textsuperscript{63,64,67,69} Even when like scores were reported there was no consistency in the studies in the severity of illness of the participants.

Stratifying the results according to the dosages administered would also be difficult as there was no consistency in the doses used. However, these drugs are commonly titrated to effect and most of the papers reported that this was what was done. More important is consistency in the target sedation level. Though most studies used the Ramsay scale to assess the level of sedation there was little agreement in the target level. This is a limitation of the available research.
If the major clinical consideration is the quality of the sedation either propofol or midazolam may be administered. However, if it is important that recovery and extubation is rapid propofol should be chosen. Nevertheless the time difference reported in many studies does not appear to be of clinical significance, being in the order of hours rather than days. It is important to note that most of these studies excluded patients with hepatic and renal impairment the very patients most likely to experience accumulation of midazolam. The most significant differences in recovery and extubation times were recorded in the critically ill general ICU patients who were sedated for longer periods. A recent study demonstrated that daily interruption of sedation until the patients woke from their sedation, was associated with decreased the duration of ventilation and length of stay. In several of the studies patients were sedated to Level 4–5 on the Ramsay scale, that is brisk response (level 4) to sluggish response (level 5), both are viewed as asleep levels. If patients were sedated more lightly it is likely that they would recover and be extubated more quickly. However, this has implications for nurses, as more lightly sedated patients can be more difficult to care for in terms of maintaining communication and comfort.

In summary, both propofol and midazolam infusions appear to provide similar quality sedation. Extubation and recovery time for patients sedated with propofol is reduced and it appears haemodynamic responses are not generally clinically significant. Future research could be directed at using a combination of agents, to make use of the synergistic effect. In this way the advantages of both agents could be best maximised. A low dose, background infusion of midazolam may provide acceptable sedation and amnesia when required, without influencing the recovery time. Propofol could be used for short-term increases in depth of sedation when required such as during suction or insertion of catheters.
REFERENCES


APPENDICES
Appendix 1

Sedation of adult critically ill ventilated patients in Intensive care units (ICUs)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>End Note No</th>
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**Inclusion / Exclusion Criteria**

The study compares effectiveness of midazolam versus propofol in adult ventilated patients in ICU.

Effectiveness evaluated by:

- Length of time from cessation of sedation till extubation.
- Ability to achieve desired sedation level
- Duration of admission to ICU
- Incidence of haemodynamic complications

**Decision:**

Include  
Reject

**Comments:**
### Appendix 2

**Critical Appraisal Form**  
**Experimental Studies**  
**Sedation of adult critically ill ventilated patients in**  
**Intensive care units (ICUs)**

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<th>Author</th>
<th>Year</th>
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<th>No</th>
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The first 4 questions must be answered “yes” for the study to be included in the meta–analysis.

- **Was the assignment to treatment groups random?**
  - Yes
  - No
  - Not clear

- **Apart from the intervention, were participants treated identically?**
  - Yes
  - No
  - Not clear

- **Were the study groups comparable at entry?**
  - Yes
  - No
  - Not clear

- **Were the outcomes measured in the same manner for all groups?**
  - Yes
  - No
  - Not clear

- **Were the participants who dropped out of the study followed up?**
  - Yes
  - No
  - Not clear  
  (*>20% not followed up*)

- **Were the outcomes measured in a reliable manner?**
  - Yes
  - No
  - Not clear

- **Was the allocation to treatment groups concealed from the allocator?**
  - Yes
  - No
  - Not clear

### Summary

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<th>Total</th>
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**Decision:**

- **Include**
- **Reject**

**Narrative summary:**

**Comments:**
## Appendix 3

### Data Extraction Form

**Experimental Studies**

**Sedation of Adult Ventilated Patients in Intensive Care Units**

<table>
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<tr>
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**Method:**

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**Setting:**

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**Participants:**

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**Number of participants:**

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<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
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**Interventions:**

**Intervention A:**

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**Intervention B:**

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**Outcome Measures:**
Length of time from cessation of sedation till extubation:

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<th>Scale</th>
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<th>Group B</th>
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Ability to achieve desired level of sedation:

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<tr>
<th>Scale</th>
<th>Group A</th>
<th>Group B</th>
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Duration of Admission to ICU:
### Incidence of HD complications:

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<thead>
<tr>
<th>Scale</th>
<th>Group A</th>
<th>Group B</th>
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### Other:

76
<table>
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<tr>
<th>Scale</th>
<th>Group A</th>
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Other:

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77
STUDY 1

THE EFFICACY OF AN ALTERNATIVE SEDATION REGIMEN COMPARED TO THE EXISTING REGIMEN FOR THE SEDATION OF ADULT VENTILATED PATIENTS IN INTENSIVE CARE
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INTRODUCTION

The systematic review indicated that infusions of both propofol and midazolam provide similar quality sedation but that extubation and recovery time for patients sedated with propofol is shorter. One of the recommendations for future research was that the effectiveness of using a combination of agents, to take advantage of the synergistic effect be investigated. In this way the advantages of both agents could be best maximised. A low dose, background infusion of midazolam may provide acceptable sedation and amnesia when required, without influencing the recovery time. Propofol could be used for short-term increases in depth of sedation when required such as during suction or insertion of catheters.

For this reason the researcher developed a proposal titled, “The efficacy of an alternative sedation regimen compared to the existing regimen for the sedation of adult ventilated patients in intensive care.” This research was to form part of the doctoral portfolio. However, after nine months the research was terminated as recruitment of subjects into the study was proving impossible. The proposal is included in the portfolio and the possible reasons for the difficulty in conducting this research are discussed.
COMMON RESEARCH PROTOCOL APPLICATION TO RESEARCH ETHICS COMMITTEE

1. Title:
The efficacy of an alternative sedation regimen compared to the existing regimen for the sedation of adult ventilated patients in intensive care.

2. Investigators
Ms J Magarey RN, CCRN, Dip Nurs, BNurs, MNurs (research).
Dr H McCutcheon PhD MPH, BA, RN, RM.
Dr M Chapman BMBS, DA (UK), FFARCSI, FANZCA, FFICANZCA.
Mr Ian Blight, RN, DipAppSc(Nurs), CCRN, GradDipIntCareNurs, BNursPrac(IntCare) MRCNA.

3. Background
The experiences of patients being treated in intensive care units (ICUs) have been likened to torture.¹ Most depend on life sustaining treatment such as artificial ventilation at some time during their admission. However, the treatment itself can be painful and distressing.² Tubes inserted to facilitate ventilation prevent speaking and inability to verbally communicate may compound distress. Many patients have suffered trauma or are admitted following operative procedures and mortality rates for critically ill patients are relatively high.³ Thus, patients may experience pain and fear death, causing extreme anxiety.⁴ Patients in intensive care are sedated so that they remain calm, are able to sleep and can tolerate life saving treatment. Sedation may also be therapeutic for example, in the treatment of head injured patients to reduce intracranial pressure. Lack of sedation or under-sedation may result in patients resisting treatment by fighting ventilation or removing tubes. There have even been reports of inadequately sedated patients sustaining fractures.⁵ Consequently sedation has become an essential component in the management of critically ill patients in ICUs and most patients in ICU receive sedation at some time during their admission.⁶

The most frequently administered drugs used for sedation of patients in ICU are benzodiazepines, and these are usually administered in combination with a narcotic such as morphine.⁷⁻⁹ However, the metabolism and excretion of these drugs is complicated by critical illness. Studies have found that continuous infusions of midazolam result in saturation of the tissues allowing subsequent doses to be available at the receptor site thus prolonging the action by days.¹⁰ Its action may also be prolonged in critical illness, particularly during shock and sepsis and elimination may fluctuate with the patients condition.¹¹ Metabolism of midazolam produces an active metabolite, α-hydroxymidazolam which is excreted by the kidneys. Accumulation of this metabolite may occur in patients with compromised renal function. The metabolism is also decreased in elderly patients with reduced hepatic or renal function.¹² The action of
morphine is also prolonged by renal and hepatic impairment, and by shock. Morphine is metabolised to an active metabolite called morphine 6 Glucuronide. This metabolite is 40 times more potent than the parent compound.13

Accumulation of sedating drugs may cause numerous problems and these include:
- prolonged sedation;
- hypotension;
- respiratory depression;
- bradycardia;
- ileus;
- increased protein breakdown;
- immunosuppression;
- renal dysfunction;
- deep vein thrombosis;
- increased cost. 14

Respiratory and central nervous system depression caused by excessive sedation may make it difficult to wean the patient from ventilation and prolong treatment which in turn may contribute to increased morbidity, particularly ventilator associated pneumonia.15,16

Circa 1995 (personal communication Zeneca Pharmaceuticals) propofol, a new sedating drug, was introduced to intensive care practice. Propofol is an equiphenol agent which has sedative and hypnotic actions but has little amnesic and no analgesia action.17 However, propofol has one major advantage over other sedative agents, even in the critically ill and elderly patient, as it has a very short redistribution half-life of 1.3 - 2.2 minutes.10 Propofol is comprised of soybean oil, egg lecithin and glycerol. 18 Its mode of action is unclear, but it may act by exerting a non-specific effect on lipid membranes.19 Nevertheless, propofol does have some side effects; for example it may cause hypotension, allergy and convulsions have been reported in susceptible individuals.20 The literature does not recommend propofol for the long-term sedation of children, due to reports of lactic acidosis and even death in paediatric patients on long-term sedation, though the link is not proven and remains controversial.9,21 Surveys of the practice of sedation in ICUs demonstrate that benzodiazepines are most commonly used, but also indicate that propofol is being used in some units.7,9,22 The main impediment to its use appears to be the cost. Propofol is expensive and a twenty-four hour infusion may cost up to six times as much as an infusion of midazolam. In addition tachyphylaxis may occur with administration of propofol necessitating increasing doses for long-term sedation, thereby further increasing cost.23

Research has demonstrated that ICU patients sedated with infusions of propofol have shorter recovery times and are able to be extubated more rapidly than patients sedated with infusions of midazolam.5,24-29 However, propofol has no analgesic properties, is a poor amnesic agent and is very expensive.17 A study by Carrasco and colleagues demonstrated that when propofol was administered with midazolam for the sedation of patients post coronary artery bypass surgery the combined drugs provided adequate sedation with reduced recovery and extubation time at significantly less cost.36 No studies
have been conducted in the general ICU population on the efficacy of sedation when these drugs are combined.

4. **Purpose of the study**

The purpose of this study is to determine if an alternative sedation regimen will provide more effective sedation than the current regimen. In particular the aim is to compare the current variable sedation regimen, with an alternative regimen. The current variable regimen consists of a continuous infusion of morphine/midazolam with bolus of the solution administered as required. The infusion is titrated by the nurse caring for the patient and bolus are administered at his/her discretion, sometimes the level of sedation is specified eg moderate, light, heavy. The alternative regimen will consist of a continuous infusion of morphine and midazolam titrated to provide the prescribed level of sedation (according to the critical illness sedation scale appendix 1) and bolus of propofol administered to supplement sedation during critical procedures such as endotracheal suctioning.

The effectiveness of sedation will be evaluated by the following outcome measures:

- length of time from cessation of sedation until extubation;
- duration of admission to the ICU (Intensive Care Unit);
- incidence of haemodynamic complications during bolus of sedation, defined as a decrease in mean arterial pressure > 20mmHg, changes in pulse rate > 10 beats per minute and treatment of these with administration of inotropic medication or bolus of intravenous fluid; and
- incidence of adverse events such as self removal of tubes or catheters, allergy, seizures and recorded periods of inadequate sedation defined as level 1 of the critical illness sedation scale.

The following hypotheses will be tested:

- Null Hypothesis 1 (H₀): Sedating patients with an alternative sedation protocol will have no effect on the length of time from cessation of sedation until extubation.
- Null Hypothesis 2 (H₀): Sedating patients with an alternative sedation protocol will have no effect on the duration of admission to the ICU.
- Null Hypothesis 3 (H₀): Sedating patients with an alternative sedation protocol will have no effect on their haemodynamic status, defined as incidents of > 20mmHg reduction in mean arterial pressure or changes in pulse rate > 10 beats per minute in response to bolus of sedation.
- Null Hypothesis 4 (H₀): Sedating patients with an alternative sedation protocol will have no effect on the incidence of adverse events such as self removal of tubes or catheters, allergy, seizures and recorded periods of inadequate sedation defined as level 1 of the critical illness sedation scale.
• Alternative Hypothesis 1 (HA): Sedating patients with an alternative sedation protocol will have an effect on the length of time from cessation of sedation until extubation.

• Alternative Hypothesis 2 (HA): Sedating patients with an alternative sedation protocol will have an effect on the duration of admission to the ICU.

• Alternative Hypothesis 3 (Hₐ): Sedating patients with an alternative sedation protocol will have an effect on their haemodynamic status, defined as incidents of > 20mmHg reduction in mean arterial pressure or changes in pulse rate > 10 beats per minute in response to boli of sedation.

• Alternative Hypothesis 4 (Hₐ): Sedating patients with an alternative sedation protocol will have an effect on the incidence of adverse events such as self removal of tubes or catheters, allergy, seizures and recorded periods of inadequate sedation defined as level 1 of the critical illness sedation scale.

Patients in Royal Adelaide Hospital (RAH) ICU are usually sedated with infusions of midazolam (0.5mg/ml) combined with morphine (1mg/ml). This is administered according to the orders prescribed by medical staff. These orders specify a rate for the infusion together with orders for bolus doses as required. For example, morphine and midazolam 1 – 10ml per hour and boli of 1-5ml prn. The infusion is then titrated by the nurse caring for the patient and boli are administered as required. Patients who are lightly sedated may be comfortable at most times, however, during suction and other critical procedures boli are frequently administered to prevent distress. The accumulation of these drugs in critical illness may result in prolonged sedation. This can extend the time taken to wean the patient from the ventilator and may increase morbidity and cost. Alternatively using propofol will increase cost and it does not provide analgesia.

For this reason patients particularly susceptible to accumulation are sometimes sedated with propofol infusions with boli as required. As indicated this is costly and may result in patients being changed from one regimen to another as their condition either changes or extubation is considered to be imminent.

The aims of the study are to determine if an alternative sedation regimen:
• is effective in reducing duration of admission;
• reduces the length of time patients take to be extubated.

Patients would be administered a background infusion of morphine and midazolam (morphine 1mg/ml and 0.5mg/ml midazolam), titrated to provide the prescribed level of sedation as evaluated using a validated sedation scale (critical illness sedation scale) and be administered slow boli of propofol to provide sedation during critical procedures. The initial bolus dose will be 0.25mg /kg and will be increased in increments of 0.25mg/kg to 1mg/kg as required to maintain comfort. In the RAH ICU it is already common practice for boli of both midazolam and propofol to be administered by nurses.
Studies have been conducted to evaluate the haemodynamic effects of sedation in the critically ill and both midazolam and propofol were reported to cause hypotension commonly treated with inotropes and fluids. In these studies the doses used to induce sedation were from 1.3mg / kg to 1mg / kg. Some investigators have found that propofol in particular may cause hypotension on induction. Induction doses ranged from 0.2mg/kg to 1mg /kg. While haemodynamic responses necessitated decreased doses in some cases, it did not influence overall fluid or inotrope requirements or necessitate cessation of sedation.

5. Subjects
Adult ventilated patients who are sedated during their admission to the intensive care unit ICU.

Inclusion criteria
All adult patients ventilated in the ICU for greater than 12 hrs and less than 10 days, who are ordered sedation. Data collected from patients who are subsequently ventilated for more than 10 days, will not be included in the analysis. This will allow sufficient time for accumulation of sedation to occur, but problems associated with prolonged ventilation and weaning will be avoided.

Exclusion criteria
The following exclusion criteria will be applied, patients:

- with neurological deficit, eg CVA, head injury;
- with neuromuscular disorders likely to cause muscle weakness such as Guillain Barré syndrome;
- receiving neuromuscular blocking agents except when administered to facilitate intubation or during an operative procedure prior to admission to ICU;
- receiving other sedating agents such as chlorpromazine and haloperidol;
- Pregnant women;
- with known allergy to midazolam or propofol;
- with tracheostomies as extubation time cannot be measured;
- ventilated for more than 10 days;
- who are prescribed MAO inhibitors.
- with hepatic or renal impairment.

Patients will be withdrawn if in the opinion of the medical officer on duty they are unable to tolerate bolus of propofol due to side effects such as hypotension.

Criteria for withdrawal from the study
Patients will be withdrawn from the study if:
- They develop a neurological deficit such a CVA;
- They require neuromuscular blocking agents except when administered to facilitate intubation or during an operative procedure prior to admission to ICU;
They receive other sedating agents such as chlorpromazine and haloperidol and propofol for the control group;
They require ventilation for > 10 days; and
If in the opinion of the medical officer that the bolus of propofol cannot be tolerated eg causing hypotension.

6. Plan and design

An experimental research design will be used in the form of a randomised controlled trial. Patients will be randomised into either a control group or to the experimental group. Patients in the control group will be sedated using the current regimen of morphine and midazolam, plus bolus as required. The experimental group will be sedated with a background infusion of morphine and midazolam at a rate titrated to provide sedation at the prescribed level, on the Critical Illness Sedation Scale (appendix 1), and will be ordered bolus of propofol to be administered prior to critical procedures.

It is proposed that a sample size of 100 subjects will be tested 50 subjects in each group. Once some preliminary data is obtained a power analysis will be performed. Randomisation will be achieved by withdrawing envelopes allocating patients to either the experimental group or the control group.

Education programs will be implemented prior to and throughout the duration of the study for all nursing staff currently working in the unit. The protocol will be discussed with the senior nurses who work as shift coordinators (approximately 50) and their cooperation in implementing the research will be sought.

The following data to will be collected:
- demographic data (age, gender, diagnosis);
- duration of ventilation;
- details regarding the sedation administered;
- details of any other drugs administered;
- hepatic and renal function (as indicated by routine daily blood analysis);
- the length of time taken until extubation from cessation of sedation;
- duration of admission to the ICU;
- haemodynamic changes and treatment required, occurring in response to the bolus of morphine and midazolam for the control group and propofol for the treatment group, defined as > 20mmHg reduction in mean arterial pressure or changes in pulse rate > 10 beats per minute in response to bolus of propofol,
- The incidence of adverse events such as self removal of tubes or catheters, seizures, allergy and recorded periods of inadequate sedation defined as level 1 of the critical illness sedation scale (appendix 1).

A data collection sheet will be attached to the patient’s charts to record these findings. The cost of the drugs administered according to each sedation regimen will also be calculated. An interview with both open and closed questions will be conducted following discharge from the ICU to record patient’s memories of ICU so the influence of the sedation protocol on the ICU experience can be evaluated.
7. Efficacy

If the alternative sedation regimen is more effective for the sedation of adult ventilated patients in intensive care its adoption may reduce the time taken to extubate patients following cessation of sedation and reduce the duration of admission to ICU. Patients may benefit from reduced morbidity. The alternative regimen may provide clinicians with a more flexible sedation regimen to maintain patient comfort. The cost of the alternative regimen may be significantly less than sedating all patients with propofol alone.

8. Ethical considerations

Patients sedated in ICU are unable to give consent, therefore consent will be obtained from the relatives of subjects and they will be given an information sheet (appendix 2 & 3). Medical staff will be asked if the patient can be included in the study. Confidentiality of patients and data will be maintained. Anonymity of the participants will be maintained and data will be stored in a locked cupboard for a period of five years. Only the investigators will have access to this data.

Approval for the study has been obtained from the Director of ICU, from the Medical research coordinator, from the ICU research committee.

9. Drugs

The drugs involved in this study, morphine, midazolam and propofol are the usual agents currently used for analgesia and sedation in the RAH intensive care unit.

10. Analysis and reporting of results

For both the experimental group and control group the demographic data will be analysed and will be presented as frequency distributions. Mean and standard deviation of extubation time and duration of admission will be calculated. A two-tailed t-test will be used to analyse the data. The t-test is chosen as it is considered to be robust to violations in assumptions of the normal distribution of data. Probability will be set at 0.05.

Details of all drugs administered to the participants will be recorded. Patients in ICU are commonly given erythromycin and amiodarone, both are cytochrome p450 3A4 inhibitors and so may potentiate sedation with midazolam. Therefore the analysis will be stratified to take account of this variable. In this way the influence of deterioration in renal and hepatic function will also be considered.

The incidence of haemodynamic complications will be recorded as episodes of > 20mmHg reduction in mean arterial pressure or changes in pulse rate > 10 beats per minute in response to boli of propofol or morphine and midazolam. The results will be submitted for publication in a refereed journal.
11. References


12. Ethical Approval

The study is supported by the Research Committee of the RAH intensive care unit.
13. Date of commencement / Time-Line

The study will commence following ethics approval and implementation of the nursing staff education program. It is anticipated it will commence in March 2001 and will take three months to complete.

14. Resource considerations

The following budget has been calculated:

**Budget**

<table>
<thead>
<tr>
<th>Budget Items</th>
<th>RAH Level 2 ($20.57 per hr)</th>
<th>3.5 hrs day for 12 weeks (294 hrs)</th>
<th>$6047.58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research assistant:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education of staff, entering of patients into study, data collection and entering of data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Printing &amp; photocopying</td>
<td>Paper $5.95 per 500 pages</td>
<td>10c copy photocopying/ printing</td>
<td>$402.84</td>
</tr>
<tr>
<td>Information sheet, consent form, protocol sheet, data collection sheets, interview forms. (up to 36 pages per patient).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>$6450.42</td>
</tr>
</tbody>
</table>

Patients will be randomised to either the control group who will be sedated with infusions of midazolam and morphine, as per the current protocol or to the alternative regimen a background infusion of midazolam and morphine with boli of propofol for critical procedures. Currently the sedation regimen is ordered at the discretion of the medical officer on duty. This means some patients receive continuous infusions of propofol for their entire admission or for 12 – 24hrs prior to planned extubation. For duration of the study patients in the control group would not be ordered propofol at all, while patients randomised to the alternative regimen would be administered low dose boli and not infusions. Therefore it is reasonable to expect that there will be a cost neutral outcome for the drugs used in the study.

The data will be collected from the subject’s medical records during their admission to ICU.
15. Details of available support

There are no other resource support considerations. The study is supported by the Research Committee of the RAH intensive care unit.

(Subsequently the investigator was awarded a grant from Abbott through the Australian College of Critical Care Nurses and had received $2500 which was returned.)
Appendix 1 Critical Illness Sedation Scale (Ciss)

**LEVEL 1 Inadequate sedation.** Agitated, distressed. Not tolerating IPPV eg coughing against the ventilator or attempting extubation.

**LEVEL 2 Light sedation.** Eyes may be closed, but open to speech, responds purposefully, quickly settles when not stimulated, tolerates ventilation when not roused.

**LEVEL 3 Moderate sedation.** Sluggish response to forehead tap or speech. eg weak flexion or grimacing.

**LEVEL 4 Heavy sedation.** No voluntary response to stimulation of any form. A weak cough on suction and spinal reflexes may be present.
Appendix 2 Royal Adelaide Hospital Consent Form

Investigators: Ms Magarey, Dr McCutcheon, Dr Chapman, Mr Blight.

1. The nature and purpose of the project has been explained to me. I understand it, and agree to allow my relative / significant other to take part.

2. I understand he / she will not directly benefit from taking part in the trial.

3. I understand that, while information gained during the study may be published, he /she will not be identified and his / her personal results will remain confidential.

4. I understand I can withdraw my relative / significant other from the study at any stage and that it will not affect his / her medical care, now or in the future.

5. I understand that consent will be sought from my relative / significant other when his / her condition allows, and that he / she may withdraw from the study.

Name ____________________________________________

Signed ____________________________________________

Date: ____________________________________________

I certify I have explained the study to the patient's relative / significant other and consider he / she understands what is involved.

Signed ____________________________________________

Judy Magarey
Appendix 3 Relative Information Sheet

Dear Sir or Madam,

I am a Doctor of Nursing Candidate at the University of Adelaide, Department of Clinical Nursing. My research involves the introduction of an alternative way of sedating patients in intensive care. This is a research project and your relative does not have to be involved. If you do not wish him or her to participate their medical care will not be affected in any way.

In the Intensive Care Unit we give drugs so that the patients do not feel pain or fight the breathing machine. The drugs make the patient sleepy and make it less likely that they will remember their time in ICU. My research involves combining the sedating drugs so that patients are kept comfortable but do not get too much sedation which can make it more difficult to get them to breathe on their own, prolonging their time on the breathing machine and in the ICU.

In ICU we usually give continuous infusions of sedating drugs (morphine and midazolam) to keep the patient calm and free of pain. The nurse caring for the patient increases or decreases the dose as necessary and often gives an increased dose prior to doing anything which may cause distress such as clearing the breathing tube with suction. In this study this method of maintaining patient comfort will be compared with an alternative method. Half the patients in the study will be kept comfortable using a new method. For the new method again the sedating drugs, morphine and midazolam will be administered at a dose, enough to keep the patient calm and free of pain. To prevent them feeling distressed during procedures such as clearing the breathing tube, they will be given a small amount of another sedating drug propofol. This drug makes the patient sleep deeply for only a few minutes. It does not take away pain or prevent patients from remembering what has happened. This drug is given now to some patients, so when it is stopped they wake up quickly. We hope that by using this method that patients may be able to breathe on their own sooner and when they no longer need intensive care be discharged to a normal ward more quickly. It is probable that patients sedated using this
new method will remember their stay in ICU more than those sedated using the usual method.

Your relative will be assessed by the nurses to ensure they are comfortable and not distressed. If they are distressed, the dose of the sedating drugs morphine and midazolam will be increased. If this is not successful at keeping them comfortable they will be withdrawn from the study and will be given the usual method of sedation. There will be no other changes to nursing or medical treatment. No details of your relatives will be revealed.

If you have any queries regarding the study please contact Judy Magarey, Royal Adelaide Hospital Phone extension 25828, or pager 1541. This study has been approved by the Royal Adelaide Hospital Research Ethics Committee. If you wish to discuss aspects of the study with someone not directly involved, you may also contact the Chairman Research Ethics Committee, Royal Adelaide Hospital on 8222 4139
Please accept in advance my thanks for your assistance.
Judy Magarey
DISCUSSION OF FACTORS CONTRIBUTING TO THE FAILURE OF THE RESEARCH

The research was commenced in March 2001 following approval by the Hospital Ethics Committee (see appendix 1), the Pharmacological Sub-committee, the ICU Research Committee and The Department of Clinical Nursing Research and Higher Degrees Committee. It was ceased in November 2001 as only one subject had been recruited.

There were a variety of factors that contributed to the failure of the research. One of the main problems was the significant number of exclusion criteria that limited the population available for recruitment. The high acuity of the unit concerned and the fact that it is a tertiary referral centre, meant that many of the patients admitted had renal or hepatic impairment or a neurological condition which meant they were excluded from the study. In retrospect a more detailed review of the admission statistics may have provided an indication of this problem to the researcher.

However, there were still sufficient numbers of suitable subjects admitted who were not entered into the study. A substantial effort was put into gaining the support of medical and nursing staff. The researcher had individually spoken to 138 of the 160 nurses listed on the roster. Those who were not spoken to in person were sent a letter and an information sheet outlining the proposal (see appendix 2) and asking them to contact the researcher if they had queries. This meant visiting the ICU at all shift times and on weekends. The consent of the consultants was gained by speaking to them individually. The registrars were not all spoken to individually and this may have contributed to the
failure of the study. However, some were spoken to and all were sent a letter and given detailed information regarding the study (see appendix 2). It was erroneously thought that the support of the consultants would filter through to the registrars. There were problems in speaking to individual registrars as their turnover was quite frequent. The researcher also had to gain the consent of the ICU research committee, which meant giving committee members a copy of the proposal and discussing it with them in a meeting.

When the study commenced it was apparent that many of the staff did not support the research. The registrars were unwilling to enter patients into the study as they considered that all short-term patients should receive propofol so that they could be extubated promptly. The systematic review demonstrated that for patients without renal or hepatic failure the difference in extubation times between patients sedated with midazolam compared to propofol was not clinically significant of the order of hours rather than days.\(^1\)\(^4\) In addition the initial study protocol indicated that patients were to be sedated lightly with the midazolam and morphine mixture and have boli of propofol to keep them comfortable during suction and turns or any other procedures where deeper sedation was deemed necessary. Despite this, the registrars considered it their right as independent medical practitioners to decide what drug to order for sedation.

Some of the nurses did not support the study. Some of the reasons for this were said to be “a nurse should not be doing this research” and “why should I do another nurse’s research”. Another reason may have been that it is more difficult to care for a lightly sedated patient than a heavily sedated one who may be perceived as not requiring
reassurance or communication. A previous questionnaire of nurses in the unit elicited the opinion that nurses do not like caring for lightly sedated patients.3

The researcher was not present full time in the unit, but worked in a Department situated on the hospital campus. This meant she was not always present when patients who fitted the inclusion and exclusion criteria were admitted. These patients were generally admitted after hours and on weekends. A letter was sent to all team leaders asking them to contact the researcher after hours if a patient was admitted who could be included in the study (see appendix 5), however, this rarely happened. In a busy ICU nursing research is not a priority when the patient is being admitted.

The researcher had applied for a grant awarded by Abbott through the Australian College of Critical Care Nurses and had received $2500 (see appendix 6). This was to be put towards employing nurses specifically to recruit subjects. It was decided that these should be ICU staff so they would have an understanding the study. However, these nurses had other duties and were unable to give dedicated time to the study and they did not work overtime. In addition they were also unable to get the registrars to recruit patients.

Several meetings were held with the nurses, senior nursing staff and the consultant in charge of research and the proposal was amended to include patients who required a depth of sedation other than light. However, this had no influence on the recruitment of patients and the study was ceased after 11 months to allow the researcher to concentrate on other research proposals.
It is possible that this research would not have been problematic if the researcher had been a doctor. Research is extremely difficult when the person undertaking it does not have control of the treatment proposed. This proposal required the support of nursing and medical staff to implement. In addition, given the complexities of the study it may have been too ambitious a project for the researcher to complete in the time available. The unit concerned does not have a well developed nursing research profile, although medical research is well supported with the services of a full time research nurse. The services of this nurse were not available to the researcher. At the time of the study only one of the senior nurses had completed studies at masters level. Few nurses in the unit concerned had conducted research.

The reasons that this study did not succeed were complex but the predominant ones were that it was perceived as a nurse infringing on the role of a doctor and lack of support for the study.
REFERENCES


APPENDICES
Appendix 1 Letter from Ethics Committee Chairman

ROYAL ADELAIDE HOSPITAL
Medical & Mental Health Services

8222 4139
25 January 2001

Ms J Magarey
DEPT OF CLINICAL NURSING
UNIVERSITY OF ADELAIDE

Dear Ms Magarey,


I am writing to advise that ethical approval has been given to the above project. Please note that the approval is ethical only, and does not imply an approval for funding of the project.

Human Ethics Committee deliberations are guided by the Declaration of Helsinki and N.H. and M.R.C. Guidelines on Human Experimentation. Copies of these can be forwarded at your request.

Adequate record-keeping is important and you should retain at least the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them if necessary, in the future. The Committee will seek a progress report on this project at regular intervals and would like a brief report upon its conclusion.

If the results of your project are to be published, an appropriate acknowledgment of the Hospital should be contained in the article.

Yours sincerely,

Dr M James
Chairman
RESEARCH ETHICS COMMITTEE
Appendix 2 Staff Information Sheet

The Efficacy Of An Alternative Sedation Regimen Compared To The Existing Regimen For The Sedation Of Adult Ventilated Patients In Intensive Care.

The aim of this study is to compare the current sedation regimen, with an alternative regimen. The current regimen consists of a continuous infusion of morphine/midazolam with boli of the solution administered as required. The alternative regimen will consist of a continuous infusion of morphine and midazolam titrated to provide sedation at the prescribed level (on the critical illness sedation scale) and boli of propofol administered to supplement sedation during critical procedures such as endotracheal suctioning.

Therefore the sedation order for treatment group should be:

- Background infusion of morphine and midazolam (morphine 1mg/ml and 0.5mg/ml midazolam), titrated to provide sedation at the prescribed level (on the critical illness sedation scale)

- boli of propofol to provide sedation during critical procedures. The initial bolus dose will be 0.25mg /kg and will be increased in increments of 0.25mg/kg to 1mg/kg as required.

Patients will be withdrawn from the study if in the opinion of the medical officer the boli of propofol cannot be tolerated eg causing severe hypotension.

The sedation order for control group should be:

- morphine / midazolam sedation infusion and boluses according to the usual ICU protocol.

Please note that where possible do not order propofol for this group as this will result in them being withdrawn from the study.

