Peri-operative and peri-partum anaemia management

Submitted by

Bernd Froessler

MD, FANZCA, MClinSc

A thesis submitted in total fulfilment of the requirements for the degree of

Doctor of Philosophy

The Joanna Briggs Institute, School of Translational Health Science,

Faculty of Health Sciences

The University of Adelaide

January 2016

Statement of Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Bernd Froessler and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signature

Date: 28/01/2016

Acknowledgements

I wish to sincerely thank Prof Alan Pearson AM for many years of supervision and tireless support.

I wish to thank Prof James Isbister for agreeing to be my associate supervisor, for his tremendous input and for reviewing this thesis.

Both my supervisors were amazing communicators and mentors along the way.

Table of Contents

List of figures

Introduction to the program of study

Anaemia in the peri-operative setting

The hospital environment challenges the human mind and body in many ways. It challenges the patient's psychological and physiological functioning and ability to cope with illness and hospitalization. It also challenges medical administration and staff to deliver quality healthcare in a dignified, respectful and culturally appropriate environment.

Admissions to hospital can become necessary as part of a disease process, trauma or a physiological state such as pregnancy. Most admissions are associated with some degree of blood loss from injuries, surgery or frequent phlebotomy, all reducing the patient's own red blood cell mass. Depending on the starting baseline haemoglobin level and the volume lost, anaemia may occur rapidly. Anaemia is defined by the World Health Organisation (WHO) as a Haemoglobin (Hb) value below 120 g/L for women, 130g/L for men and between 110-105 g/L in the 2nd and 3rd trimester of pregnancy.(1)

In addition to anaemia resulting from peri-procedural blood loss, it can also be pre-existing. Most commonly anaemia is caused by iron deficiency (ID). This can occur as a result of a range of acute or chronic medical conditions, nutritional deficiencies, physiological loss during menstruation or pregnancy, medication or be exercise induced. Imbalances of intake, absorption, loss, and utilisation of iron will disturb the delicate and tightly controlled iron metabolism eventually resulting in iron deficiency anaemia (IDA). Diagnosis is not always straight forward. Once iron loss exceeds iron intake, bone marrow stores

become insufficient which will result in iron depletion. Iron depletion is generally present in non-anaemic states, may not cause any symptoms and will not be reflected in the mean corpuscular volume of red blood cells. The transition to iron deficiency and microcytosis often occurs at a later stage. (Figure 1) Red cell indices can help identify the condition, but might be completely absent particularly in older people.(2)

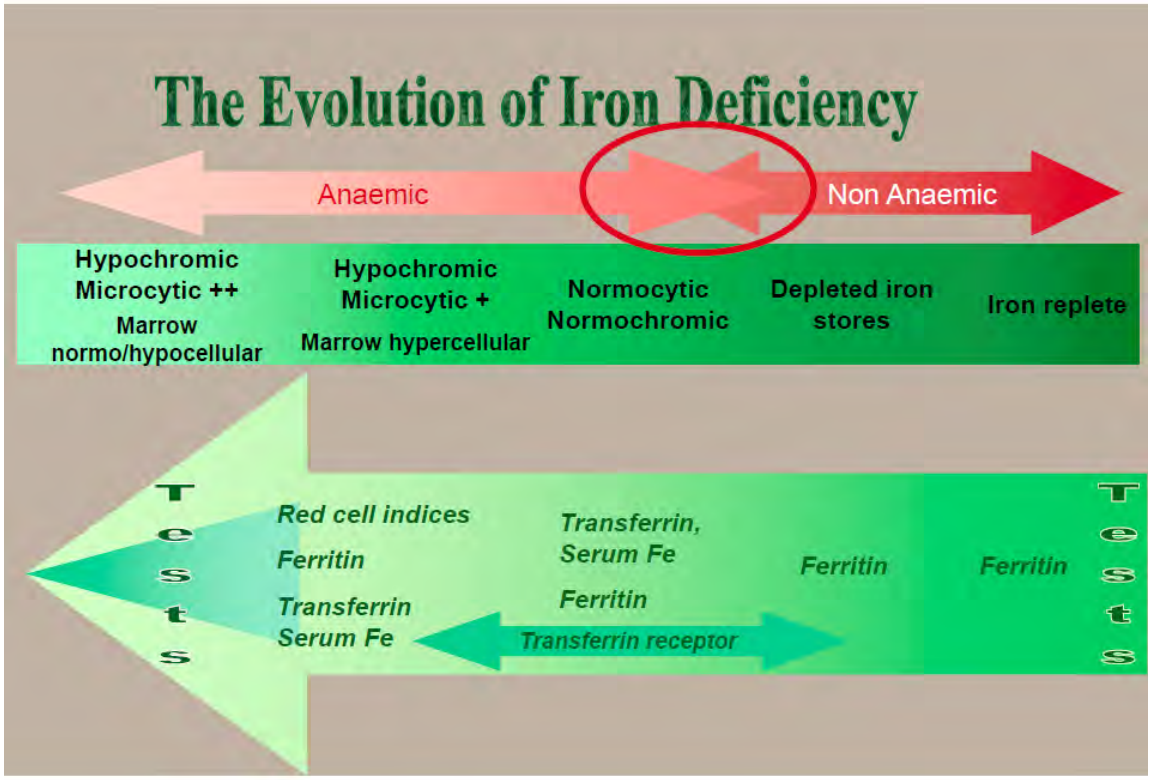

Figure 1: The evolution of Iron Deficiency (with compliments of Professor James Isbister)

The prevalence of anaemia is high. Globally around 25% of people are affected.(3) Patients with inflammatory bowel disease, bowel cancer, menorrhagia, and chronic diseases, such as osteoarthritis are most affected. In addition pregnant women, the very young and the rapidly growing make up a substantial proportion. In patient subgroups the incidence can be as high as 74 %.(4)

Iron depletion

Iron depletion, ID and IDA are all associated with adverse outcomes. (5, 6) Iron is at the core of red blood cell production and involved in many other cellular and enzymatic processes.(7) Furthermore it is vital for foetal development and growth.(8) Low iron stores negatively impact on cardiac, cognitive and immune function.(9-11) Overall aerobic capacity and productivity are reduced. (12) Symptoms often occur late, particularly in the younger population, are often discounted as “normal tiredness”, or misunderstood and misinterpreted by clinicians. As ID progresses to IDA and haemoglobin drops, symptoms may become more severe. Adaptation occurs, however once oxygen delivery and tissue oxygenation become severely impaired, organ ischemia and dysfunction may result. Organ tolerance varies with heart and central nervous tissues being most sensitive.(13)

The detection, evaluation and treatment of ID with or without anaemia remains challenging for many clinicians. Many advances in understanding iron homeostasis, various stages and types of ID and IDA have been made.(14) The separation of possible causes of ID into, physiologic, environmental, pathologic (decreased absorption vs increased loss), drug-related, genetic and iron restricted erythropoiesis allows direct investigation and treatment modalities.(14, 15) These advances will hopefully aid clinicians to overcome those challenges - an urgent need because of the massive burden the condition poses to society.(16)

Blood transfusion

Blood has always been surrounded by mystic theories and its admirable attributes are already mentioned in Greek mythology.(17) In Goethe's "Faust" Mephisto describes blood as a very special juice ('Blut ist ein ganz besonderer Saft'). (18)

The practice of blood transfusion was explored in the early 17th century and initially performed with animal blood, first animal to animal but eventually animal to human transfusion was explored . (17) The experiments continued in England and France, with multiple deaths occurring from the intervention. The French parliament banned the practice in 1670 which led to a cessation of transfusion across Europe. (19)

Red blood cell (RBC) transfusion became part of clinical medicine again in the early 18th century. High mortality rates amongst women suffering post-partum haemorrhage encouraged an obstetrician, James Blundell, to perform the first human to human transfusion in 1818, with several more in the following years.(20) The lack of understanding about its function and compatibility resulted in disastrous outcomes and death for many recipients.(21) In the early 20th century it was clear that there was a potential link between haemorrhage, transfusion and survival. At this time blood transfusions were administered frequently to women who had bled during child birth. Karl Landsteiner's discovery and the introduction of ABO typing made transfusion safer.(22) The development of reliable anticoagulation and prolonged storage in plastic bags after donation introduced a new era of transfusion medicine. (23) Allogeneic

RBC transfusion is today a frequently prescribed treatment modality with approximately 800,000 units issued each year in Australia alone. (24)

One has to differentiate between ID/IDA and the acutely bleeding patient where blood loss occurs suddenly, can be significant and might be ongoing. The management of acute or massive blood loss is beyond the scope of this thesis which focuses on “elective” peri-operative and peri-partum anaemia and transfusion events that account for approximately eighty percent of RBC’s prescribed. But even elective RBC transfusion has been an assumed mainstay of medical practice. After the widespread use of transfusion therapy in World War II and the Spanish civil war, blood transfusion became a lucrative business for clinicians and even more lucrative for the newly introduced blood banking sector. The perception of unlimited availability, the widely promoted safety of allogeneic donor blood and its efficacy in rapid haemoglobin correction led to often unscrutinised and inappropriate prescribing practices. The overuse and misuse of RBC transfusion was lamented throughout the 20th century.(25, 26) It wasn’t until the AIDS epidemic in the 1980s and the transmission of the virus that a temporary shift in transfusion practice occurred, putting the recipient at the centre of the intervention.(27) (28) Interest in “bloodless surgery” grew, initially aimed at the Jehovah’s witness population which also drove research into perfluorocarbon-based oxygen carriers. Multiple authors called for careful consideration of transfusion appropriateness and reminded the divided medical community of available treatment strategies and anaemia tolerance, aimed at the reduction of RBC use.(28, 29)