Note: If a patient requires paralysing agents (other than to facilitate intubation) or other agents for sedation they will be withdrawn from the study.

If you have any queries regarding this study or would like a copy of the proposal please contact:

Judy Magarey 25828 page 1541
Frank Donnelly ICU page 22906
Peter Lorimer ICU
Marianne Chapman ICU
Appendix 3 PROTOCOL (Treatment Group)

The efficacy of an alternative sedation regimen compared to the existing regimen for the sedation of adult ventilated patients in intensive care

This patient is a participant in a study to investigate the efficacy of a new sedation regimen. Therefore the following protocol applies:

- **A continuous infusion of morphine / midazolam titrated to provide** the prescribed level of sedation on the Critical Illness Sedation Scale (CISS) (**do not give bolus doses of this infusion**).

- **Record the CISS hourly on the observation chart.**

<table>
<thead>
<tr>
<th>CRITICAL ILLNESS SEDATION SCALE (CISS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL 1 Inadequate sedation.</td>
</tr>
<tr>
<td>LEVEL 2 Light sedation.</td>
</tr>
<tr>
<td>LEVEL 3 Moderate sedation.</td>
</tr>
<tr>
<td>LEVEL 4 Heavy sedation.</td>
</tr>
</tbody>
</table>

- **Administer slow bolus doses of propofol as ordered if required for procedures such as turns, suction.**

- **Record all bolus doses and any adverse haemodynamic responses (MAP ↓ > 20mmH and or Pulse ↑ > 10BPM or other) occurring during or immediately following the administration (prior to the procedure) on the data collection sheet.**

- **Record periods of inadequate sedation (level 1 on CISS) or other adverse events such as self removal of tubes, allergy or seizures on the data collection sheet.**

**Note if the patient requires paralysing agents (other than to facilitate intubation) or other agents for sedation they will need to be withdrawn from the study.**
Appendix 4 Protocol (Control Group)

The efficacy of an alternative sedation regimen compared to the existing regimen for the sedation of adult ventilated patients in intensive care

This patient is a participant in a study to investigate the efficacy of a new sedation regimen. Therefore the following protocol applies:

- Administer morphine / midazolam sedation according to the usual ICU protocol
- Record the CISS hourly on the observation chart.

<table>
<thead>
<tr>
<th>CRITICAL ILLNESS SEDATION SCALE (CISS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL 1 Inadequate sedation.</td>
</tr>
<tr>
<td>LEVEL 2 Light sedation.</td>
</tr>
<tr>
<td>LEVEL 3 Moderate sedation.</td>
</tr>
<tr>
<td>LEVEL 4 Heavy sedation.</td>
</tr>
</tbody>
</table>

- Record periods of inadequate sedation (Agitation, distress. not tolerating IPPV eg coughing against the ventilator or attempting extubation, level 1 on sedation scale) on the data collection sheet
- Record all bolus doses of sedation and any adverse haemodynamic responses (MAP ↓ > 20mmH and or Pulse ↓ > 10BPM or other) occurring during or immediately following the administration (prior to the procedure, such as suction) on the data collection sheet.
- Record adverse events such as self removal of tubes, allergy or seizures on the data collection sheet.

Note if the patient requires paralysing agents (other than to facilitate intubation) or other agents for sedation they will need to be with drawn from the study.
Appendix 5 Letter to Team Leaders

The efficacy of an alternative sedation regimen compared to the existing regimen for the sedation of adult ventilated patients in intensive care.

Dear Team Leader / Coordinator as you know a randomised controlled trial to compare the current sedation regimen, with an alternative regimen has commenced. Below are the inclusion and exclusion criteria for the study. If you admit a patient who you think will be eligible to enter the study can you please contact one of the research team so consent can be requested from the relatives.

Monday to Friday Frank Donnelly (page 22906) or Peter Lorimer
After hours till 8 PM or weekends till 8 PM Judy Magarey phone 25828, page 1541, Mobile 041 7807481

Inclusion criteria
All adult patients ventilated in the ICU for greater than 12 hrs and less than 10 days, who are ordered sedation.

Exclusion criteria
The following exclusion criteria will be applied:

- Patients with neurological deficit, eg CVA, head injury;
- Patients with neuromuscular disorders likely to cause muscle weakness such as Guillain Barre syndrome;
- Patients receiving neuromuscular blocking agents except when administered to facilitate intubation or during an operative procedure prior to admission to ICU;
- Patients receiving other sedating agents such as chlorpromazine and haloperidol;
- Pregnant women;
- Known allergy to midazolam or propofol;
- Patients with tracheostomies as extubation time cannot be measured;
- Patients ventilated for more than 10 days;
- Patients who are prescribed MAO inhibitors.
- Patients with hepatic or renal impairment.

Patients will be withdrawn if in the opinion of the medical officer on duty they are unable to tolerate bolus of propofol due to side effects such as hypotension.

Thankyou

Judy Magarey
Appendix 6 Letter from the Australian College of Critical Care Nurses

Ms Judy Magarey
Department of Clinical Nursing
Level 3
Eleanor Harrald Building
Royal Adelaide Hospital
North Terrace
Adelaide  5000

April 3rd, 2001

Dear Judy,

Thank you for your application and research proposal for the Abbott Research Grant. I apologise that it has been so long since you have received formal notification about this.

The Australian College of Critical Care Nurses (ACCCN) Ltd are very excited about the support from Abbott Australasia in providing significant funding towards critical care nursing research. We have been pleased with the response and interest in this grant and the standard of those proposals received has been high.

The Board of ACCCN Ltd requested representatives from Abbott Australasia and the ACCCN Research Advisory Panel to review and make recommendations in regards to the received proposals. I have attached the written feedback from the Research Advisory panel in regards to your proposal.

I am pleased to inform you that you have been successful in being awarded partial funding of $2,500 towards the conduct of this project. Abbott has requested that you acknowledge the grant in any written reports related to this project.

Congratulations. We wish you every success with this project and look forward to receiving information about the outcome of the study.

Yours sincerely,

[Signature]

ACCCN Director and Manager, Education and Research Fund
STUDY 2

A DESCRIPTIVE STUDY TO EXPLORE PATIENTS’ MEMORIES OF THEIR STAY IN AN INTENSIVE CARE UNIT (ICU) AND TO INVESTIGATE THE ASSOCIATION OF THEIR MEMORIES WITH THE SEDATION REGIMES USED
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ABSTRACT

The purpose of this study was to investigate the memories of patients who were ventilated from 12 hours to ten days in the ICU. In particular to investigate the incidence of dreams, nightmares and confusion as recalled by the patients and to determine if there was an association between these memories and the sedation regime that the patient received, with regard to the type of sedation agent used, and depth of sedation applied.

The study was conducted in two stages. In the first stage descriptive data about the patients' memories were collected by a means of a questionnaire, with a target sample of 50 participants. Data were then collected from the patients records concerning demographics (age, gender, diagnosis), duration of admission and ventilation, the duration and depth of sedation, time awake prior to extubation and prior to discharge from the ICU, drugs administered and documented nightmares, confusion or hallucinations. Data were analysed using SPSS.

Forty-two percent of patients stated that they remembered being in the ICU, but only 24% - 29% remembered the specific experiences of intermittent positive pressure ventilation (IPPV) or endotracheal suction. Anxiety, pain, thirst and nausea were remembered by 20-29% of participants and these experiences appear to have caused was moderate to high distress. Nightmares, hallucinations and confusion were remembered by 10%-27.5% of participants, but those who remembered these experiences found them highly distressing. Fifty-five percent of the participants remembered the nurses speaking to them and most (71%) found them reassuring.

There was no statistically significant relationship between memory of the ICU, and the sedation regime administered or memories of nightmares, dreams and hallucinations and the sedation regime administered.
There was no statistically significant relationship between variables such as age or time in the ICU, APACHE II score and memory. Seventy eight percent of patients were ventilated for some time without sedation and 65% were observed to be awake while on ventilation. However, there was no statistically significant relationship between this and memories.

In the second stage of the study patients who reported hallucinations, dreams or delusions in the questionnaire and indicated that they would like to be interviewed were invited to participate in an open-ended semi-structured interview. The qualitative data in the form of typed interview transcripts were analysed using the phases described by Leininger. The themes that developed were, blackness and colour, powerlessness and purpose, reality and unreality and death. Participants described horrifying paranoid delusions. Some of the experiences described possibly had a basis in reality for example being unable to speak or move. Participants related how the presence of loved ones reassured them and helped them return to reality when they were confused. One participant suffered continuing embarrassment relating to attacking a doctor in a confused state and another was continuing to suffer flashbacks and nightmares.

The results of the study indicate that while the patients commonly indicated that they remembered the ICU (42%), memories of specific experiences such as artificial ventilation were only remembered by 20 – 29% of the sample. The participants found that some of the experiences were very distressing, in particular nightmares, hallucinations and confusion. This finding was supported by the themes that developed from the qualitative data and these were blackness and colour, powerlessness and purpose, reality and unreality and death. However, it appears that the contact provided by nurses and loved ones is important in providing reassurance and orientating patients in the ICU.
Definition of Terms

Confusion: A mental state characterised by disorientation regarding, time, place, person or situation.¹

Delirium: An acute organic mental disorder characterised by confusion, disorientation, restlessness, clouding of the consciousness, incoherence, fear, anxiety, excitement, and often by illusions; hallucinations, usually of visual origin; and at times delusional.¹

Explicit memory: Consciously remembered events.²

Extubation: Removal of the endotracheal tube.

Implicit memory: Unconsciously remembered events². Memories may be elicited by cues. For example, a patient may feel a sense of unexplained panic when watching a medical program on TV.

IPPV: Intermittent Positive Pressure Ventilation, artificial ventilation.

Nightmare: A dream...that arouses feelings of intense inescapable fear, terror, distress, or extreme anxiety...¹
INTRODUCTION

Context of the Study

The first component of this portfolio was a systematic review of the effectiveness of midazolam and propofol, for the sedation of adult ventilated patients, with particular reference to: the ability to achieve a chosen sedation level, recovery and extubation time, duration of admission to the ICU and the incidence of haemodynamic complications. None of these variables take into account the experiences of patients who are sedated in an ICU. Some studies analysed in the systematic review reported on the incidence of agitation, but none reported whether patients remembered their experiences or whether particular drugs or regimes were related to an increase in the incidence of confusion, agitation and hallucinations as recalled by the patient.

Midazolam and propofol were chosen as the subject of the systematic review as they are the most common agents used to sedate adult patients in ICUs.\textsuperscript{3-5} Midazolam is a more effective amnesic agent than propofol\textsuperscript{6} and anecdotal evidence suggests that both ICU nurses and doctors believe this is beneficial. However, recently it has been proposed that the absence of explicit or real memories may in fact increase distress, as patients are unable to reject dreams, hallucinations or nightmares as internally generated.\textsuperscript{2} Sometimes, patients express concern that they have “lost time”\textsuperscript{7} and may worry about what happened during the time that they are unable to recall. It is possible that patients who are more lightly sedated or have a period of time in the ICU in which they are “awake” and are able to assimilate real memories may suffer less distress.

Use of propofol has been related to agitation, confusion and hallucinations.\textsuperscript{8} It is often used to induce sleep or deep sedation and because of its extremely short re-distribution half-life patients may wake rapidly and may become agitated. As it is not an effective amnesic agent it is possible that distress relating to this agitation may be remembered. A
survey conducted in 1996 found that the most common agents used for sedation were benzodiazepines. However, anecdotal evidence suggests propofol which was first used in Australian ICUs in the 1990s, may now be the most common drug used for short-term sedation. Much of the research conducted on patients’ memories of their ICU experiences was carried out prior to the widespread use of propofol. Thus it is timely to further investigate patients’ memories.

There are many studies that have investigated the recall of ventilated ICU patients, but none appear to have related the recall of dreams, nightmares and hallucinations to the sedation regime that the patient received. In particular factors such as the depth of sedation, periods of wakefulness prior to extubation and time in the unit following extubation prior to discharge need to be considered as these may have an influence on patients’ memories.

**Purpose of the study**

The purpose of this study was to investigate the memories some patients have of their experiences in the ICU. In particular, to investigate the incidence of dreams, delusions and confusion as recalled by the patients and to investigate the relationship of these to the sedation regime the patient received, with regard to the type of sedation agent used, and depth of sedation applied. The findings of this study may be useful to assist nurses and doctors in ICUs to make decisions regarding the agents used and how they are administered. It may also inform those caring for sedated patients about the possible psychological implications of their sedation practice.

**Statement of the Research Questions**

The research questions were:

- What memories do patients have of their experiences in ICU?
• What memories do patients have of dreams, nightmares and confusion?
• Is there a relationship between the sedation regime and these memories?

**Significance of the Study**

The findings of this study will be used to inform clinicians about the influence current sedation regimes have on the patients' recall of their stay in the ICU and in particular to illuminate what if any influence chosen regimes have on the incidence of hallucinations, dreams, and delusions.

**Assumptions**

Assumptions on which this study is based are that some patients will remember their experiences in ICU and in particular dreams, hallucinations and nightmares and that patients will complete the questionnaire honestly and accurately. A further assumption was that memories of dreams, nightmares and hallucinations which caused distress were still remembered by the patients when they responded to the questionnaire.

**Summary**

The first component of the portfolio, a review of the effectiveness of the sedation agents, midazolam and propofol highlighted that none of the research evaluated the patients' experiences. Both midazolam and propofol have been related to confusion agitation and hallucinations, but midazolam is an effective amnesic agent while propofol is not. Surveys conducted in the 1980s and the early 1990s indicated that benzodiazepines were the most common agents used for sedation of adult patients in ICUs. However, anecdotal evidence suggests that propofol may be used more commonly particularly for the sedation of short-term patients. Although there have been many studies investigating the memories of ICU patients, most were performed prior to the widespread use of propofol. Therefore, it is timely to further investigate the memories of ICU patients. In addition, previous studies have not specifically related memories and in particular those of hallucinations, nightmares and confusion to the sedation regime used. Thus the purpose of this study was to investigate these matters.
LITERATURE REVIEW

Introduction

There have been numerous studies investigating patients’ recall of their experiences in the ICU. Most researchers used either questionnaires or interviews that were completed from a few hours to months following discharge. The research indicates that approximately 50% of patients have no explicit memories of their experiences in the ICU. Factors related to poor recall, include age greater than 60 yrs, the administration of medications such as benzodiazepines, severity of illness and artificial ventilation.

Common Memories

Common memories of ICU include pain and discomfort, discomfort from equipment such as catheters, noise and inability to sleep, fear and anxiety, thirst, and difficulty with communication. Fontes Pinto Novaes and colleagues evaluated the stressors of ICU as perceived by the patients, relatives and health care team. Pain and being unable to sleep were the stressors ranked highest by the patients. However, some studies have reported positive findings, such as patients being made to feel secure and receiving reassurance from nurses. The support of relatives and loved ones as remembered by the patient, is also reported to be extremely important. Relatives are trusted and provide a link with reality, in addition they are able to facilitate communication between the patient and the nurses.

Researchers have found that while many patients initially claim to have no recall of their time in the ICU, memories may be elicited by use of cues, for example using a timetable of events recorded during the patient’s stay in the ICU. This finding may be explained by the differences between explicit (consciously remembered) and implicit memories (unconsciously remembered). Explicit memory involves conscious recall of a particular event such as a patient remembering tracheal suction being performed or a particular relative visiting. Conversely implicit memory may subconsciously influence
actions even although there is no conscious recollection of events. For example, a patient may feel a sense of unexplained panic when watching a medical program on TV. Artificial ventilation and sedation have also been reported to influence re-call. With the increasing acuity of patients in acute hospitals they are less likely to remain in ICU following extubation, and therefore patients may not have extended conscious periods in the ICU in which to consolidate memories or to make sense of fragmented memories.

**Nightmares and hallucinations**

Studies indicate that from 26% to 73% of ICU patients suffer nightmares, hallucinations, paranoid delusions or confusion. These are commonly recounted by those patients who have no explicit memories of ICU. Jones, Griffiths and Humphris propose that the absence of real memories means patients have no clues with which to reject vivid delusions and hallucinations as internally produced. This has important implications for the psychological well being of patients following discharge from the ICU. Indeed the incidence of post-traumatic stress in ICU patients is higher in those without explicit memories of the ICU. Even following discharge and recovery patients may be unable to distinguish between reality and delusions. Nightmares may continue for months and are a major feature of post traumatic stress syndrome. Conversely, Schelling and colleagues investigating posttraumatic stress in survivors of Adult Respiratory Distress Syndrome (ARDS) found a higher incidence was related to more memories of traumatic episodes in the ICU. The mean duration of ventilation for these patients was 23 days and the duration of ICU treatment was 31 days. It has also been reported that hostages in solitary confinement and in fear of their lives report vivid hallucination like those suffered by ICU patients.

Nightmares, delusions and confusion are all characteristics of the “ICU syndrome”. This term was first used by McKegney to describe the delirium common in ICU patients. It is a complex disorder and there are many factors which may contribute to
its development, including hypoxia, hypercapnia, pain, sleep deprivation, fear, and drugs administered.\textsuperscript{30,31} One of the major predictors is age with the elderly more likely to suffer from ICU syndrome. This may be due to increased sensitivity of the brain to hypoxia and choline (the main component of acetylcholine a neurotransmitter substance).\textsuperscript{32}

Dreams and hallucinations can be terrifying, the dream world becomes the patient’s reality, so that they may fear for their lives.\textsuperscript{24} Nightmares may also cause patients to fear sleep, further exacerbating the problem of sleep deprivation.\textsuperscript{11} Of concern is that patients report a reluctance to tell nurses about nightmares, thus staff may be unaware of their distress.\textsuperscript{8,19,31,33} This reluctance may be due to embarrassment about the content of nightmares, or a fear that they are losing their sanity.\textsuperscript{33} Some patients experience frightening flashbacks and the dreams and delusions are often remembered with clarity and in detail although actual events are not recalled.\textsuperscript{8}

There have been many studies investigating the memories of ICU patients following discharge, however, most do not report how many of the subjects were actually ventilated or what sedative regime was followed. Therefore, the influence of these factors on patient’ memories and the incidence of nightmares and hallucinations has not been reported.

\section*{The influence of sedative agents on nightmares}

In 1996 the most common agents used for the sedation of ICU patients in Australia were a combination of benzodiazepines and narcotics.\textsuperscript{4} Specifically midazolam and morphine. Midazolam is an amnesic agent but has also been reported to cause nightmares.\textsuperscript{2} In a study of the effects of anaesthesia on sleep and dreams it was reported that two thirds of the patients who received benzodiazepines as a pre medication had
post operative dreams and half of these were nightmares. Morphine may also cause mental clouding and delirium although this is reported to be rare.

The sedative propofol was introduced to Australia in the 1990s. Anecdotal evidence suggests that this agent is now commonly used for ICU sedation. It is important to note that it does not produce the profound amnesia of midazolam. Hall-Smith, Ball and Coakley collected narrative data from 26 patients as part of a follow up program for ICU patients. Hall Smith, Ball, and Coakley state that reports of nightmarish hallucinations from patients sedated with propofol resulted in the unit in question “rarely” using this agent for sedation.

Cheng states that “unfortunately the previous studies that examined recall in the ICU do not provide insight on the impact of specific sedative regimes in different clinical situations.” Thus there is a need for further research to explore the memories of ICU patients in relation to the sedation regime administered; in particular, the incidence of nightmares, dreams and delusions so that this can be taken into account when sedation is administered.

**Summary**

Sedation is administered to promote comfort, reduce anxiety and to facilitate treatment, but the relationship of these agents to nightmares, hallucinations and confusion has not been investigated. Lack of explicit memory may increase the risk of post-traumatic stress syndrome. In addition some patients complain of feeling they have lost part of their lives in a black hole or of finding the inability to remember distressing. Explicit memories of the ICU may help them to make sense of their experiences.
METHODS

Research Design Stage 1

The study was conducted in two stages. The first stage was conducted using a descriptive design. Polit and Hungler state that “the purpose of a descriptive study is to observe, describe, and document aspects of a situation” and that this design may also be used to describe the relationship between variables. As the purpose of the study was to describe the memories patients had of their stay in ICU and to investigate whether there was a relationship between these and the sedation regime used, a descriptive design was chosen.

The population investigated was patients who had been discharged from the 20 bed adult general ICU of an 800 bed public teaching hospital in South Australia. The aim was to recruit a convenience sample of 50 of the most recently discharged patients. A convenience sample is the weakest form of sampling having the highest risk of bias. However, it was thought that a convenience sample would be the only practical method of gaining a sample from the target population. Although the research hospital has a large ICU with a high turnover, only patients who were ventilated and sedated for at least 12 hours were included. Many patients had to be excluded due to factors that may influence memory or the likelihood of hallucinations and confusion, for example, head injuries or drug and alcohol abuse. In addition, the mortality rate is high in ICUs also limiting the study population. Long-term patients who are a distinct group and are often ventilated for long periods without sedation were also excluded. Therefore, to obtain a sample of patients who were discharged within the last two years and large enough for analysis, a convenience sample with a target of 50 participants was chosen. Given the restrictions gaining this number of participants was a realist goal. Questionnaires were sent in increments as the lists of names were generated by the information services staff.
(10 as a pilot and then 31, 73 and finally another 11) until a sample 50 patients had responded. The inclusion and exclusion criteria defined the target population. All were intubated, ventilated and sedated. The research question related to memories of these experiences. Thus the inclusion and exclusion criteria were designed to reduce heterogeneity of the sample in terms of their experiences of the ICU. This was considered important because homogeneity of the population improves the reliability of the results.37

A questionnaire does not allow any interaction with the participant but this may also reduce the possibility of bias.38 This technique of collecting data does not require as many resources as interviewing and is less time consuming.38 However, there is the possibility of sampling bias as the sample was “self selecting”, patients who did not respond to the questionnaire may have had very different memories to those who did.39

Although the recall of patients may not be reliable, it is not possible to collect prospective data on the experiences of patients who were intubated and sedated and cannot communicate. Retrospective data were also collected from the patients’ medical records. One disadvantage of this method was that missing data could not be obtained from other sources, such as by asking staff directly due to the time that had elapsed since the discharge of the participants. Data could have been collected prospectively during the admissions of all patients who fitted the inclusion criteria. Although this may have provided more reliable data, it would have been extremely time consuming and labour intensive and beyond the resources available for this study.

**Ethical Issues**

Approval for the study was obtained from the hospital medical ethics committee (appendix 1) and the ICU research committee at the hospital where the research was conducted. Participation in the study was voluntary and the return of a completed
questionnaire implied consent. Anonymity was maintained by using numbers to identify the participants and data remained confidential. Each questionnaire was coded for the purposes of identifying those patients who responded. However, this information was kept confidential and only the researcher had access to the names or any other information that could identify the participants. No information that could identify an individual was used in the analysis of the data. On completion of the study all data were kept secure in a locked cupboard and will remain secured for a period of seven years. Participants were assured that all data would remain confidential and that no information would be published or reported that could identify an individual.

Recruitment of Participants

The aim was to recruit a convenience sample of 50 patients to participate in stage one of the study. Subjects were identified using the Australian Patient Management System (APMS). The APMS is a patient information database that was established in 1980. It was originally a system produced by IBM® that was adapted for use in Australia by information technology staff at the research hospital. Data is entered into the APMS by nurses, doctors and ward clerks in all departments of the study hospital. The information is subsequently coded for funding purposes, using case mix codes. Following ethics approval an information technology staff member conducted a search of the APMS database using the inclusion and exclusion criteria. Those used for the initial search were:

Inclusion criteria

Patients:

- greater than 18yrs of age (as the research unit is an adult unit);
- admitted to the ICU for at least 24hrs;
- sedated and ventilated for at least 12 hrs but less than 10 days; and who were
- alive on discharge from hospital.
The reason for these criteria was that patients with prolonged conscious periods and long admissions would be excluded as their experiences could be very different from that of the general ICU population. For example, patients with Guillain Barré may be ventilated without sedation for months. It is likely that patients who had long-term admission in the ICU would have been managed with tracheostomies and may be more likely to remember being ventilated, having endotracheal suction and interactions with the nurses. In 1999-2000 the average length of stay in the ICU was 292.6 hours (median 46.6 hours) and there were 1188 admissions.40

Exclusion criteria

Those used for the initial search were patients:

- known to be addicted to alcohol or drugs;
- with dementia;
- who had suffered disorders affecting the central nervous system;
- with an existing psychological disorder;
- with a permanent tracheostomy or dysphasia;
- who had been admitted following a drug overdose.

Patients with alcohol or drug addictions may experience nightmares, hallucinations and confusion not related to their ICU experience or sedation. Central nervous system injury may also impair memory and cause confusion. Communication would be impaired in patients with a permanent tracheostomy or dysphasia, impeding interviews. In the unit where the research was conducted, patients are commonly not sedated following drug overdose, thus these were also excluded from the study.

Once suitable participants were identified on the APMS print out, they were given an identification number so that data from the returned questionnaires could be matched to data collected from records and so that patients who consented to interviews could be identified. Patients were then sent a letter of introduction from the medical director of
ICU and the researcher inviting participation (appendices 2 & 3). The questionnaires were labelled with the patient’s study identification number.

When the questionnaire (appendix 4) was returned the following information was collected from the notes of the patients who had responded:

- demographic data (age, gender, diagnosis);
- duration of ventilation;
- details regarding the sedation administered;
- details regarding depth of sedation and periods of time during the admission to the ICU in which the patient was not sedated and appeared orientated;
- details of any other sedating drugs administered;
- details of recorded periods of confusion and reports of nightmares, dreams or delusions;
- duration of admission to the ICU;
- admission APACHE score, as severity of illness has been reported to influence memories of ICU.

APACHE II is a severity of disease classification system. It was developed in the USA and uses 12 physiological measurements (eg pH, temperature and heart rate), age and previous health status to calculate the severity of disease. Increasing score correlates with risk of hospital death, although it is important to note that it cannot be used to provide predictions for individual patients.41 A range of 0-71 is possible.42 In the ICU in which the study was conducted, APACHE II scores are calculated by the medical consultant using data from the first 24 hours of admission.

The patients’ case notes were examined in the medical records department of the study hospital. Information regarding the patient demographics and duration of admission to the ICU was recorded directly from the ICU admission records. The nursing and medical notes were examined for any recorded episodes of confusion or reports of dreams, nightmares or hallucinations.
The following information was collected from the patients’ special observation charts which are stored in ICU:

- the most common level of sedation recorded using the CISS;
- the duration in hours of sedation and ventilation;
- the duration in hours of ventilation without sedation;
- the time in hours that the patient was observed to be awake while ventilated;
- the time in hours that they remained in ICU following extubation.

In the ICU nurses caring for the patients enter information on the special observation charts on an hourly basis. Observations, drugs administered, fluid balance and nursing activities such as pressure area care are recorded on these special observation charts. Therefore, data such as the duration of sedation and ventilation was calculated in hours. These charts were also examined for any records of hallucinations, nightmares or confusion. APACHE II scores were obtained from the ICU computerised database. All information was recorded on the data collection tool (appendix 5). The data collected was analysed to determine whether there was a relationship between the sedation regimes used for the patient and recall, in particular of hallucinations, dreams or nightmares.

**Data Gathering Instrument**

The questionnaire was designed to collect data regarding memories patients had of their ICU experience and also to investigate memories of dreams, nightmares, hallucinations and confusion. It was developed using information gained from previous studies that identified the most significant memories patients had of their ICU experience.9-11,13,22,23 The questionnaire contained 14 structured questions each with a space provided for comments. Within the questionnaire a number of different response designs were used, dichotomous responses, semantic differential scales, visual analogue scales and modified Likert scales. These were chosen as the response designs that best fitted the questions asked. In addition the mixture of response designs encouraged the participants to consider their responses to each question in its own right, rather than
giving the same response throughout. For each experience, such as whether the participant remembered feeling pain while in ICU a dichotomous, closed response- yes or no was offered. Then if the participant remembered the particular experience they were asked to rate the distress it caused on a semantic differential scale. For a semantic differential scale respondents rate a given concept along a continuum between two extreme evaluations (eg not distressing and extremely distressing). They were then asked to rate the severity on a visual analogue scale and the frequency of the experience on a modified Likert scale. Burns and Grove state that the Likert scale may include statements such as rarely, seldom, sometimes, occasionally and usually. The categories of rarely, frequently and constantly were chosen as the most appropriate. Likert scales are usually comprised of a negative or positive statement with which the respondent indicates a level of agreement. The Likert scale was modified by asking the questions directly, for example, “How commonly do you remember feeling thirsty?”, rather than “Indicate whether you agree with this statement, I felt thirsty constantly”.

Questions one and two, related to whether the participant remembered being in the ICU and how long they thought they stayed. Questions three to eight, were designed to investigate memories of ventilation, tracheal suction, anxiety, pain, thirst and nausea. These were commonly reported in previous research of patients’ memories of their experiences in ICU. Questions nine and ten asked whether the participant remembered nurses speaking to them, if they found this reassuring and if any other nursing actions would have made their time in ICU less distressing. In question 11 participants were asked if they remembered having dreams while in ICU. Question 12 asked about memories of nightmares, the degree of distress these caused and if they continued following discharge from ICU. Questions 13 and 14 investigated memories of confusion and hallucinations the degree of distress these caused. Participants who experienced dreams and nightmares were then asked whether they would consent to an interview. The final question (15) was open-ended and asked participants whether they had any other comments or memories that they wished to highlight.
The questionnaire was designed to flow logically and care was taken to avoid using medical jargon. During the design of the questionnaire issues of reliability and validity were considered. “Reliability is the degree of consistency or dependability with which a tool measures the attribute that it is designed to measure” and validity is the ability of a tool to measure what it is designed to measure. The tool was designed using the results of previous studies and was reviewed by several expert committees. These were the research and higher degree committee of the Department of Clinical Nursing The University of Adelaide, the research committee of the ICU in which the research was conducted and the hospital ethics committee. Following feedback some changes were made to improve the design of the instrument. In addition the tool was piloted on 10 participants. Piloting of a questionnaire enhances its reliability and validity by helping to identify difficulties relating to comprehension, language and clarity. No changes were made following the piloting of the questionnaire.

Analysis

Data from the questionnaire were entered on a database and statistical analysis was undertaken using Statistical Package for Social Sciences (SPSS) version 10.0 for Macintosh. Results are presented using frequency distributions. Possible associations between memories, hallucinations, nightmares and sedation regimes were calculated using the Chi Square statistic, Fisher’s exact probability test and the Mann-Whitney U test. Non-parametric tests were used as the population was not normally distributed and some of the data were ordinal and nominal. Chi-Square is a non-parametric statistic used to determine whether the frequency in each category is different from that which could be expected by chance. For example, memory of the ICU (yes or no) and sedation agent (propofol or midazolam or other). If the numbers in the sample result in an expected frequency of less than five in more than 20% of the cells in the crosstabulation, Fisher’s exact test is used. Mann-Whitney U test is used to test differences between two independent groups on a continuous measure. For example memory of the ICU (yes or no) and age.
Summary

This descriptive study was designed to investigate the memories patients had of the ICU, in particular dreams, nightmares and hallucination and the relationship of these to the sedation regime with which the patient was treated. Ethics approval was obtained and the study was conducted in two stages. In the first stage of this study descriptive data were collected by a questionnaire, with a target sample of 50 responses. This tool was designed to collect data regarding memories of:

- ventilation and tracheal suctioning;
- anxiety pain, thirst, nausea;
- nurse speaking to them and the reassurance provided by nurses; and
- dreams, nightmares, confusion and hallucinations.

Data were then collected from the patients records concerning demographics (age, gender, diagnosis), duration of admission and ventilation, the duration and depth of sedation, time awake prior to extubation and prior to discharge from the ICU, drugs administered and documented nightmares, confusion or hallucinations. Data were analysed using SPSS.

Stage 2 Method

In the second stage of the study patients who reported hallucinations, dreams or delusions in the questionnaire and indicated that they would like to be interviewed were invited to participate in an open-ended semi-structured interview. They were asked to sign a written consent form and were provided with a written information sheet (Appendices 6 & 7). Participants were advised that if during the interview they felt in any way distressed due to memories of their ICU experiences, the interview would be ceased and they could be referred to the ICU social worker for counselling if desired. They were also informed that they could withdraw from the study at any time. Simple questions such as “Can you tell me about the dreams or nightmares that you experienced while in the ICU?” were used to start the discussion. This interview was used to collect qualitative data about their experiences of dreams, nightmares and
hallucinations while in ICU or immediately following discharge. Open-ended, semi-structured interviews were conducted and taped. The qualitative data in the form of typed interview transcripts were analysed using the phases described by Leininger: “the entire material collected was studied to give a sense of the whole, indicators and categories were then identified, recurrent patterns derived, and themes and summative research findings abstracted.”

It was thought that information gained from the interviews would provide more detailed information regarding the patients’ experiences of confusion, nightmares and hallucinations and would provide personal descriptions which would generate a more complete understanding of these experiences. Burns and Grove state that interviewing is “…a flexible technique that can allow the researcher to explore greater depth of meaning than can be obtained with other techniques.” Open-ended, semi-structured interviews were chosen as a method, as this allows responses relating to the chosen subject to be recorded, but does not bias these so feelings and experiences are recorded in the participants’ own words. Interviews started with the question “On your questionnaire you indicated that you recalled having nightmares while you were in the ICU. Can you tell me about these nightmares?” Then if required the participant was asked to describe how these nightmares made them feel. The process was repeated to gain information regarding confusion and hallucinations. When necessary participants were prompted to continue by the interviewer paraphrasing their descriptions and asking them to expand further. For example, “you say that you had no idea that you were in the ICU, but thought you were fishing with your father, can you tell me more about that memory”.

Thematic Analysis

Thematic analysis of the interview was conducted using the principles outlined by Leininger. This is a method that has frequently been used in nursing research. It may be used to analyse qualitative data, which is then used to provide rich descriptions,
complimenting quantitative analysis such as in the study by Pincombe, Brown, Ballantyne, Thorne and McCutcheon. Thematic analysis is a method of analysis in which “raw data are analysed by identifying themes and bringing together components or fragments of ideas or experiences, which are often meaningless when viewed alone.” Leininger developed the following sequential steps for thematic analysis:

Step 1 Identify and list descriptors (pieces of raw data) of nursing observations and experiences or domain under study.

Step 2 Combine raw data and descriptors into meaningful sequential units or into larger units, known as patterns.

Step 3 Identify mini or micropatterns and determine how they relate to patterns and themes.

Step 4 Synthesize several patterns to obtain a broad, comprehensive, and holistic view of the data as themes and subthemes.

Step 5 Formulate theme (or pattern) statements to test or reaffirm further nursing phenomena.

Step 6 Use the confirmed themes for hypothesis, decisions and nursing interventions.

Five data sets were used, set one comprised raw data from transcribed interviews, set two had numbered units in a margin, set three comprised initial coding of text with a word or short sentence, set four comprised codes with reference to text units and finally a fifth set with themes. This is the process outlined by McCutcheon, FitzGerald and Walsh. In this inductive process themes emerge from the text. Analysis continued until no new information or differences were found in the data. This is defined by Morse as saturation.

Summary

In the second phase of the study open semi-structured interviews were conducted to collect qualitative data about patients’ memories or nightmares, hallucinations and
confusion. This data were analysed using a thematic analysis, based on the steps described by Leiniger. 47

RESULTS

Stage 1

Summary of procedures

Patients who met the inclusion criteria were identified on the Australian Patient Management System (APMS). The questionnaire was piloted on ten participants, but no changes were made. One hundred and twenty-five questionnaires were sent by post in four batches (including the pilot) until a sample of 50 participants was obtained. It was predicted that a sample of 50 would be sufficient for analysis of the data using the Chi-square statistic. A self-addressed envelope with a brightly coloured stamp was supplied for participants to return the questionnaires. It was hoped these strategies would improve the response rate by prompting patients to return the questionnaires. Reminder letters and personal phone calls may have improved the response rate, but it was thought to be inappropriate to pressure patients, particularly as they had been ill enough to warrant admission to the ICU.

A search was conducted of the Australian Patient Management System (APMS) using the inclusion and exclusion criteria. The first print out supplied the researcher with 100 potential subjects. It listed the patient’s names, unit record numbers, diagnoses, ages, hours of ventilation, admission and discharge dates, home addresses and phone numbers. The printout was examined to ascertain if the patients met the inclusion criteria. Of the 100 potential participants only 41 could be included as the search terms used for the APMS were not sensitive enough to exclude patients suffering from disorders and injuries affecting the central nervous system. In addition drug overdose and long term tracheostomy had not been included as exclusion criteria. A further two searches of the APMS were conducted yielding another 168 potential participants,
however only 84 were suitable. Thus a total of 125 questionnaires were distributed. Participants were allocated an identification number when the questionnaire was sent. The APMS was only able to identify those patients alive on discharge and notification was subsequently received that two patients sent the questionnaire had died since discharge. Another three were returned unopened with the patient unknown at the indicated address. Four of the participants who returned the questionnaires were subsequently excluded as examination of their case notes revealed that they did not meet the inclusion criteria. One was not ventilated, two were ventilated for periods exceeding ten days and one had suffered neurological injury. Thus the number of questionnaires sent to eligible participants was 115, fifty-one were returned (response rate 44%). The data were analysed using the Statistical Package for Social Science (SPPS) for Macintosh version 10.0.

**Analysis of Questionnaire**

**Memory of ICU**

The first question related to the participants’ overall memory of ICU. Forty-three percent of participants (n=22) remembered their time in ICU while the remaining 57% (n=29) had no memory of their time in ICU (see Figure 1).
From question 2 it had been planned to determine if there was a correlation between the remembered time with the actual duration of admission. However, many of the participants provided a time they had been told by relatives or doctors, rather that their actual remembered time. Therefore no further analysis was done. The only reliable method of collecting data on this would be to speak to the patient immediately following discharge, but this too would be influenced by previous communications.

**Memory of Artificial Ventilation**

Question three was designed to investigate memory of artificial ventilation (Intermittent Positive Pressure Ventilation, IPPV). Twenty-four percent (n=12) of participants answered yes to this question, while 77% (n=39) answered no (see Figure 2).
The participant who remembered IPPV (n=12) were then asked to record on average how distressing they found the experience by indicating on a semantic differential scale from 1 – Not distressing, to 6 – Extremely distressing (see Table 1). The mean score was 3.58 and there were multiple modes. IPPV was only slightly above moderately distressing for those who remembered it, but there was variation in the responses.

Table 1 IPPV Distress scale 1-6

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Multiple modes exist. The smallest value is shown

Comments regarding this question varied. Two of the participants remembered nurses encouraging them to make some respiratory effort: “hear the beep Diane (pseudonym),
that means you need to breathe” (Patient Identity no. 121), “I found it hard work, if it hadn’t been for the nurse consistently insisting for me to breathe. I would have found it easier to relax and fade away”. Participant 53 Another participant remembered being told that they were going to be on the machine “to help them breathe for a while” (Patient Identity no. 106).

Several other comments related to distress regarding an inability to communicate, one could hear his family talking but couldn’t respond while another indicated that he appreciated being offered a board to write on so he could communicate while intubated.

Only two participants commented on the physical discomfort of artificial ventilation, one writing “I had a tube which was extremely distressing” (Patient Identity no. 36), and the other “felt like I had lumps in my throat and felt like pulling the machine out”. (Participant 103).

**Memory of Endotracheal Suction**

Question four was concerned with memories of endotracheal suction. Twenty percent (n=10) of participants remembered endotracheal suction, while 80% (n=41) had no memory of the experience (see Figure 3). Participants were then asked to rate the average distress the experience caused on a semantic differential scale from 1 – Not distressing, to 6 – Extremely distressing.
As can be seen from Table 2 the mean score was 3.78, while the mode was 6. One participant who remembered suction did not answer this question. Although the mean indicates only moderate distress was caused by this procedure the mode was six indicating the most common response was maximum distress.

With regard to this question one participant stated that suction made him feel better "clearing the tube offered some relief" (Patient Identity no. 53), another said the
distress although severe was only brief, while another said they only vaguely remembered the experience.

Memory of Anxiety (Question 5)

Of the 51 participants 29% (n=15) remembered feeling anxious while in ICU, the remainder 71% (n=36), had no memory of anxiety (see Figure 4).

Figure 4 Memory of anxiety

Again participants were asked to rate the average distress the experience caused on a semantic differential scale, from 1 – Not distressing, to 6 – Extremely distressing (see Table 3). The mean rating was 4.2 and the mode 5. This indicates that most participants found this experience quite distressing.

Table 3 Anxiety Distress Scale 1-6

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Several comments regarding this experience related to participants’ fear of what was going to happen and disorientation. One participant stated that he didn’t know where he was, while another wrote “I’ve never had anything like this before so I didn’t really know what was going on or what was going to happen next” (Patient Identity no. 6). Another wanted to know how he got to be in ICU.

Several of the participants wrote about particular experiences that caused distress, these included “waking up and not being able to talk” and for another fear relating to “swelling in his throat” delaying removal of the tube, “not knowing when I would come off the tube was very distressing” (Patient Identity no. 53). One participant stated that he was “struggling to keep alive” (Patient Identity no. 10). There was an interesting comment from a patient who had been admitted following an assault, his wrote “I wanted to get a bit of my own back on the person who stabbed me, but knowing I couldn’t gave me that anxious ‘want to get out’ feeling” (Patient Identity no. 106).

**Memory of Pain (Question 6)**

Twenty percent (n=10) of the participants remembered experiencing pain while in the ICU while 80% (n=41) had no memory of pain (see Figure 5).
Again participants who remembered pain were asked to rate the average distress the experience caused, from 1 – Not distressing, to 6 – Extremely distressing (see Table 4). The mean rating was 4.1 and there were multiple modes. This indicates that although the experience most commonly caused above moderate distress there was variation in the responses.

Table 4 Pain Distress Scale 1-6

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Multiple modes exist. The smallest value is shown

Participants who remembered pain were then asked to rate the severity of the pain on a visual analogue scale from, 1- No pain to 10- Worst imaginable pain (see Table 5). The mean rating was 7 and there were multiple modes indicating the remembered pain was severe but that there was a wide variation in responses.
Table 5 Pain Scale 1-10

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Multiple modes exist. The smallest value is shown.

Participants were also asked to rate the frequency of pain by choosing a category from rarely, frequently and constantly. Only two categories were selected by the patients who reported remembering pain (n=10), four reported suffering pain rarely and six frequently (see Figure 6).

**Figure 6 Frequency of Pain**

There were several written comments relating to memory of pain. Two described when the pain occurred, "when staff tried moving me by my broken ribs" (Patient Identity no. 21) and "I felt pain at its worst when coughing which put strain on the operation wound" (Patient Identity no. 1). One participant described how his predominant
memory of ICU was of being in pain "I can’t remember a lot of ICU but what I can I was in a fare (sic) bit of pain’ (Patient Identity no. 67). One participant described how memory of the pain is causing continuing distress, "I do have very bad sleeping problems, which to date I haven’t done anything about yet, and that’s when I constantly think about the pain, which I didn’t deserve in the first place” (Patient Identity no. 106). One participant described how the pain he felt was reflected in a hallucination “in one of my hallucinations I was shot in the chest, took me about 3 days to work out I wasn’t” (Patient Identity no.10).

Memory of Thirst (Question 7)

Twenty nine percent (n=15) of the participants remembered feeling thirsty, the remaining 71% (n = 36) had no memory of thirst (see Figure 7).

Figure 7 Memory of Thirst

Participants were asked to rate the average distress the experience caused from 1 – Not distressing, to 6 – Extremely distressing (see Table 6). The mean rating was 3.54 and
the mode 4. Thus the experience was moderately distressing for those who remember it, but there was variation in the responses.

Table 6 Thirst Distress Scale 1-6

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Participants were then asked to rate the frequency of thirst. The most commonly chosen category was frequently with 60% (n=9) participants choosing this category. One participant did not indicate the frequency of thirst, 21% (n=3) chose rarely and 13% (n=2) chose constantly (see Figure 8).

Figure 8 Frequency of Thirst
There were only two comments regarding memory of thirst. Both these stated that crushed ice to relieve thirst was appreciated (*Patient Identity nos. 2 & 75*).

**Memory of Nausea (Question 8)**

Twenty-two (n=11) percent of participants remembered feeling nauseated, while 78% (n=40) had no memory of nausea (see Figure 9). Participants were then asked to rate how distressing the experience was, from 1 – Not distressing, to 6 – Extremely distressing (see Table 7). The mean rating was 3.20 and there were multiple modes. Thus nausea was only moderately distressing for those who remembered it, but there was variation in the responses. One participant who remembered nausea did not rate the experience.

**Figure 9 Memory of Nausea**
Participants were then asked to rate the frequency of nausea, from the categories of rarely, frequently and constantly. Only two categories were chosen 73% (n=8) indicated rarely and 18% (n=2) frequently, 9% did not indicate the frequency.

**Figure 10 Frequency of Nausea**

There were two comments relating to the memory of nausea one participant that was admitted with burns stated that “due to the smoke etc in lungs and airway I wanted to spit up mucus (sic) which made me feel nausea” (Patient Identity no. 51). Another
participant stated that she only felt the nausea "when I was awake which wasn't long" (Patient Identity no. 121).

**Memory of Nurses (Question 9)**

Fifty-five percent (n=28) of participants remembered the nurses speaking to them, while 43% (n=22) had no such memory and one participant did not respond to this question (see Figure 11).

**Figure 11 Memory of Nurses Speaking**

Participants were then asked whether they found the nurses speaking to them reassuring. Seventy-one percent (n=20) of the participants who remembered the nurses speaking to them found this reassuring, 11% (n=3) were neutral, 11% (n=3) did not answer and 7% (n=2) did not find it reassuring (see Figure 12).
Many of the written comments indicated patients had positive memories of the nurses speaking to them. Several commented on the reassurance this provided. For example, “very reassuring the nurses were wonderful, without them I would have freaked out” (Patient Identity no. 53), “it was good to know that someone was with me all the time” (Patient Identity no.16), “it was nice to know that I was being taken care of” (Patient Identity no. 67) and “to hear a friendly soft voice was comforting” (Patient Identity no. 121).

There were two comments relating to how the staff were fun and the use of humor. A man who was admitted post oesophagectomy wrote “sometimes we had a good laugh” (Patient Identity no. 75) and a women admitted following burns wrote “I found the staff to be caring and a lot of fun” (Patient Identity no. 79).

Two participants commented on how they found it comforting to be told what was happening to them, “yes it was good to know what was going on” (Patient Identity no. 18) and “yes I found it real good as the Drs and Nurses explained everything they were doing” (Patient Identity no. 7). Another participant wrote “very important to always speak to the patient and act confidently” (Patient Identity no.13). One patient
who had been transferred from a country hospital remembered the nurse explaining that she was in a different hospital (Patient Identity no. 102).

There were two comments from patients who were confused while in ICU. One said he did not find the nurses talking to him reassuring as "I thought they wanted to kill me" and another explained "it was hard to distinguish real nursing staff from hallucinated ones" (Patient Identity no. 10). One young patient complained that the staff spoke too softly and he could not hear or understand what they were saying "...I couldn't hear what they were saying" and "I couldn't comprehend what the nurse were talking to me about but I remember voices and hazes around me that also made it frustrating" (Patient Identity no. 106).

**Possible nursing action to reduce nursing distress**

Eighty-two percent (n=23) of the patients who remembered the nurses speaking to them did not think the nurses could have done any thing else to reduce distress, while 14% (n=4) said additional actions could have been taken and one participant did not answer this question (see Figure 13).

**Figure 13 Nursing Action To Reduce Distress**

- **No answer**: 4%
- **Yes**: 14%
- **No**: 82%
Actions stated by those who thought nurses could do more were “let the patient know immediately they are on morphine for pain and the potential for hell (sic) like hallucinations. Lower stress levels i.e. sit next to family member if possible”, (Patient Identity no. 10) and “I could only communicate by writing on a pad and it was some time before they realised this option” (Patient Identity no. 53). Another two participants stated that nurses could do more but they were not specific about what they could do.

Dreams in the ICU (Question11)

Twenty-two percent (n=11) of the participants remembered having dreams while in ICU, 78% (n=40) had no memory of dreams (see Figure 14).

![Figure 14 Memory of Dreams](image)

Of the 11 patients who remembered having dreams while in the ICU, seven stated that these continued after discharge from the unit. The time these continued for was from one to 21 days, with a mean of 8.2 and a mode of seven. Two patients did not give a
time that dreams continued. One participant who did not remember having dreams in ICU stated that they still dream about their ICU experience even though the questionnaire was completed five months since they he was discharged from hospital (Participant 11).

**Memory of Nightmares (Question 12)**

Ten percent (n=5) of patients remembered having nightmares while in the ICU, while the remaining patients had no such memories (see Figure 15).

![Figure 15 Memory of Nightmares](image)

Participants were then asked to rate the distress the nightmares caused on a scale from 1 – Not distressing, to 6 – Extremely distressing. For the five participants who remembered nightmares the mean distress rating was five, the mode was four, the minimum four and the maximum six (see Table 8). This indicates that the participants who recalled nightmares found them quite distressing with most common rating four and the mean just below the maximum rating.
Table 8 Nightmare distress Scale 1-6

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Multiple modes exist. The smallest value is shown

Of the five patients who remembered having nightmares four said they continued after discharge from the ICU. Two did not state how long they continued, the others stated 4-5 days and for about one week. One participant stated “I wasn’t keen to go to sleep” (Patient Identity no. 53). Eight participants who did not remember having nightmares while in the ICU wrote that they suffered nightmares following discharge from the unit. Five wrote that they experienced dreams and nightmares in the ward or high dependency unit, while three indicated they were still suffering from nightmares about their experiences in ICU. One participant wrote “I am still having nightmares about when I took my last breath” (Patient Identity no. 43). Another man who suffered from upper airway obstruction wrote “I frequently have nightmares of the 10 minute period while I was being stabilised before going into ICU” (Patient Identity no. 73). Two patients complained that they now have difficulty sleeping “I have a fear of sleeping now, it is one big fight each night” (Patient Identity no. 78) and “I do have very bad sleeping problems...and that is when I constantly think about the pain, which I didn’t deserve in the first place” (Patient Identity no. 106).

Memory of Confusion (Question 13)

Twenty seven point five percent of patients (n=14) remembered feeling confused while in the ICU, while 72.5% (n=37) had no such memory (see Figure 16).
Participants were then asked to rate the distress the confusion caused on a scale from 1 – Not distressing, to 6 – Extremely distressing. The mean rating was 4.38 and the mode 6. Thus most participants who remembered being confused found that this experience severely distressing. Indicating a maximal score on the distress scale (see Table 9).

**Table 9 Confusion distress Scale 1-6**

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Memory of Hallucinations (Question 14)

Sixteen percent (n=8) of the participants remembered having hallucinations, while 84% (n=43) had no such memory (see Figure 17).

Figure 17 Memory of Hallucinations

Participants were then asked to rate the distress the hallucinations caused on a scale from 1 – Not distressing, to 6 – Extremely distressing. The mean rating was 4.13 and the mode 5. Thus the most common rating indicated severe distress, with the mean also indicating a high level of distress.

Table 10 Hallucinations Distress Scale 1-6

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</table>
Other Comments and Memories

The participants were then asked if there were any other comments or memories that they wanted to highlight. Twenty of the participants took the opportunity to thank the staff of the ICU and of the hospital. Five of these had indicated that they had no memory of ICU, however, some of the thanks were from the families of the patients. Comments included: “my family would like to thank all for looking after them & my partner was very impressed with my care in the unit” (Patient Identity no. 23), “just a big thankyou to all concerned for giving me and my family back my life. My wife and I now have a chance to see our 60th wedding anniversary” (Patient Identity no. 119), “…I feel very grateful and appreciate the nurses involved who took good care of me, I just don’t know how to thank everybody. I was given a second chance” (Patient Identity no. 40), “glad to be alive” (Patient Identity no. 103), “The care I was given was outstanding” (Patient Identity no. 18), “all the staff and doctors were brilliant, my family and I could not find a thing to complain about” (Patient Identity no. 111), “I don’t think I could have been looked after better anywhere else in the world” (Patient Identity no. 9), and “all the staff were extremely kind & respectful to me & I felt completely relaxed with them around” (Patient Identity no. 2).

There were two negative comments relating to staff: “I would only have some criticism of one nurse and she wasn’t assigned to me”, and “After three operations I lost all confidence both with all medical staff and myself. I was extremely anxious all of the time and needed constant reassurance...even when I was in a confused state it was easy to pick up inexperienced staff which only made things worse” (Patient Identity no. 13).

One participant took the opportunity to ask questions, about her time in ICU “I would like to know how when and why I got to ICU... I need answers” (Patient Identity no. 40) Another wrote, “I was shocked to realize the time I had lost” (Patient Identity no. 36).
Two patients wrote that they had been frightened by experiencing blurred vision, when recovering from the sedation (Participant 18 & 51). One women, wrote that she is distressed by the knowledge that she exposed herself by kicking off the bedclothes (Participant 76). Another women wrote "My husband has been very much affected by seeing me on the life support system" (Patient Identity no. 121). One participant related the frustration she felt in the sick role "When I finally awoke I became frustrated that the decisions had been made for me and I realized how people with disabilities would feel" "...I know how frustrated I felt that no one got my opinion but made decisions for me. I felt totally dis-empowered because decisions were being made for me, without my consultation" (Patient Identity no. 79). One participant’s major concern was the constant changes in temperature induced by the air conditioning.

**Summary of the questionnaire results**

Forty-two percent of patients stated that they remembered being in the ICU, but only 24% to 29% remembered the specific experiences of IPPV or endotracheal suction. Anxiety, pain, thirst and nausea were remembered by 20-29% of participants. The mean level of distress and these experiences appear to have caused was from 3.20 to 4.20 indicating moderate to high distress. Tracheal suction had the highest mode at 6.0 indicating that those who remembered this most commonly rated the distress it caused at the maximum level. Nightmares, hallucinations and confusion were remembered by 10%-27.5% of participants and these experiences appear to have been distressing with means of 4.13 to 5. Although only 10% of patients remembered having nightmares this experience had the highest mean for the distress it caused (mean 5) indicating those who remembered the experience found it highly distressing. Fifty-five percent of patients remembered the nurses speaking to them and most (71%) found them reassuring. A review of the data indicated that predominantly the same group of respondents remembered multiple experiences, however, there were some individuals that remembered only one experience such as feeling anxiety. There were many informative
responses written in the comments sections, indicating the importance of the nursing actions in reassuring and comforting patients.

**Analysis of Data Obtained from Patient Records**

The next phase of the study was the collection of information from the patients' records. The information collected was:

- demographic data (age, gender, diagnosis);
- duration of ventilation, sedation and admission to the ICU;
- periods of time during the admission to the ICU in which the patient was not sedated and appeared awake, ventilation time without any sedation; time in ICU following extubation;
- Sedation agent/s administered and depth of sedation;
- details of recorded confusion and reports of nightmares or dreams;
- Admission APACHE score, as severity of illness has been reported to influence memories of ICU.

**Demographic Data**

The mean age of the participants was 59 years, while the oldest participant was 84 years and the youngest 23 years, the median age was 66 years (see Figure 18). Sixty-five percent (n=33) of the participants were male and 35% (n=18) female. The distribution of the ages of the participants was skewed towards the 60-70 year age group. This is consistent with the aging of the Australian population. This may have had an influence on the results as it has been reported that older patients are less likely to remember their time in the ICU.
The most common diagnosis was trauma, followed by abdominal aortic aneurysm surgery and cardiac disorders (cardiac failure and cardiac arrest). Post gastro-intestinal (GIT) surgery and upper airway obstruction were also common diagnoses. Upper airway obstruction included patients with airway obstruction from allergy (contrast medium, drugs and bee sting) and infection such as tonsillitis (see table 11).
Table 11 Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>abdominal aortic aneurysm</td>
<td>8</td>
<td>15.7</td>
</tr>
<tr>
<td>cardiac</td>
<td>8</td>
<td>15.7</td>
</tr>
<tr>
<td>renal surgery</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>trauma</td>
<td>9</td>
<td>17.6</td>
</tr>
<tr>
<td>GIT surgery</td>
<td>6</td>
<td>11.8</td>
</tr>
<tr>
<td>burns</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>facial surgery</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>acute respiratory failure</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>thoracic surgery</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>upper airway obstruction</td>
<td>5</td>
<td>9.8</td>
</tr>
<tr>
<td>oesophageal varices</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>gynae surgery</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Key:
- Cardiac: cardiogenic pulmonary oedema, cardiac failure, cardiac arrest
- GIT: post gastrointestinal surgery
- Gynae surgery: complications eg bleeding post gynaecological surgery

Duration of Ventilation, Sedation and Admission to the ICU

The mean duration of admission was four days with a maximum of 11 days and a minimum of one. The mean duration of ventilation was sixty hours, the maximum 211 hours and the minimum duration was 12 hours. The mean duration of sedation was 48 hours with a minimum duration of seven hours and a maximum of 196 hours. All data were taken to the nearest hour (see Table 12).
Table 12 Duration of Admission, Ventilation and Sedation.

<table>
<thead>
<tr>
<th></th>
<th>Duration of Admission days</th>
<th>Duration of artificial ventilation hours</th>
<th>Duration of Sedation hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Mean</td>
<td>4.22</td>
<td>60.71</td>
<td>48.20</td>
</tr>
<tr>
<td>Median</td>
<td>3.00</td>
<td>41.00</td>
<td>31.00</td>
</tr>
<tr>
<td>Mode</td>
<td>3</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>3.08</td>
<td>51.19</td>
<td>42.79</td>
</tr>
<tr>
<td>Minimum</td>
<td>1</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Maximum</td>
<td>13</td>
<td>211</td>
<td>196</td>
</tr>
</tbody>
</table>

Multiple modes exist. The smallest value is shown.

Time Ventilated Without Sedation, Time Awake While Ventilated, Time in ICU Following Extubation (see Table 13)

Seventy-eight percent (n=40) of patients were ventilated for some period of time without sedation. The mean time patients were ventilated without any sedation being administered was 11.8 hours, while the minimum was zero hours and the maximum 118 hours. This does not necessarily mean that the patient was awake even though they were recorded as being ventilated without sedation, as the elimination of drugs such as morphine and midazolam is frequently prolonged in the critically ill. Therefore the time in hours that the patient was documented as being “awake” while being ventilated was also recorded. Sixty-five percent of patients were observed to be awake while ventilated. The mean time of artificial ventilation (IPPV) while awake was three hours, while the minimum was zero hours and the maximum 20 hours (note this data were not available for two patients). The time following removal of the endotracheal tube (extubation), until discharge from the ICU was also recorded. The mean was 27 hours while the maximum was 244 hours and the minimum was two hours. All data were taken to the nearest hour as this information is recorded hourly on the observation chart.
Table 13 Time Ventilated Without Sedation, Time Awake While Ventilated, Time in ICU Following Extubation

<table>
<thead>
<tr>
<th></th>
<th>Ventilated with no sedation hours</th>
<th>Time documented as awake on IPPV hours</th>
<th>Recorded time in ICU following extubation hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Mean</td>
<td>12</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Mode</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>21</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Minimum</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Maximum</td>
<td>118</td>
<td>20</td>
<td>244</td>
</tr>
</tbody>
</table>

Sedation Agent/s Administered and Depth of Sedation

Thirty nine percent of patients were sedated with propofol (n=20), 29% (n=15) were sedated with midazolam, while 28% (n= 14) received both and 3.9%(n=2) were administered both and another agent such as ketamine (see Figure 19).

Figure 19 Sedation Agent Administered
Seventy percent (n=36) of patients also received morphine. All patients who were administered midazolam, received infusions of morphine. It is common practice in this ICU to mix these agents in one syringe for continuous infusion. Only 35% (n=7) of patients who were administered propofol also received morphine.

The patient’s level of sedation is recorded on the observation chart hourly using the Critical Illness Sedation Scale (Appendix 8). The number of hours at each level was calculated and the most commonly charted level for each patient was recorded. Forty-one percent of patients were predominantly lightly sedated 41% (n=21), while 33% (n=17) received moderate sedation, 23% (n=12) were most commonly heavily sedated and one patient was inadequately sedated for most of the time (according to the CISS) (see Figure 20).

**Figure 20 Level of Sedation**
Documented Confusion and Nightmares

The nursing notes were then examined to ascertain if there was any confusion, dreams or nightmares documented. Confusion was documented in 31% (n=16) of patient’s notes, while nightmares were only documented in one patient’s notes. When this data were compared to the patients’ memories it was found that only five of patients who reported feeling confused (27.5%, n=14) were documented as confused at some time during their time in ICU, while 30% (11 of 37) of patients who did not report confusion were documented as confused.

APACHE II

The highest APACHE II score was 32 and the mean was 17 (see Table 14). One patient did not have an APACHE II score recorded. Hospital death rates have been reported to approximately 84% for patients with APACHE II scores of 35+, although this varies with the disease, while the hospital death rate for patients with APACHE II scores of 5-9 is approximately 3.9%. Thus the patients in this study were at the less severe end of the severity of illness scale. This is to be expected as patients ventilated for greater than ten days and those who died were excluded from the study. The mean APACHE II score for patients in the unit where the research was conducted was 21.2 (median 19) for 1999-2000.

Table 14 APACHE II Scores

<table>
<thead>
<tr>
<th>N</th>
<th>Valid</th>
<th>Missing</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
<th>Std. Deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td></td>
<td>1</td>
<td>17.00</td>
<td>18.00</td>
<td>11</td>
<td>7.70</td>
<td>3</td>
<td>32</td>
</tr>
</tbody>
</table>

Multiple modes exist.
The smallest value is shown
Time elapsed since discharge from the hospital

The time in months, since discharge from the hospital until the return of the questionnaire was calculated. The mean time that had elapsed since discharge was 7.1 months while the maximum was 15 months and the minimum 1 month (see Table 15).

Table 15 Time from discharge months

<table>
<thead>
<tr>
<th>N</th>
<th>Valid</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Summary

The mean age of participants was 59 years and the majority (65%) of participants were male. There was a broad range of disorders from medical conditions such as respiratory failure to surgical conditions and trauma. The mean duration of ventilation was 4.22 days, ventilation time was 60.71 hours and duration of sedation 48.2 hours. The majority of patients were ventilated for some time without sedation (78%) and observed to be awake while on ventilation (65%). The most common agent administered for sedation was propofol and the predominant level of sedation was light. Confusion was documented in 31% of patients. A similar percentage of patients who remembered feeling confused were documented as confused at some time during their admission as those who did not remember confusion. The mean APACHE II score was 17 and the time since discharge ranged from one to 15 months.
**Analysis of possible associations between memories and sedation regimes**

**Chi-squared ($X^2$) and Fisher’s exact probability test**

One of the stated aims of the study was to investigate if there was an association between the sedation regime and memories, therefore the data were analysed using the chi-squared test for independence. Chi-squared ($X^2$) is a non-parametric statistic that is used to determine if the frequency observed in each category is different from the frequency that might be expected by chance.\(^3\)

The possible association between whether the patient remembered any of their time in ICU (yes or no) and the following variables was tested:

- Age of the patient and memory of ICU (<60 years or > 60 years)
- Time in ICU (0-2 days, 3-4 days or > 5 days)
- Duration of ventilation (<48 hrs or > 48 hrs)
- Duration of sedation (<48 hrs or > 48 hrs)
- Duration of artificial ventilation without any sedation (nil, 1-5 hrs or > 5 hrs)
- If the patient was recorded by staff as awake at any time during artificial ventilation (yes or no)
- The type of sedation agent administered (propofol, midazolam, both or other)
- Level of sedation according to the CISS
- Time since discharge (≤ 6 months or > 6 months)
- Creatinine elevated > 0.12 mmol/L
- APACHE score (0-10, 11-20, 21+)

One of the assumptions that should not be violated when performing the $X^2$ is that at least 80% of the cells should have expected frequencies of 5 or more, or for a one by one or two by two table frequencies of at least ten.\(^4\) For this reason, the above variables were divided into categories, for example ages <60 years and > 60 years, that would ensure a cell expected frequency of five or more.
There was no statistical significance in the results of the $X^2$, meaning there were no statistically significant associations between these variables. The results of the above analyses are in appendix nine.

Fisher's exact probability test is used when a two by two table violates the assumption of an expected frequency of at least ten in each cell. Therefore, this test was used to evaluate if there was an association between the patient receiving either propofol or midazolam and:

- Memories of nightmares, confusion and hallucination.
- Memory of pain.

Fisher's exact probability test was also used to determine if there was an association between: memory of anxiety and the sedation agent used.

- memory of pain and whether morphine was administered.

Again the results were not statistically significant, meaning that there were no statistically significant associations between these variables.

Chi-square and Fisher's exact test were also used to determine if there was an association between patients remembering the ICU and dreams, nightmares, hallucinations and confusion. Again there were no statistically significant associations between these variables. The results of the above analyses are in also in appendix 9.