Despite strict mandatory screening of the donor and the product by the blood services and an increased safety profile for the transmission of infectious

diseases, allogeneic RBC transfusion (ABT) is not without risk. Peri-operative allogeneic transfusion adversely impacts on patient outcomes, such as, increased length of stay (LOS), increased infection rates, increased occurrence of transfusion related lung injury (TRALI), transfusion associated circulatory overload (TACO) and mortality.(30, 31) One needs to separate adverse events from ABT in which causation is clear from ABT related risk factors responsible for adverse patient outcome. To assure identification of the former, the importance of surveillance was recognized.(32) Haemoviligance systems were designed and implemented *"to prevent the occurrence or recurrence of transfusion related unwanted events, to increase the safety, efficacy and efficiency of blood transfusion, covering all activities of the transfusion chain from donor to recipient. The system should include monitoring, identification, reporting, investigation and analysis of adverse events, near-misses and reactions related to transfusion and manufacturing".*(33) The latter have become more apparent since 1999 after the results from a randomised controlled study in the critically ill showed that a more restrictive transfusion approach benefited the patient.(34) Additional evidence from the Jehovah's witness population, where the administration of blood products was no option, strengthened a view that the time had come to question liberal transfusion approaches.(35-38) From then on multiple research projects were directed to answer this question, directly comparing restrictive versus liberal transfusion strategies in surgical and non-surgical settings.(39-42) Systematic review data from this research activity led to the conclusion that restrictive transfusion strategies are safe in most clinical setting.(43-46)

It is important to point out that ABT has never been completely safe, is a transplant and associated with a wider range of potential hazards than any other therapeutic intervention. This message is taking a long time to get through and the point has been made by several experts for decades. (27, 47)

Regardless of the well described risks of ABT and the strong evidence supporting a review of transfusion thresholds ABT remains a default position for many clinicians. ABT still occurs in 10% of hospital admissions and the procedure has been identified as one of the five most over prescribed medical treatment modalities.(48) Calls for abandoning a “laissez faire approach” assuming the benefits of ABT while accepting the risks remained largely unheard.(49) Many transfusion events could be avoided if more attention was spent on modifiable factors, such as optimising pre-operative haemoglobin values and the patient’s iron status.

Most countries from around the world are facing significant demographic changes over the next two decades (50). These changes come as the result of a dramatic increase in the older population and a decrease of the young due to an ongoing decline in birth rates in the western world. More complex surgery in the elderly in addition to many serious medical conditions requiring transfusion is likely to lead to an increase in demand for blood products.(51) The shrinking pool of donors compounds the problem and demand threatens to outstrip a safe supply of a high quality product.(50, 52, 53) This looming shortfall has to be addressed urgently to guarantee the sustainability of fresh blood products in the blood supply. Fresh blood products currently account for 33% of the blood budget in Australia. (Figure 2) Additionally, even bigger problems for the sector arise from the substantial annual growth in demand for intravenous

immunoglobulin (IVIg). IVIg demand exceeds Australia's current plasma collection capacity, which is now growing at a rate of approximately 6.7 % per annum. The annual shortfall is supplemented with imported finished products, sourced by the National Blood Authority (NBA) using competitive procurement processes. Known and unknown infection risks from blood transfusions, an inventory at risk and ever-increasing cost should be drivers for change (54).

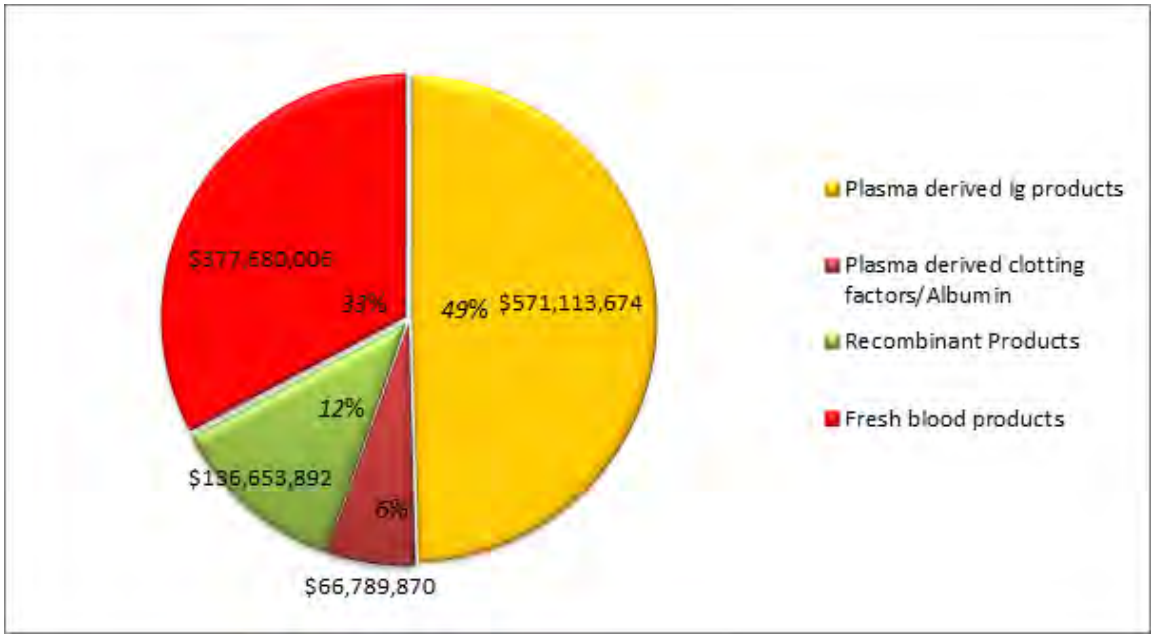

Figure 2: Distribution and cost for fresh blood products and plasma and recombinant products in Australia (2013-14). Source: National Blood Authority

The need for practice change

The need for change has also been recognized and endorsed by the World Health Organization (World Health Alliance Resolution A63.R12) supporting the implementation of Patient Blood Management (PBM) (55). Some countries have taken action to advocate a more efficient and appropriate blood utilization (56), but uptake of clinical practice change remains slow (57). The transfusion approach should be "individualised" and tailored to the needs of the patient,

backed by the latest evidence. Patients' age, co-morbidities and the underlying cause should direct the clinician to the appropriate treatment approach. However, rigid interpretation of guidelines, dogma and beliefs often misguide clinicians and transfusion practices vary immensely.

This thesis discusses and focuses on preoperative and peri-partum haematological optimisation, the addressing and avoidance of intra-operative anaemia with the utilisation of cell salvage (58) and the treatment of iron deficiency within the broader concept of patient blood management.

The term Blood Management was created in the late nineties, supported by the foundation of organisations and societies such as the Network for Transfusion Alternatives (NATA) and the *Society for the Advancement of Blood Management* (SABM). The potential misconception of the term "blood management", determined by the view and responsibilities of either the clinician (patient) or the blood bank (product), sparked a discussion initiated by Professor James Isbister, at the NATA meeting in 2005. He called on health care professionals to embrace the patient as the centre of attention in transfusion medicine. As one of the pioneers in blood management, he renewed his call that "transfusion therapy should be recipient-oriented", which he had advocated since the mid-eighties. (28) By the inclusion of the word 'patient' to the term blood management, PBM became a brand and a broader uptake of the concept occurred.

PBM is a patient focused comprehensive approach with the aim to improve clinical outcome. PBM is relevant to all sectors of medicine where blood

products are prescribed and transfused. Due to the overlap of care and shared responsibilities it is essential that a multidisciplinary approach is taken.

In the peri-operative setting a three pillar strategy was developed to address important factors in all three phases of the time around surgery, pre-operative, intra-operative and post-operative. (Figure 3) These principles applied in the peri-surgical period enable treating physicians to have the time and tools to provide patient-centred evidenced-based patient blood management to minimize allogeneic blood transfusions.

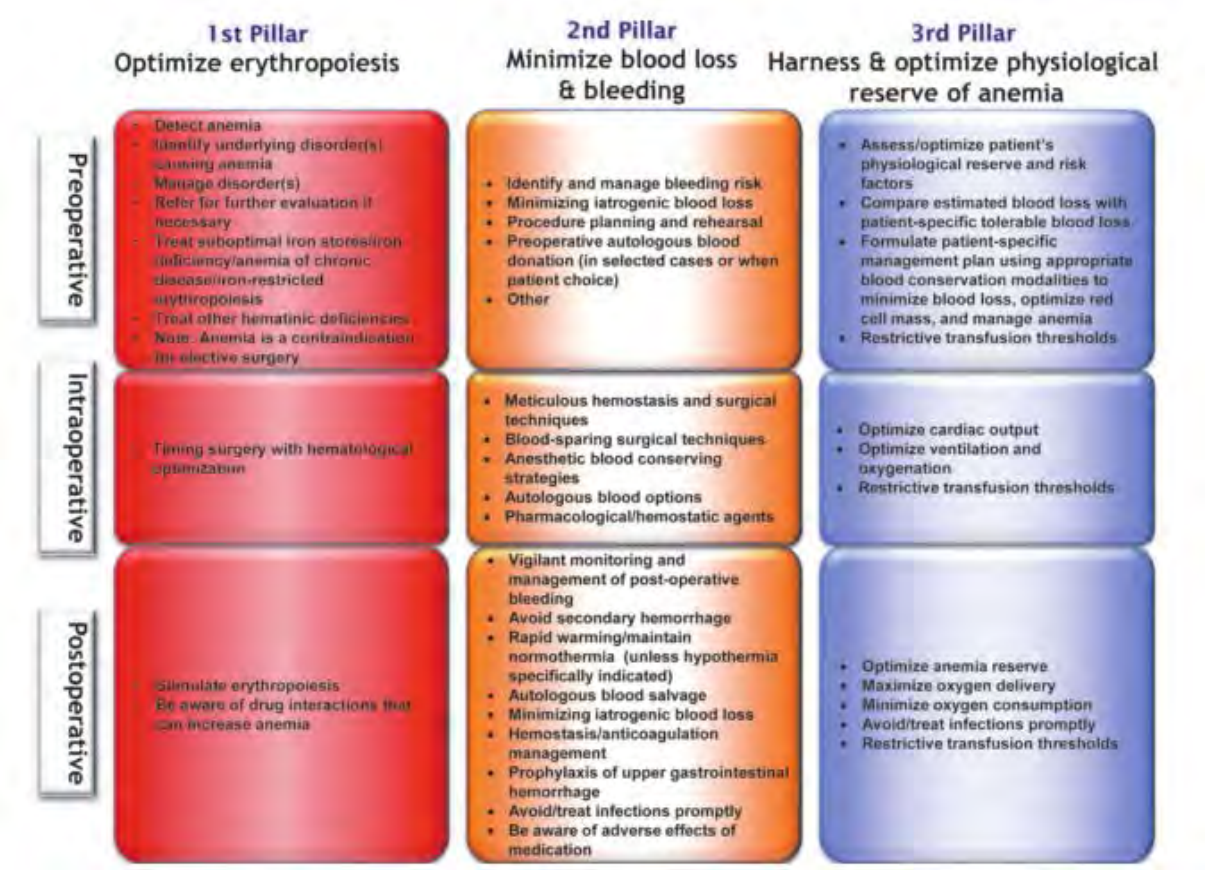

Figure 3: The pillars of patient blood management. *Cited with permission from Hofmann A, Friedman D, Farmer S, for the Western Australia Department of Health. Western Australian Patient Blood Management Project 2008–2012: Analysis, Strategy, Implementation and Financial Projections. Perth: Western Australia Department of Health, 2007:1–154.*