**Mann-Whitney U Test**

The Mann-Whitney U Test is a non-parametric test to determine the differences between two independent groups on a continuous measure. A non-parametric test was chosen because the data were not normally distributed. Non-parametric tests are also used when the data is measured on nominal or ordinal scales. Thus this test was performed on memory and the following variables:

- Age;
- Time in ICU in days;
- Duration of ventilation in hours;
- Duration of sedation in hours;
- Time recorded as awake on IPPV in hours;
- Duration of artificial ventilation without any sedation in hours;
- Time since discharge until return of the questionnaire in months;
- APACHE score.

None of the results were statistically significant, indicating there were no statistically significant differences found in the listed variables between the participants who remembered the ICU and those who did not (appendix 10).

Summary

One of the purposes of the study was to determine if there was a statistically significant association between memories and the sedation regime administered. Statistical analysis did not indicate any significant associations between any of the variables tested. This suggests that for patients in this study memory was not influenced by any of the variables such as age or time in the ICU and that the sedation agent used did not influence the likelihood of the patient having memories of nightmares, confusion, hallucinations, pain or anxiety. In addition the results do not indicate that there is an association between implicit memory of the ICU and memories of dreams, nightmares and hallucinations for these participants. However, it is important to note that the sample may have been too small to demonstrate a statistically significant relationship between these variables.
Stage 2

Interviews and Thematic Analysis

In the second stage of this study qualitative data were collected using semi-structured interviews and thematic analysis was undertaken. Fourteen patients consented to interviews however, two could not be contacted and two did not have any memories of dreams nightmares or hallucinations. Another two participants were excluded following their interviews, as it was found on examination of the medical records that they did not meet the inclusion criteria. Despite the APMS indicating that both had been ventilated for less than ten days, one had not been ventilated at all and the other had been ventilated for more than a month; data from these patients were excluded from all analysis (also for the questionnaires). Thus eight participants were included this phase of the study. Of these six interviews were conducted either in the participant’s home or work place. Four lived in the metropolitan area, one lived in the “Iron Triangle” and one on York Peninsular. Two interviews were conducted by phone as one participant lived in Leigh Creek and for another the phone interview was more convenient. The interviews lasted from 15 minutes to one hour.

Participants’ Profiles

There were six male and two female participants. Pseudonyms have been used to protect their anonymity.

The first participant Mr Andrew Barter, is a 56 year old, married self-employed mechanic who suffered severe burns to his hands and airways as result of a work accident. When the interview was conducted it was seven months since Andrew had been discharged from the hospital, but he had only recently returned to work and for convenience the interview was conducted in his workshop. His business had been closed down for several months during his recovery but the doctors had informed his insurance company that he was fit to return to work. However, Andrew was finding it
difficult to manage due to soreness of his hands and continuing infection. Andrew has a son who only recently was diagnosed with a severe illness. As this son usually assisted his father in the business, this had added to the strain. Although it had been some time since his discharge many of his memories had remained clear.

Participant two, is Mr Edward Wright, a 65 year old man who appeared much older than his age. He had an extensive medical history and had been in the ICU for two days due to a severe allergic reaction following a carotid endarterectomy. Edward had been discharged from ICU seven months prior to the interview that was conducted in the sitting room of his home.

The third participant is Mr Alan Field, a 62 year old man who suffered a ruptured abdominal aortic aneurysm. He then had a cardiac arrest and was resuscitated by his wife. Alan lived in the country and was retrieved by helicopter to be treated at the hospital. He had only been discharged three months prior to the interview and his memories were still very clear. Alan was recovering well and was feeling fit and happy. The interview was conducted at the kitchen table of Mr Field’s home.

Participant four is Mr Rocky Taylor, who described himself as “hard to get along with”, he is 84 years old and after several myocardial infarcts showed few signs of slowing down. He had been variously employed in the racing industry and as a farm hand. Rocky had been retrieved to the ICU by helicopter following a myocardial infarction that was complicated by pulmonary oedema. He had been in the ICU for four days, ten months prior to the interview. The interview was conducted in the sitting room of his unit, which was filled with exercise equipment-used by Rocky.

Mr Tony McArthur, the fifth participant is a 61 year old Scot who although he had lived in Australia for some time and raised a family here, still retained a strong accent. Tony had been admitted to ICU following facial surgery performed for severe sleep apnoea.
He was in the ICU for five days and suffered severe confusion and hallucinations. Tony had very detailed memories of his time in the ICU. He was only discharged one month prior to the interview, which lasted one hour. It was conducted at the kitchen table in Tony’s home.

Participant six Mrs Helen Smales, is a 43 year old women married women with several school age children who was admitted to the ICU seven months previously due to complications following a hysterectomy. Her interview lasted only 15 minutes as she did not remember much about her time in ICU. She was still unsure how much of what she remembered was reality. Helen had returned to work as a schoolteacher and said she had not found her ICU admission very stressful. The interview was conducted in the dining room of Helen’s family home.

The final two interviews were conducted using a conference phone. Craig Jones is a 34 year old man who had been assaulted and sustained stab wounds to his chest. The attack was unprovoked and Craig is still extremely angry about what had happened. His memories of ICU included horrific dreams, nightmares and flashbacks. It was 12 months since Craig had been discharged however, he was still suffering from nightmares and flashbacks despite counselling, but he was keen to participate in the interviews.

The final interview was with Mrs Debbie Ryan, a 36 year old women who was transferred to the ICU from a private hospital with complications following bowel surgery performed for Crohn’s disease. She had a keen sense of humour and joked about her experiences in the ICU, even though it had been a harrowing time for her. Debbie had been discharged five months prior to the interview, so her memories were still very clear.
The interviews were transcribed from the recordings and then rechecked. A copy of the original transcriptions was retained unchanged. The next set was cleaned of all information that could identify individual participants who were given pseudonyms and the text units were numbered. A further set was used for the initial coding, meanings were identified by a word or short sentence. For example, Tony said:

My son, was at the side of the bed, and was crying. And I thought what’s wrong with ya, he’s like “Well we thought we lost ya dad”, and I can still remember that. As far as I was concerned, that was the first part that was real, that happened. (8.p10.l19-22)

This passage was highlighted and given the code “returning to reality”. Alan wrote

I was aware my wife was there, and I could see foggy that this person from Pirie, I recognised her, my sister-in-law ...and I must have thought, it was coming back to me then that, I must have thought that I was, you know, in the hospital. (5.p5.l13-18)

This passage was highlighted and coded as “recognition -coming back”. When all the interviews had been studied and given codes (mini or micropatterns), they were studied to see how the codes linked in sub-themes (patterns, data set four ). These two codes were put under the sub-theme of “returning to reality”. Once all sub-themes had been developed these were studied to see if they linked in themes (data set five). The sub-theme “returning to reality’ fitted under the theme of “reality” and then “reality and unreality” with other sub-themes such as “hanging on to reality”. The transcripts were re-read with each step to check that meaning was not lost and that the codes, themes and sub-themes represented the meanings found in the text. For referencing, participants were allocated a number from one to eight, page numbers of the transcribed interviews were identified by p. and line numbers l).
When the data were analysed the following sub-themes and themes become apparent:

**Table 15 Sub-themes and Themes**

<table>
<thead>
<tr>
<th>Sub-themes</th>
<th>Themes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blackness</strong></td>
<td>Blackness and Colour</td>
</tr>
<tr>
<td>Vibrant colour</td>
<td></td>
</tr>
<tr>
<td>I can’t see</td>
<td></td>
</tr>
<tr>
<td><strong>Is this forever?</strong></td>
<td>Powerlessness and Purpose</td>
</tr>
<tr>
<td>No control</td>
<td></td>
</tr>
<tr>
<td>Purpose-Acceptance</td>
<td></td>
</tr>
<tr>
<td><strong>Hanging on to reality</strong></td>
<td>Reality and Unreality</td>
</tr>
<tr>
<td>Familiar faces - reassurance and returning to reality</td>
<td></td>
</tr>
<tr>
<td>Trusting</td>
<td></td>
</tr>
<tr>
<td>Caring nurses and uncaring</td>
<td></td>
</tr>
<tr>
<td>Flashbacks</td>
<td></td>
</tr>
<tr>
<td>Rationalising unreality</td>
<td></td>
</tr>
<tr>
<td>Funny things</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td>The onlooker</td>
<td></td>
</tr>
<tr>
<td>Not knowing</td>
<td></td>
</tr>
<tr>
<td>Coming and going</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td><strong>Fishing with the dead</strong></td>
<td>Death</td>
</tr>
<tr>
<td>Deadly intrigue</td>
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</tr>
<tr>
<td>Fear of death and terror</td>
<td></td>
</tr>
</tbody>
</table>

**Theme - Blackness and Colour**

**Sub-theme Blackness**

Several participants spoke about blackness. This blackness was an absence of colour and light, that appeared to make those who experienced it fearful and was related to being isolated from the world.

Tony said

*Everything was covered in a black blanket apart from me. I can remember being in the middle of this black blackness and (5.p*
2.1 27-29) ...the whole thing was black. Total blackness that is what it were like (sic) (5.p 3.1 14-15)

Edward spoke of how he saw himself as composed of coloured and black blocks. Thus his world appeared to change from blackness and colour and back again.

...and um, these blocks kept turning and I was able to see when the block was sort of facing outside in the world, but sometimes it would turn into the wall and everything would go black (2.p1.117-18) The bricks were sort of different colours when I saw them, The black ones I didn’t like that was sort of unnerving. (2.p5.111-13)

He related how this blackness made him feel he had died.

...there was a lot of this blackness, you see and I ...honestly thought I’d gone, you know gone to the other side and I was sort of ...especially when I couldn’t get my face around to any light” (2.p4.18-12)

Edward also spoke of blackness and not being able to see.

Everything was black. I couldn’t open my eyes. (2.p9.116)

This experience caused severe distress and he was only reassured when his wife explained that it was the effect of the drugs.

Sub-theme Colours

In contrast to the blackness associated with fear, several participants spoke of colour which was associated with more pleasant memories. This colour was described as vivid or like the rainbow. To Helen it was associated with peace.

Like I was just looking up at this white space but then it became colourful-peaceful and colourful all the time. (6.p1.113-15) and
sort of like rainbow colours. Just soft and ...moving but softly not sharply. (6,p2.123-24)

Helen was the only participant that spoke of peace in her memory of the ICU, but for Tony the colours were associated with pleasant memories.

"Um, I had this thing right in front of me, with nothing but beautiful forest, there were trees and there were bushes and e-e-e it was, not psychedelic, but I think you might know what I mean the colours were just beautiful.(5,p4.125-28) and the whole wall in front of me, was the most vivid colours imaginable. (5,p11,130,p12,11)

Sub-theme I Can’t …

Two of the participants had distressing memories of not being able to see. Experiencing an absence of colour and light. Edward could not open his eyes and for Andrew it was a blurring of vision.

Andrew:

Everything was very blurred, which was a bit concerning. Um… and my wife was there. I asked her “I can’t see, I can’t see. (1,p1.112-14)

The blurred vision could have been related to the drugs such as sedatives and narcotics.

Theme - Powerlessness and Purpose

Sub-theme Is This Forever?

Several participants had fears that they would remain in the same condition forever.

Andrew:

I couldn't see, and it went through my mind that I would be like that for the rest of my life. (1,p4.15-6)

Debbie expressed the fear at the thought of not getting any better and planned to commit suicide.
... I thought if I am going to be like this for the rest of my life, like on this breathing machine and things, I was scheming up ways of how I would probably do myself in. (8.p12.19-12)

Sub-theme No Control

Several of the participants experienced a loss of control. This was related to an inability to move or communicate and control what was happening to them

Andrew:

...just could not work out, what was happening to me. That was the biggest thing about it. I just couldn’t work it out. But I’m a fairly practical sort of person, and I mean you gotta (sic), you work everything out and you’ve got a plan. And I had no control over it and I just did not know what was going on, you know. Until the wife come in and told me “You’re in Intensive Care and you know, you’re on drugs” and this kind of stuff. (1.p8.l5-9)

Tony also expressed this experience.

It was obvious that I couldn’t do anything, there was too many things that were around me. (5.p2.115-16)

In ICU it is quite common for the patient to be surrounded by equipment and staff. Tubes and monitoring equipment effectively tether the patient to the bed, preventing movement and contributing to feelings of powerlessness.

Debbie found she was unable to communicate and felt isolated.

And it’s quite strange because I couldn’t speak to them or I couldn’t get anything... yeah, like I couldn’t say “Hey it’s me over here”. I couldn’t say that. And I felt like I was paralysed to the bed. (8.p4.11-4)

Helen too related a similar experience.
I remember waking up and seeing my husband and immediately knowing that I couldn’t speak. I mean I tried to speak and realised that I couldn’t. (6.p3.125.p4.11-3)

Patients in the ICU are often unable to communicate verbally due to the presence of an endotracheal tube facilitating ventilation. Drugs such as muscle relaxants may be used to paralyse patients facilitating treatment and sedatives may also make the patients feel weak. The patients are often rendered powerless and this powerlessness combined with the inability to communicate is very isolating.

Tony was distressed that he had attacked the doctor. He saw this as out of character something over which he had no control.

I mean to attack somebody, it must have frightened me. Um, because, like I say like most blokes I can get angry but I am not going to attack anybody. (5.p15.18-10)

His purpose now was to move on, to escape his memories:

I wanted the operation to work, so it would be different... now hopefully ...we’ll sell the house, and we’ll actually get away. (5.p16.16-10)

Tony was reassured that hypoxia and drugs may cause patients to become confused and paranoid, but this memory was still the most distressing of his experiences.

Craig was still experiencing a sense of loss of control as he was still suffering flashbacks and nightmares. These were sometimes related to remembering the attack, but the nightmare of the demons was also recurring. This was despite the fact that he was being counselled by members of the Victims of Crime Association.
Sub-Theme Purpose-Acceptance

Both Rocky and Tony expressed feelings that there was a purpose in their experiences and this appeared to help them accept their situations. For both these appeared to be almost religious experiences.

Tony:

\[ I\ remember\ praying,\ I'm\ not\ a\ religious\ bloke,\ but\ you\ know,\ 
He\ did\ look\ after\ me,\ that\ was\ the\ way\ it\ was\ meant\ to\ be.\ 
\]

(5.p15.l27-29)

Rocky:

\[ I'm\ a\ spiritual\ person.\ I\ believe\ I\ was\ put\ on\ earth\ to\ serve\ a\ 
purpose\ and\ whatever\ it\ is,\ when\ it's\ finished,\ that's\ when\ I'm\ 
finished.\ (4.p9.l2-4)\]

Participants appeared to experience both a sense of powerlessness and purpose. Powerlessness was implied by the inability to control what was happening to them, being unable to speak or move. Debbie sought to gain control by planning suicide. Rocky and Tony felt a sense of purpose that appeared to in part develop from not being able to control their situations. The feeling that it was “the way it was meant to be” and “when it is finished it is finished”.

Theme – Reality and Unreality

Sub-theme Hanging on to Reality

Tony spoke about having to hang onto what he knew was real. This was viewed as an imperative to maintain his sanity.

\[ You\ seem\ to\ pick\ on\ one\ thing\ that\ was\ real,\ to\ me\ my\ bed\ was\ 
real,\ and\ that\ was,\ ...,\ if\ I\ fell\ off\ the\ bed,\ I\ could\ get\ back\ into\ it\ 
and\ it\ would\ be\ OK.\ (5.p7.l6-9)\]

In concentrating on what he knew was real he was able to maintain some hold on reality.
Sub-theme Familiar faces Reassurance and Returning to Reality

For some, familiar faces brought reassurance or helped them to return to “reality”.

Debbie:

yeah, because it’s a familiar face they could probably reassure you that you’re fine. You know, that there’s nothing going on. Although, I mean, they could’ve said “There’s nothing going on” etc till they were blue in the face but I wouldn’t have believed them. (8.p15.1-9)

For both Alan and Tony it was recognising a relative that first made them realise what had happened to them.

Tony:

My son, was at the side of the bed, and was crying. And I thought what’s wrong with ya, he’s like “Well we thought we lost ya dad”, and I can still remember that. As far as I was concerned, that was the first part that was real, that happened. My son was there, and he was crying... that’s when I knew I was in hospital. (5.p10.119-27)

Both these extracts demonstrate the importance of allowing relatives and loved ones to visit as this may reassure patients and help them orientate to their surroundings.

Sub-theme Trusting

For Debbie a return to reality was associated with being able to trust the nurses who she had believed were trying to kill her.

And that just took me a while when my awareness um...became more stable, of reality, I was able to realize that I could actually start to trust these people that were looking after me. (8.p8,121-23)
This trust allowed Debbie to rest facilitating recovery.

**Sub-theme Nurses Caring and Uncaring**

Many of the participants spoke of reassurance and comfort given by the nurses

Helen:

*They were terrific in Intensive Care. They were wonderful. Very comforting.* (6.p8.117-18)

Edward:

*I know the nursing was first class.* (2.p8.110)

Alan:

*That was reassuring you know, that there was someone there the whole time.* (3.p12.116-17)

Craig related that a nurse showed lack of compassion when he woke with severe pain and swore.

*I was just waking up and I swore pretty badly and one of the nurses come over and told me to jam it up, told me to shut up and stop using that language.* (7.p5.110-12)

But he also experienced care from one particular nurse

*I think she went beyond the course of her duty to help me out.*

(7.p6.123.p711)

**Sub-theme Flashbacks**

For Craig the realisation of where he was and what had happened was related to frightening flashbacks of the assault.

*I had some pretty bad flash backs during, late at night when the curtains were pulled across... Um, I think it was something I remembered that night, that flashed, yeah, that's all I remember so I s'pose (sic) that's why it kept on playing on my mind.*

(1.p2.17-22)
Sub-theme Rationalising Unreality

Several of the participants spoke of how they tried to rationalise the hallucinations they experienced.

Alan:

\[And\ I\ was\ laying\ (sic)\ there,\ and\ I\ was\ sort\ of\ clock-watching\ a\ bit.\ The\ ceiling\ seemed\ the\ most\ comfortable\ place\ to\ look\ at,\ and\ then\ of\ course\ out\ comes\ this\ foggy\ mist\ again.\ I\ used\ to\ think\ Oh\ perhaps\ that’s\ because\ I\ might\ have\ used\ the\ bedpan\ and\ it\ smells\ a\ bit\ and\ to\ me\ it\ might\ have\ been\ you\ know\ Aerogard\ stuff.\ (3.p10,l23-24,p11,l1-9)\]

This rationalising made it easier for them to accept what they were seeing.

Sub-theme Funny Things

Not all hallucinations were frightening, some were described as funny, silly, weird or eerie.

Tony:

\[Some\ of\ it\ was\ weird,\ some\ was,\ I\ wouldn’t\ say\ frightening.\]
\[Some\ of\ it\ was\ funny.\ (5.p7,l3-6)\]

Debbie described a time when she was convinced that some of her friends that she had not seen for many years were also being nursed in the ICU.

\[It\ was\ a\ really\ eerie\ sort\ of\ feeling.\ ...I\ don’t\ know...I\ don’t\ know\ why\ they\ even,\ I\ don’t\ know\ why\ they\ came\ up\ in\ my\ memory.\ It\ was\ really\ strange\ because\ I\ hadn’t\ had\ anything\ to\ do\ with\ them\ for\ such\ a\ long\ time.\ (8.p4,l15-19)\]

For Alan although the hallucinations were not frightening they made him anxious.
I didn’t have real bad, awful dreams but it was the anxiety of it all, you know, I couldn’t work out what the stuff was coming out of the ceiling at me, and the bowls of fruit hanging up and – turned out to be other things later. The bowls of fruit was um, I think it was a fan or something that was sitting there. (3.p2.15-10)

Fans are sometimes used in the ICU particularly for febrile patients, it is interesting to observe how common objects may be perceived by confused patients.

Sub-theme Confusion
Debbie described how in her drugged state she found reality like ward rounds confused her.

A lot of the time you’re under these drugs and the doctors and things come in and say, and they go off, and say “ah yes, such and such and such and such” and they’ll mention drugs and all that sort of thing, which they have to do, to tell you what they’re doing but I guess in a way it stressed me because I couldn’t grasp what they were saying because I was so highly drugged. It confused me even more, of what they were actually doing. (8.p5.16-13)

Ward rounds occur several times a day in the ICU and are often attended by several doctors, nurses and allied health staff such as physiotherapists. It is important to acknowledge how confusing this must be to a sick and drugged patient.

The same participant described how she mostly felt confused when she was alone and how it helped to have someone there with her.

Sub-theme The onlooker
Several of the participants described how they felt like onlookers. It was as though they were watching what was going on, but were not part of it. Although they did not understand what was going on the rationalised what they saw.
Tony:

I got the impression that like a hall of mirrors, that when you was in the what the one bed, there was a mirror in front of ya, where people sort of disappear, and they, they were always doing and saying the same thing. Um, it was sort of a routine. You went in at one o’clock, they said ‘Good Morning, oh, Good Afternoon” etc etc. Everybody was saying the same thing, at the same time.(5.p6.11-8)

Andrew:

...not knowing what people were doing pacing up and down, I didn’t have any idea where I was. I will never forget that. I just couldn’t work out what was going on. People were walking past and it just seemed like it was a set time, like every five minutes on the minute, they were pacing past. And it went through my mind, it must be a row of people, and they’re walking up and down checking on them all at once. (1.p10.114-18)

In the ICU the beds are mostly positioned in a long lines and nurses and doctors often walk from one bed to the next checking patients or handing over to new staff. When a patient is sedated or drifting in and out of sleep they may be woken by someone walking past this may make it seem like people are “pacing past”.

Sub-theme Not knowing

Nearly all of the participants described experiences of “not knowing” that caused anxiety. Not knowing they were in hospital, or which ward they were in, or how they got there, or what was going to happen to them. Several wondered about time they had “lost”.

Rocky:

I wanted to know what the hell I was doing there. (4.p9.23)

Andrew:

I had no idea what was going to happen to me. (1.p5.111-12)

Helen:
And I thought “what the heck’s going on here?” I had no idea that I had been out for three days. (6,p7.115-17)

These extracts demonstrate the importance of talking to patients and telling them what is happening. This may have to be repeated when patients are confused or drifting in and out of consciousness.

**Sub-theme Coming and Going**

Several participants described how they drifted in and out of consciousness or from unreality to reality.

Andrew:

* I was very confused. I just couldn’t comprehend what was sort of going... I must have been drifting sort of in and out and in and out. (1,p2.123-25)

In the unit in which the research was conducted, bolus of sedatives and narcotics are often administered when the patient becomes restless, or to prevent discomfort during a turn or suctioning. This may easily result in patients “drifting” in and out of consciousness.

**Sub-theme Pain**

Craig was the only patient who spoke of experiencing pain. This was associated with not knowing why he was in the ICU. In his confused state he was unable to understand why he had pain or what was happening to him.

* I was in so much pain, I couldn’t move, I didn’t know why I was there. (7,p5.116-17)

These sub-themes demonstrate both the reality and unreality of the participants’ experiences. There were stark illustrations of reality, pain, caring and uncaring nurses. Participants moved between the “real” world and unreality, coming and going. They described the confusion as an unreal experience and related how things appeared funny or weird. Familiar faces reassured and helped them return to reality. There was as sense of an unreality in losing touch with what was happening to them. For Craig the flashbacks were both real and unreal. In the flashbacks he re-experienced the attack
which had caused his injuries. He knew the flashbacks were not real but they dominated his consciousness.

**Theme - Dreaming of death**

**Sub-theme Fishing with the Dead**

Two of the participants described vivid dreams of seeing people they knew were dead. This caused anxiety, as even in their confused states they knew that the people they were seeing were dead.

Tony:

> Yeah, I went fishing with me dad, and that one did frighten me, because my dad has been dead for ten years. (5.p4.110-11)

Rocky:

> And I dreamt I was dead one night. There was one night there that I dreamt(sic) I was dead. I’ll never forget that. And I’m meeting all these people that that had passed on that I knew. That was unreal, that was. I tell you what, when I come to, I really thought I must have died and I didn’t even, you know, it was that real. Strange isn’t it? (4.p6.16-11)

Seeing those who are dead is often associated with impending death or may make the person who experiences it think they have already died.

**Sub-theme Deadly Intrigue**

Several participants described how they thought people were trying to kill them. Some of their nightmares and hallucinations were horrifying and dramatic. Some devised elaborate schemes to escape those “plotting to kill them”.

Alan:

> And the people moving around, they all seemed to have, I suppose they were going about their business with different papers and things, and they was moving around and I kept, it
was sort of concerning a bit that they was plotting against me. (3.p1.123-25)

Debbie:

I thought that they were going to kill me – that the nursing staff were going to kill me and sell my body parts overseas. (8.p1.116-18) And I thought that he was going to actually overdose me with this injection and put me out and then they would take my body parts, which I really didn’t have a lot left that were any good anyway (laughter) and that they were going to sell them overseas. (8.p2.113-17)

Tony described how he fought with his assailants who later turned out to be doctors, nurses and security staff. He even remembered ripping the shirt from a doctor’s back. He spent a lot of time planning his escape.

I was terrified, um, I really, I, I, really thought he was trying to kill me. (5.p2.114) Yep, um... I can remember them shouting for security, (pause) um...(short pause) one of the security guards stands out, plain as day...tall, skinhead, you know, shaved head, had an accident, stands out plain as day. (5.p1.122-28)

I am saying to the guy, “You’re not killing me, You’re not fooling me. (5.p10.l6-7)

And

I wanted to get out of bed, that was the most important thing, so I kept on undoing this and undoing that and they would come back and fasten it up, and I am thinking to myself, how can I outwit them, um, like if they took the bandages off this way, it
would make it look as though they are still on. And you know, um, I can’t remember I got out once I think. (5.p9.12-10)

Debbie described dramatic dreams and thoughts related to fear of death. And my imagination went really wild. Like I thought you know “I wonder if he is in part of the Mafia” because he had like an ethnic background. It just seemed very secretive and ... that was really strange too. Um... I think I was probably frightened because of my initial thought of dying. (88.p8.111-16)

Although these hallucinations and thoughts appeared very real to those who experienced them, they were almost melodramatic when described. Given the exposure of the modern society to drama from television, video games, radio and the media generally, it is not surprising that these dramatic images that enter the subconscious emerge in dreams, nightmares and hallucinations. The ICU is commonly viewed as a dramatic place dealing with life and death.

Sub-theme Fear of Death and Terror

Several participants described horrifying nightmares about dying.

Rocky:

This particular terrible nightmare I had when I was going up this road. It was a big wide road. And it seemed like miles ahead I see this big building. When I got closer, this big bloke standing there with a long gown on, you got no idea how fearsome he looked. And he had big wide hands. And anyway he come over, he said “I’ve been waiting for you” he said. “I’m going to take you far” or something. And he reached out to get me, and that was it, that was where I sort of.......(4.p1.112-20)
Craig:

They were just really unusual, ah, foreign sort of demonic dreams(7.P3,L18-19). ... like demons with red eyes telling me I am going to hell. (7.P4,L2-3)

The descriptions of these memories were very clear, and had been horrifying for the participants.

Alan believed he was dying. This belief was sometimes based on the fact that he realised he was in the ICU.

Well, a couple of times there I sort of thought Oh gee I don’t think I am going to make it. (3.p2.l24-25)

In all these sub-themes there was a reference to death. Trying to escape death, fearing death and hell, and dreaming of the dead. The two participants who dreamed of being with those they knew were dead, related this to their own death, fearing that they may also be dead.

Diagrammatic Representation of Themes of the Participants’ Memories

Figure 21 is a diagrammatic representation of some of the images described by the participants and the themes that developed. One of the participants described the experience as a “Rubik’s cube”, this is how Edward described himself:

And um, these blocks kept turning and I was able to see when a block was sort facing outside in the world but sometimes it would turn into the wall and everything would go black, and I could feel parts of me shifting. But I didn’t seem to have any control over how I shifted, or um how I was able to turn so I could actually see what was going on. Um, it was a bit like that, you know those games you play shifting blocks around?
Other participants described moving from unreality to reality, or from blackness and colour or feeling loss of control and later a sense of purpose. These themes seem to oppose each other, but are part of a continuum, therefore they are depicted in this way in the diagram. Some of the images described by the participants can be see on the faces of the blocks.

Figure 21 Diagrammatic Depiction of the Thematic Analysis
Information from Case Notes

Only two of the participants who were interviewed were documented in the case notes as having been confused, but all experienced this to some degree and several had horrific nightmares and hallucinations associated with severe paranoia. Tony was described as combative and the incident with security staff was described in his notes. The incident was documented just as Tony had described, security staff had been called and forcibly restrained Tony after he had torn the shirt from a doctor’s back. Blackness and colour were common in the memories of the participants. The blackness was commonly a frightening and isolating experience, where colour was associated with more pleasant memories. Participants described feeling powerless and fearing that they would never regain their faculties. Some of the memories were described as weird, funny or silly. There was also a strong sense of the unreality of their experiences. Several described how they rationalised what they saw, including hallucinations. In some of the hallucinations it is possible for one who has worked in ICU to see threads of reality. For example drugs may mean that the patient is unable to open their eyes or move and intubation may prevent speech. Other memories such as Rocky’s big bloke who had come to get him, may also have some relationship to reality. The bloke may have been a nurse or orderly moving him to ICU, or perhaps the anaesthetist who intubated him. Many memories were positive and there were stories of how participants found familiar faces a comfort and how the presence of loved ones gave them strength and helped them return to reality. Although most were glowing in their praise of the nurses, for Craig a strong memory was the lack of compassion shown by one nurse.

There was no evidence in the notes that any of the participants had told any of the staff about their nightmares, confusion and hallucinations. The nursing and medical notes were examined and there was no record that any of these experiences had been described to the staff.
DISCUSSION

Restatement of the Problem
The purpose of this study was to investigate the memories patients have of their experiences in the ICU. In particular to investigate the incidence of dreams, delusions and confusion as recalled by the patients themselves and to determine if there is an association between these and the sedation regime the patient received, with regard to the drugs used, and duration and depth of sedation.

Brief Summary of Procedures
The study was conducted in two stages. For the first stage a questionnaire was distributed by post to 125 patients who had been ventilated and sedated in the ICU in order to gain a sample of at least 50 participants. The questionnaire responses were analysed using descriptive statistics. Data were then collected from the medical records of the participants regarding demographics, diagnosis and detailed information regarding the sedation administered.

In the second stage of the study patients who remembered hallucinations, dreams or delusions in the questionnaire were invited to participate in semi-structured interviews. These were used to collect qualitative data about their experiences of dreams, nightmares and hallucination while in ICU or immediately following discharge and a thematic analysis of the transcripts was undertaken.
Major Findings and their Significance to Clinical Practice

Questionnaires and medical records

In table 16 some of the findings from this study are compared with findings from other studies.

Table 16 ICU experiences

<table>
<thead>
<tr>
<th>Experience</th>
<th>This study percentage recall</th>
<th>Previous studies percentage recall</th>
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<tbody>
<tr>
<td>Time in ICU</td>
<td>43%</td>
<td>50% 199017 (n=100)</td>
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<td></td>
<td>66% 199424 (n=54)</td>
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<td>72% 199922 (n=76)</td>
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<tr>
<td>IPPV</td>
<td>24%</td>
<td>16.3% of IPPV patients 198813 (n=49)</td>
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<td></td>
<td></td>
<td>32% of IPPV patients 197910 (n=22)</td>
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<td></td>
<td></td>
<td>52% 198912 (n=158)</td>
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<td></td>
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<td></td>
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<td>62% 199922 (n=76)</td>
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<tr>
<td>Pain</td>
<td>20%</td>
<td>40% 198812 (n=60)</td>
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<td>36% 198912 (n=158)</td>
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<td></td>
<td></td>
<td>43% 199922 (n=76)</td>
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<tr>
<td></td>
<td></td>
<td>69% pain or discomfort, 31% intense pain16 (n=26)</td>
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<td></td>
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<td>71% 199012 (n=24)</td>
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<tr>
<td>Thirst</td>
<td>29%</td>
<td>13% 198813 (n=76)</td>
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<td></td>
<td></td>
<td>66% 198813 (n=60)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22%</td>
<td>13.3% 198813 (n=60)</td>
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</table>
Some possible reasons for differences in memories of ICU may be variations in the methods used to collect data and differences in the inclusion criteria. Most studies used interviews to collect data. These were conducted from 48 hours following discharge\textsuperscript{11,16} to 5 days\textsuperscript{25}, at three months\textsuperscript{24} and from two months to four years.\textsuperscript{12} In this study, the questionnaires were completed by participants from one to 15 months following discharge. Chi-square did not indicate a statistically significant association between the time since discharge and memory. Therefore, the results of this study did not support the theory that there is a relationship between these variables. Perhaps if the data were collected using interviews the results of the study may have been different.

Some studies appeared to include all patients as participants\textsuperscript{13} others included patients with specific disorders\textsuperscript{12,25} while others used a convenience sample.\textsuperscript{16} In this study patients likely to have impaired memory such as those with neurological disorders and those with psychiatric disorders were excluded as was also the case for several other studies.\textsuperscript{10,22} The aim of this study was to investigate the experiences of short-term patients, those ventilated for less than 10 days this was not the case in any other study.

In this study all patients were ventilated and this was the case in only one other study.\textsuperscript{12} In the study by Jones\textsuperscript{10} 22\% (of n=100) were ventilated, Green\textsuperscript{16} 62\% (of n=26), Bion\textsuperscript{13} 81\% (of n=60) and by Turner\textsuperscript{11} 68\% (of n=100). In the remaining studies the numbers were not reported.

The administration of sedation may also influence recall. In the study by Bion\textsuperscript{13} 78\% received midazolam, in the study by Turner\textsuperscript{11} 36\% received no sedation while the remaining studies did not report on the sedation administered. In the study by Bion\textsuperscript{13} 90\% of patients who received midazolam had impaired memory of the ICU, while this percentage was only 34\% of those who did not have midazolam. Other studies have indicated that administration of sedation did not influence memory.\textsuperscript{16,24} Turner reported that the administration of sedation had no influence on the ability to sleep or fear of
No previous study has reported on the depth of sedation or particular agents used and memory. In this study all patients received sedation of some type. However, chi-square indicated there was no statistically significant association between the type of sedation received, or the depth of sedation and memory. This may have been due to the size of the sample.

Age has been reported to have an influence on recall. This appears to be related also to gender and the type of illness. However, a statistically significant association was not found in this study. The mean age was 59 years comparable with several previous studies 53.3 years and 62 years, but significantly older than patients in the study by Turner 38.1 years. In 2000-2001 the average age of patients admitted to the unit in which the study was conducted was 57 (median 56) close to the mean age of participants in this study. The hospital is a major trauma centre and conducted 544 retrievals in 2000-2001 many of whom would have suffered trauma. Exclusion of patients who suffered from head injuries from the study sample would have increased the mean age as these are most common in people less than 30 years of age. This would have contributed to the skewing of the data towards the 61-70 year age group.

The severity of illness as calculated by an APACHE II score has also been reported to influence recall. However, a statistically significant relationship was not found in this study. This may have been due to the exclusion criteria used. Patients were ventilated for less than 10 days, which would exclude many of the more seriously ill patients. The mean APACHE II was 17, which is comparable with the only mean APACHE II score of 12.27 reported in previous studies. The average APACHE II score of patients admitted to the study unit in 1999-2000 was 21.2. Patients who died had to be excluded from this study and as the APACHE II is a severity of illness score it would be expected that these people would have had higher scores. This would account for the lower mean APACHE II for the participants in the study.
Another factor that\(^{12}\) has been demonstrated to influence recall is the duration of ventilation, again a statistically significant relationship was not found in this study, which may have been due to the restricted duration of ventilation. Again, it is important to note that the sample may have been too small to demonstrate a statistically significant relationship between these variables.

In this study a lower percentage of patients remembered pain than in previous studies. All patients in this study were sedated to some degree, although most were predominantly lightly sedated. Seventy percent had infusions of morphine. Although only 35% of patients who were sedated with propofol received morphine, there was no statistically significant association between the sedation agent received and reports of pain. Sixty-five percent of patients had undergone surgical procedures or suffered trauma. In the study by Puntillo all the patients had undergone surgery (19 of the 24 thoracoabdominal surgical procedures), the sample was purposeful, and “some” received sedation and all but two morphine.\(^{25}\) Green reported that 65% of patients received sedation, while equal proportions of patients who received analgesia such as alfentanil or morphine or who did not receive analgesia reported pain.\(^{16}\) Simini did not report on the analgesia given.\(^{22}\) Bion and Bergbom-Engberg did not report whether analgesia was administered.\(^{12,13}\)

Several studies have attempted to quantify the degree of pain suffered. Turner\(^{11}\) found pain caused moderate to severe distress in 22% (22/100) of patients, Puntillo found that 63% (15/24) of patients remembered moderate to severe pain.\(^{25}\) Green found 50% (13/26) recalled pain as tolerable or causing discomfort, while 31% (8/26) recalled intense pain.\(^{16}\) Simini asked patients to state their worst memory, pain was reported by 8% (6/76).\(^{22}\) In this study the mean pain score on a visual analogue scale was 7, but pain was only reported by 20% of patients (10/51). Pain was reported to be rarely
experienced by 8% and frequently by 12%. No other study has reported on the frequency of the experience.

The percentage of patients remembering thirst and nausea were comparable with previous studies. Although none have attempted to quantify the experience.

Only 43% of participants indicated that they remembered being in the ICU 55% indicated that they remembered the nurses speaking to them and 71% of these found this reassuring. Previous studies have also indicated that most patients gain reassurance from the nurses.\textsuperscript{10,16}

Nightmares (10%), hallucinations (27.5%) and confusion were fairly common experiences for patients in this study and were related to a high level of distress. Recorded observations by staff did not appear to reliably report confusion. Previous studies have reported that from 26\%\textsuperscript{12} to 38\%\textsuperscript{16} of patients reported nightmares and hallucinations. Previous researchers have postulated that these cause more distress for patients with no explicit memories of the ICU. Distress following discharge from the ICU was not investigated as this was beyond the scope of this study. Such a study would need to investigate the issue of post-traumatic stress syndrome. No statistically significant association was demonstrated between memory of the ICU and the incidence of dreams, nightmares, hallucinations and confusion. In addition no statistically significant association was demonstrated between the agent administered or the depth of sedation and these experiences.

The majority of patients were ventilated for some time with out receiving sedation (78\%, mean 11.8 hours, maximum 118 hours) and 65\% were recorded as being awake while ventilated (mean 3hrs, maximum 20 hours); this did not have any statistically significant association with whether the patient remembered being in the ICU.
**Questionnaire Summary**

The practice of sedation may have changed in the past decade but the results of this study are comparable with many previous studies. Many patients have no memory of the ICU and even fewer remember ventilation. The percentage of patients remembering pain and anxiety was lower than that reported by previous investigators. Dreams, nightmares, hallucinations and confusion were all reported by patients who had no explicit memory of being in the ICU. However, they were no more common in this group. There did not appear to be a statistically significant association between the agent administered for sedation or its depth and memories. It was common for patients to be ventilated for periods of time without sedation and to be observed to be “awake”, but this did not appear to influence explicit memory.

**Interviews**

Many studies have reported that confusion, nightmares and hallucinations are commonly experienced by patients in ICU. It has been reported that staff are often not necessarily aware that the patient was suffering “mental changes”. In addition some researchers have reported a reluctance by patients to tell staff that they are experiencing, confusion, nightmare or hallucinations. Granberg, Bergbom and Lundberg state that “patients often try to disguise and deny symptoms of delirium, because they believe they are going crazy.”

In this study all the eight patients interviewed had experienced confusion, nightmares or frightening hallucinations. Yet for only two was there any indication that this had been recognised by the staff according to documentation in the notes.

Two studies have investigated patient’s experiences of confusion and unreal experiences in the ICU using qualitative methods. Laitinen used a phenomenological-hermeneutic approach to investigate the memories of ten patients who had undergone coronary bypass surgery and Granberg, Engberg and Lundberg, used a hermeneutic approach to
study the experiences of 19 patients who had been ventilated in a general ICU. Both describe how participants suffered paranoid delusions like patients in this study. Granberg also found several patients reported seeing fantasies with “strong colours”. Several patients reported that when they were with relatives or a nurse, things became “normal” or that the hallucinations disappeared. This study also found that participants reported that a familiar face helped them return to reality. Russell reporting on a study that used questionnaires to study patients’ experiences of intensive care also reported that one patient was embarrassed to think about what he had done in the ICU while confused.

Some of the nightmares and hallucinations experienced by patients in this study were quite horrific. The impact of these on recovery and the emotional well being of the patient cannot be positive. In addition it appears staff may often be unaware that patients are suffering confusion, hallucinations or nightmares.

**Implications for Practice**

Anecdotal evidence suggests that nurses sometimes assume that patients will not remember any of their time in ICU and so it is not worth talking to sedated patients. Although the majority of patients in this study did not have implicit memory of ICU most remembered nurses talking to them and found this reassuring. This indicates the importance of nurses talking to their patients. Thirst was among the next most common memory, for those who remembered this experience it occurred frequently and caused a high degree of distress. Therefore nursing actions like providing ice chips and maintaining moisture of the oral mucosa are extremely important. Anxiety was also frequently remembered emphasising the importance of providing reassurance. Confusion, nightmares and hallucinations are fairly common and cause a high degree of distress. Nurses need to be more aware of this so they can act to minimise distress by actions such as, orientating patients frequently, explaining routines and encouraging
relatives to stay with their loved ones. Nurses need to encourage patients who can talk to discuss any nightmares and hallucinations with staff. Talking with patients about their perceptions of what is happening will assist in the detection of confusion, so this can be documented. It is important that the potential for drugs to potentiate confusion or cause hallucinations is not disregarded. Patients need to be reassured that these experiences are common and it does not mean they are going mad. The interviews demonstrated the degree of distress these experiences caused. Several participants recounted how the presence of loved ones helped them return to reality and reassured them as nothing else could. Therefore, it may be beneficial to allow family and loved ones to stay with those who are experiencing confusion.7

A number of participants were still experiencing difficulty in sleeping, were having nightmares or were concerned about their ICU experiences. Three patients who responded to the questionnaire were referred to the ICU social worker for follow up on request. This was because of continuing nightmares and sleeping problems, or wanting to know what had happened to them in their lost time (none of these had consented to be interviewed). After ICU, patients are generally followed up by their individual clinic. It may be beneficial for some patients if an ICU specific follow-up service was available. This should be conducted by staff who have insight into the experiences that ICU patients have and can explain to patients what happened to them. Patients may feel more at ease to discuss their experiences with someone who was there, rather than a doctor who does not work in the ICU. Encouraging patients to visit the ICU following their stay may allow them to make sense of some of their memories. Patients may need help to recover psychologically as well as physically. They may also benefit from a period of time in ICU following extubation, when they are awake and able to orientate themselves to their surroundings. This could be particularly important for those who suffer confusion and hallucinations in ICU.
Although for the majority of patients there was documentation indicating that they were “awake” while ventilated this did not appear to be related to the likelihood of remembering the experience. This is the time when most nurses do talk to their patients. However, patients commonly recalled how they drifted in and out of consciousness and from reality to unreality. Nurses need to talk to patients even if they do not know whether they can hear and keep explaining what has happened and where they are. The effects of drugs and devices should be explained frequently. For example “you may feel that you can’t see properly” or “you have a tube in your throat so you will not be able to speak”. It is also important to explain every day events to the patient for example, ward rounds and handovers.

Pain was remembered by 20% of patients and was indicated to be severe on the pain scale. The administration of analgesia is important, however in this study this did not have a statistically significant association with the likelihood of remembering this experience. Likewise, particular sedation regimes did not appear to influence memories or the likelihood of nightmares, hallucinations and confusion.

Patients remembered individual nurses not only for their use of humour and compassion but one also for her lack of compassion. Many patients remember being in the ICU and the nursing care they are provided with needs to be compassionate and not just technical. The community expects that nurses provide not just technical expertise but that they are “caring”.

Although no statistically significant association was found between the agent used or the depth of sedation and memories, it is important that nurses observe patients themselves. Nurses may be able to detect clinically important reactions to the sedation regime chosen for individual patients.
**Limitations**

One of the limitations of the study was that data involving patients' memories was collected by questionnaire from one to 15 months since discharge from hospital. Patients may have forgotten their experiences and although the target sample was fifty, one hundred and twenty-five questionnaires were distributed to gain this sample (response rate 44%). Interviewing patients earlier post discharge may have resulted in a higher number of participants. The statistical analysis was limited by the number of participants. However, to gain more it would have meant collecting data from patients who had been discharged prior to the last two years or accessing those who were admitted to another ICU. The sample was not randomly selected which reduces the reliability and generalisability of the results. The results may have been biased as the participants self selected; those who did not respond may have had different memories. In addition the questionnaire was quite short and directed to the study question and its internal consistency was not tested. The data regarding the patients’ sedation regime was collected retrospectively from the medical records. This also reduces the reliability of the data.

**Conclusions**

This study indicated that 43% of short-term ventilated patients remember being in the ICU. Common explicit memories are anxiety and thirst. A significant number of patients, even those who had no other memory of the ICU, remembered the nurses and found most of them reassuring. There was no statistically significant association between the memory and nightmares, hallucinations and confusion or any of these variables and the sedation regime administered. In addition although many patients in this study were documented as awake while ventilated and as ventilated without sedation, for significant periods of time, no statistically significant association was found between this and memory of the ICU.
Confusion was a common experience and it appears nurses and doctors are often unaware that patients are experiencing these phenomena. Patients may experience horrific hallucinations and nightmares of which death appears to be a common theme. A feeling of powerlessness was commonly described and patients may drift from reality to unreality. Providing constant reassurance and explaining every day ICU happenings, may assist patients to understand what they are experiencing. For those who are experiencing confusion a loved one may provide an important link with reality. Some may require individual assistance to recover from these experiences.

**Recommendations for Further Investigation**

This study considered the memories of short-term patients. Future research should investigate the memories and experiences of long-term patients because this group of patients may suffer more from confusion, nightmares and hallucinations. In addition the benefits of an ICU follow up service for those who have suffered distressing confusion or who are experiencing continuing problems such as difficulty in sleeping or flashbacks should be investigated. It was not the purpose of this study to examine the incidence or effect of nightmares continuing following discharge, this matter requires further investigation.
REFERENCES


Appendix 1 Letter from Research Ethics Committee

Ms J Magarey
Clinical Lecturer
DEPT OF CLINICAL NURSING
ADELAIDE UNIVERSITY

Dear Ms Magarey,

Re: "A study to explore patients' memories of their stay in an Intensive Care Unit (ICU) and to investigate the relationship of these memories to the sedation regimes."
RAH Protocol No: 010411

I am writing to advise that ethical approval has been given to the above project. Please note that the approval is ethical only, and does not imply an approval for funding of the project.

Human Ethics Committee deliberations are guided by the Declaration of Helsinki and N.H. and M.R.C. Guidelines on Human Experimentation. Copies of these can be forwarded at your request.

Adequate record-keeping is important and you should retain at least the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them if necessary, in the future. The Committee will seek a progress report on this project at regular intervals and would like a brief report upon its conclusion.

If the results of your project are to be published, an appropriate acknowledgment of the Hospital should be contained in the article.

Yours sincerely,

Dr M James
Chairman
RESEARCH ETHICS COMMITTEE
Appendix 2 Introduction Letter from Director of the ICU

Dr P Thomas
Director Intensive Care

Dear

I would like to introduce Judy Magarey who is a nurse with extensive experience in Intensive care. She is conducting research into the memories patients have of their time in Intensive Care. In particular the effect the drugs given patients to keep them calm have on these memories and dreams or nightmares experienced. As you were recently a patient in the Intensive care Unit at Royal Adelaide Hospital, it would be appreciated if you could participate in this study. Judy has my support in undertaking this research, however, your participation is entirely voluntary.

Yours sincerely

Dr P Thomas
Appendix 3 Introduction Letter from Investigator

Dear Sir or Madam,

I am a Doctor of Nursing Candidate at The University of Adelaide, Department of Clinical Nursing and I am investigating the memories patients have of their time in an Intensive Care Unit. In particular I am interested in the effect the drugs we give patients to keep them calm have on these memories and dreams or nightmares experienced.

As you were recently a patient in the Intensive care Unit at Royal Adelaide Hospital I would be very grateful if you could complete the attached questionnaire and return it in the enclosed envelope. Your participation is voluntary. If you do not wish to participate your ongoing or future medical care will not be affected in any way.

There are no immediate benefits to you from participating in the study, but it will help nurses and doctors to understand more about the experiences of patients in ICU. The results of the study will be published but any information that could identify you will remain strictly confidential.

Note that if you complete and return the questionnaire, you may be asked to take part in an interview about your experiences. If you are selected for this it will be explained and your further consent for the interview will be sought.

If you have any queries please contact Judy Magarey, Royal Adelaide Hospital Phone extension 25828. This study has been approved by the Royal Adelaide Hospital Research Ethics Committee. If you wish to discuss aspects of the study with someone not directly involved, you may also contact the Chairman Research Ethics Committee, Royal Adelaide Hospital on 8222 4139.

Please accept in advance my thanks for your assistance.

Judy Magarey
Appendix 4 Patient Questionnaire

1. Do you remember any of your time in the intensive care unit?

   Yes [ ] No [ ]

   Even if at this stage you do not remember being in the intensive care unit, please continue with the questionnaire as the questions may prompt some memories.

2. How long do you think you stayed in ICU?

3. Do you remember being on the breathing machine?

   Yes [ ] No [ ] (if no go to question 4)

   If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

   1  2  3  4  5  6
   Not distressing  Extremely distressing

   Comments: ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
4. Do you remember the breathing tube being cleared with suction?

Yes [ ] No [ ] (if no go to question 5)

If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

1 2 3 4 5 6
Not distressing Extremely distressing

Comments: ____________________________________________________________
__________________________________________________________

5. Do you remember feeling anxious while in the ICU?

Yes [ ] No [ ] (if no go to question 6)

If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

1 2 3 4 5 6
Not distressing Extremely distressing

Comments: ____________________________________________________________
__________________________________________________________
__________________________________________________________
6. Do you remember experiencing pain while in the ICU?

Yes [ ] No [ ] (if no go to question 7)

If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

1 2 3 4 5 6
Not distressing Extremely distressing

Please indicate the severity of the pain at its worst was by circling a number on the scale below.

1 2 3 4 5 6 7 8 9 10
No pain Worst pain imaginable

How commonly do you remember feeling in pain?

Rarely [ ] Frequently [ ] Constantly [ ]

Comments: ____________________________________________

_______________________________________________________

_______________________________________________________
7. Do you remember feeling thirsty while in the ICU?

Yes [ ] No [ ] (if no go to question 8)

If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

1 2 3 4 5 6
Not distressing Extremely distressing

Please indicate the severity of the thirst at its worst was by circling a number on the scale below.

1 2 3 4 5 6 7 8 9 10
No thirst Worst thirst imaginable

How commonly do you remember feeling thirsty?

Rarely [ ] Frequently [ ] Constantly [ ]

Comments:
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
8. Do you remember feeling nauseated while in the ICU?

Yes [ ] No [ ] (if no go to question 9)

If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

1 2 3 4 5 6
Not distressing Extremely distressing

Please indicate the severity of the nausea at its worst was by circling a number on the scale below.

1 2 3 4 5 6 7 8 9 10
No nausea Worst nausea imaginable

How commonly do you remember feeling nauseated?

Rarely [ ] Frequently [ ] Constantly [ ]

Comments: ____________________________________________________________
__________________________________________________________

9. Do you remember the nurses speaking to you?

Yes [ ] No [ ]
If yes, did you find this reassuring?

Comments: ____________________________________________

______________________________________________________

10. Is there any thing you think the nurses could have done to make your time in ICU less distressing?

______________________________________________________

______________________________________________________

11. Do you remember having dreams while in the ICU?

Yes □  No □  (if no go to question 12)

Did these continue after you were moved from the ICU, if so for how long?

______________________________________________________

12. Do you remember having nightmares while in the ICU?

Yes □  No □  (if no go to question 13)

If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

1  2  3  4  5  6
Not distressing  Extremely distressing
Did these continue after you were moved from the ICU, if so for how long?

13. Do you remember feeling confused while in the ICU?

Yes [ ] No [ ] (if no go to question 14)

If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

1 2 3 4 5 6
Not distressing Extremely distressing

14. Do you remember having hallucinations while in ICU?

Yes [ ] No [ ] (if no go to question 15)

If your answer was yes, please indicate on average how distressing you found the experience by circling a number on the scale below.

1 2 3 4 5 6
Not distressing Extremely distressing
If you experienced dreams or nightmares during your time in the ICU or immediately following your discharge from the ICU, would you consent to being interviewed in person by Judy Magarey? If so please give a contact number below.

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

• Do you have any other comments or memories you would like to highlight?

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

Thank you for your participation in this survey.

Please return the completed questionnaire in the stamped, self addressed envelope provided.
### Appendix 5 Data Collection Tool

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<td>Dreams</td>
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<table>
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<th>Other (drugs, alcohol)</th>
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Appendix 6 Information Sheet

Dear Sir or Madam,

I am a Doctor of Nursing Candidate at The University of Adelaide, Department of Clinical Nursing. In the Intensive Care Unit we give drugs so that the patients do not feel pain or fight the breathing machine. The drugs make the patient sleepy and make it less likely that they will remember their time in ICU. My research involves investigating the effect that these drugs have on the memories patients have of their ICU experience and in particular dreams or nightmares experienced.

In the interview I would like to hear about your experiences of dreams, nightmares and confusion while you were in ICU and immediately following discharge. The discussion will be unstructured but basic questions "Can you tell me about the dreams or nightmares that you experienced while in the ICU?", will be used to start the discussion. There is no intention to upset you by causing you to remember your ICU experiences. However, if the interview causes you any distress it will not be continued and if you wish you can be referred to Mr Carl Phillipson the ICU social worker for counselling.

You can withdraw from the study at any stage or refuse to answer any questions and this will not effect your care now or at any time in the future.

There are no immediate benefits to you from participating in the study, but it will help nurses and doctors to understand more about the experiences of patients in ICU. The results of the study will be published but any information that could identify you will remain strictly confidential.

If you have any queries regarding the study please contact Judy Magarey, Royal Adelaide Hospital Phone extension 25828. This study has been approved by the Royal Adelaide Hospital Research Ethics Committee. If you wish to discuss aspects of the study with someone not directly involved, you may also contact the Chairman Research Ethics Committee, Royal Adelaide Hospital on 8222 4139.

Please accept in advance my thanks for your assistance.

Judy Magarey
Appendix 7 Consent Form

**Project title:** A study to explore patients’ memories of their stay in an intensive care unit (ICU) and to investigate the relationship of these memories to sedation regimes.

**Researcher:** Judy Magarey

This is to certify that I,

(Print Name)

agree to participate as a volunteer in the above named project. I give permission to be interviewed and for those interviews to be tape recorded.

I agree that the information may be published, provided my name and any information which may lead to the identity of myself or any other person or institution will remain confidential.

I understand that I can withdraw from the study at any stage or refuse to answer any questions without prejudice to any further care I may require.

I have been informed about the aims and purposes of this study by the researcher and have been given the opportunity to ask any questions I desire and all such questions have been answered to my satisfaction.

________________________________________________________

participant researcher

Date __________________________
### Appendix 8 Critical Illness Sedation Scale (CISS)

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<th>LEVEL</th>
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<th>Description</th>
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<td>1</td>
<td>Inadequate sedation.</td>
<td>Agitated, distressed. Not tolerating IPPV eg coughing against the ventilator or attempting extubation.</td>
</tr>
<tr>
<td>2</td>
<td>Light sedation.</td>
<td>Eyes may be closed, but open to speech, responds purposefully, quickly settles when not stimulated, tolerates ventilation when not roused.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate sedation.</td>
<td>Sluggish response to forehead tap or speech. eg weak flexion or grimacing.</td>
</tr>
<tr>
<td>4</td>
<td>Heavy sedation.</td>
<td>No voluntary response to stimulation of any form. A weak cough on suction and spinal reflexes may be present.</td>
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Appendix 9 Chi-Square Tests

Any memory * Ages Crosstabulation

Count

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<td>&gt;60</td>
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<tr>
<td>Any memory</td>
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Chi-Square Tests

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N of Valid Cases 51

a Computed only for a 2x2 Table
b 0 cells (.0%) have expected count less than 5. The minimum expected count is 9.49.
### Any memory * Time in ICU Crosstabulation

#### Count

<table>
<thead>
<tr>
<th></th>
<th>Time in ICU</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-2 days</td>
<td>3-4 days</td>
</tr>
<tr>
<td>Any memory yes</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>

#### Chi-Square Tests

<table>
<thead>
<tr>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>3.884</td>
<td>2</td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>3.913</td>
<td>2</td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td>.248</td>
<td>1</td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>51</td>
<td></td>
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</tbody>
</table>

0 cells (0%) have expected count less than 5. The minimum expected count is 6.90.
Any memory * Duration of ventilation Crosstabulation

<table>
<thead>
<tr>
<th>Duration of ventilation</th>
<th>Total</th>
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<tbody>
<tr>
<td>&lt;or=48</td>
<td>&gt;48</td>
</tr>
<tr>
<td>Any memory</td>
<td></td>
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<tr>
<td>yes</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
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</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>.888</td>
<td>1</td>
<td>.346</td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>.426</td>
<td>1</td>
<td>.514</td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>.896</td>
<td>1</td>
<td>.344</td>
</tr>
<tr>
<td>Linear-by-Linear</td>
<td>.871</td>
<td>1</td>
<td>.351</td>
</tr>
<tr>
<td>Association</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

N of Valid Cases 51

a Computed only for a 2x2 Table
b 0 cells (.0%) have expected count less than 5.
The minimum expected count is 8.63.
Any memory * DURATION OF SEDATION Crosstabulation

Count

<table>
<thead>
<tr>
<th>Duration of sedation hours</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;OR=48</td>
<td></td>
</tr>
<tr>
<td>&gt;48</td>
<td></td>
</tr>
<tr>
<td>Any memory yes</td>
<td>17</td>
</tr>
<tr>
<td>No</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
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</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>1.343</td>
<td>1</td>
<td>.246</td>
<td></td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>.730</td>
<td>1</td>
<td>.393</td>
<td></td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>1.371</td>
<td>1</td>
<td>.242</td>
<td></td>
</tr>
<tr>
<td>Fisher's Exact Test</td>
<td></td>
<td></td>
<td>.362</td>
<td>.197</td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td>1.317</td>
<td>1</td>
<td>.251</td>
<td></td>
</tr>
</tbody>
</table>

N of Valid Cases 51

a  Computed only for a 2x2 Table
b  0 cells (.0%) have expected count less than 5.
   The minimum expected count is 6.90.
Any memory * Artificial ventilation with no sedation Crosstabulation

Count

<table>
<thead>
<tr>
<th></th>
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<tr>
<td></td>
<td>Nil</td>
<td>1-5</td>
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<tr>
<td>Any memory yes</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>3.156</td>
<td>2</td>
<td>.206</td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>3.221</td>
<td>2</td>
<td>.200</td>
</tr>
<tr>
<td>Linear-by-Linear Assn.</td>
<td>1.958</td>
<td>1</td>
<td>.162</td>
</tr>
</tbody>
</table>

N of Valid Cases 51

a 1 cells (16.7%) have expected count less than 5.
The minimum expected count is 4.31.
## Memory of IPPV * Awake on IPPV Crosstabulation

### Count

<table>
<thead>
<tr>
<th>Memory of IPPV</th>
<th>Awake</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>50</td>
</tr>
</tbody>
</table>

### Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>2.351</td>
<td>1</td>
<td>.125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>1.389</td>
<td>1</td>
<td>.239</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>2.250</td>
<td>1</td>
<td>.134</td>
<td></td>
<td></td>
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<tr>
<td>Fisher's Exact Test</td>
<td></td>
<td></td>
<td></td>
<td>.163</td>
<td>.120</td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td>2.304</td>
<td>1</td>
<td>.129</td>
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<td></td>
</tr>
</tbody>
</table>

**N of Valid Cases** 50

---

*a* Computed only for a 2x2 Table  
*b* 1 cells (25.0%) have expected count less than 5.  
The minimum expected count is 3.84.
Any memory * APACHE chi square Crosstabulation

Count

<table>
<thead>
<tr>
<th></th>
<th>APACHE chi square</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-10</td>
<td>11-20</td>
</tr>
<tr>
<td>Any memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>23</td>
</tr>
</tbody>
</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>4.920</td>
<td>2</td>
<td>.085</td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>4.989</td>
<td>2</td>
<td>.083</td>
</tr>
<tr>
<td>Linear-by-Linear</td>
<td>.178</td>
<td>1</td>
<td>.673</td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a 1 cells (16.7%) have expected count less than 5.
The minimum expected count is 4.40.
Any memory * propofol or midazolam Crosstabulation

<table>
<thead>
<tr>
<th></th>
<th>propofol or midazolam</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>propofol</td>
<td>midazolam</td>
</tr>
<tr>
<td>Any memory</td>
<td>yes</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>19</td>
</tr>
</tbody>
</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>1.318</td>
<td>1</td>
<td>.251</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>.652</td>
<td>1</td>
<td>.419</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>1.325</td>
<td>1</td>
<td>.250</td>
<td>.318</td>
<td>.210</td>
</tr>
<tr>
<td>Fisher's Exact Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td>1.281</td>
<td>1</td>
<td>.258</td>
<td>.318</td>
<td>.210</td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Computed only for a 2x2 table

b 0 cells (.0%) have expected count less than 5. The minimum expected count is 7.31.
### Memory of nightmares * propofol or midazolam Crosstabulation

#### Count

<table>
<thead>
<tr>
<th></th>
<th>propofol or midazolam</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory of nightmare</td>
<td>yes</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>propofol</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>midazolam</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>

#### Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>2.763</td>
<td>1</td>
<td>.096</td>
<td>.234</td>
<td>.148</td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>1.116</td>
<td>1</td>
<td>.291</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>3.901</td>
<td>1</td>
<td>.048</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher's Exact Test</td>
<td></td>
<td></td>
<td></td>
<td>.234</td>
<td>.148</td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td>2.684</td>
<td>1</td>
<td>.101</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Computed only for a 2x2 table
b 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.37.
Memory of confusion * propofol or midazolam Crosstabulation

Count

<table>
<thead>
<tr>
<th>Memory of confusion</th>
<th>propofol or midazolam</th>
<th>midazolam</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>16</td>
<td>35</td>
</tr>
</tbody>
</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>.748</td>
<td>1</td>
<td>.387</td>
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<td></td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>.227</td>
<td>1</td>
<td>.633</td>
<td></td>
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</tr>
<tr>
<td>Likelihood Ratio</td>
<td>.762</td>
<td>1</td>
<td>.383</td>
<td></td>
<td>.460</td>
</tr>
<tr>
<td>Fisher’s Exact Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.319</td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td>.727</td>
<td>1</td>
<td>.394</td>
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<td></td>
</tr>
</tbody>
</table>

N of Valid Cases 35

a Computed only for a 2x2 table

b 2 cells (50.0%) have expected count less than 5. The minimum expected count is 4.11.
Memory of hallucinations * propofol or midazolam Crosstabulation

<table>
<thead>
<tr>
<th>Memory of hallucinations</th>
<th>Propofol</th>
<th>Midazolam</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>16</td>
<td>35</td>
</tr>
</tbody>
</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>.781</td>
<td>1</td>
<td>.377</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>.123</td>
<td>1</td>
<td>.726</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>.821</td>
<td>1</td>
<td>.365</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher's Exact Test</td>
<td></td>
<td></td>
<td></td>
<td>.608</td>
<td>.370</td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td>.759</td>
<td>1</td>
<td>.384</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Computed only for a 2x2 table
b 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.83.
Memory of pain * Morphine Crosstabulation

<table>
<thead>
<tr>
<th>Memory of pain</th>
<th>Morphine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>yes</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>5</td>
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<tr>
<td></td>
<td>yes</td>
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<td>No</td>
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</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>51</td>
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</table>

Chi-Square Tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>2.540</td>
<td>1</td>
<td>.111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>1.456</td>
<td>1</td>
<td>.228</td>
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<td></td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>2.374</td>
<td>1</td>
<td>.123</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher's Exact Test</td>
<td></td>
<td></td>
<td>.135</td>
<td>.116</td>
<td></td>
</tr>
<tr>
<td>Linear-by-Linear</td>
<td>2.490</td>
<td>1</td>
<td>.115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Computed only for a 2x2 table
b 1 cells (25.0%) have expected count less than 5. The minimum expected count is 2.94.
Any memory * Memory of nightmares Crosstabulation

Count

<table>
<thead>
<tr>
<th></th>
<th>Memory of nightmares</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
<td>No</td>
</tr>
<tr>
<td>Any memory</td>
<td>yes</td>
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<td></td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
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<td>5</td>
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Chi-Square Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
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<td>1</td>
<td>.423</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>.106</td>
<td>1</td>
<td>.744</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>.636</td>
<td>1</td>
<td>.425</td>
<td>.641</td>
<td>.368</td>
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a Computed only for a 2x2 table
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Any memory * Memory of confusion Crosstabulation

Count

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Chi-Square Tests

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<tr>
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N of Valid Cases 51

a Computed only for a 2x2 table
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Count

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Chi-Square Tests

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a Computed only for a 2x2 table
b 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.45.
### Appendix 10 Mann-Whitney U tests

#### Age

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* a Grouping Variable: Any memory

#### Documented time in ICU days

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* a Grouping Variable: Any memory

#### Duration of IPPV hours

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<th>Z</th>
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<tbody>
<tr>
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* a Grouping Variable: Any memory

#### Sedation time hours

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* a Grouping Variable: Any memory
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<td>Wilcoxon W</td>
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a Grouping Variable: Any memory

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a Grouping Variable: Any memory

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<th>Recorded time in ICU following extubation</th>
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a Grouping Variable: Any memory

<table>
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<th>APACHE Score</th>
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a Grouping Variable: Any memory
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a Grouping Variable: Any memory
STUDY 3

A STUDY TO INVESTIGATE THE ASSOCIATION BETWEEN THE CRITICAL ILLNESS SEDATION SCALE (CISS), INDEPENDENT CLINICAL JUDGMENT AND THE BISPECTRAL INDEX OF EEG FOR THE ASSESSMENT OF SEDATION OF VENTILATED PATIENTS IN AN INTENSIVE CARE UNIT (ICU)
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ABSTRACT

The purpose of this study was to determine the reliability of the Critical Illness Sedation Scale (CISS) (appendix 1) for the assessment of sedation of ventilated ICU patients, when compared to independent clinical judgment and the objective measure of the Bispectral Index of the electroencephalogram (BIS). BIS was measured by the “Aspect Medical Systems A-2000™” BIS monitoring system. The monitor processes the electroencephalogram (EEG) and displays a number between 0-100 that relates to the level of sedation. The study used a prospective design with a convenience sample. A total of two hundred clinical assessments were made by the team-leaders and patient-care nurses. Each of these ratings were compared with four BIS measurements, BIS at the time of the assessment, BIS mean, BIS base and BIS difference. The results demonstrated that there was a moderate, positive correlation between CISS measurements performed by the nurse caring for the patient and the BIS recordings (r 0.408, r 0.447, r 0.374 & r 0.495) and a weak positive correlation between CISS assessments performed by the team-leaders using the headings of the CISS and the BIS recordings. When the results were analysed according to the educational qualifications of the nurses caring for the patient; it was found that the strongest positive correlations between the CISS assessments and the BIS were for those assessments performed by the graduate nurses (GNs). There was a strong positive correlation between the CISS assessments performed by the nurse caring for the patient and those performed by the team-leader. Kruskal-Wallis Tests indicated a significant difference in the rank of the BIS scores for each level of the CISS assessment by the patient-care nurse. However, error plots of the means for each CISS level for assessments performed by the patient care nurse demonstrated overlapping
of the confidence intervals for the means of the BIS recordings at levels 2-4 of the CISS. The results indicate that the BIS may be useful for the assessment of the sedation in ICU patients, particularly for those who are heavily sedated when a clinical scale is not as useful in discriminating levels of sedation.
DEFINITION OF TERMS

Bispectral Index of EEG (BIS)  A processed EEG measurement that uses time domain, frequency domain and higher order bispectral analysis, to display a number between 0 and 100 which can be used to measure the depth of sedation.¹

Critical Illness Sedation Scale (CISS)  A scale developed to assess the level of sedation in adult ventilated patients.