Preoperative

The main focus of the first pillar is a meticulous planning process for major surgical procedures and the timely assessment of patients scheduled for surgery. Depending on the extent of surgery and the underlying disorder this should be done at least 4-6 weeks prior to the operation. The detection and evaluation of anaemia by appropriate investigations will determine a management approach and guide decision making on the potential need for further investigation and/or delaying surgery.(59) Considering the close link between preoperative anaemia, perioperative haemorrhage and RBC transfusion the necessity for patient optimisation should be high and shared between disciplines involved in a patient's care, including the primary care physicians. (60) (61) At the time of referral for surgical specialist review, important investigations could be conducted and waiting list time utilized to schedule procedures and/or initiate treatment.

Intraoperative

Intraoperative strategies should be discussed and agreed on. There is no "one size fits all" approach. Meticulous haemostasis is often inappropriately labelled an "alternative approach" or "transfusion alternative" but should be a given a high priority. The use of cell salvage (CS), acute normovolaemic haemodilution (ANH) and pharmacological haemostatic agents, such as Tranexamic acid (TXA), has to be decided on a case to case basis and is in part dependent on institutional availability. More recent guidelines have also included Point of Care *in vitro* haemostasis monitoring devices to aid the "real time" haemostasis decision making and administration of blood products.(62)

Postoperative

Many of these approaches should flow on into the postoperative period. Anaemia tolerance is important for the whole of PBM, especially if a patient has a non-correctable anaemia in the short or long-term. However in the postoperative setting acute (surgery related) anaemia tolerance is particularly important and requires careful patient monitoring and optimisation. Anaemia has been shown to be an independent risk factor, but there is a large body of evidence that transfusion to correct the anaemia would pose an even higher risk to patients in many cases.(47) This underpins the importance of evidence-based transfusion strategies.(63)

Adherence to the three pillar principles will contribute to better patient outcomes, the avoidance of inappropriate transfusion events and a reduction in transfusion related morbidity and mortality. In general, PBM is a broad concept and should be considered in the majority of clinical settings.(64) Essentially, this thesis can only consider some, but very important, aspects of PBM. The main focus is the optimisation and preservation of erythrocytes around the time of surgery. The majority of work embodied in this thesis was devoted to the correction of pre-existing ID and IDA, in particular with IV iron. Therefore it is about optimising red cell production and the utilisation of the patient's own physiological compensatory reserves. One project included in the thesis examines intraoperative cell salvage, a technology that facilitates the conservation of erythrocytes by intraoperative collection of shed blood and its re-infusion.

The treatment of chlorosis with iron was described in a review in the late 19th century and goes back hundreds of years.(65) Parenteral iron became available not much later but caused many problems due the quick release and the toxicity of free iron.(66) Safer variations of high molecular weight iron dextran (HMW ID) followed in the 1950's (67) but despite its efficacy concerns remained due to the potential anaphylactic reactions caused by the high molecular carrier dextran. Low molecular weight iron dextran (LMW ID) replaced the HMW ID in the early 1990's and offered a yet safer alternative. Dextran free forms of intravenous (IV) iron were developed and released onto the European and American markets. Further improvements and modifications have led to the availability of IV preparations, ferric carboxymaltose and iron isomaltoside, which can be given at a reasonably large dose over a short infusion time and result in a low incidence of serious adverse events.

An increasing number of studies report the safe and successful administration of IV iron in a wide range of clinical settings.(68-71) The use of IV iron results often in a satisfactory outcome without allogeneic transfusion.(38) Inexperience with IV iron, logistical difficulties in arranging administration, a misconception regarding the rapidity of the response and anecdotal fear of serious adverse reactions appear to be preventing widespread use of the therapy despite current evidence based recommendations.(62, 72)

Program of study reported in this thesis

Between 2011 and 2013 the author conducted a Systematic Review (SR) and completed a Master of Philosophy at the Joanna Briggs Institute, School of

Translational Health Science.(73) The objective of this systematic review was to critically appraise, synthesise and present the best available evidence related to the effectiveness and economic aspects of intravenous iron administration on the correction of iron deficiency anaemia in the peri-operative period. The SR found insufficient data to make firm conclusions about the efficacy of pre-operative intravenous iron administration for the correction of anaemia based on clinical trial settings. Neither could the review establish firm conclusions on the potential cost savings of intravenous iron supplementation.

The aim of undertaking this PhD program of study was in part to provide further evidence into a clinical area of great importance. The thesis includes in chronological order four peer-reviewed journal articles published during candidature

Froessler B, Collingwood J, Hodyl NA, Dekker G. Intravenous ferric carboxymaltose for anaemia in pregnancy. BMC Pregnancy Childbirth. 2014;14:115.

Froessler B, Dekker G, McAuliffe G. To the rescue: the role of intravenous iron in the management of severe anaemia in the peri-partum setting. Blood Transfus. 2015 Jan;13(1):150-2.

Froessler B, Weber I, Hodyl NA, Saadat-Gilani K. Dynamic changes in clot formation determined using thromboelastometry after reinfusion of unwashed anticoagulated cell-salvaged whole blood in total hip arthroplasty. Blood Transfus. 2015 Jul;13(3):448-54.

Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial. Ann Surg. 2016 Jan 27. PubMed PMID: 26817624. Epub 2016/01/29. Eng.

All four publications focus on aspects of Patient Blood Management.

Publication 1:

Froessler B, Collingwood J, Hodyl NA, Dekker G. Intravenous ferric carboxymaltose for anaemia in pregnancy. BMC Pregnancy Childbirth. 2014;14:115.

BMC Pregnancy & Childbirth

RESEARCH ARTICLE Open Access

Intravenous ferric carboxymaltose for anaemia in pregnancy

Bernd Froessler[1,2*], Joshua Collingwood[3], Nicolette A Hodyl[4] and Gustaaf Dekker[5,6]

Abstract

Background: Iron deficiency is a common nutritional deficiency amongst women of childbearing age. Peri-partum iron deficiency anaemia (IDA) is associated with significant maternal, fetal and infant morbidity. Current options for treatment are limited: these include oral iron supplementation, which can be ineffective and poorly tolerated, and red blood cell transfusions, which carry an inherent risk and should be avoided. Ferric carboxymaltose is a new treatment option that may be better tolerated.
The study was designed to assess the safety and efficacy of iron deficiency anaemia (IDA) correction with intravenous ferric carboxymaltose in pregnant women with mild, moderate and severe anaemia in the second and third trimester.

Methods: Prospective observational study; 65 anaemic pregnant women received ferric carboxymaltose up to 15 mg/kg between 24 and 40 weeks of pregnancy (median 35 weeks gestational age, SD 3.6). Treatment effectiveness was assessed by repeat haemoglobin (Hb) measurements and patient report of well-being in the postpartum period. Safety was assessed by analysis of adverse drug reactions and fetal heart rate monitoring during the infusion.

Results: Intravenous ferric carboxymaltose infusion significantly increased Hb values ($p < 0.01$) above baseline levels in all women. Increased Hb values were observed at 3 and 6 weeks post infusion and up to 8 weeks post-infusion. Ferritin values increased significantly after the infusion. Only 4 women had repeat ferritin values post-partum which remained above baseline levels. Fetal heart rate monitoring did not indicate a drug related negative impact on the fetus. Of the 29 (44.6%) women interviewed, 19 (65.5%) women reported an improvement in their well-being and 9 (31%) felt no different after the infusion. None of the women felt worse. No serious adverse effects were found and minor side effects occurred in 13 (20%) patients.

Conclusions: Our prospective data is consistent with existing observational reports of the safe and effective use of ferric carboxymaltose in the treatment of iron deficiency anaemia in pregnancy.

Keywords: Pregnancy, Iron deficiency, Peri-partum anaemia, Intravenous ferric carboxymaltose, Red blood cell transfusion

Background

Iron deficiency is recognized as a common nutritional deficiency amongst women of childbearing age in both the developed and developing world [1]. Peri-partum iron deficiency anaemia (IDA) is associated with significant maternal, fetal and infant morbidity. Poor outcomes for the fetus and infant include: preterm birth, fetal growth restriction, intrauterine fetal death, low Apgar scores and infection [2]. Women with iron deficiency are also at risk of adverse effects requiring medical interventions such as red blood transfusion [3], cardiovascular problems, reduced physical and cognitive performance, reduced immune function, tiredness and increased depressive episodes [4]. Peri-partum maternal iron deficiency has also been associated with childhood developmental problems [5] and negative mother-infant interactions such as an increase in negative statements and decreased responsiveness [6].