Electroencephalogram (EEG)  A graphic chart on which is traced the electric potential produced by brain cells, detected by electrodes placed on the scalp. The resulting brain waves are called alpha, beta, delta and theta rhythms.²

Electromyogram (EMG)  A record of the intrinsic electrical activity in skeletal muscle.²

Team-leader  A nurse with the overall responsibility for 4-6 patients for the particular shift.

Graduate Nurse  Registered nurse in their first year of practice.
INTRODUCTION

Context of the Study

This study comparing the clinical assessment of sedation by the nurses with recordings of the BIS monitor forms the final component of the portfolio. The accurate assessment of sedation continues to be one of the most challenging issues encountered in the ICU. The numerous problems associated with over and under-sedation were discussed in the systematic review. The BIS monitoring system consists of a small portable monitor (weighing 1.4Kg) that may be mounted on an IV pole. It monitors the BIS via a sensor placed on the patient’s forehead. In the ICU where the study was undertaken, the current sedation protocol suggests that the CISS should be used hourly to assess sedation. However, anecdotal evidence suggests that this is commonly forgotten, or the headings from level 1 “inadequate sedation to level 4 “heavy sedation” are applied without reference to the descriptions. It was important to determine if the CISS had any relationship to objective measurements produced by the BIS. This would provide information on the potential role of the BIS in the assessment of sedation in the unit in which the research was conducted.

Statement of the Research question

The research question: Is clinical judgement of the level of sedation accurate when compared to an objective measure?
Significance of the Study

The information gained from the study will aid in the development of the sedation protocol, with the aim of providing the most appropriate level of sedation for the individual by titration of sedation to a reliable scale. It will provide information on the potential for use of the BIS monitor in helping staff to accurately assess the individual patient's level of sedation or support the use of the CISS and clinical judgment.

LITERATURE REVIEW

Sedation in the ICU and Problems relating to its use

Ventilated patients in ICU are commonly sedated to facilitate treatment such as artificial ventilation, to promote comfort, to ensure distressing events are not remembered and sometimes as part of the treatment, for example for the management of raised intracranial pressure. Indeed, most patients admitted to ICUs are ventilated at some time during their admission. A survey conducted in 1996 found the most common agents used for the sedation of adult ventilated patients in Australia were benzodiazepines and these were usually administered in combination with analgesia, specifically midazolam and morphine. Around 1995, propofol was introduced to intensive care practice for sedation of ventilated patients in Australia (personal communication Zeneca Pharmaceuticals) and anecdotal evidence suggests that this agent is now also in common use. Propofol has no analgesic action, so critically ill patients particularly those recovering from trauma or surgery, commonly require analgesic medication such as morphine. Both benzodiazepines and narcotics have the potential to accumulate in the critically ill, resulting in prolonged sedation.
Midazolam has an active metabolite $\alpha$-hydroxymidazolam which will accumulate in renal failure and shock. Reduced hepatic perfusion may also interfere with metabolism prolonging its action. In addition, research indicates that continuous infusions result in saturation of the tissues, meaning any further dose remains available to the receptor sites resulting in prolongation of the action by days. Morphine also has an active metabolite morphine - 6 glucuronide which is up to 40 times as potent as the parent compound. The metabolism is also influenced by hepatic function and reduced metabolism may occur with age related deterioration in function or due to reduced hepatic blood flow in shock.

These factors all make the sedation of critically ill ventilated patients problematic. Sedation is essential to facilitate treatment and reduce distress, but over sedation may be associated with complications such as prolonged sedation, hypotension, respiratory depression, bradycardia, ileus, increased protein breakdown, immunosuppression, renal dysfunction, vein thrombosis and increased cost. Under-sedation may also be distressing and dangerous to the patient. Agitation occurs in as many as 74% of adult ICU patients and to a severe or dangerous degree in as many as 46%. Some researchers have reported that memories of frightening or painful events may contribute to psychiatric sequelae. Therefore, providing adequate sedation and pain relief without over-sedating the patient is of great importance.
Assessment of Sedation - Sedation Scales

Clinical assessment scales such as the Ramsay\textsuperscript{13}, Riker sedation-agitation scale (SAS)\textsuperscript{14}, the Sheffield scale\textsuperscript{15} the Comfort scale\textsuperscript{16} and CISS, appear to be the most common method used to assess the level of sedation in ICU patients.\textsuperscript{6,10,17,18} These scales typically apply a score to a clinical description of the level of sedation. Shelly states that an ideal sedation scale, should be “accurate, reproducible, simple, minimal work required, easy to chart, minimally invasive, no discomfort to patient, relevant to the individual, not time consuming”.\textsuperscript{10} In addition the chosen scale must be able to provide consistency in patient assessment from one shift to the next, so it must be easily understood and able to be used by any staff member however inexperienced.\textsuperscript{15}

For a sedation scale to be used in intensive care to assess critically ill patients, it is essential that it is both reliable and valid. Reliability is the capacity of a tool to reproduce results on repeated measurement and can be tested by calculating correlation between raters or by repeating the test.\textsuperscript{19} Validity is the ability of a tool to measure what it is designed to measure.\textsuperscript{20} Many scales have been developed which vary in their complexity and ease of use.\textsuperscript{10,13-16,21,22}

The scale named the Critical Illness Sedation Scale (CISS), was developed in 1996 and was tested for reliability and validity compared to the Ramsay scale and a visual analogue scale (VAS).\textsuperscript{23} Forty-three independent simultaneous ratings were performed, by an intensivist, the investigator and the bedside nurse on a total of 22 patients. Correlations were analysed using Spearman’s correlation coefficient.
Table 1 Results of Correlations validation of CISS

<table>
<thead>
<tr>
<th>Scale</th>
<th>Raters</th>
<th>Correlation</th>
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<tbody>
<tr>
<td>VAS</td>
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<td>0.83</td>
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<tr>
<td></td>
<td>Nurse V Investigator</td>
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<td>Investigator V Intensivist</td>
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<td>Investigator V Intensivist</td>
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All correlations were significant (P < 0.0001)

The possible range of correlation may vary from -1 to +1. Good reliability is reflected by a correlation of 0.8 or above; for new instruments a reliability of +0.70 is considered acceptable. The total percentage agreement between raters was analysed and the overall rating for the CISS was 84%, for the VAS 7% and for the Ramsay it was 51%. To determine validity, correlations between the Ramsay and the CISS were calculated, for all the raters, these were high (Spearman’s rho, Intensivist, +0.79, Investigator +0.87 and Bedside nurses +0.90, P < 0.0001).

The results demonstrated that by all measures the CISS was a reliable scale and that it had good criterion validity when compared to the Ramsay scale. The CISS is part of the current protocol for administration and assessment of sedation in the ICU where this study was conducted study.

**Objective Methods of Assessing Sedation – The Bispectral Index of the EEG**

Scales by their nature are subjective measures of a patient’s level of sedation and there have been many attempts to develop an objective method of assessment. These
have included, measurement of the r-r interval on the electrocardiogram (ECG)\textsuperscript{25} and use of the electroencephalogram (EEG).\textsuperscript{26} These methods have failed to provide a reliable, practical and objective method of assessing the depth of sedation. Recently it has been suggested that a new method, the Bispectral Index of the EEG (BIS) may be the solution to the problem. The EEG measures electric potential produced by the brain cells, resulting in waves called alpha, beta, delta and theta waves\textsuperscript{2} but produces a large amount of information that is complex and requires expert interpretation.\textsuperscript{27} BIS is a processed EEG parameter obtained by multivariate discriminate analysis.\textsuperscript{28} It was derived from bifrontal EEG recordings of > 5000 subjects sedated with different types of anaesthetics.\textsuperscript{29} Shapiro states that BIS has the following characteristics:

- It provides information regarding interactions between cortical and subcortical areas that change with increasing amounts of hypnotic drugs;
- It is an empirical, statistically derived measurement that was accomplished by analysing a large data base of EEGs from subjects who had received hypnotic agents;
- The BIS measures the state of the brain, not a concentration of a particular drug;
- In general a BIS of 100 reflects an awake state, 80 reflects some sedation, 60 reflects a moderate hypnotic level, and 40 reflects a deep hypnotic level.\textsuperscript{27}

Studies have shown that when the BIS is less than 70 there is very low probability of recall and when the BIS is below 60 subjects are unconscious.\textsuperscript{30} The BIS has been tested extensively in the anaesthetic setting, as a guide for the titration of anaesthesia with the objectives of controlling the depth of anaesthesia\textsuperscript{30-32} and predicting recovery
time.\textsuperscript{33,34} BIS does not correlate well with somatic or autonomic responses, because it indicates the level of sedation at the time and does not predict an individual response to autonomic stimuli or pain.\textsuperscript{35} However, it appears to reliably measure the sedative component of anaesthesia. This would suggest that it may be valuable to reliably measure the depth of sedation in ICU patients. BIS has been extensively tested in measuring depth of sedation produced by both propofol and midazolam.\textsuperscript{25,30,36,37} the predominant drugs used for sedation in Australian ICUs.\textsuperscript{4} Testing has indicated that even in the presence of drug interactions such as when opioids are administered the BIS is still able to reliably monitor the depth of sedation.\textsuperscript{35}

Nevertheless, there are several potential problems that may reduce the accuracy of the BIS. Alternating current (AC) interference may be a potential source of error\textsuperscript{32}, such as from a warming blanket or pacemaker impulse\textsuperscript{38} and electromyographic (EMG) activity may increase the BIS. The influence of the EMG on BIS readings has not been determined as it is difficult to differentiate between muscle activity associated with increased wakefulness and non-specific muscle activity.\textsuperscript{18} In addition, other factors that depress cerebral activity such as hypothermia and cerebral ischaemia will decrease the BIS.\textsuperscript{35} However, in the ICU it is the actual level of sedation that is significant, rather than a response to a particular agent; it is immaterial what is causing the depressed conscious state. For example, a patient in a coma from metabolic causes may have a depressed BIS; this patient may not be able to breathe spontaneously or maintain their airway in the same manner as if they were sedated with midazolam. Effectively it does not matter what is causing the depressed BIS; drugs or pathology, the patient still has a depressed conscious state. Another factor that may result in inaccurate BIS readings is unilateral brain injury. If the fronto-
temporal sensor is applied to the injured side it may result in a BIS that does not relate
to the patient’s true state of consciousness.39

**Use of the BIS to Assess the Sedation Of ICU Patients**

Recently some researchers have investigated use of BIS monitoring to assess sedation of patients in the ICU setting.28,40-45 In 1996 Shah published two studies reporting on the use of the BIS in an ICU setting.28,43 In the first study 22 male surgical patients in an adult ICU, sedated with a variety of drugs including propofol, midazolam, and lorazepam administered in association with analgesics such as morphine and meperidine were each monitored with the Aspect Medical Systems BIS monitor from four to six hours. During this time the subjects were assessed hourly for their response to verbal commands. The assessments were divided into groups of non-responders and responders. A total of 107 observations were recorded. A logistic regression model was developed using the Statistical Package for Social Sciences (SPSS) to predict the probability of the response to verbal command for each BIS (see figure 1). The probability of each observation being a responder was estimated and plotted. An increase in the BIS (x axis) is positively related to an increased likelihood of response to verbal command (y axis). Also on the diagram is the confidence interval for BIS 62-73. The confidence interval is narrow but the percentage for the confidence interval was not reported.
They found that BIS monitoring was able to predict responsiveness to verbal command in ICU patients regardless of the sedation or analgesia administered.

Also in 1996, Shah published the results of another study on the use of the BIS in an ICU. In this study the correlation of the BIS with the Ramsay sedation scale was tested. Twenty-two adult males were studied in a surgical ICU. The patients were sedated but the report did not state the drugs used. The Ramsay scale (appendix 2) was modified to assess response to mild shaking (1- no response to mild shaking, 2- response to mild shaking, 3- response to name only when called repeatedly, 4- lethargic, 5- alert, 6- agitated). The BIS was recorded for one minute every hour at the time of the assessment using the modified Ramsay scale (MRSS). Linear regression analysis of the results comparing MRSS versus BIS gave an r=0.71. However, 79.5% of the observations were in the 3-6 range of the MRSS indicating that most subjects
were not heavily sedated. In addition some of the standard deviations of the mean BIS scores associated with the levels on the MRSS overlapped considerably (see table 2).

Table 2 MRSS versus BIS

<table>
<thead>
<tr>
<th>MRSS</th>
<th>No of Observations</th>
<th>BIS (mean± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>61.7 ± 13.1</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>62.0 ± 8.6</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>77.2 ± 14.3</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>87.0 ± 10.5</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>90.6 ± 9.1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>94.1</td>
</tr>
</tbody>
</table>

*p< 0.05 vs MRSS 1, + p<0.05 vs MRSS 2, 0 p< 0.05 vs. < MRSS3

The researchers used this data to classify the BIS into low MRSS of 1, medium MRSS of 2 and 3 and high MRSS of 4-6.

In 1999 Triltsch investigated the correlation of the BIS with the Ramsay scale in neurological ICU patients. Seventy-two sedated patients were monitored for six minute periods at which time they were also assessed using a modified Ramsay Scale. A total of 225 observations were made. Mean BIS measurements were recorded and they found that the MRSS was strongly correlated to mean BIS scores (r=0.629, p<0.001).

In 1998 Riker reported on the correlation of the BIS with the Sedation-Agitation Scale (SAS) (developed in 1994) and a visual analogue scale in a study with a sample of thirty-nine adult post cardiac surgery patients. Assessments were made as the
patients recovered and were extubated with analysis resulting in a correlation coefficient of $r=0.59$ $p<0.001$. In a later publication reporting on the same study the results were further analysed to exclude the possible effect of raised EMG. A mean EMG was calculated for all BIS readings and BIS scores were divided into those with low EMG (less than the mean) and those with high EMG (greater than the mean). Mean EMG was 39dB (dB a measure of interference). Correlation between the SAS and BIS for readings with a lower EMG was better than those with elevated EMG (low $r=0.35$, $p=0.018$, n=46, high $r=0.18$, $p=0.20$, n=49).

De Deyne and colleagues reported on the relationship of the BIS to the Ramsay score of 18 deeply sedated (unresponsive on the Ramsay Scale, score=6) patients. They found a wide range of average BIS scores in these patients but 15 of them had scores of less than 60. The average for the whole sample was 31. The correlation was weak between duration of sedation; doses of morphine, and midazolam administered and the average BIS. They argued that the Ramsay Scale is a poor discriminator of the level of sedation in the deeply sedated patient and that an objective measure such as the BIS should be employed to prevent over-sedation. They also indicated that BIS scores of below 60 may indicate unnecessarily deep sedation.

In a further study by some of the same investigators, 14 patients, heavily sedated with propofol and piritramide (a narcotic) were monitored with the BIS and assessed with the Ramsay Scale. They found that although all were sedated heavily (level 6) on the Ramsay Scale a wide range of BIS scores were recorded. At the commencement of sedation these varied from 20 – 88. However, in this study they found that although there was no correlation between the dose of sedation and the BIS, the BIS decreased
significantly in 10 of the 14 patients by day five of the study. These results are consistent with the fact that narcotics can accumulate in the critically ill. It could be expected that the actual dose of sedation delivered would not correlate with the BIS as there is wide variation in responses between individuals; blood levels do not correspond to the action at receptor sites and the presence of active metabolites and severity of illness must be considered.\textsuperscript{5,10}

In 1999 Simmons, Riker, Prato, and Fraser reported on a study describing the sedation of 63 patients. The sedation levels varied from very deep to mild agitation. They found that average BIS scores correlated well with the Sedation and Agitation Score (SAS)\textsuperscript{(r̂ =0.21 p<0.001). The coefficient of determination (r²) is a statistical test used to evaluate the proportion of variance.\textsuperscript{47} It is an indication of how likely it is that one score will accurately predict the other. An r² of 0.221 indicates that an assessor is 22\% better off using the relationship of the BIS to predict the SAS, than if it were not used.\textsuperscript{47} The average BIS scores for each level of sedation were also reported. Although there was an increase in the BIS associated with the scores on the scale the confidence intervals overlapped significantly particularly at the lower levels. This means that the mean BIS was not as reliable a predictor of the SAS level at deeper levels of sedation.

In 2000 Kaplan and Bailey reported on a comparative study investigating use of the BIS. Patients in a surgical ICU were studied for a four-month period.\textsuperscript{48} In the first two months sedation was titrated according to changes in patients' vital signs in response to stimulation. In the following two months infusions were titrated to a BIS of 70 - 80. Sedation costs were calculated per patient and the number of patients who
remembered painful or frightening experiences was recorded. Use of the BIS resulted in an 18% reduction in the cost of sedatives and less patients in the second two months remembered frightening or painful experiences (18% versus 4%). The demographics were similar for both groups, but other factors may have contributed to the difference, for example changes in the personnel, the fact that staff were not blinded to the treatment protocol and that the sample was not randomised. However, the results of the study do support continued investigation of use of the BIS in the ICU setting.

The current protocol in the unit where this study was undertaken recommends that the CISS is used to assess sedation. Although this scale was tested for reliability and validity during its development, it has not been tested against an objective measure such as the BIS. The purpose of this study was to investigate whether clinical assessment using the CISS headings (clinical judgement) and full CISS correlate positively with objective measurement using the BIS and to determine the strength of the correlation.

**Summary**

Both over and under-sedation are associated with significant problems for critically ill patients and accurate assessment of sedation is integral to delivering the optimal sedation level for the individual. However, the assessment of the level of sedation of the ventilated patient is problematic. Until recently the recommended method of assessing sedation in these patients was use of clinical scales such as the Ramsay Scale. These scales by their nature are subjective. The BIS monitor is a processed EEG parameter designed to give a reading between 0-100 that correlates with the
level of sedation.\textsuperscript{1} This has been used in the anaesthetic setting to help control the level of anaesthesia.\textsuperscript{34,49-51} It has been widely tested in patients receiving propofol and midazolam often administered with narcotics. These are the same drugs used to sedate patients in the ICU. Recent studies have demonstrated a relationship between the BIS and the Ramsay Scale and the Sedation and Agitation Scale.\textsuperscript{42-45} However, some researchers have demonstrated a broad range of BIS scores in patients who were assessed as heavily sedated according to the Ramsay scale.\textsuperscript{40,41} A study by Kaplan and Harvey demonstrated that when the BIS was used to assess the sedation level and as a guide to titrate infusions; drug utilisation and costs were significantly reduced.\textsuperscript{48}

This study was designed to investigate if there was a relationship between the level of sedation indicated by assessing patients with the CISS and the level of sedation indicated by the BIS monitor.
METHOD

Overview of the Research Design

The study used a prospective design with a convenience sample. The aim of the study was to compare BIS measurements of the level of sedation with nurses' clinical assessments using the CISS of adult, ventilated patients. The goal was to collect from 80 to 100 measurements. The nurse caring for the patient and the team-leader carry out hourly independent, simultaneous assessments of the patient's level of sedation. The patient care nurse used the CISS with the headings and descriptions and the Team-leader used a modified scale giving headings only without the descriptions as anecdotal evidence suggests this is common practice. An Aspect Medical Systems A-2000™ was used to continuously monitor the BIS and readings recorded on the trend were compared with the clinical assessments of sedation. Details of the qualifications of the nurses were also recorded.

Participants

A convenience sample of adult ventilated patients sedated with infusions of midazolam or propofol, for whom sedation was being titrated by the nurses according to the CISS were recruited for this study. Patients with neurological deficit or neuromuscular disorders, eg CVA, head injury, were excluded from the study. This is because the level of sedation cannot be accurately measured using the CISS scale as a motor response is required, in addition unilateral cerebral damage may cause inaccuracies in the BIS measurement. Patients were also excluded if they had been admitted following drug overdose as they are not usually administered sedation. Other
exclusions were patients receiving neuromuscular blocking agents except when administered to facilitate intubation or during an operative procedure prior to admission to ICU; again as sedation cannot be accurately measured using the CISS scale. Patients who could not have the monitoring electrode applied, eg. a patient suffering from burns to the forehead were also excluded. Infectious patients were not included as the monitor had to be easily moved from one patient bay to another. Patients were not included if they required a warming blanket or had a pace maker in situ as these can cause AC interference.38

**Ethical Issues**

Approval for the study was obtained from the hospital medical ethics committee (appendix 3) and the ICU research committee at the hospital where the research was conducted. Patients sedated in ICU are unable to give consent, therefore this was obtained from the relatives of subjects and they were given an information sheet (appendix 4 & 5). Although the information sheet stated that patients would be monitored for eight hours all relatives consented to monitoring for up to 24 hours. This was the time limit chosen for monitoring as the Zipprep™ disposable electrodes used in the study are not recommended for greater than 24 hours use. Participation by the bedside nurse was voluntary and information sheets and instructions were also given to these nurses (appendix 6). Confidentiality of patients, nurses and data were maintained and only the researcher has access to the data this will be stored in a locked cupboard for a period of five years. Anonymity of the participants was maintained by using numbers to identify the participants and the nurses doing the assessments. Data were aggregated so no individual can be identified. At the time this
study was being conducted there were several other studies underway in the ICU. Therefore, the ethics committee were concerned that relatives of seriously ill patients may be asked to consent to their loved one being entered in more than one study and this was considered to be unacceptable. Thus relatives were only asked to consent to this study if their relative had not already been entered in a study. Suitable patients were identified by the researcher.

**Procedures**

When consent was gained the study was explained to the nurses caring for the patient and Aspect Medical Systems A-2000™ BIS machine was set up at the patient’s bedside. An Aspect Medical Systems A-2000™ printer was attached to the BIS monitor to record trends. Data from any previous patient was cleared, and the time on the BIS monitor was synchronised with the clock in the patient’s room. The monitor was then set to record the BIS and a trend of the BIS and the electromyogram. The smoothing rate was set on 30 seconds. This is the recommended setting as trends are smoother and easier to analyse. The smoothing rate indicates the time over which the BIS is averaged for each displayed reading. The machine can be set for a smoothing time of 15 seconds or 30 seconds. The filter was set to “on” to remove potential AC interference such as from the ECG monitor. If interference does occur it can still be detected on the raw ECG printout. The sites where the electrodes were to be positioned on the patient’s face were identified and these areas were cleaned with alcohol and allowed to dry. The Zipprep™ disposable electrode was then applied (see diagram in the information sheet, appendix 4.) It is a pre-jelled electrode applied directly to the skin. “Circle one” was applied to the forehead approximately 4 cm
above the nose and “circle three” to the temple between the eye and the hairline. “Circle two” is attached to “circle one”, so will be automatically positioned correctly. Firm pressure was applied to the edges of the sensors to ensure adhesion. Then the three circles were pressed firmly for 5 seconds to ensure contact. The Zipprep™ is a specific BIS electrode developed to maintain low electrode/skin impedance. Within the gel–liquid hydrogel is a polymer disk containing small flexible tines. These tines part the dead-cells layer of the epidermis when the electrode is gently pressed onto the skin. This prevents the need to abrade the skin as is necessary when applying other electrodes such as those used for ECG monitoring. The electrode does not cause any pain, although sometimes small, indentations may be seen on the skin after removal, however, these appear to disappear quite quickly.

When the electrode was connected to the monitor the sensor was checked. To monitor accurately the sensor must pass an impedance test. To pass, the impedance must be less than 7.5 kilo ohms. If the sensor did not pass the impedance test, it was reapplied (this was only necessary in one case). The sensors for all patients passed the impedance test. The face of the BIS monitor was then covered with a piece of paper to avoid biasing the bedside nurse’s perception of the level of sedation.

Patients were monitored for a minimum of one hour or for up to twenty hours (it is not recommended to use the BIS electrode for greater than 24 hours as the tines may cause irritation). The team-Leader and the nurse caring for the patient were asked to perform hourly assessments of sedation. It was requested of the nurses that the assessments be performed simultaneously and independently without any discussion and the exact time of the assessment was recorded using the clock in the patient’s bay.
However, this was not enforced in any way. Simultaneous assessment allowed the correlation between the clinical measurements to be analysed. The nurse caring for the patient used the Critical Illness Sedation Scale and the Team-leader used the headings of this scale without the descriptions (appendix 7). The bedside nurse was requested to observe the electrode site for any signs of irritation and to notify the investigator if this occurred.

**The Data Gathering Instrument**

The BIS is a continuously processed EEG parameter that objectively measures the level of sedation. It is a statistically derived measurement that was accomplished by analysing a large database of EEGs from subjects who had received hypnotic agents. The BIS is a non-invasive form of monitoring and only requires the use of a sensor strip with three electrodes similar to ECG electrodes which are currently used on all patients in ICU. The “Aspect Medical Systems A-2000™” BIS monitoring system was checked by the Biomedical Department of the hospital to ensure safety prior to use. The printer was used to print 12 hour trends of the BIS and the EMG. A raw EEG was also provided. Where a patient was monitored for more than 12 hours two overlapping trends were printed.

As previously described the CISS is a clinical scale that was designed at the study hospital in 1996. It has four levels ranging from inadequate sedation to heavy sedation. The nurse caring for the patient was asked to use a copy of this scale attached to their data collection sheet to perform the assessments (appendix 8). The Team-leader was requested to use a copy of the scale with the headings but no descriptions for their assessments. In the unit where the research was conducted the
CISS is supposed to be used for assessment of sedation. However, anecdotal evidence indicates that assessments are commonly made without any reference to the written descriptions. Thus it was decided to use the headings without the descriptions for the Team-leaders clinical assessments. This assessment was called “clinical judgment”. Although these headings may act as a prompt, anecdotal evidence suggests that they are commonly used to assess sedation without any reference to the descriptions.

**Statistical Analysis**

Data were entered on a database and statistical analysis undertaken using the Statistical Package for Social Sciences (SPSS). Four BIS readings were recorded for each of the pairs of clinical assessment on the CISS. The trends were examined and the BIS at the exact time of each assessment was recorded. This was documented as the BIS at the time of the assessment. For example 1820 hours on the trend below (see figure 2). The trend was then examined back in time from this measurement to find the nadir occurring immediately prior to the “at time measurement”, this was documented as the BIS base reading. The difference between these two was also calculated and recorded. Then the BIS reading for each ten minutes for the last 60 minutes were recorded and a mean was calculated. Therefore four BIS measurements were recorded for each pair of nursing assessments:

- BIS at time of assessment
- BIS base
- BIS mean
- BIS difference
All BIS measurements were rounded to the nearest whole number except for the BIS difference measurement. This increased the ease of calculations and a difference in the BIS by less than one would have little clinical significance.

**Figure 2 BIS trend**

![Graph showing BIS trend]

Correlation using Spearman’s correlation (rho) was calculated between the CISS assessments, clinical judgments and BIS measurements. Correlation analysis is used to analyse the strength and direction of the linear relationship between two variables.\(^5\) Pearson’s correlation is not recommended if either of the variables are not normally distributed or not measured on an interval or ratio scale.\(^5\) Spearman’s rho was used as the measurements conducted by the nurses were scored on an ordinal scale.\(^4\) The BIS measurements were converted into categorical data, using the guidelines developed by Aspect Medical Systems (Table 3). Each measurement was considered to be an independent rating as a patient’s level of sedation can change from deep to awake in a short period of time, sometimes in a matter of minutes. Therefore, the nurses should not be influenced by the previous reading when assessing a patient’s level of sedation.

EMG was also calculated from the trend recording. The scale for this parameter extends from 0-80dB. Increased wakefulness usually results in an increased EMG
from increased muscle activity. The significance of raised EMG scores has not been determined and for many of the readings the EMG was so low that it did not register on the scale. Therefore EMG for each BIS measurement was calculated and categorised as <30, 31-40, >41-50, >51-60, >61dB according to the EMG scale on the trend. For mean calculations the highest EMG for each of the six 10 minute recordings was recorded, for the difference the highest EMG was recorded.

### Table 3 Range Guidelines

<table>
<thead>
<tr>
<th>BIS</th>
<th>Clinical endpoints and sedation ranges</th>
<th>Clinical situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Awake, Sedated</td>
<td>Awake or resting state</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sedated for special procedures; conscious sedation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Response to vigorous stimulation during surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emergence from general anaesthesia</td>
</tr>
<tr>
<td>60-70</td>
<td>Light hypnotic effects, Very low probability of recall</td>
<td>Short surgical procedures requiring deep sedation or light anaesthesia</td>
</tr>
<tr>
<td>40-60</td>
<td>Deep hypnotic effects, Unconscious</td>
<td>Maintenance range during general surgical procedures</td>
</tr>
<tr>
<td>0-40</td>
<td>EEG suppression</td>
<td>High dose opioid anaesthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgical procedures where deep anaesthesia is required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barbiturate coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Profound hypothermia</td>
</tr>
</tbody>
</table>

The correlation between the assessments conducted by the nurses caring for the patient and the Team-leaders’ assessments was also analysed using Spearman’s rho.
RESULTS

Major Findings

Eleven patients were entered into the study however, three had to be excluded after they were later found to have neurological problems. All were sedated with continuous infusions of midazolam and morphine; one was also receiving propofol. Duration of sedation ranged from one to eight days.

Thirty-eight nurses participated in the study. Of these 19 (51%) had a University post graduate qualification in intensive care nursing, 14 (35%) had a hospital certificate in intensive care nursing, three (8%) were registered nurses without any formal critical care qualifications and two were graduate nurses. In the unit where the research was conducted there are 200 nurses, 65% hold an intensive care qualification either a hospital certificate or university qualification; 30% are registered nurses without an intensive care qualification and 5% are graduate nurses (personal communication Jones 2002).