* Correspondence: bernd.froessler@health.sa.gov.au
[1]Department of Anaesthesia, Lyell McEwin Hospital, Haydown Road, Elizabeth Vale 5112, South Australia, Australia
[2]Discipline of Acute Care Medicine, University of Adelaide, Adelaide, South Australia, Australia
Full list of author information is available at the end of the article

Progression from iron deficiency to iron deficiency anaemia (IDA) in pregnancy is common, due to the increased demand for iron during pregnancy, required to support maternal haemoglobin mass expansion, as well as the growing fetus and placenta [7]. This is further aggravated by blood loss associated with delivery. Deliveries by both caesarean section and vaginal deliveries that require instrumentation/intervention represent an even greater risk [4] increasing a woman's vulnerability for peri-partum blood transfusion [3], chronic iron deficiency anaemia and iron store depletion, all compromising maternal well-being. However, this recognition has not resulted in a universal approach of iron supplementation [8].

Iron deficiency is potentially both preventable and treatable. Effective management strategies that allow women to replenish iron stores, both antenatal or during labour, restore haemoglobin values and are likely to enhance the health of the mother and infant [9]. For many decades the mainstay treatment of IDA has been oral iron and red blood cell (RBC) transfusions. However, oral iron supplementation can lead to significant side effects resulting in non-compliance in many patients [10] and the risks for RBC transfusion are well described and should be avoided whenever possible [11]. Intravenous iron formulations offer an alternative approach in the presence of moderate or severe anaemia, intolerance of or non-adherence to oral iron and malabsorption states [12]. Intravenous iron is less commonly used as fear of anaphylaxis with iron dextran formulations, and long infusion time with iron polymaltose, have led to reluctance amongst clinicians [13]. The development of dextran free parenteral iron formulations with an improved safety profile, and a more rapid delivery time suggests that intravenous iron should be considered as a mainstay treatment for moderate to severe IDA [14].

Iron Sucrose and Ferric Carboxymaltose are dextran free intravenous iron alternatives. When compared to oral iron in pregnancy iron sucrose is superior with respect to the rate of both haemoglobin increase and iron store replenishment, combined with a good safety profile [12,15,16]. Serious adverse effects are rare with iron sucrose, however minor side effects occur in up to 18% of patients which may in part be attributed to its non-physiological physical properties (high pH and high osmolarity). Ferric carboxymaltose is a newer dextran-free iron formulation with a near neutral pH, physiological osmolarity and increased bioavailability which allows for single dose, short 15 minute infusion time and higher dosing (up to 1000 mg) [17]. These properties make ferric carboxymaltose an attractive alternative to iron sucrose in terms of risk profile, efficacy, patient comfort and convenience, staff and institutional resource utilization.

To date, there are few clinical studies using ferric carboxymaltose in pregnant women. The primary aim of this study was to assess the use of intravenous ferric carboxymaltose in the correction of iron deficiency anaemia in pregnant women. The secondary aims were to determine the extent and severity of adverse effects of ferric carboxymaltose, and to evaluate the perceived quality of life of women in the post-partum period.

Methods

After approval by the Queen Elizabeth Hospital, Lyell McEwin Hospital & Modbury Hospital Human Research and Ethics committee (Reference number 2011160) this prospective study was performed between July 2011 and September 2012. Informed consent was waived by the ethics committee for data collection, as ferric carboxymaltose was being used as our routine clinical treatment modality in this setting.

Pregnant women with documented IDA, defined as Hb < 115 g/dl, who consecutively presented as outpatients in the Women's Assessment Unit at the Lyell McEwen Hospital (Elizabeth Vale South Australia) to receive ferric carboxymaltose infusions were recruited to this study. A total of 65 women were included. Due to the limited availability of safety data for its use in pregnancy, we adopted a longer infusion protocol (30 min) than recommended by the manufacturer (15 min). Maternal blood pressure was taken every five minutes during infusion and foetal heart rate was assessed before and after infusion. According to routine antenatal care blood samples were collected to measure haemoglobin, and in some cases ferritin levels, prior to infusion and then again, where clinically indicated, at up to three post-infusion visits (at approximately 3, 6 and 8 weeks). Haemoglobin and ferritin concentrations were determined in the hospital laboratory using Sodium lauryl sulphate (SLS) method for Hb analysis (Sysmex XE2100 analyser) and direct chemiluminometric sandwich immunoassay (Siemens ADVIA Centaur XP) for ferritin analysis. Women were observed for one hour post infusion, before being discharged home. Medical and pathology data were collated from case notes and electronic laboratory reports, as well as transfusion data linkage reports. A telephone interview was conducted after all 65 patients delivered to evaluate well-being after the infusion. Patients were asked to place themselves into 1 of 4 allocated categories (worse, no different, better or much better), which reflected degrees of perceived change in symptomatology since infusion.

The data were analysed using Graph Pad Prism 5, using p values of ≤0.05 to indicate significance. Available pre-infusion, post-infusion and post-partum haemoglobin, ferritin and transferrin saturation levels were compared using one-way ANOVA tests. Tukey's multiple comparison tests were used to assess changes in levels across the time points measured with Dunn's

multiple comparison test used for post hoc analysis when necessary.

Results

The characteristics of the women receiving ferric carboxymaltose for iron deficiency anaemia are outlined in Table 1. A total of 65 women received a ferric carboxymaltose infusion for antenatal iron deficiency anaemia, with pre-infusion haemoglobin data available for all 65 women. Following infusion, haemoglobin values were repeated by the obstetric team as required and data were available for 88% of women: 31 women (48%) at visit 1 (3 weeks post infusion), 26 women (40%) at visit 2 (6 weeks post infusion) and a total of 20 (31%) women had a blood test at visit 3 (8 weeks post infusion; post-partum). All women responded to the treatment with increased Hb values.

Of the 65 women entered into the study, 18 (27.7%) women were defined as having severe anaemia (Hb <90 g/dl), while 12 women (18.5%) were defined as having moderate anaemia (90–94 g/dl) and the remaining 35 (55.8%) women had mild anaemia (95–116 g/dl)

Changes in haemoglobin concentration over the post-infusion period are presented in Figure 1. The pre-infusion haemoglobin level was significantly lower than haemoglobin values measured at all subsequent visits ($p < 0.01$ in each case). There was a significant increase in haemoglobin levels from 3 to 6 weeks post-infusion (average increase 12 g/dl; $p < 0.01$). By 8 weeks post-infusion, these values had returned back to levels comparable with those observed at 3 weeks post-infusion, which were still significantly higher than pre-infusion levels. When IDA severity was included in the analysis, a similar pattern of results emerged (Table 2). For all three severity groups, haemoglobin levels increased post infusion at 3 and 6 weeks, to be significantly higher than baseline levels ($p < 0.01$ in all cases). However, the post-partum haemoglobin levels were only significantly higher than baseline in the women with mild IDA ($p < 0.01$), while haemoglobin levels in the moderate and severe groups had reverted back to pre-infusion levels. The analysis of the post-partum haemoglobin levels, however, was limited by small numbers in each group at this time point (mild n = 11, moderate n = 3, severe n = 4).

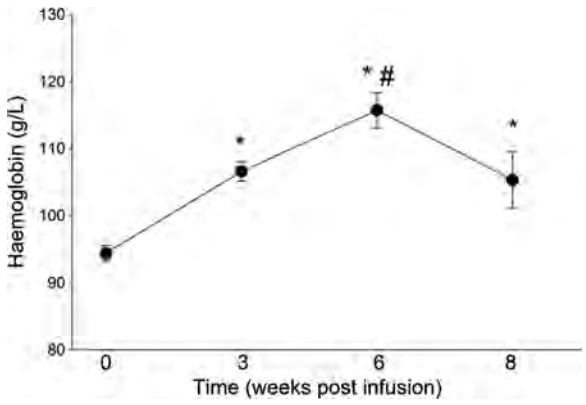

Figure 1 Mean ± SEM haemoglobin levels (g/L). *$p < 0.01$ compared to baseline (pre-infusion), #$p < 0.01$ compared to 3 weeks.

Table 1 Demographic information of women in the study

Age (years)	28.3 ± 7.3
BMI	28.3 ± 8.2
Gravidity	4 ± 3
Parity	2 ± 2
Mode of delivery	
Vaginal	38 (58.4%)
Elective Caesarean	19 (29.2%)
Emergency Caesarean	4 (6.2%)
Instrumental	4 (6.2%)
Oral iron supplements	31 (48%)
Iron intolerance	10 (15%)
Blood loss (ml)	413 ± 340
Gestational age at intervention (weeks)	34.3 ± 3.6
Haemoglobin at booking (12 weeks)	113.4 g/L
Ferritin at booking (12 weeks)	17 μg/L

Data are presented as n (%) or mean (± standard deviation).

Ferritin values increased significantly after the infusion (Table 3). As there was no strict protocol, post-partum ferritin levels were available for only 2 patients. However, despite the limitation, these values indicate reasonably replenished iron stores, with mean (±SD) levels of 151 μg/L (± 4.2).

All adverse reactions are presented in Table 4. No serious adverse effects were recorded in any of the 65 women receiving an infusion. Minor side effects occurred in 13 (20%) patients. One patient required medication with Metoclopramide for nausea and vomiting. All other adverse events were self-limiting. Fetal heart rate monitoring did not indicate a drug related adverse effect on the fetal heart pattern. Red blood cell transfusions were required by 3 women (4.6%) in the study cohort, all of whom had a significant peri-partum haemorrhage.

Follow-up interview by telephone was conducted on 29 (44.6%) women in the post-partum period. Of these women, 19 (65.5%) reported an improvement in their wellbeing (48.3% reported feeling “much better”, 17.2% reported “a little better”, and 9 (31%) reported feeling “no different”) after the infusion. One woman was unwilling to provide information. None of the women reported feeling worse.

Table 2 Haemoglobin levels (g/L) across the testing period for women in the study, split by severity of iron deficiency anaemia at study enrolment

	Gestational age at entry	Pre-infusion	3 weeks post infusion	6 weeks post infusion	8 weeks post infusion (post-partum)
Mild ≥95 g/L	34 (4)	102.1 (1.0) n = 31	108.3 (3.9)* n = 28	120.6 (2.9)* n = 18	113.1 (4.2)* n = 11
Moderate 90-94 g/L	36 (2)	92.6 (0.4) n = 14	105.8 (3.0)* n = 13	108.4 (3.8)* n = 5	92.7 (12.4) n = 3
Severe <90 g/L	34 (3)	83.7 (0.9) 20	100.2 (3.3)* n = 17	110.0 (8.1)* n = 5	93.3 (8.1) n = 4

Data are presented as means (SEM). *p < 0.01 compared to pre-infusion haemoglobin levels.

Discussion

This is the first prospective study reporting on ferric carboxymaltose infusions in pregnancy. The key finding of our study is that in women presenting with IDA relatively late in pregnancy, a ferric carboxymaltose infusion prior to delivery significantly increased haemoglobin levels and improved iron stores. Further, we demonstrate that ferric carboxymaltose appears to be a safe and effective treatment modality for the correction of IDA, as no serious adverse events and only few minor adverse events reported. Reassuringly, patient satisfaction rating and improvement in perceived wellbeing assessed in the postnatal period was high

Many women develop iron deficiency during pregnancy, a condition that can have serious maternal and fetal implications [14]. In our cohort, first trimester booking bloods showed only discrete anaemia with mean Hb of 113.4 g/L, but all women studied developed moderate to severe IDA. The low mean ferritin at booking of 17 μg/L represent profound iron deficiency and reiterates the importance of ferritin as a screening tool. This finding should generally result in the initiation of iron supplementation. For some women oral iron supplementation appears to be sufficient to maintain adequate iron stores. However many women develop moderate to severe IDA despite oral iron supplementation (as demonstrated in the current study where 48% of women were on oral iron), or due to drug intolerance (15% in the current study), non-adherence or pre-disposing pathology such as malabsorption or inflammatory bowel disorders. For those women intravenous iron administration may be a more effective treatment modality.

To date no prospective, controlled clinical study has been performed using ferric carboxymaltose in pregnant women. A recent Cochrane review concluded that large, good quality trials, assessing clinical outcomes (including adverse effects) as well as the effects of treatment by severity of anaemia are required [18]. In the absence of these studies, observational safety and efficacy data may help identify potential benefits and risks. Two recent retrospective observational studies comparing ferric carboxymaltose to different intravenous iron preparations highlighted the safety and efficacy of ferric carboxymaltose [19,20].

The rapid delivery option of a large single dose of ferric carboxymaltose offers a promising treatment modality for pregnant women who need correction of iron deficiency and anaemia, over other IV iron formulations that have low dosage limits, such as iron sucrose (200 mg). The properties of ferric carboxymaltose may also reduce the burden on the patient and the health care system.

In obstetrics, red blood cell transfusions currently account for 3–4% of all transfusion events and the majority of these occur following post-partum haemorrhage (PPH) [21]. PPH is the leading cause of maternal mortality in obstetrics, and is estimated to occur at a rate of 13.1% [9]. Despite its enormous clinical utility, RBC transfusion is a treatment with well described adverse events and risk, and should ideally be avoided. Additionally blood is both costly and in ever increasingly short supply [22-24]. In the present cohort, only three patients (4.6%) required a RBC transfusion following a significant PPH. A recent large retrospective study revealed much higher transfusion rates of 7.5% in women with clinical PPH [25]. The current data suggests that improving Hb, even at a late stage of the third trimester may have shielded some mothers in our cohort from the risks of an allogeneic transfusion. This does not only spare resources, but also optimizes the health of women

Table 3 Ferritin levels (μg/L) across the testing period for women in the study

	Booking	Pre infusion	Post infusion
Ferritin μg/L	13.5 (13) n = 47	6.5 (3.9) n = 25	194 (316)* n = 24

Data are presented as means (SD). *p < 0.05 compared to pre-infusion levels.

Table 4 Number of women experiencing a drug related adverse events following infusion with ferric carboxymaltose (total number of women infused n = 65)

Adverse event	n (%)
Any adverse event	13 (20)
Local (injection site irritation)	
Slight burning sensation	5 (8)
Systemic	
Hypotension	1 (1.5)
Headache	4 (6)
Nausea/Vomiting	1 (1.5)
Pruritus	2 (3)

throughout and beyond her pregnancy into the challenging post-partum period [4,26].

Conclusion

The data from this prospective case series is consistent with existing retrospective data that ferric carboxymaltose administration in the second and third trimester of pregnancy is likely to be safe and effective. In our study ferric carboxymaltose successfully corrected IDA prior to delivery. The intervention prevented significant post-partum anaemia in all women resulting in post-partum haemoglobin values higher than their pre-treatment antenatal values. Despite moderate to severe anaemia at presentation, labour associated blood loss was tolerated well resulting in low peri-partum RBC transfusion rates. No serious adverse events were recorded. Well-being also improved for the majority of women after the infusion.

Abbreviations

IDA: Iron deficiency anaemia; Hb: Haemoglobin; RBC: Red blood cell; PPH: Post-partum haemorrhage.

Competing interests

BF has received lecture honoraria or travel support in the last 5 years from New South Wales Department of Health, South Australia Department of Health, Australian Red Cross Blood Service, Australian National Blood Authority, Vifor Pharma Ltd., Glattbrugg, Switzerland, Fresenius Kabi GmbH, Bad Homburg, Germany.

No support was received from any organization for the submitted work; No other relationships or activities that could appear to have influenced the submitted work. JC, NH and GD have no conflict-of-interest to declare.

Authors' contributions

BF participated in the design, acquisition of data, communicated with participants and drafted the manuscript. JC participated in the design, acquisition of data and revising the manuscript critically for important intellectual content. NH performed the statistical analysis and helped to draft the manuscript. GD conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

Acknowledgement

I would like to thank all midwifes, in particular Michelle Marsh, in Women's Assessment Unit, who collected the information during the infusion.

Author details

[1]Department of Anaesthesia, Lyell McEwin Hospital, Haydown Road, Elizabeth Vale 5112, South Australia, Australia. [2]Discipline of Acute Care Medicine, University of Adelaide, Adelaide, South Australia, Australia. [3]Ballarat Base Hospital, Drummond Street, North Ballarat, VIC, Australia. [4]NHMRC Peter Doherty Research Fellow, Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, South Australia, Australia. [5]Department of Obstetrics and Gynaecology, Lyell McEwin Hospital, Elizabeth Vale, South Australia, Australia. [6]Robinson Institute, Lyell McEwin Hospital, Elizabeth Vale, South Australia, Australia.

Received: 1 October 2013 Accepted: 6 March 2014
Published: 25 March 2014

References

1. Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L, Irlam J, Isaacs W, Sive A, Tomlinson M: **Maternal iron deficiency anemia affects postpartum emotions and cognition.** *J Nutr* 2005, **135**(2):267–272.
2. Lone FW, Qureshi RN, Emmanuel F: **Maternal anaemia and its impact on perinatal outcome in a tertiary care hospital in Pakistan.** *East Mediterr Health J* 2004, **10**(6):801–807.
3. Ehrenthal DB, Chichester ML, Cole OS, Jiang X: **Maternal risk factors for peripartum transfusion.** *J Womens Health* 2012, **21**(7):792–797.
4. Bodnar LM, Cogswell ME, McDonald T: **Have we forgotten the significance of postpartum iron deficiency?** *Am J Obstet Gynecol* 2005, **193**(1):36–44.
5. Beard J: **Recent evidence from human and animal studies regarding iron status and infant development.** *J Nutr* 2007, **137**(2):524S–530S.
6. Perez EM, Hendricks MK, Beard JL, Murray-Kolb LE, Berg A, Tomlinson M, Irlam J, Isaacs W, Njengele T, Sive A, Vernon-Feagans L: **Mother-infant interactions and infant development are altered by maternal iron deficiency anemia.** *J Nutr* 2005, **135**(4):850–855.
7. Gautam CS, Saha L, Sekhri K, Saha PK: **Iron deficiency in pregnancy and the rationality of iron supplements prescribed during pregnancy.** *Medscape J Med* 2008, **10**(12):283.
8. Milman N: **Postpartum anemia II: Prevention and treatment.** *Ann Hematol* 2012, **91**(2):143–154.
9. Roberts CL, Ford JB, Thompson JF, Morris JM: **Population rates of haemorrhage and transfusions among obstetric patients in NSW: a short communication.** *Aust N Z J Obstet Gynaecol* 2009, **49**(3):296–298.
10. Khalafallah A, Dennis A, Bates J, Bates G, Robertson IK, Smith L, Ball MJ, Seaton D, Brain T, Rasko JE: **A prospective randomized, controlled trial of intravenous versus oral iron for moderate iron deficiency anaemia of pregnancy.** *J Intern Med* 2010, **268**(3):286–295.
11. Shander A, Javidroozi M, Perelman S, Puzio T, Lobel G: **From bloodless surgery to patient blood management.** *Mt Sinai J Med* 2012, **79**(1):56–65.
12. Froessler B, Cocchiaro C, Saadat-Gilani K, Hodyl N, Dekker G: **Intravenous iron sucrose versus oral iron ferrous sulfate for antenatal and postpartum iron deficiency anemia: a randomized trial.** *J Matern Fetal Neonatal Med* 2013, **26**(7):654–659.
13. Chertow GM, Hsu CY, Johansen KL: **The enlarging body of evidence: obesity and chronic kidney disease.** *J Am Soc Nephrol* 2006, **17**(6):1501–1502.
14. Khalafallah AA, Dennis AE: **Iron deficiency anaemia in pregnancy and postpartum: Pathophysiology and effect of oral versus intravenous iron therapy.** *J Pregnancy* 2012, **2012:**10.
15. Bayoumeu F, Subiran-Buisset C, Baka NE, Legagneur H, Monnier-Barbarino P, Laxenaire MC: **Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route.** *Am J Obstet Gynecol* 2002, **186**(3):518–522.
16. Bhandal N, Russell R: **Intravenous versus oral iron therapy for postpartum anaemia.** *Bjog* 2006, **113**(11):1248–1252.
17. Milman N, Bergholt T, Byg KE, Eriksen L, Graudal N: **Iron status and iron balance during pregnancy. A critical reappraisal of iron supplementation.** *Acta Obstet Gynecol Scand* 1999, **78**(9):749–757.
18. Reveiz L, Gyte Gillian ML, Cuervo Luis G, Casasbuenas A: **Treatments for iron-deficiency anaemia in pregnancy**. In *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2011.
19. Christoph P, Schuller C, Studer H, Irion O, De Tejada BM, Surbek D: **Intravenous iron treatment in pregnancy: comparison of high-dose ferric carboxymaltose vs. iron sucrose.** *J Perinat Med* 2012, **40**(5):469–474.
20. Myers B: **Diagnosis and management of maternal thrombocytopenia in pregnancy.** *Br J Haematol* 2012, **158**(1):3–15.
21. Catling S: **Blood conservation techniques in obstetrics: a UK perspective.** *Int J Obstet Anesth* 2007, **16**(3):241–249.
22. Ferraris VA, Davenport DL, Saha SP, Austin PC, Zwischenberger JB: **Surgical outcomes and transfusion of minimal amounts of blood in the operating room.** *Arch Surg* 2012, **147**(1):49–55.
23. Greinacher A, Fendrich K, Brzenska R, Kiefel V, Hoffmann W: **Implications of demographics on future blood supply: a population-based cross-sectional study.** *Transfusion* 2011, **51**(4):702–709.
24. Pfenniger A, Schuller C, Christoph P, Surbek D: **Safety and efficacy of high-dose intravenous iron carboxymaltose vs. iron sucrose for treatment of postpartum anemia.** *J Perinat Med* 2012, **40**(4):397–402.
25. Bonnet MP, Deneux-Tharaux C, Dupont C, Rudigoz RC, Bouvier-Colle MH: **Transfusion practices in postpartum hemorrhage: a population-based study.** *Acta Obstet Gynecol Scand* 2013, **92**(4):404–413.
26. Bergmann RL, Richter R, Bergmann KE, Dudenhausen JW: **Prevalence and risk factors for early postpartum anemia.** *Eur J Obstet Gynecol Reprod Biol* 2010, **150**(2):126–131.