Correlation between Clinical Assessments using the CISS and BISS

A total of two hundred clinical assessments were made by the nurses. One hundred and nine by the nurses caring for the patient and 91 by the team-leaders. There were 79 paired simultaneous recordings. The results of Spearman’s correlation between the clinical assessments using the CISS and the BIS are in the table below.
Table 4 Correlation between CISS & BIS

<table>
<thead>
<tr>
<th></th>
<th>BIS Mean</th>
<th>BIS At time</th>
<th>BIS Base</th>
<th>BIS difference</th>
</tr>
</thead>
</table>
| Patient care nurse CISS  | r= +0.408*  
                        | n= 109        | p=0.000   | r= +0.374*  
                        | n= 109        | p=0.000   |
| Significance             | **significant at 0.01**  
| (2 tailed)               |           |           | r= +0.495*  
                        | n= 109        | p=0.000   |
| Team-leader              | r= +0.105  
                        | n=90        | p=0.326   | r= +0.117    
                        | n=90        | p=0.006   |
| Significance             | r= +0.288**  
                        | n=90        | p=0.006   | r= +0.263**   
| (2 tailed)               |           |           | n=90        | p=0.12       |

From these results it can be seen that there is a moderate positive correlation between the patient-care nurses CISS assessments and the BIS and a weak positive correlation between the Team-leaders CISS assessments and the BIS measurements. This means that the CISS assessment by the bedside nurse was more closely related to the BIS than the team-leaders assessments.

**Correlation between Clinical Assessments using the CISS**

There was a strong positive correlation between the clinical assessments by the patient-care nurse using the CISS with descriptions and the team-leader using the headings of the CISS for assessment of the level of sedation (r =+0.646 p=0.000 significant at the 0.01 level). This means that the team-leader using the headings only and the patient-care nurse using the full CISS predominantly chose the same level of sedation for each assessment.
Correlation between Patient–Care Nurses’ Clinical Assessments using the CISS and the BIS according to qualifications

The correlation between the patient-care nurses’ observations using the CISS and the BIS was analysed according to the qualifications of the nurses (see table 5).

**Table 5 Correlation between CISS and BIS for Patient-care Nurse according to qualifications**

<table>
<thead>
<tr>
<th>Qualifications of Patient Care Nurse</th>
<th>BIS Mean</th>
<th>BIS At time</th>
<th>BIS Base</th>
<th>BIS difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>University Intensive care qualification n=19 assessments n=51</td>
<td>r= +0.121</td>
<td>r=+0.270</td>
<td>r=+0.037</td>
<td>r=+0.260</td>
</tr>
<tr>
<td></td>
<td>p= 0.397</td>
<td>p= 0.055</td>
<td>p= 0.0797</td>
<td>p= 0.066</td>
</tr>
<tr>
<td>Hospital critical care Certificate n=14 assessments n=24</td>
<td>r= -0.374</td>
<td>r= -0.155</td>
<td>r= -0.110</td>
<td>r= -0.175</td>
</tr>
<tr>
<td></td>
<td>p= 0.072</td>
<td>p= 0.469</td>
<td>p= 0.608</td>
<td>p= 0.413</td>
</tr>
<tr>
<td>RN n=3 assessments n=19</td>
<td>r= +0.438</td>
<td>r=+0.437</td>
<td>r=+0.437</td>
<td>r=+0.438</td>
</tr>
<tr>
<td></td>
<td>p= 0.061</td>
<td>p= 0.061</td>
<td>p= 0.061</td>
<td>p= 0.061</td>
</tr>
<tr>
<td>Graduate nurse n=2 assessments n=15</td>
<td>r=+0.947</td>
<td>r=+0.801</td>
<td>r=+0.554</td>
<td>r=+0.747</td>
</tr>
<tr>
<td></td>
<td>p= 0.000</td>
<td>p= 0.000</td>
<td>p= 0.032</td>
<td>p= 0.001</td>
</tr>
</tbody>
</table>

Correlation is significant at the 0.01 level (2-tailed).

The strongest positive correlations between the CISS and the BIS were for those observations performed by the graduate nurses. As there were only two graduate nurses no conclusions can be drawn from this result. There was a moderate positive correlation between the CISS and the BIS for those observations performed by the RNs without any intensive care qualification. There was a weak positive correlation between the BIS (mean at time and difference) and the CISS assessments performed
by patient care nurses with a university intensive care qualification and poor positive correlation between the BIS and CISS measurements performed by patient care nurses with a hospital certificate. The correlations between the BIS and CISS assessments indicates that the measurements performed by the graduate nurses and those nurses without intensive care qualifications are more accurate than those performed by nurses with a hospital certificate or University qualification.

*Correlation between Team-leader' Clinical Assessments using the CISS headings and the BIS according to qualifications*

The Team-leader is required to have an intensive care qualification. Therefore the Team-leaders either had a hospital intensive care qualification or a university qualification. The correlation between the Team-leaders’ observations using the CISS and the BIS was analysed according to the qualifications of the team-leaders (see table 6).

**Table 6 Correlation between CISS and BIS for Patient-care Nurse according to qualifications**

<table>
<thead>
<tr>
<th>Qualifications of TL</th>
<th>BIS Mean</th>
<th>BIS At time</th>
<th>BIS Base</th>
<th>BIS difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>University Intensive care qualification n=19 Assessments n=36 Significance (2 tailed)</td>
<td>r= +0.274</td>
<td>r= +0.636</td>
<td>r= +0.358</td>
<td>r= +0.666</td>
</tr>
<tr>
<td></td>
<td>p=0.106</td>
<td>p=0.000</td>
<td>p=0.032</td>
<td>p=0.000</td>
</tr>
<tr>
<td>Hospital critical care Certificate n=14 Assessments n=54 Significance (2 tailed)</td>
<td>r= +0.081</td>
<td>r= +0.102</td>
<td>r= -0.023</td>
<td>r= -0.024</td>
</tr>
<tr>
<td></td>
<td>p=0.563</td>
<td>p=0.461</td>
<td>p=0.866</td>
<td>p=0.866</td>
</tr>
</tbody>
</table>

Correlation is significant at the .05 level (2-tailed)

For the Team-leaders the strongest positive correlations were found between the CISS observations and the BIS for those observations performed by those with university intensive care qualifications. The positive correlation between the BIS and the CISS
varied, for the four different BIS recordings. For the CISS and mean BIS it was weak, for the BIS at the assessment time and difference it was strong and for the BIS base it was moderate. There were no statistically significant correlations between the CISS measurements and the BISS for assessments performed by team leaders with hospital certificates.

This indicates that the most accurate assessments were performed by the team-leaders with university qualifications and that the BIS scores most likely to correlate with the clinical assessments, were the BIS at the time of assessment and the BIS difference.

**Electromyogram**

The influence of the EMG has been considered by the researchers separating BIS readings into those with an EMG of less than and greater than a mean of 39dB. In this study the EMG readings were calculated from the trend and divided into readings according to the EMG scale on the trend <30, 30-40,>40-50, >50-60,>60dB. As the scale extended from 0-80dB the BIS readings were then divided into those with high EMGs -greater than 40dB and low EMGs as less than 40 (see table 7). An EMG of 40dB was considered to be the half way mark and was close to the reading chosen by the researchers in the study which considered EMG readings.
Table 7 BIS and CISS correlation according to EMG readings

<table>
<thead>
<tr>
<th></th>
<th>BIS Mean EMG &lt; 40db</th>
<th>BIS Mean EMG &gt; 40db</th>
<th>BIS at time EMG &lt; 40db</th>
<th>BIS at time EMG &gt; 40db</th>
<th>BIS base EMG &lt; 40 db</th>
<th>BIS base EMG &gt; 40 db</th>
<th>BIS diff EMG &lt; 40 db</th>
<th>BIS diff EMG &gt; 40 db</th>
</tr>
</thead>
<tbody>
<tr>
<td>CISS Patient care nurse</td>
<td>r=0.102 p=0.553</td>
<td>r=+0.487 p=0.000</td>
<td>r=+0.189 p=0.152</td>
<td>r=+0.404 p=0.013</td>
<td>r=+0.153 p=0.28</td>
<td>r=+0.117 p=0.523</td>
<td>r=+0.304 p=0.021</td>
<td>r=+0.370 p=0.022</td>
</tr>
<tr>
<td>Sig n=109</td>
<td>36</td>
<td>60</td>
<td>59</td>
<td>37</td>
<td>64</td>
<td>32</td>
<td>58</td>
<td>38</td>
</tr>
<tr>
<td>CISS Team Leader Sig n=90</td>
<td>r=0.051 p=0.797</td>
<td>r=0.077 p=0.593</td>
<td>r=+0.251 p=0.096</td>
<td>r=+0.158 p=0.371</td>
<td>r=+0.188 p=0.186</td>
<td>r=+0.386 p=0.043</td>
<td>r=+0.357 p=0.016</td>
<td>r=+0.034 p=0.848</td>
</tr>
<tr>
<td>28</td>
<td>51</td>
<td>45</td>
<td>34</td>
<td>51</td>
<td>28</td>
<td>45</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

For the assessments conducted by the patient-care nurse the readings with the higher EMGs (except for the base BIS) are more strongly positively correlated with the CISS. For the Team-leaders there are only two statistically significant correlations between the CISS and the BIS, the base BIS >40dB EMG (negative correlation) and the BIS difference <40dB EMG. There is a negative correlation between the base BIS and the CISS readings for those readings with a higher than 40dB EMG. For the assessments conducted by the patient-care nurse it would appear that the BIS readings (mean, at time and difference) are more likely to correlate when the EMG is high. However, for the base BIS reading this was not the case for measurements performed by both the team-leaders and patient-care nurse.

**Kruskal-Wallis Tests**

Several studies have reported an analysis of variance between the BIS scores for each level of a clinical assessment scale using analysis of variance (ANOVA). This test is based on a number of assumptions these are: that the dependent variable is measured...
on a interval or ratio scale, that the scores are obtained using random sampling of the population (though Pallant states this is often not the case in real-life research) and independence of observations, that the population from which the samples were taken are normally distributed and that samples are obtained from populations of equal variance. Sampling for this study was by convenience rather than random and the samples are not normally distributed (see appendix 9 Skewness and Kurtosis). For these reasons a non-parametric test, the Kruskal-Wallis Test, was used to compare the scores for the BIS for each level of the CISS assessment by the patient-care nurse. For each of these there was a significant difference in the rank of the BIS scores for each level of the CISS assessment by the Patient-care nurse (See tables 9-12).

**Table 9 Kruskal Wallis Test for CISS & BIS at time of assessment**

<table>
<thead>
<tr>
<th>CISS Patient-care Nurse</th>
<th>N</th>
<th>Mean Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>BISS at assessment time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>98.06</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>69.79</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>50.68</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>41.29</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td></td>
</tr>
</tbody>
</table>

**Test Statistics**

<table>
<thead>
<tr>
<th></th>
<th>BISS at assessment time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
<td>29.488</td>
</tr>
<tr>
<td>df</td>
<td>3</td>
</tr>
<tr>
<td>Asymp. Sig.</td>
<td>p=0.000</td>
</tr>
</tbody>
</table>

a Kruskal Wallis Test  
b Grouping Variable: CISS Patient-Care Nurse
### Table 10 Kruskal Wallis Test for CISS & BIS Mean

<table>
<thead>
<tr>
<th>CISS Patient-care Nurse</th>
<th>N</th>
<th>Mean Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BISS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>99.00</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>67.74</td>
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<tr>
<td>3</td>
<td>41</td>
<td>47.70</td>
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<td>4</td>
<td>38</td>
<td>45.42</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td></td>
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</table>

**Test Statistics**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
<td>26.555</td>
</tr>
<tr>
<td>df</td>
<td>3</td>
</tr>
<tr>
<td>Asymp. Sig.</td>
<td>p=0.000</td>
</tr>
</tbody>
</table>

a Kruskal Wallis Test  
b Grouping Variable: CISS Patient-Care Nurse

### Table 11 Kruskal Wallis Test for CISS & Base BIS

<table>
<thead>
<tr>
<th>CISS Patient-care Nurse</th>
<th>N</th>
<th>Mean Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base BISS at time of CISS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>92.50</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>63.93</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>51.76</td>
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<tr>
<td>4</td>
<td>38</td>
<td>44.68</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td></td>
</tr>
</tbody>
</table>

**Test Statistics**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
<td>18.929</td>
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<tr>
<td>df</td>
<td>3</td>
</tr>
<tr>
<td>Asymp. Sig.</td>
<td>p=0.000</td>
</tr>
</tbody>
</table>

a Kruskal Wallis Test  
b Grouping Variable: CISS Patient-Care Nurse
Table 12 Kruskal Wallis Test for CISS & BIS difference

<table>
<thead>
<tr>
<th>Ranks</th>
<th>CISS Patient Care Nurse</th>
<th>N</th>
<th>Mean Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between peak and Lowest</td>
<td>1</td>
<td>9</td>
<td>97.06</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>21</td>
<td>68.00</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>41</td>
<td>51.20</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>38</td>
<td>41.96</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>109</td>
<td></td>
</tr>
</tbody>
</table>

Test Statistics

<table>
<thead>
<tr>
<th></th>
<th>Difference between peak and Lowest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
<td>26.559</td>
</tr>
<tr>
<td>df</td>
<td>3</td>
</tr>
<tr>
<td>Asymp. Sig.</td>
<td>p=0.000</td>
</tr>
</tbody>
</table>

a Kruskal Wallis Test
b Grouping Variable: CISS Patient-Care Nurse

This indicates that the mean BIS recordings were significantly different from the assessments at each level of the CISS.

Error plots for the BIS means for each level of CISS assessment by the Patient-care nurse were generated (see Figures 3-6) (see appendix 10). The confidence intervals for the mean BIS for each level of CISS assessments are illustrated.
Figure 3 Error plot of Means of BIS for CISS assessments by the Patient-Care Nurse BIS Mean

Figure 3 is an error plot illustrating the mean BIS recordings for each level of the CISS. The recordings used in this analysis were the mean BIS scores (calculated over the hour prior to the assessment). The mean BIS scores decrease as the level of sedation increases according to CISS assessments. According to the Kruscal-Wallis test the mean rank for each level of the CISS is significantly different. However, the confidence intervals for means of levels 2-4 on the CISS overlap. This indicates that when the CISS is used assessments do not discriminate well between levels defined according to the mean BIS.
Figure 4 Error plot of Means of BIS for CISS assessments by the Patient-Care Nurse BIS At Assessment Time

Figure 4 is an error plot illustrating the mean BIS recordings for each level of the CISS. The recordings used in this analysis were the BIS scores at the time of the CISS assessment. Again the mean BIS scores decrease as the level of sedation increases according to CISS assessments and according to the Kruscal-Wallis test the mean rank for each level of the CISS is significantly different. The confidence intervals for means of levels 2-4 on the CISS still overlap. However, the overlap between levels 2 and 3 is not as great. Therefore, if the BIS at the time of the assessment, is related to the CISS assessments, there is better discrimination between the levels.
Figure 5 Error plot of Means of BIS for CISS assessments by the Patient-Care Nurse BIS Base

The error plot in figure 5 illustrates the mean BIS recordings for each level of the CISS using the base BIS scores. The mean BIS scores decrease as the level of sedation increases according to CISS assessments. Again according to the Kruscal-Wallis test the mean rank for each level of the CISS is significantly different. However, the confidence intervals for means of levels 2-4 on the CISS all overlap. The means for each level of the CISS are much closer for the Base CISS. This indicates that when the CISS is used assessments do not discriminate well between levels defined according to the base BIS.
The error plot in figure 6 illustrates the mean BIS recordings for each level of the CISS using the difference BIS scores. Like the BIS mean, at time and base, the mean BIS scores decrease as the level of sedation increases according to CISS assessments. Again according to the Kruscal-Wallis test the mean rank for each level of the CISS is significantly different. However, like the BIS mean and base the confidence intervals for means of levels 2-4 on the CISS all overlap. Thus when the sedation is moderate to heavy, CISS assessments do not discriminate well between levels defined according to the BIS difference.

The error plots of the means for the patient-care nurses’ assessments using the CISS and the BIS at the time of assessment, BIS mean, BIS base and BIS difference all demonstrate that the 95% confidence intervals for the means overlap at the lower levels of the CISS. This indicates that for more heavily sedated patients as indicated by the CISS there is more variation in the BIS recorded. The confidence intervals for
the means for each level of the CISS overlap least for the BIS recording taken at the time of assessment. The CISS discriminates best between the levels of sedation according to the BIS, when the BIS is recorded at the time of assessment.

Summary

The results of this study demonstrated that there was a moderate, positive correlation between CISS measurements performed by the nurse caring for the patient and the BIS recordings and a weak positive correlation between CISS assessments performed by the team-leaders using the headings of the CISS and the BIS recordings. When the results were analysed according to the qualifications of the nurses caring for the patient, it was found that the strongest positive correlations between the CISS assessments and the BIS were for those assessments performed by the GNs. The weakest correlations were for those assessments performed by nurses with a hospital intensive care qualification. For the assessments performed by the team-leaders positive correlations between the CISS assessments and the BIS recordings were only found between assessments performed by those with university qualifications. There was a strong positive correlation between the CISS assessments performed by the nurse caring for the patient and those performed by the team-leader. The influence of the EMG was conflicting, with the assessments performed by the patient-care nurse those with a higher EMG (except for the base) were more strongly correlated with the BIS and for the only significantly correlated assessments performed by the team-leaders the opposite was the case (BIS base and difference). Kruskal-Wallis Tests indicated a significant difference in the rank of the BIS scores for each level of the CISS assessment by the Patient-care nurse. Meaning that there was a significant difference in the rank of the mean BIS for each level of the CISS. However, error
plots of the means for each CISS level for assessments performed by the patient care nurse demonstrated overlapping of the confidence intervals for the means of the BIS recordings at levels 2-4 of the CISS. This indicates that it is not as easy to discriminate between the deeper levels of sedation using the CISS.
DISCUSSION

The aim of this study was to determine if there is a statistically significant positive correlation between clinical measurements by the nurses using the CISS and the objective measurements of the BIS monitor. As was found in several other studies there was a correlation between clinical assessments using a sedation scale and recordings of the BIS.\textsuperscript{42,43,45} Overall the strongest positive correlations were between assessments performed by the nurse caring for the patient and the BIS. This is not surprising as it could be expected that a nurse who spends an eight to nine hour shift with one patient would be able to assess the patient’s level of sedation more accurately. In addition, this group of nurses used the full CISS scale with its descriptions and the team-leaders only used the headings of the CISS. However, this scale has been used in the unit since 1996 so one would expect team-leaders to be familiar with the descriptions, however over time they may have become more complacent about its use. All team-leaders must have an intensive care qualification and should become familiar with unit protocols working as a patient care nurse prior to being allocated team-leader duties. In addition the full CISS descriptions are written on every special observation chart.

The strongest correlations were between the BIS mean and the BIS at the time of the CISS assessment. This is consistent with the study performed by Simmons and colleagues who found that the SAS (Sedation Agitation Scale) correlated best with the BIS average between the stimulated BIS and the baseline.\textsuperscript{44} The patient’s level of sedation can vary markedly in a short period of time and in response to stimulation. Therefore, it could be expected that the mean which was calculated using six ten
minute readings from the previous hour would not show good correlation with the hourly assessment. The BIS base was the lowest recording prior to the assessment and since nurses perform clinical assessments by stimulating the patient it could be expected that this reading would not correlate well.

It is difficult to draw any conclusions from the differences found in the correlations according to the qualifications of the nurse, as different numbers of assessments were performed by each nurse and the numbers of nurses with each qualification varied. A more controlled study would be necessary to draw any conclusion, such as, that less qualified nurses assess the sedation level of patients in the ICU more accurately. However, it may be that nurses who are less qualified follow the protocol more closely and assess the patient by strictly using the written descriptions for each level of the scale. For the team-leaders those with university qualifications may have had more recent exposure to the problems relating to sedation, as university courses have only been available in this state since 1996 at which time the hospital ceased conducting a hospital certificate program. The nurses without university qualifications and the GNs may be less complacent and may not rely as heavily on recall of the descriptions of the levels to guide their assessments.

The significance of the EMG on the BIS recording has not been resolved. Higher BIS readings are associated with more muscle movement and higher EMGs. Several studies have shown that clinical assessment scales do not discriminate levels of sedation well at deeper levels. For this reason, it could be expected that BIS readings with higher EMGs would correlate more closely with the assessment scale than those with low EMGs. The results of this study were contradictory, but for the assessments
performed by the patient care nurse this was the case for the BIS mean and BIS at time of assessment. This is in contrast to the study by Simmons and colleagues who found a stronger positive correlation between the SAS and BIS for readings with a lower EMG than those with elevated EMG.

Although the Kruskal-Wallis tests demonstrated a statistically significant difference for the rankings of the means of the BIS recordings the confidence intervals on the error plot charts demonstrated overlapping for the deeper levels of sedation. The least overlap occurred when the means for the BIS at time of assessment was analysed. The CISS discriminates best between the levels of sedation according to the BIS, when the BIS is recorded at the time of assessment.

Below is an error plot of the means from the study performed by Simmons and colleagues. Like this study there is overlap of the confidence intervals at all levels but particularly at the deeper levels of sedation (1-3).

**Figure 7 Mean Bispectral Index Values for each level of the SAS**

![Brain Index Scale Chart](https://via.placeholder.com/150)

**Figure 2.** Mean Bispectral Index values (horizontal bars) ± the 95% confidence intervals (vertical bars) for each Sedation-Agitation Scale value for each patient at baseline.
This is consistent with the results of this study. Indicating that assessments using the SAS also do not discriminate well between the deeper levels of sedation measures by the BIS.

A similar result can be seen on the study by Shah and colleagues (see table 13). Note that on the Ramsay scale 1 indicates the deepest level of sedation.

Table 13 MRSS and BIS

<table>
<thead>
<tr>
<th>MRSS</th>
<th>No of Observations</th>
<th>BIS (mean± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>61.7 ± 13.1</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>62.0 ± 8.6</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>77.2 ± 14.3**</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>87.0 ±10.5***</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>90.6 ± 9.1**</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>94.1</td>
</tr>
</tbody>
</table>

*p<0.05 vs MRSS 1, +p<0.05 vs MRSS 2, 0p<0.05 vs. < MRSS 3

The means for each level of sedation on the clinical assessment scale are pictured below (see figures 8 and 9). Illustrating the rank levels of the means for each sedation level on a clinical scale can be deceptive if the confidence intervals are not also illustrated. These diagrams make it look like the means for each level of sedation on the clinical scale increase as the BIS score rises and that these are discrete measurements.
Several studies have indicated that clinical scales are poor discriminators of the depth of sedation when the patient is heavily sedated; the results of this study also support this view.\textsuperscript{40,41} The BIS may be a useful tool for assessment of sedation for those patients for whom heavy sedation is necessary.

The results of this study were consistent with those of previous studies and indicate that the BIS readings did have some positive correlation with the clinical scale in use in the unit in which the research was conducted. The CISS is only used in two ICUs and the correlation between this scale and the BIS had not previously been studied.
Limitations

One of the main limitations of this study was that the BIS measurements were calculated from the trend print out. Data downloaded from the BIS machine to a computer may have been more accurate but was not available to the researcher. In addition, the nurses performing the assessments may not have accurately recorded the assessment times. In future a time clock could be used to accurately record the time of the assessment. Another limitation of the study is that the BIS machine calculates the BIS every minute, so recordings would lag behind the clinical assessments. In addition, the clinical assessments were performed by various nurses. A stronger correlation between the scales may have resulted if there was only one trained assessor performing these measurements. However, the aim of this study was to investigate the situation as it occurs in every day practice. There were only two graduate nurses involved in the study, if more of these nurses had been involved in the study the results may have differed. In addition the majority of the assessments were on the lower levels of the CISS, perhaps if more assessments of lightly sedated patients were collected it may have influenced the results. Another potential limitation is that it would have been possible for a nurse to be both a patient care nurse and on another shift to act as the team-leader, however, this did not occur.

Implications for Practice

The results of this study indicate that the BIS may be useful in the assessment of sedation in the ICU setting. There is also an indication that patients who are heavily sedated vary considerably in their level of hypnosis as indicated by the BIS. Over-sedation may be difficult to avoid in patients who require heavy sedation and are not
responding. Benzodiazepams and narcotics accumulate in critical illness increasing the possibility of over-sedation. Nurses who are responsible for administering and titrating sedation may find the BIS useful in providing an objective measure of sedation of these patients.

**Conclusion**

The study indicated that the CISS was moderately positively correlated with BIS recordings. The strongest correlations were for assessments performed by the nurse caring for the patient. There was a statistically significant difference in the means of the BIS recordings for each level of the CISS assessments, however, the confidence intervals overlap particularly at the deeper levels of sedation.

**Recommendations for further investigation**

Future studies should aim to investigate the use of the BIS in the management of heavily sedated patients. Over-sedation is associated with significant complications and once a patient becomes unresponsive it is difficult to use a clinical scale that relies on responsiveness to assess sedation. Future studies could be designed to further investigate the assessment of sedation by staff with different qualifications.
REFERENCES


APPENDICES
Appendix 1 Critical Illness Sedation Scale (CISS)

LEVEL 1 Inadequate sedation. Agitated, distressed. Not tolerating IPPV eg coughing against the ventilator or attempting extubation.

LEVEL 2 Light sedation. Eyes may be closed, but open to speech, responds purposefully, quickly settles when not stimulated, tolerates ventilation when not roused.

LEVEL 3 Moderate sedation. Sluggish response to forehead tap or speech. eg weak flexion or grimacing.

LEVEL 4 Heavy sedation. No voluntary response to stimulation of any form. weak cough on suction and spinal reflexes may present.
Appendix 2 The Ramsay Scale

Awake Levels

1. Patient anxious and agitated or restless or both.
2. Patient cooperative, orientated and tranquil.
3. Patient responds to commands only.

Asleep levels (Dependent on response to a glabella tap or loud auditory stimulus)

5. Sluggish response.
6. No response.
Appendix 3 Ethics Letter

8222 4139

20 August 2001

Ms J Magarey
DEPT OF CLINICAL NURSING
ROYAL ADELAIDE HOSPITAL

Dear Ms Magarey,

Re: "A study to investigate the relationship between the Critical Illness Sedation Scale (CISS) independent clinical judgment and the Bispectral Index of EEG for the assessment of sedation of ventilated patients in an Intensive Care Unit (ICU)."
RAH Protocol No: 010809

I am writing to advise that ethical approval has been given to the above project. Please note that the approval is ethical only, and does not imply an approval for funding of the project.

Human Ethics Committee deliberations are guided by the Declaration of Helsinki and N.H. and M.R.C. Guidelines on Human Experimentation. Copies of these can be forwarded at your request.

Adequate record-keeping is important and you should retain at least the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them if necessary, in the future. The Committee will seek a progress report on this project at regular intervals and would like a brief report upon its conclusion.

If the results of your project are to be published, an appropriate acknowledgment of the Hospital should be contained in the article.

Yours sincerely,

Dr N James
Chairman
RESEARCH ETHICS COMMITTEE
Appendix 4 Relative Information Sheet

Dear Sir or Madam,

I am a Doctor of Nursing Candidate at the University of Adelaide, Department of Clinical Nursing. My research involves methods used to assess the level of sedation of patients in ICU. This is a research project and your relative does not have to be involved. If you do not wish him or her to participate their medical care will not be affected in any way.

In the Intensive Care Unit we give drugs so that the patients do not feel pain or fight the breathing machine. The drugs make the patient sleepy (sedated) and make it less likely that they will remember their time in ICU. The level of sedation must be assessed accurately to ensure that patients are not over-sedated as this may make it more difficult to get them to breathe without assistance from the ventilator. My research involves comparing the scale currently used in the Royal Adelaide ICU to assess sedation (how asleep patients are), with measurement obtained from a machine called the Bispectral Index of the electroencephalogram. (BIS), to check the reliability of the scale.

The BIS measures electrical activity produced by the brain. These brain waves are analysed by the machine to assess the level of sedation. The BIS is not an invasive monitor and only a sticky strip be applied to the forehead of the patient (see the attached photo). This strip is similar to those used to measure the patient’s heart rhythm. The BIS is a relatively new monitor for the assessment of sedation of ICU patients but has been used for some time in the operating theatre to assess the level of anaesthesia. It provides a reliable measurement of sedation (how asleep the patient is). The monitor will only need to be applied for eight hours. The patient will be observed closely for any signs of irritation from the electrodes and if these occur, the electrodes will be removed and the patient withdrawn from the study.

There will be no other changes to nursing or medical treatment. No details of your relatives will be revealed.

If you have any queries regarding the study please contact Judy Magarey Royal Adelaide Hospital Phone extension 25828. This study has been approved by the Royal Adelaide Hospital Research Ethics Committee. If you wish to discuss aspects of the study with someone not directly involved, you may also contact the Chairman Research Ethics Committee, Royal Adelaide Hospital on 8222 4139

Please accept in advance my thanks for your assistance.

Judy Magarey
BIS Sensor in Place

Aspect Medical Systems A-2000™

From Aspect Medical Systems
http://www.aspectms.com/clinical/sld
Appendix 5 Consent Form

Investigators: Ms Magarey, Dr McCutcheon, Dr Chapman.

1. The nature and purpose of the project has been explained to me. I understand it, and agree to allow my relative / significant other to take part.

2. I understand he / she will not directly benefit from taking part in the trial.

3. I understand that, while information gained during the study may be published, he / she will not be identified and his / her personal results will remain confidential.

4. I understand I can withdraw my relative / significant other from the study at any stage and that it will not affect his / her medical care, now or in the future.

Name

______________________________

Signed

______________________________

Date:

______________________________

I certify I have explained the study to the patient’s relative / significant other and consider he / she understands what is involved.

Signed

______________________________

Judy Magarey
Appendix 6 Instructions for Nurses

A study to investigate the relationship between the Critical Illness Sedation Scale (CISS), independent clinical judgment and the Bispectral Index of EEG for the assessment of sedation of ventilated patients in an intensive care unit (ICU).

Instructions:

Please:

- Assess the patient’s sedation level hourly (if possible). It does not have to be exactly every hour, but leave at least 45 minutes between ratings.
- Use the same process you would usually follow to assess the level of sedation.
- Document the level of sedation at the time of the assessment.
- Assess the patient independently using the scale or headings provided.
- Do not discuss your rating with the other assessor.
- Record the exact time of the assessment using the clock in the patient’s bay.
- At the end of the shift put the evaluation sheet in the envelope labelled “Judy Magarey”.
- If for some reason a new nurse is performing the assessment start a new assessment sheet and complete an information sheet on years of experience etc. You will find extra copies in the envelope.

Please note no individual will be identified in the findings of the research. Anonymity will be maintained.

If you have any problems please ring Judy Magarey Phone 25828 mobile 0417807481

Thanks
Appendix 7 Critical Illness Sedation Scale (CISS) Headings

Only for Assessments by Team-leader

LEVEL 1 Inadequate sedation.

LEVEL 2 Light sedation.

LEVEL 3 Moderate sedation.