doi:10.1186/1471-2393-14-115
Cite this article as: Froessler *et al.*: Intravenous ferric carboxymaltose for anaemia in pregnancy. *BMC Pregnancy and Childbirth* 2014 **14**:115.

Publication 2:

Froessler B, Dekker G, McAuliffe G. To the rescue: the role of intravenous iron in the management of severe anaemia in the peri-partum setting. Blood Transfus. 2015 Jan;13(1):150-2.

Froessler, B., Dekker, G. & McAuliffe, G. (2015). To the rescue: the role of intravenous iron in the management of severe anaemia in the peri-partum setting. *Blood Transfusion, 13*(1), 150-152

Publication 3:

Froessler B, Weber I, Hodyl NA, et al. Dynamic changes in clot formation determined using thromboelastometry after reinfusion of unwashed anticoagulated cell-salvaged whole blood in total hip arthroplasty. *Blood Transfus* 2015; 13:448-454.

Froessler, B., Weber, I., Hodyl, N.A., & Saadat-Gilani, K. (2015). Dynamic changes in clot formation determined using thromboelastometry after reinfusion of unwashed anticoagulated cellsalvaged whole blood in total hip arthroplasty.
Blood Transfusion, 13(3), 448-454

Publication 4:

Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial. Ann Surg. 2016 Jan 27. PubMed PMID: 26817624. Epub 2016/01/29. Eng.

Froessler, B., Palm, P., Weber, I., Hodyl, N.A., Singh, R. & Murphy, E.M. (2016).
The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial.
Annals of Surgery, 264(1), 41-46

Conclusion

Significance and contribution to knowledge

The program of research as reported in the publications included in this thesis highlight the importance of appropriate anaemia management in various clinical settings. Simple but effective pharmacological (IV iron) and technical interventions (cell salvage) to enhance and preserve the patient's own red cell mass led to reduction or avoidance of allogeneic RBC transfusion in our patients. Thereby, risk minimisation and improved outcomes were achieved. The overall significance is substantial and has led at least at a local level to practice change. The presented work adds to a growing body of evidence that anaemia management is at the core of PBM.

Problems encountered

However, despite the enormous prevalence of iron deficiency with or without anaemia, the clear association between allogeneic RBC transfusion and adverse outcomes, the demonstrated safety of restrictive transfusion approaches, the increased health care cost and the growing shortage of blood products, clinicians around the world often ignore the importance of appropriate anaemia management.

Decades after the AIDS crisis blood transfusions were listed in 2013 as one of the five most overused treatment modalities. (48) The AMA also highlighted the danger of unnecessary transfusions. It appears that a considerable number of clinicians have adopted a more restrictive transfusion approach, as RBC consumption is decreasing in many countries. In Australia 21% fewer RBC's were issued over the last 4 years. (NBA, personal communication) Tolerating

anaemia by applying restrictive transfusion strategies challenges the patients' physiological reserves. Provisions to support the individual by addressing co-morbidities have to be made and limitations and risk to be kept in mind. However, it needs to be understood that restrictive transfusion strategies are only one aspect of a comprehensive PBM approach.

PBM has to reflect sound clinical practice. Modifiable conditions like ID and IDA must be treated appropriately to capitalise on the outcome benefits offered by the implementation of the perioperative three pillar strategy. Translational gaps continue to exist. In part this may be caused by clinicians' ongoing struggle in understanding iron metabolism and diagnosis of iron deficiency, functional iron deficiency and the anaemia of chronic disease.

The diagnosis of ID can be difficult. Bone marrow aspiration remains the gold standard. The invasive nature of the test in combination with patient discomfort, cost and accessibility make this, however, a limited diagnostic tool. In longstanding iron deficiency red cell indices are often reduced and a standard full blood count will help to make the diagnosis. In certain age groups in combination with specific disorders (e.g. women with heavy menstrual bleeding) 80% with microcytosis will also be iron deficient.(2) The presence of other nutrional deficiencies may balance these changes out, which is often the case in the elderly.(74) Without inflammation serum ferritin provides a reliable tool. By increasing the cut-off from 15 µg/L to 30 µg/L sensitivity increased from 25% to 92%. The new cut-offs and reference intervals were adopted by many colleges and societies. (75) (76, 77) (Accessed 11/12/15) Ferritin levels

between 30-300 µg/L make interpretation of suspected ID more difficult and higher reference values in combination with other laboratory parameters, such as C-reactive protein (CRP) and Transferrin saturation, (TSAT), have been recommended for patients with acute or chronic inflammation, chronic disease, cancer, renal disease and hepatic disorders. (74, 78, 79)

Future directions

Governments, professional societies, clinicians and patients have recognised the value and importance of PBM. Patient safety is vital and the paradigm shift from a (blood) product focus to a patient focused approach has occurred. However, we are far from a universal implementation of PBM. To ensure that PBM becomes “Standard of Care” many jurisdictions and professional organisations have introduced or are developing guidelines to assist health professionals with the implementation of good clinical practices around PBM in surgical and non-surgical settings. (62, 80-82)

Although this thesis concentrates on the perioperative setting James P. Isbister has recently proposed that the three pillar matrix has a broader application. (64)

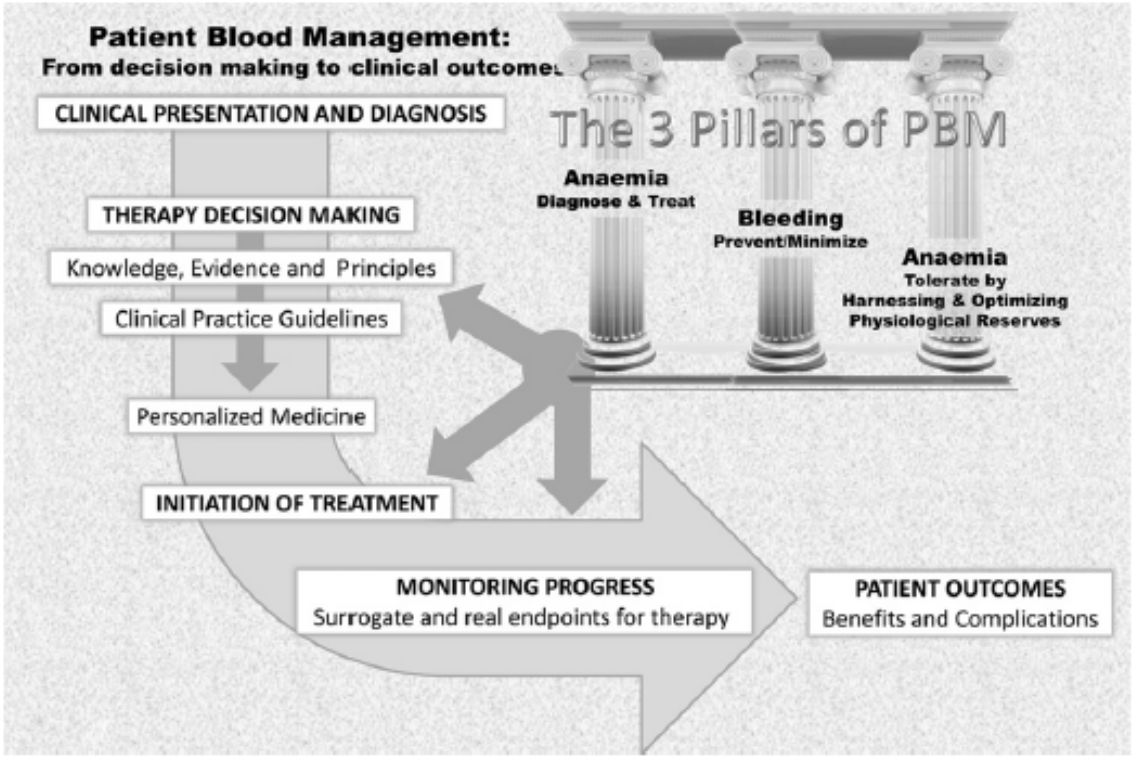

Figure 4: The three pillars of patient blood management: From decision making to clinical outcomes. Cited with permission from; Isbister JP. The three-pillar matrix of patient blood management--an overview. *Best Pract Res Clin Anaesthesiol* 2013; 27:69-84.

In Australia PBM guidelines were established and published by the National Blood authority (NBA) in 2012 and replaced clinical practice guidelines from 2002, published by National Health and Medical Research Council (NHMRC). Blood and blood products were also included in 2011 into the National Safety and Quality Health Service (NSQHS) standards, to ensure the safe and appropriate administration of blood and blood products to patients. The systematic review which provided the evidence for the development of the PBM guidelines, conducted by the NBA, highlighted an independent association between pre-operative anaemia and increase of morbidity and mortality. Enormous variability in anaemia management and RBC transfusion practice

became apparent. In 2014 the Health Minister of Australia engaged the Australian Commission on Safety and Quality in Health Care (the Commission) to facilitate a National Patient Blood Management Collaborative (the collaborative).(80) The collaborative includes 12 teams from health services around Australia and aims to reduce unnecessary clinical variation and morbidity and mortality associated with pre-operative anaemia. The focus is on three major surgical subgroups (gastrointestinal, orthopaedic, and gynaecological) where the prevalence of ID and IDA is high. The aim is to establish detection and treatment pathways in order to reduce unnecessary clinical variation and morbidity and mortality associated with pre-operative anaemia.

We have come a long way in the last 15 years of PBM. However, we have a long way to go to achieve widespread application of PBM principles and strategies. Guidelines and government initiatives can only be as good as the clinician applying the best practice approach.

A search for the term ‘Patient Blood Management’ today gives 9,680,000 results. A multitude of published trial results and editorials have emphasized the negative impact of transfusion, IDA and the outcome and financial benefits of good clinical medicine offered by applying a comprehensive PBM approach. Yet, we continue to come across many patients who remain untreated and who potentially suffer the consequences from receiving inappropriate RBC transfusions. Many misconceptions remain (83). A recent editorial titled “Non-treatment of preoperative anaemia is substandard clinical practice” (84) reminds clinicians of their individual ethical responsibilities. The ‘Choosing wisely campaign’ launched in the United States and Canada (85) (86) could offer

different approach to win over doctors in an attempt to avoid harm and provide best practice(87). This is, hopefully a timely wake up call for many of us.

Appendix:

Statement of Authorship

Statement of Authorship

Title of Paper	Intravenous ferric carboxymaltose for anaemia in pregnancy
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Publication Style
Publication Details	Froessler, B., J. Collingwood, N. A. Hodyl and G. Dekker (2014). "Intravenous ferric carboxymaltose for anaemia in pregnancy." BMC Pregnancy Childbirth 14: 115. DOI 10.1186/1471-2393-14-115

Principal Author

Name of Principal Author (Candidate)	Bernd Froessler		
Contribution to the Paper	Study design, interpreted data, wrote manuscript and acted as corresponding author.		
Overall percentage (%)	85%		
Signature		Date	16/12/15

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);
II. permission is granted for the candidate in include the publication in the thesis; and
III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Joshua Collingwood		
Contribution to the Paper	Collected data, revised manuscript.		
Signature		Date	16/12/15

Name of Co-Author	Nicolette A Hodyl		
Contribution to the Paper	**Performed analysis,** interpreted data, revised manuscript		
Signature		Date	16/12/15

Name of Co-Author	Gustaaf Dekker		
Contribution to the Paper	Helped to evaluate and edit the manuscript.		
Signature		Date	16/12/15

Please cut and paste additional co-author panels here as required.

Statement of Authorship

Title of Paper	To the rescue; the role of intravenous iron in the management of severe anaemia in the peri-partum setting
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Publication Style
Publication Details	Froessler, B., Dekker, G., McAuliffe, G. (2014). "To the rescue: the role of intravenous iron in the management of severe anaemia in the peri-partum setting " Blood Transfusion, Trasfusione del Sangue DOI 10.2450/2014.0220-14

Principal Author

Name of Principal Author (Candidate)	Bernd Froessler		
Contribution to the Paper	Collected and interpreted data, wrote manuscript and acted as corresponding author		
Overall percentage (%)	90		
Signature		Date	16/12/15

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);
II. permission is granted for the candidate in include the publication in the thesis; and
III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Georgina McAuliffe		
Contribution to the Paper	revised manuscript		
Signature		Date	16/12/15

Name of Co-Author	Gustaaf Dekker		
Contribution to the Paper	Helped to evaluate and edit the manuscript.		
Signature		Date	16/12/15

Please cut and paste additional co-author panels here as required.

Statement of Authorship

Title of Paper	Dynamic changes in clot formation using Thromboelastometry after reinfusion of unwashed anticoagulated cell salvaged whole blood in total hip arthroplasty
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Publication Style
Publication Details	Froessler, B., I. Weber, N. A. Hodyl and K. Saadat-Gilani (2015). "Dynamic changes in clot formation determined using thromboelastometry after reinfusion of unwashed anticoagulated cell-salvaged whole blood in total hip arthroplasty." Blood Transfus 13(3): 448-454.

Principal Author

Name of Principal Author (Candidate)	Bernd Froessler		
Contribution to the Paper	Study design, performed analysis on samples, interpreted data, wrote manuscript and acted as corresponding author		
Overall percentage (%)	85%		
Signature		Date	16/12/15

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);

II. permission is granted for the candidate in include the publication in the thesis; and

III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Ingo Weber		
Contribution to the Paper	Recruitment, performed analysis on samples, helped in data interpretation and manuscript evaluation.		
Signature		Date	16/12/15

Name of Co-Author	Nicolette A Hodyl
Contribution to the Paper	**Performed cytokine and statistical analysis**, interpreted data, revised manuscript

Signature		Date	16/12/15

Name of Co-Author	Khaschayar Saadat-Gilani		
Contribution to the Paper	Study design, performed analysis on samples, revised manuscript		
Signature		Date	16/12/15

Please cut and paste additional co-author panels here as required.

Statement of Authorship

Title of Paper	The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: a randomized controlled trial
Publication Status	☑ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Publication Style
Publication Details	**Annals of Surgery _ Volume XX, Number X, Month 2016**

Principal Author

Name of Principal Author (Candidate)	Bernd Froessler		
Contribution to the Paper	Study design, wrote ethics application, recruitment, follow up, statistical analysis, interpreted data, wrote manuscript and acted as corresponding author		
Overall percentage (%)	85%		
Signature		Date	24/12/15

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

I. the candidate's stated contribution to the publication is accurate (as detailed above);
II. permission is granted for the candidate in include the publication in the thesis; and
III. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Peter Palm		
Contribution to the Paper	Recruitment, follow up, manuscript evaluation.		
Signature		Date	24/12/15

Name of Co-Author	Ingo Weber		
Contribution to the Paper	Recruitment, manuscript evaluation.		
Signature		Date	24/12/15

Name of Co-Author	Nicolette A Hodyl		
Contribution to the Paper	Study design, statistical analysis, revised manuscript		
Signature		Date	24/12/15

Name of Co-Author	Rajvinder Singh		
Contribution to the Paper	Study design, manuscript evaluation		
Signature		Date	24/12/15

Name of Co-Author	Elizabeth Murphy		
Contribution to the Paper	Study design, recruitment, follow up, revised manuscript		
Signature		Date	24/12/15

Please cut and paste additional co-author panels here as required.

References

1. World Health Organization. Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers. 2001 [cited 2015 12/05/2015]. Available from: http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf
2. Galloway MJ, Smellie WSA. Investigating iron status in microcytic anaemia2006. 791-3 p.
3. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public health nutrition. 2009 Apr;12(4):444-54.
4. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. Alimentary pharmacology & therapeutics. 2006 Dec;24(11-12):1507-23.
5. Rattehalli D, Pickard L, Tselepis C, Sharma N, Iqbal TH. Iron deficiency without anaemia: Do not wait for the haemoglobin to drop? Health Policy and Technology. 2013;2(1):45-58.
6. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet. 2011 Oct 15;378(9800):1396-407.
7. Cairo G, Bernuzzi F, Recalcati S. A precious metal: iron, an essential nutrient for all cells. Genes Nutr. 2006;1:25-39.
8. Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW, et al. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. BMJ. 2013;346:f3443.
9. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. Nat Rev Cardiol. 2011;8(9):485-93.
10. Jauregui-Lobera I. Iron deficiency and cognitive functions. Neuropsychiatric disease and treatment. 2014;10:2087-95.
11. Ekiz C, Agaoglu L, Karakas Z, Gurel N, Yalcin I. The effect of iron deficiency anemia on the function of the immune system. Hematol J. 2005;5(7):579-83.
12. Brownlie Tt, Utermohlen V, Hinton PS, Giordano C, Haas JD. Marginal iron deficiency without anemia impairs aerobic adaptation among previously untrained women. Am J Clin Nutr. 2002 Apr;75(4):734-42.
13. Meier J, Gombotz H. Pillar III – Optimisation of anaemia tolerance. Best Practice & Research Clinical Anaesthesiology. 2013;27(1):111-9.
14. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015 May 7;372(19):1832-43.
15. Pratt JJ, Khan KS. Non-Anaemic Iron Deficiency - a disease looking for recognition of diagnosis: a systematic review. Eur J Haematol. 2015.
16. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014 Jan 30;123(5):615-24.
17. Shannon L. Farmer JI, Leahy MF. History of blood transfusion. In: Jabbour N, editor. Transfusion Free Medicine and Surgery. 2nd ed: Wiley-Blackwell; 2014.
18. Goethe JWv. Faust. Eine Tragödie. 1. Auflage ed. Tübingen: Cotta; 1808.
19. Myhre BA. The first recorded blood transfusions: 1656 to 1668. Transfusion. 1990;30(4):358-62.
20. Farr AD. The first human blood transfusion. Medical History. 1980;24(2):143-62.
21. Spence RK, Erhard J. History of patient blood management. Best Practice & Research Clinical Anaesthesiology. 2013 3//;27(1):11-5.