LEVEL 4 Heavy sedation.
### Appendix 8 Data collection sheets

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<thead>
<tr>
<th>Patient Sticker</th>
<th>Date</th>
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Nurse

<table>
<thead>
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<th>Clinical Judgement</th>
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Nurse

<table>
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Name ________________________________

Please tick the appropriate boxes

Graduate Nurse [ ]

Level 1 RN non CCRN [ ] Years Registered [ ]

CCRN [ ]

Critical Care Qualification:

Hospital Certificate [ ]

Graduate Diploma [ ]

Graduate [ ]

Level 1 [ ]

Level 2 [ ]

Level 3 [ ]

Other: ____________________________________________
Patient Sticker

Diagnosis

Consent: 

Time sedated 

Drugs:

- Propofol
- Morphine
- Midazolam

Other:

Comments:
### Appendix 9 Assessment of Distribution of BIS Scores

#### Descriptive Statistics

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<thead>
<tr>
<th></th>
<th>N</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Skewness</th>
<th>Kurtosis</th>
<th>Std. Error</th>
<th>Statistic</th>
<th>Std. Error</th>
<th>Statistic</th>
<th>Std. Error</th>
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<td>121</td>
<td>38</td>
<td>100</td>
<td>68.13</td>
<td>16.61</td>
<td>.530</td>
<td>.220</td>
<td>-.658</td>
<td>.437</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BISS at time</td>
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<td>100.0</td>
<td>68.34</td>
<td>21.42</td>
<td>.278</td>
<td>.220</td>
<td>-1.333</td>
<td>.437</td>
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<td>Base BISS</td>
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<td>97.0</td>
<td>53.51</td>
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<td>-.473</td>
<td>.437</td>
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<td>Difference BIS</td>
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<td>32.5</td>
<td>98.5</td>
<td>60.92</td>
<td>19.68</td>
<td>.557</td>
<td>.220</td>
<td>-.960</td>
<td>.437</td>
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<td>Valid N (listwise)</td>
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### Appendix 10 Mean BIS for each level of CISS Assessment by Patient Care Nurse

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<th>Statistic</th>
<th>Std. Error</th>
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<tr>
<td>1 Mean 95% Confidence Interval for Mean</td>
<td>Lower Bound: 94.78</td>
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<tr>
<td></td>
<td>Upper Bound: 101.48</td>
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<tr>
<td></td>
<td>Median: 99.00</td>
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<tr>
<td></td>
<td>Std. Deviation: 8.71</td>
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<tr>
<td></td>
<td>Minimum: 73</td>
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<tr>
<td></td>
<td>Maximum: 100</td>
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</tr>
<tr>
<td>2 Mean 95% Confidence Interval for Mean</td>
<td>Lower Bound: 73.19</td>
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<td></td>
<td>Upper Bound: 80.38</td>
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<tr>
<td></td>
<td>Median: 77.00</td>
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<tr>
<td></td>
<td>Std. Deviation: 15.80</td>
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<tr>
<td></td>
<td>Minimum: 39</td>
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<td></td>
<td>Maximum: 97</td>
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<tr>
<td></td>
<td>Range: 58</td>
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<tr>
<td>3 Mean 95% Confidence Interval for Mean</td>
<td>Lower Bound: 64.90</td>
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<td>Upper Bound: 70.11</td>
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<td></td>
<td>Median: 59.00</td>
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<td>Std. Deviation: 16.50</td>
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<td>4 Mean 95% Confidence Interval for Mean</td>
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<td>Upper Bound: 63.55</td>
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<td>Variance: 87.770</td>
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<td></td>
<td>Std. Deviation: 9.37</td>
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<tr>
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<td>Minimum: 38</td>
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<td></td>
<td>Maximum: 77</td>
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<tr>
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<td>Range: 39</td>
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PORTFOLIO CONCLUSION
CONTENTS

Portfolio Conclusion ................................................................. 1
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CONCLUSION

This portfolio of research is comprised of studies conducted using various research methods and techniques. These include a systematic review, questionnaires, interviews and a clinical comparative study. This enabled the researcher to investigate different aspects of the sedation of adult patients in the ICU. The results provide broad insight into the topic and present many potential areas for future research aimed at improving the practice relating to the sedation of adult patients in the ICU.

The objective of the systematic review was to present the best available evidence relating to the sedation of adult ventilated patients in intensive care units (ICUs). Specifically regarding the effectiveness of midazolam compared to propofol. The evidence presented in the review supported the view that infusions of both propofol and midazolam provide similar quality sedation. In relation to the mode of administration, studies agreed that bolus of midazolam do not provide as good quality sedation as infusions of propofol. The review also concluded that patients sedated with infusions of propofol recover and are extubated in a shorter time from the cessation of sedation. The most significant differences in recovery and extubation times were recorded in the critically ill general ICU patients who were sedated for longer periods.1-3

Several potential research topics emerged from the review. It was concluded that a study could be directed at investigating the use of a combination of agents, to take advantage of the synergistic effect and the potential benefits of each individual agent. This was the aim of the first study of the portfolio that was not completed. Despite this the topic may still
have some potential, as it appears that propofol and midazolam are still the main sedation agents used in the ICU. However, in the future when propofol is no longer a patented agent, the cost implications of using this agent will be less significant. In addition, some new sedation and analgesic agents are being introduced. For example, dexmedetomidine an $\alpha_2$ agonist agent which provides sedation, analgesia and anxiolysis without causing significant depression of respirations or the conscious state.$^4$ Nevertheless, its potential side effects of hypotension and heart rate reduction may limit its usefulness. Remifentanil is another agent that appears to be ideal for treating critically ill patients.$^5$ It has a rapid onset and short half-life and is not dependent on organ elimination, so does not accumulate in patients with organ failure. Use of agents such as these may make it easier for clinicians to provide optimal sedation and pain relief for patients in the ICU without causing problems such as over-sedation.

The majority of the studies that investigated the effectiveness of propofol and midazolam used the Ramsay sedation scale to measure the patients' clinical response to the agents.$^1$ $^6$$^{14}$ However, this scale does not measure confusion, anxiety or comfort. One of the aims of the second study in this portfolio was to investigate if there was an association between the agents used and participant's memories of the ICU. It also aimed to investigate the memories some patients have of their experiences in the ICU. The results indicated that despite the fact that practice of sedation may have changed recently with the introduction of propofol, the percentage of patients who remember their time in the ICU in this study was consistent with the results of previous studies. Anxiety and thirst were among the most common memories. A significant number of patients remembered
the nurses talking to them and found this reassuring. This was despite that fact that most patients indicated that they did not remember being in the ICU. This emphasises the importance of nurses talking to their patients even when the patient cannot respond.

The study did not find any statistically significant associations between memory and nightmares, hallucinations and confusion or any of these variables and the sedation administered. However, confusion was a common and distressing and it appeared that nurses and doctors were often unaware that patients are experiencing these phenomena. Some participants described horrific hallucinations and nightmares. Future research should be aimed at how nurses can detect when patients are experiencing these phenomena and how they may be prevented or the distress minimised. Non-pharmacological methods of calming and reassuring patients and preventing the ICU syndrome, such as promoting sleep, reducing noise, and providing natural light should be implemented. It would be useful to summarise and appraise the research already conducted on this topic.

Although it was not the aim of the study to investigate the incidence of nightmares following discharge from the ICU, several participants complained of continuing distress and inability to sleep and asked to be referred to the social worker. The incidence of these experiences and the impact they have on recovery should be further investigated. There may be a role for post discharge clinics to help patients make sense of their memories of ICU and come to terms with their experiences. The nurses and doctors of the ICU usually only see a patient they have cared for when they visit the unit. It is important for the
development of good practice that ICU staff know how the care they provide impacts on individuals.

The final study of the portfolio was the study that investigated the association between the critical illness sedation scale (CISS), independent clinical judgment and the bispectral index of EEG for the assessment of sedation of ventilated patients in an intensive care unit (ICU). The results indicated that the CISS was moderately positively correlated with BIS recordings. There was a statistically significant difference in the means of the BIS recordings for each level of the CISS, however, the confidence intervals overlap particularly at deeper levels of sedation. Future studies could be designed to investigate the use of the BIS in the management of heavily sedated patients.

Another finding of this study was that the strongest positive correlations between nurses' assessments of sedation and the BIS were for those assessments performed by the least qualified staff. A future study could be designed to further investigate factors that influence the accuracy of assessment and how these may be improved.

ICU is a dynamic area of nursing practice and it can be expected that in the future the ways in which patients are sedated and assessed in the ICU will change. New agents with different actions and side effects will be introduced and the BIS technology will probably be further refined. While the research presented in this portfolio has generated many questions for future research, the results have also contributed to the existing evidence relating to this important aspect of ICU practice.
REFERENCES


ATTACHMENTS

Publications


NOTE:
This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:
https://doi.org/10.1046/j.1440-172X.2001.00295.x

NOTE:

This publication is included in the print copy of the thesis held in the University of Adelaide Library.
Propofol or midazolam – which is best for the sedation of adult ventilated patients in intensive care units?

A systematic review

Judith M Magarey • RN, Critical Care Cert, DipNurs, BNurs, MNurs (research)
Doctor of Nursing Student at Adelaide University
Department of Clinical Nursing, Adelaide SA

This paper was awarded the Best Nursing Review paper at the Australian and New Zealand Scientific Meeting on Intensive Care in Canberra 2000.

Abstract: Intensive care patients are commonly sedated to maintain comfort and to facilitate life saving therapy. Although sedation is ordered by medical staff, nurses are usually responsible for its administration and titration and thus the question of which drug regime should be chosen is an important practice issue for nurses. This is a report on a systematic review that was conducted to compare the effectiveness of two of the most common drugs used for the sedation of adult ventilated patients in Australian intensive care units (ICUs) – propofol and midazolam. All randomised controlled trials (RCTs) which compared propofol with midazolam for the sedation of adult ventilated patients in ICUs were included in the study. The outcome measures evaluated were the quality of sedation achieved, the length of time from cessation of sedation till extubation, recovery time, duration of admission to the ICU and the incidence of haemodynamic complications. Meta-analysis was used to compare results of studies where subjects had the same characteristics and the outcome criteria were measured in the same manner.

The review found that infusions of both midazolam and propofol appear to provide similar quality sedation, that extubation time and recovery time is shorter in patients sedated with propofol and that haemodynamic complications related to either drug regime are not usually clinically significant.


INTRODUCTION

Since intensive care developed as a distinct specialty in the 1960s, sedating drugs have been used to relieve anxiety and distress and to enable patients to tolerate therapy such as artificial ventilation.

The word sedation means a “calm and restful state”. Many drugs have been used to produce sedation or anxiolysis, including opiates, benzodiazepines, anaesthetics and neuroleptic agents. However, each of these agents may have a range of actions, including hypnosis (producing sleep), analgesia (relieving pain) and amnesia (loss of memory). They also have various side effects. Therefore, the drug chosen will depend on the action required and the anticipated side effects. Accumulation may result in over-sedation, causing respiratory depression and extending the time taken to wean a patient from ventilation. Other complications associated with over-sedation include hypotension, ileus, immunosuppression and renal dysfunction all contributing to increased morbidity.

Surveys of ICUs in the United Kingdom, North America and Australia have shown that the drugs most frequently used to sedate intensive care patients are benzodiazepines – these are usually administered in combination with narcotics. However, they also indicated that propofol was being used in some units.

One of the most common benzodiazepines used is midazolam – this is often administered in combination with morphine. Midazolam is a relatively short acting benzodiazepine which is rapidly distributed into peripheral tissues. The predicted half-life of midazolam is normally from 30 minutes to 2 hours.

However, its action is extended in renal failure due to accumulation of an active metabolite (hydroxymidazolam). Shock and reduced hepatic perfusion can also interfere with metabolism, prolonging its action. If it is administered in continuous infusions, the peripheral tissues become saturated and the action may be extended to days. Elderly patients are also at greater risk of accumulation due to reduced metabolism. Thus midazolam may easily accumulate in the critically ill, causing over-sedation and the associated complications.

In approximately 1995 [Zeneca Pharmaceuticals – personal communication], propofol was introduced in Australia for sedation of ventilated patients in intensive care units (ICUs). Propofol is an alpha2 agonist agent that has sedative and hypnotic actions, but has little amnesic and no analgesia action. However, propofol has one
major advantage over other sedative agents – even in the critically ill, those with hepatic or renal impairment and elderly patients – as it has a very short redistribution half-life of 1.3-2.2 minutes11.

Nevertheless, propofol does have some side effects. It may cause hypotension, and allergy and convulsions have been reported in susceptible individuals11. Currently it is not recommended for the long-term sedation of children, due to reports of lactic acidosis and even death in paediatric patients on long-term propofol sedation11, though the link is not proven and remains subject to some controversy.

The main impediment to its use appears to be the cost. Propofol is expensive and a 24 hour infusion may cost up to six times as much as an infusion of midazolam. In addition, tachyphylaxis may occur with administration of propofol, necessitating ever increasing doses for long-term sedation, thereby further increasing cost. Despite this fact, propofol may provide safer sedation for intensive care patients, particularly those with renal or hepatic impairment.

**OBJECTIVE OF THE REVIEW**

The objective of the review was to present the best available evidence relating to the sedation of adult ventilated patients in ICUs. The specific questions addressed were:

- Which sedative agent is the most effective; midazolam or propofol?
- How should it be administered; by bolus or continuous infusion?

Thus outcome measures were chosen to evaluate the effectiveness of the alternative regimes on: firstly, the quality of sedation provided by the alternative agents, secondly, the duration of admission to the ICU and weaning and recovery time and, finally, the incidence of haemodynamic complications.

**Quality of sedation**

The aim of sedation in the ICU is to promote anxiolysis. Both midazolam and propofol can produce various levels of sedation and hypnosis. Therefore, the first question considered by the review was which drug provides the best quality of sedation? The outcome measure used to evaluate quality of sedation was the ability to achieve a chosen sedation level, as evaluated by use of a recognised sedation scale or, if a scale was not used, by expert observation.

Although several different objective methods of assessing sedation levels have been investigated, such as lower oesophageal contractility and Bispectral index of the electroencephalogram (EEG)10, currently, the recommended method to assess the level of sedation is clinical observation using a recognised scale1. The scale most commonly used in research appears to be the Ramsay scale, which was first published in 1974 (Figure 1)11. Despite the fact that it has not been extensively tested for reliability and validity, the Ramsay scale is often considered to be the gold standard for assessing sedation in ICU10.

**Duration of admission, recovery and weaning time**

One of the main complications of sedation is over-sedation which may prolong weaning times and increase morbidity1. The outcome measures that were considered in order to assess the probability of over-sedation were:

- Time from cessation of sedation until awakening (recovery) and extubation; and
- Duration of admission to the ICU.

**Haemodynamic complications**

Cardiovascular system (CVS) depression, in particular hypotension, may limit the usefulness of some sedating drugs. In order to compare the propensity of propofol or midazolam to cause CVS depression, the incidence of haemodynamic complications was evaluated, in particular changes in heart rate and blood pressure. Thus the outcome measure considered was:

- the incidence of haemodynamic complications during sedation (changes in heart rate and blood pressure).

**METHODS**

**Criteria for considering studies: types of participants and studies**

The review considered randomised controlled trials (RCTs) which evaluated the effectiveness of midazolam and propofol as sedation for adult ventilated patients in ICUs. This method of research was chosen because RCTs are considered to be be less susceptible to bias and the best form of evidence when the effectiveness of treatment is being evaluated.

The data were analysed for each specific subgroup, such as critically ill and post-cardiac surgery patients, and combined when appropriate. For example, when the duration of sedation was similar, the data was combined. Studies conducted on paediatric patients or during anaesthesia were excluded. Studies done on patients in recovery units or cardiac units and who were not ventilated were also excluded, as sedation in this population must be managed in an entirely different manner to avoid the possibility of respiratory depression.

Patients in ICUs are commonly administered narcotics with sedation. This factor may complicate the question because narcotics such as morphine also act as sedatives15,16,90. Although the review did not specifically target the issue of narcotics, studies were examined to establish which narcotics were administered, so the possible influence on sedation could be evaluated.

Any study in which patients received paralysing agents was excluded. This is because evaluation of the quality of sedation, extubation time, recovery time, haemodynamic responses and length of admission may all be complicated by the use of paralysing agents. It is not possible to use a sedation scale to assess consciousness if the patient is paralysed and many factors variably influence the metabolism and excretion of these drugs; these...
include renal and hepatic function, temperature, use of other drugs and pH. In addition, some paralysing agents such as pancuronium may also cause haemodynamic variations such as tachycardia and hypertension.

Interventions of interest were those relating to the sedation of adult ventilated patients in intensive care and included:
- Use of midazolam versus propofol with or without concurrent administration of narcotics;
- Continuous infusions versus intermittent bolus administration of propofol or midazolam.

**Search strategy**
The search sought all published and unpublished studies relating to the research question but, due to resource and time limitations, non-English articles were excluded from the search. The databases searched included:
- CINAHL
- MEDLINE
- Current Contents
- The Cochrane Library
- Expanded Academic Index
- EMBASE
- Papers First
- Proceedings First
- Dissertation Abstracts International.

The initial search terms were:
- sedation
- intensive
- care
- therapy
- ventilation
- mechanical ventilation
- propofol
- midazolam
- propofol and midazolam

In addition the reference lists and bibliographies of the relevant articles were also examined to identify new articles. In order to locate unpublished research, the Australian and The New Zealand Scientific Meeting on Intensive Care conference proceedings were searched from 1994 and several experts were contacted. When a relevant poster or conference presentation abstract was located, the author was contacted in writing requesting details of the paper in order to establish if the article had been published.

Two hundred and eleven papers that appeared to meet the inclusion criteria were retrieved. One hundred and sixty seven papers were found to be general discussion papers or did not compare propofol with midazolam. These were not included in the study. Of the remaining 44, eight were found to be duplicates. A total of 36 studies were included in the review.

An appraisal form based on the work of the Cochrane Collaboration and the Centre for Reviews and Dissemination was used to evaluate the methodological quality. Studies which fulfilled the following criteria were included in the analysis.
- Was the assignment to treatment groups random?
- Apart from the intervention, were participants treated identically?
- Were the study groups comparable at entry?

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<th>No. located</th>
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</tr>
<tr>
<td>Propofol infusions versus midazolam infusions</td>
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<td>5</td>
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<tr>
<td>Post-cardiac surgery</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Propofol infusions versus midazolam infusions</td>
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<td>2</td>
</tr>
<tr>
<td>Medical conditions and following general surgery</td>
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<td>Post-trauma injury or neurological surgery</td>
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</table>

- Were the outcomes measured in the same manner for all groups?
- Seventeen studies fulfilled the conditions and were considered in the analysis (Table 1).

**Data synthesis**
Data from studies that compared propofol with midazolam were combined for meta-analysis where appropriate. Where possible, standardised mean differences and their 95 per cent confidence intervals were calculated for each study included in the review. Meta-analysis was used to estimate the effectiveness and relative value of the different interventions. Raw data were requested from authors where standard deviations or mean scores were not published. Where statistical pooling was not appropriate or the data were not suitable, the findings of studies were considered in a narrative summary. Study results were also considered for homogeneity, which was evaluated by assessing if the confidence interval lines overlap and the chi-square test. Possible reasons for heterogeneity were then further investigated. In particular, the studies were evaluated to see if they had the same types of participants, interventions and outcome measures.

**RESULTS**
All studies were evaluated for their relevance to the question and their methodological rigour. The results were considered in specific subgroups:
- Quality of sedation
- Time from cessation of sedation until extubation
- Time from cessation of sedation until recovery
Quality of sedation

The first variable considered by this study was the ability of the sedation regime to achieve a chosen sedation level as evaluated by a recognised scale. Most studies reported data relating to the quality of sedation as the mean percentage of time at ideal sedation, as evaluated by the Ramsay scale. Typically, levels 2-4 or 2-5 were considered ideal. Most of the data was not suitable for meta-analysis as few studies reported standard deviations.

For critically ill, general ICU patients, the results were contradictory, with two studies reporting that infusions of propofol produced significantly better quality sedation, another that midazolam produced better sedation, and a fourth finding no difference. There are several possible reasons for the differences between the studies. Firstly, three studies used the Ramsay scale to assess the quality of sedation, but the fourth used a visual analogue scale. Secondly, the ideal sedation level on the Ramsay scale was considered to be 2-5 in one study, 2-4 in a second and was not reported in a third. Thus, no conclusions could be drawn about which regime provides the best quality of sedation in critically ill, general ICU patients.

None of the studies that compared infusions of midazolam with propofol in post-cardiac surgery patients reported a significant difference in the quality of sedation provided by the different regimes. The reasons for the agreement in results may be because the patient groups are homogeneous and the majority of studies aimed at the same sedation level (Ramsay 2-4).

Both studies that compared propofol infusions with bolus of midazolam in post-cardiac surgery patients demonstrated that propofol infusions provided better quality sedation than bolus of midazolam.

In studies that compared propofol infusions with midazolam infusions in post-operative patients, the results were again conflicting. One study reported the propofol provided better tolerance of ICU and another reported that both drugs provided similar quality sedation. One possible reason for the different results may be that in one study, patients were administered bolus of analgesia and in the other, infusions.

The single study that compared the efficacy of propofol infusions with midazolam infusions in surgical and medical patients found both regimes were equally effective.

Thus regarding which drug infusions provide the best quality of sedation – propofol or midazolam – the overall results were inconclusive. But midazolam bolus do not provide as good quality sedation as infusions of propofol (Table 2).

Time from cessation of sedation until extubation

The studies that compared infusions of propofol with midazolam in general ICU, critically ill patients demonstrated that this group took less time to wean from ventilation when propofol was used for sedation. However, meta-analysis revealed non-homogeneity between the studies. Though all patients were considered to be critically ill, there was considerable variation in the diagnoses of patients, even within studies. Patients with renal failure (which greatly influences the excretion of midazolam) were only excluded in one study and patients with hepatic failure were excluded from two. In addition, differences in the procedures used to wean patients from ventilation would have a considerable influence on the variation between final results.

Five studies which compared infusions of propofol with midazolam in post-cardiac surgery patients reported extubation times (time from cessation of sedation until extubation). However, meta-analysis did not demonstrate homogeneity. This may be due to the short sedation time of only 4 hours in the study by Searle et al. In addition, all other studies excluded patients with renal and hepatic disease. When this study was excluded from the meta-analysis, the results revealed homogeneity and shorter extubation times for those patients sedated with propofol (Figure 2).

Table 2. Quality of sedation summary.

<table>
<thead>
<tr>
<th>Group</th>
<th>Studies (references)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically ill, general ICU</td>
<td>23, 24, 46, 57</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Post-cardiac surgery infusions</td>
<td>43, 44, 45</td>
<td>No significant differences</td>
</tr>
<tr>
<td>Post-cardiac surgery propofol infusions versus midazolam bolus</td>
<td>46, 47</td>
<td>Propofol infusions significantly better than bolus of midazolam</td>
</tr>
<tr>
<td>General post-operative</td>
<td>53, 54</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Surgical &amp; medical</td>
<td>55</td>
<td>Inconclusive</td>
</tr>
</tbody>
</table>
Two studies that compared propofol infusions with midazolam bolus in post-cardiac surgery patients reported extubation times and, although the meta-analysis revealed non-homogeneity in the results of studies, patients sedated with propofol were extubated significantly sooner. Possible reasons for the non-homogeneity may include the different inclusion criteria for the participants and the different dosage of the sedative agents used (Table 3).

Overall, all studies reported shorter extubation times for those patients sedated with infusions of propofol.

**Time from cessation of sedation until recovery**

Four studies that compared propofol infusions with midazolam infusions in critically ill, general ICU patients reported recovery times. In two studies, recovery time was defined as the time from cessation of sedation until the patient could follow a specific command or respond to simple orders. In the remaining studies, the method used to assess recovery was not reported. Although all studies reported shorter recovery times for patients sedated with propofol, meta-analysis did not demonstrate homogeneity. As with the extubation times, this may be explained by the variation in the diagnoses of patients, varying practices between units and the different methods used to measure recovery time.

Three studies that compared propofol infusions with midazolam infusions in post-cardiac surgery patients reported recovery times. All reported shorter recovery times for patients sedated with propofol infusions but meta-analysis did not demonstrate homogeneity. Again, this heterogeneity may be due to the different manner in which recovery time was measured. In the one study, it was measured as the time till the patient could raise their arm in response to command, while in another it was measured at the time taken to reach a Modified Glasgow Coma Score of greater than 16. None of the studies performed on post-surgery patients included in the initial analysis reported recovery times.

From these results, it can be concluded that patients sedated post-cardiac surgery and general ICU patients with propofol infusions have recovery times which are significantly shorter than those who are sedated with infusions or bolus of midazolam (Table 4).

**Duration of admission to the ICU**

Only one study that was included in the initial analysis reported duration of admission to the ICU. This study reported a shorter length of stay for patients sedated on propofol. However, it is difficult to interpret the significance of this result given the varying diagnoses and lack of results from similar studies.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Critically ill general ICU</td>
<td>30, 35, 37</td>
<td>Shorter admission time with propofol</td>
</tr>
<tr>
<td>Post-cardiac surgery</td>
<td>39, 43-45</td>
<td>Shorter admission time with propofol</td>
</tr>
<tr>
<td>Extracorporeal surgery</td>
<td>39, 40, 44, 45</td>
<td>Shorter admission time with propofol</td>
</tr>
<tr>
<td>Propofol sedated patients in post-cardiac surgery</td>
<td>39, 40, 44, 45</td>
<td>Shorter admission time with propofol</td>
</tr>
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**Haemodynamic complications**

The final outcome measure evaluated was the incidence of haemodynamic complications. The data reported were extensive and included changes in:

- mean arterial pressure (MAP)
- diastolic blood pressure (DBP)
- systolic blood pressure (SBP)
- heart rate (HR).

Some studies also reported the incidence of adverse events such as hypertension and hypotension and requirements for treatment with inotropes and vasodilators and volume expanders.

Several studies performed on critically ill general ICU patients reported that propofol was more likely to cause a decrease in HR. Nevertheless, cardiovascular depression was not clinically significant, limiting the usefulness to similar numbers of patients in both regimens. One study reported that propofol caused a greater decrease in MAP and SBP which necessitated fluid loading in significantly more patients. The authors stated that since fluid and vasoactive requirements were similar for both groups prior to induction of sedation, the effect could not be attributed solely to hypovolaemia.

Another study found all differences between the groups in the MAP at any point in time were small. One reason for the variation in results could be that patients in these studies were critically ill, with many factors complicating their haemodynamic responses, including the use of drugs such as inotropes and their physiological condition. Many critically ill patients are already very unstable prior to the induction of sedation. In addition, different doses of the sedating agents were administered between studies. It appears that overall propofol infusions may cause more cardiovascular complications (decreased HR and BP) than infusions of midazolam but the effects were generally not clinically significant.

The results of studies conducted on post-cardiac surgery patients demonstrated that propofol is perhaps more likely to cause hypotension accompanied by a decreased heart rate but that midazolam can also cause hypotension on induction of sedation and an increase in heart rate during maintenance. These haemodynamic responses did not appear to necessitate ceasing the sedation, but doses were decreased in some studies.

In most cases, haemodynamic changes did not influence the overall inotrope or fluid requirements. One study reported that cardiovascular depression was treated with fluids and inotropes, with more patients in the propofol group requiring the latter. Nevertheless, the overall inotrope requirements did not differ between the groups. In several studies, less vasodilators were required for patients sedated with propofol. Again, one possible

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<td>Critically ill general ICU</td>
<td>30, 35, 37</td>
<td>Shorter recovery time with propofol</td>
</tr>
<tr>
<td>Post-cardiac surgery</td>
<td>39, 43-45</td>
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<td>Extracorporeal surgery</td>
<td>39, 40, 44, 45</td>
<td>Shorter recovery time with propofol</td>
</tr>
<tr>
<td>Propofol sedated patients in post-cardiac surgery</td>
<td>39, 40, 44, 45</td>
<td>Shorter recovery time with propofol</td>
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</table>
cause of the variation in results of the studies may be the different doses administered. The numbers included in the studies were all small, varying from 15 to 42 in each group. Two studies used a closed loop arterial pressure controller which may also have influenced the results.45,49.

The two studies that compared propofol infusions with bolus of midazolam in post-cardiac surgery patients reported no significant difference in the BP and HR between the study groups.45,49.

For general post-operative patients, the only one study included in the initial analysis investigated haemodynamic complications - this reported no statistical difference between the groups in the SBP, but reported that patients receiving propofol had a significant decrease from their baseline SBPs. There was also a decrease in the MAP evident in the first 5 minutes. Patients receiving propofol also had a decreased heart rate. The results of this study supports those seen in other studies.25,24.

In a study with medical and surgical patients, adjustments to infusion rates due to hypotension were required in more patients receiving propofol than those receiving midazolam. This again supports the indication that propofol is more likely to cause hypotension.

Overall, it appears that propofol is more likely to cause hypotension and decreased heart rate (Table 5).

**OVERALL LIMITATIONS AND CONFounding FACTORS**

A possible cause of the varying results may be that few of the studies were double blinded which can lead to possible bias in those assessing the patient’s response. Nevertheless, it may not be practical to double blind in studies comparing infusions of midazolam with propofol. This would mean either covering lines (which is potentially hazardous, as air cannot be seen), or running infusions at set rates with placebo infusions, which would mean the sedation could not be easily titrated to effect. Another possible action to reduce this bias would be to have the assessor unaware of the drug being infused. However, in most studies, the nurse caring for the patient continually assessed the quality of sedation, so again this may not be practical.

**ADMINISTRATION OF NARCOTICS**

A confounding factor that may have influenced the results of the studies in the review is the administration of narcotics. These are commonly administered for their analgesic action but they also act as sedatives. The studies included in the review were examined to establish which narcotics were administered and, in particular, to detect differences in dosages and patterns of administration between the study groups. For critically ill, general ICU and surgical patients, no significant differences were detected between the study groups.

Most studies that compared propofol infusions with midazolam infusions in post-cardiac surgery patients reported no differences between the groups in the administration of analgesia. Only one study reported a significant difference in the morphine requested, although the mean dose administered in each group was similar. In this study, patients were administered analgesia if they acknowledged pain when questioned by nurses; it was not reported whether a background infusion was administered. There was no indication as to whether there was control over the questioning technique or timing. Fifty three per cent of patients sedated with midazolam requested analgesia while only 33 per cent of patients sedated with propofol requested analgesia. In the other studies, analgesia was administered routinely which is common practice when caring for post-operative patients.

In studies that compared propofol infusions with bolus of midazolam, the patients sedated with midazolam boli required more analgesia. This is not a surprising finding as the studies demonstrated that bolus of midazolam provided poorer quality sedation.

From this summary, it can be concluded that it is unlikely that the administration of analgesia influence the results of the review, as for most studies there was no difference between the groups in the patterns of administration or doses administered.

**CONCLUSION AND IMPLICATIONS FOR PRACTICE**

The evidence provided by the review supports the view that infusions of both propofol and midazolam provide a similar of quality sedation. However, for some groups, for example the

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<tbody>
<tr>
<td>Critically ill, general ICU</td>
<td>23, 24, 26</td>
<td>Differences in propofol group vs placebo group</td>
</tr>
<tr>
<td>Post-cardiac surgery infusions</td>
<td>39, 40, 42-45</td>
<td>Differences in propofol group vs placebo group</td>
</tr>
<tr>
<td>Propofol vs midazolam</td>
<td>65, 47</td>
<td>No significant difference in MAP between groups</td>
</tr>
<tr>
<td>General post-operative</td>
<td>42</td>
<td>Propofol in critical care, MAP, depressor from placebo</td>
</tr>
<tr>
<td>Midazolam surgical</td>
<td>45</td>
<td>No additional propofol required</td>
</tr>
</tbody>
</table>
critically ill, general ICU patients, the results are conflicting. Many reported no significant difference between the two drugs during infusions. One possible reason for this is that sedating drugs vary in their actions. Midazolam is an effective amnestic agent, while propofol has little amnestic action. They also vary in onset of action in producing hypnosis and the duration of action. These different actions are not evaluated separately by the Ramsay scale. Future research into the quality of sedation provided by either propofol or midazolam should be directed towards clarifying these variables.

In relation to the mode of administration, infusions of sedation are preferable. Studies agreed that bolus of midazolam do not provide as good quality sedation as infusions of propofol.

Regarding the time from cessation of sedation till extubation and recovery time, the results were fairly conclusive, with most studies reporting a shorter time till extubation and recovery for patients sedated with infusions of propofol. This was demonstrated best in studies conducted in post-cardiac surgery units where participants had a greater degree of homogeneity. There was not enough data to draw any conclusions regarding duration of admission. Nevertheless, it may be that a shorter recovery and extubation time lead to a reduced duration of admission in the ICU.

Although many of the studies produced conflicting results on the incidence of haemodynamic complications, reports of hypotension related to induction of sedation were quite common. The influence of propofol or midazolam on haemodynamic variables appears to be less significant as the infusion progresses. Few studies reported having to cease sedation due to haemodynamic response. Propofol may have some advantages in the post-cardiac surgery patient where hypertension must be avoided.

If the major clinical consideration is the quality of the sedation, either propofol or midazolam may be administered. However, if it is important that recovery and extubation is rapid, propofol should be chosen. However, the time difference reported in many studies does not appear to be of clinical significance, being hours rather than days — most of these studies excluded patients with hepatic and renal impairment. They are the very patients most likely to experience accumulation of midazolam.

The most significant differences in recovery and extubation times were recorded in the critically ill, general ICU patients who were sedated for longer periods. A recent study demonstrated that daily interruption of sedation until the patients woke was associated with a decreased duration of ventilation and length of stay. In several of the studies, patients were sedated up to level 4-5 on the Ramsay scale, both are viewed as asleep levels. If patients were sedated more lightly, it is likely that they would recover and be extubated more quickly. However, this has implications for nurses, as more lightly sedated patients can be more difficult to care for in terms of maintaining communication and comfort.

In summary, both propofol and midazolam infusions appear to provide similar quality sedation. Extubation and recovery time for patients sedated with propofol is shorter and it appears haemodynamic responses are not generally clinically significant. Future research could be directed at using a combination of agents to make use of the synergistic effect. In this way, the advantages of both agents could be best maximised.

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REFERENCES