22. Landsteiner K. Ueber Agglutinationserscheinungen normalen menschlichen Blutes. Wein Klin Wschr. 1901;14:1132–6.
23. Hoffman R. Hematology. Sixth Edition ed. Philadelphia: Saunders; 2013.
24. National Blood Authority. Red cells issued by the Blood Service. Canberra2013.
25. ABUSE of transfusion therapy. The New England journal of medicine. 1951;245(19):745-6.
26. Crosby WH. Misuse of blood transfusion. Blood. 1958;13(12):1198-200.
27. Isbister JP. Strategies for avoiding or minimizing homologous blood transfusion: a sequel to the AIDS scare. Med J Aust. 1985 May 27;142(11):596-9.
28. Isbister JP. The paradigm shift in blood transfusion. Med J Aust. 1988 Mar 21;148(6):306-8.
29. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. Ann Intern Med. 1992 Mar 1;116(5):393-402.
30. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation. 2007 Nov 27;116(22):2544-52.
31. Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg. 2009 May;208(5):931-7.
32. Engelfriet CP, Reesink HW, Brand B, Levy G, Williamson LM, Menitove JE, et al. Haemovigilance systems. Vox Sang. 1999;77(2):110-20.
33. World Health Organization. Haemovigilance 2015 [cited 2015 11/12/2015]. Available from: http://www.who.int/bloodsafety/haemovigilance/en/.
34. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999 Feb 11;340(6):409-17.
35. Reyes G, Nuche JM, Sarraj A, Cobiella J, Orts M, Martin G, et al. [Bloodless cardiac surgery in Jehovah's witnesses: outcomes compared with a control group]. Rev Esp Cardiol. 2007 Jul;60(7):727-31.
36. Habler O, Voss B. [Perioperative management of Jehovah's Witness patients. Special consideration of religiously motivated refusal of allogeneic blood transfusion]. Anaesthesist. 2010 Apr;59(4):297-311.
37. Shander A, Javidroozi M, Naqvi S, Aregbeyen O, Çaylan M, Demir S, et al. An update on mortality and morbidity in patients with very low postoperative hemoglobin levels who decline blood transfusion (CME). Transfusion. 2014;54(10pt2):2688-95.
38. Froessler B, Dekker G, McAuliffe G. To the rescue: the role of intravenous iron in the management of severe anaemia in the peri-partum setting. Blood Transfus. 2015 Jan;13(1):150-2.
39. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011 Dec 29;365(26):2453-62.
40. Carson JL, Carless PA, Hébert PC. OUtcomes using lower vs higher hemoglobin thresholds for red blood cell transfusion. JAMA. 2013;309(1):83-4.
41. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014 Oct 9;371(15):1381-91.
42. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. New England Journal of Medicine. 2013;368(1):11-21.

43. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ. 2015;350:h1354.
44. Jairath V, Kahan BC, Gray A, Dore CJ, Mora A, James MW, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet. 2015 Jul 11;386(9989):137-44.
45. Spahn DR, Spahn GH, Stein P. Evidence base for restrictive transfusion triggers in high-risk patients. Transfusion medicine and hemotherapy : offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie. 2015 Mar;42(2):110-4.
46. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012;4:CD002042.
47. Shander A, Javidroozi M, Ozawa S, Hare GM. What is really dangerous: anaemia or transfusion? Br J Anaesth. 2011 Dec;107 Suppl 1:i41-59.
48. Goodnough LT. Blood management: transfusion medicine comes of age. The Lancet. 2013;381(9880):1791-2.
49. Isbister JP, Shander A, Spahn DR, Erhard J, Farmer SL, Hofmann A. Adverse blood transfusion outcomes: establishing causation. Transfus Med Rev. 2011 Apr;25(2):89-101.
50. Greinacher A, Fendrich K, Brzenska R, Kiefel V, Hoffmann W. Implications of demographics on future blood supply: a population-based cross-sectional study. Transfusion. 2011 Apr;51(4):702-9.
51. Hofmann A, Farmer S, Shander A. Five drivers shifting the paradigm from product-focused transfusion practice to patient blood management. Oncologist. 2011;16 Suppl 3:3-11.
52. Gombotz H. Patient blood management: A patient-orientated approach to blood replacement with the goal of reducing anemia, blood loss and the need for blood transfusion in elective surgery. Transfusion Medicine and Hemotherapy. 2012;39(2):67-72.
53. Leahy MF, Mukhtar SA. From blood transfusion to patient blood management: a new paradigm for patient care and cost assessment of blood transfusion practice. Intern Med J. 2012 Mar;42(3):332-8.
54. Goodnough LT, Shander A. Patient blood management. Anesthesiology. 2012 Jun;116(6):1367-76.
55. Organization WH. World Health Assembly Resolution 63.12 on Availability, Safety and Quality of Blood Products. 2010.
56. Spahn DR, Theusinger OM, Hofmann A. Patient blood management is a win-win: a wake-up call. Br J Anaesth. 2012 Jun;108(6):889-92.
57. Isbister JP. Clinicians as gatekeepers: what is the best route to optimal blood use? Dev Biol (Basel). 2007;127:9-14.
58. Froessler B, Weber I, Hodyl NA, Saadat-Gilani K. Dynamic changes in clot formation determined using thromboelastometry after reinfusion of unwashed anticoagulated cell-salvaged whole blood in total hip arthroplasty. Blood Transfus. 2015 Jul;13(3):448-54.
59. Goodnough LT, Maniatis A, Earnshaw P, Benoni G, Beris P, Bisbe E, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth. 2011 Jan;106(1):13-22.
60. Myers E, O'Grady P, Dolan AM. The influence of preclinical anaemia on outcome following total hip replacement. Archives of orthopaedic and trauma surgery. 2004 Dec;124(10):699-701.

61. Minck S, Robinson K, Saxon B, Spigiel T, Thomson A. Patient blood management -- the GP's guide. Aust Fam Physician. 2013 May;42(5):291-7.
62. Leal-Noval SR, Munoz M, Asuero M, Contreras E, Garcia-Erce JA, Llau JV, et al. Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the "Seville Document". Blood Transfus. 2013 Oct;11(4):585-610.
63. Hare GM. Tolerance of anemia: understanding the adaptive physiological mechanisms which promote survival. Transfus Apher Sci. 2014 Feb;50(1):10-2.
64. Isbister JP. The three-pillar matrix of patient blood management--an overview. Best Pract Res Clin Anaesthesiol. 2013 Mar;27(1):69-84.
65. Stockman R. The treatment of chlorosis with iron and some other drugs. Br Med J. 1893;1:881-5.
66. Nissim J. Intravenous administration of iron. Lancet. 1947;1::49-51.
67. Baird IM, Podmore DA. Intramuscular iron therapy in iron-deficiency anaemia. Lancet. 1954 Nov 6;267(6845):942-6.
68. Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. Transfusion. 2009 Dec;49(12):2719-28.
69. Filippatos G, Farmakis D, Colet JC, Dickstein K, Luscher TF, Willenheimer R, et al. Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial. European journal of heart failure. 2013 Jul 18.
70. Bisbe E. Role of iron replacement in the management of preoperative anemia. Transfusion Alternatives in Transfusion Medicine. 2012 //;12(3-4):150-6.
71. Froessler B. Intravenous Iron Sucrose for the anaemic peri-operative patient. National Scientific Congress of the Australian Society of Anaesthetists; Darwin2009.
72. Auerbach M, Macdougall IC. Safety of intravenous iron formulations: facts and folklore. Blood Transfus. 2014 Jul;12(3):296-300.
73. Froessler B, Tufanaru C, Cyna A, Pearson A. Preoperative anaemia management with intravenous iron: a systematic review. The JBI Database of Systematic Reviews and Implementation Reports. 2013 2013-11-14;11(10):33.
74. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet. 2015 Aug 24.
75. Goddard AF, James MW, McIntyre AS, Scott BB, British Society of G. Guidelines for the management of iron deficiency anaemia. Gut. 2011 Oct;60(10):1309-16.
76. Pavord S, Myers B, Robinson S, Allard S, Strong J, Oppenheimer C. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol. 2012 Mar;156(5):588-600.
77. RCPA. Iron studies standardised reporting protocol: The Royal College of Pathologists of Australasia; 2013 [11/12/2015]. Available from: http://www.rcpa.edu.au/Library/Practising-Pathology/Iron-Studies-Standardised-Reporting-Protocol.
78. Beris P, Munoz M, Garcia-Erce JA, Thomas D, Maniatis A, Van der Linden P. Perioperative anaemia management: consensus statement on the role of intravenous iron. Br J Anaesth. 2008 May;100(5):599-604.
79. Stein J, Dignass AU. Management of iron deficiency anemia in inflammatory bowel disease - a practical approach. Annals of gastroenterology : quarterly publication of the Hellenic Society of Gastroenterology. 2013;26(2):104-13.
80. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. Anesthesiology. 2015 Feb;122(2):241-75.

81. National Blood Authority. Patient blood management guidelines: Module 2 – Perioperative. 2012 [11/12/2015]. Available from: http://www.blood.gov.au/pbm-module-2.
82. European Guide on Good Practices for Patient Blood Management 2015 [cited 2015 11/12/2015]. Available from: http://www.europe-pbm.eu/about.
83. Munoz M, Gomez-Ramirez S, Kozek-Langeneker S, Shander A, Richards T, Pavia J, et al. 'Fit to fly': overcoming barriers to preoperative haemoglobin optimization in surgical patients. Br J Anaesth. 2015 Jul;115(1):15-24.
84. Spahn DR, Zacharowski K. Non-treatment of preoperative anaemia is substandard clinical practice. Br J Anaesth. 2015 Apr 15.
85. American Board of Internal Medicine Foundation. Choosing Wisely 2015 [cited 2015 15/12/15]. Available from: http://www.abimfoundation.org/Initiatives/Choosing-Wisely.aspx.
86. Hurley R. Can doctors reduce harmful medical overuse worldwide? Bmj. 2014;349:g4289.
87. Murphy MF. The Choosing Wisely campaign to reduce harmful medical overuse: its close association with Patient Blood Management initiatives. Transfus Med. 2015 Oct 16.