Prevention of oral mucositis in head & neck cancer patients: 
A systematic review

Thesis submitted in partial fulfilment for the Masters of Philosophy (Clinical Science)

THE UNIVERSITY OF ADELAIDE

School of Population Health and Clinical Practice

Discipline of Nursing

The Joanna Briggs Institute

Supervisors: Dr Craig Lockwood and Emeritus Professor Judy Lumby

Dr Joanne Bowen

August 2012
# Table of Contents

Table of Figures ................................................................................................................................................................... v

Exegesis ................................................................................................................................................................................ vii

Declaration ........................................................................................................................................................................... ix

Acknowledgements............................................................................................................................................................. x

Chapter 1. Introduction .................................................................................................................................................... 1

1.1 Context of the review ............................................................................................................................................ 1

1.2 Scope of review .................................................................................................................................................... 11

1.3 Justification of review approach ................................................................................................................... 13

1.4 Assumptions and limitations of approach ................................................................................................ 13

Chapter 2. Systematic review protocol ................................................................................................................... 15

2.1 Statement of review question ........................................................................................................................ 15

2.2 Objectives of review ........................................................................................................................................... 15

2.3 Inclusion criteria .................................................................................................................................................. 15

2.3.1 Types of studies ................................................................................................................................ 15

2.3.2 Types of participants ................................................................................................................................. 16

2.3.3 Types of interventions ............................................................................................................................... 16

2.3.4 Types of comparisons ............................................................................................................................... 16

2.3.5 Types of outcome measures ................................................................................................................... 16

2.4 Review methods ................................................................................................................................................... 17

2.4.1 Search strategy ............................................................................................................................................. 17

2.4.2 Assessment of methodological quality .................................................................................................... 20

2.4.3 Data extraction ............................................................................................................................................. 20

2.4.4 Data synthesis .............................................................................................................................................. 20

Chapter 3. Results ........................................................................................................................................................... 21

3.1. Description of studies ....................................................................................................................................... 21

3.1.1. Summary of interventions of included studies .............................................................................. 22
3.1.2. Summary of outcomes reported in included studies ............................................ 24

3.2 Review findings........................................................................................................ 25

3.2.1 Accelerated radiotherapy ................................................................. 25

3.2.2 Amifostine ................................................................................. 28

3.2.3 Allopurinol .............................................................................. 37

3.2.4 Aloe Vera ............................................................................... 37

3.2.5 BCoG lozenge ..................................................................... 41

3.2.6 Benzydamine ..................................................................... 41

3.2.7 Chlorhexidine ..................................................................... 42

3.2.8 Chemotherapy ..................................................................... 43

3.2.9 Dead Sea products ......................................................... 43

3.2.11 Epidermal growth factor .................................................. 44

3.2.10 Flurbiprofen ..................................................................... 44

3.2.11 Fluconazole ....................................................................... 45

3.2.12 Glutamine ........................................................................ 46

3.2.13 Glycerin payayor................................................................. 46

3.2.14 Granulocyte colony stimulating factor .................................... 47

3.2.15 Granulocyte macrophage colony stimulating factor .......... 50

3.2.16 Honey .............................................................................. 51

3.2.17 Indigowood root extract .......................................................... 55

3.2.18 Iseganan hydrochloride .......................................................... 55

3.2.19 Keratinocyte growth factor .................................................. 56

3.2.20 Low level laser therapy ....................................................... 56

3.2.21 Misoprostol ...................................................................... 57

3.2.22 Morning radiotherapy ............................................................. 58

3.2.23 Orgotein ............................................................................ 60

3.2.24 Perio-Aid Tratamiento® ............................................................ 60
3.2.25 Pilocarpine .................................................................................................................................................. 60
3.2.26 Prednisone .................................................................................................................................................. 63
3.2.27 Providone iodine ...................................................................................................................................... 63
3.2.28 PTA ................................................................................................................................................................. 66
3.2.29 Qingre Liyan Decoction .......................................................................................................................... 68
3.2.30 Salt and bicarbonate ............................................................................................................................... 68
3.2.31 Selenium....................................................................................................................................................... 68
3.2.32 Sucralfate ..................................................................................................................................................... 69
3.2.33 Vitamin E...................................................................................................................................................... 74
3.2.34 WF10 ............................................................................................................................................................. 74
3.2.35 Wobe-Mugos E ........................................................................................................................................... 74
3.2.36 Zinc ................................................................................................................................................................. 77

Chapter 4. Discussion and Conclusions.................................................................................................................. 79
4.1 General Discussion .............................................................................................................................................. 79
4.2 Implications for Practice ................................................................................................................................ 88
4.3 Implications for Research ................................................................................................................................ 88
4.4 Conclusion .............................................................................................................................................................. 89

References .......................................................................................................................................................................... 91

Appendix 1 - Clinical appraisal instruments ...................................................................................................... 114
Appendix 2 - Data extraction instrument ............................................................................................................ 117
Appendix 3 - Detailed search strategies ............................................................................................................... 119
  a. PUBMED .............................................................................................................................................................. 119
  b. EMBASE ............................................................................................................................................................... 119
  c. CINAHL ................................................................................................................................................................. 120
  d. CENTRAL ............................................................................................................................................................ 120
  e. Web of Science .................................................................................................................................................. 121

Appendix 4 – Included studies ........................................................................................................................................ 122
Appendix 5 – Excluded studies
**Table of Figures**

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1.</td>
<td>Therapeutic index of strategies used to treat head and neck cancer.</td>
<td>6</td>
</tr>
<tr>
<td>Figure 2.</td>
<td>Systematic review workflow.</td>
<td>21</td>
</tr>
<tr>
<td>Figure 3.</td>
<td>Incidence of severe mucositis in accelerated/hyperfractionated radiotherapy vs conventional radiotherapy for head and neck cancer.</td>
<td>27</td>
</tr>
<tr>
<td>Figure 4.</td>
<td>Incidence of severe oral mucositis with subcutaneous amifostine vs nothing in radiotherapy with or without chemotherapy for head and neck cancer.</td>
<td>35</td>
</tr>
<tr>
<td>Figure 5a.</td>
<td>Incidence of severe mucositis in patients treated with intravenous amifostine vs nothing during radiotherapy with or without chemotherapy for head and neck cancer.</td>
<td>36</td>
</tr>
<tr>
<td>Figure 5b.</td>
<td>Incidence of any mucositis in patients treated with intravenous amifostine vs nothing during radiotherapy with or without chemotherapy for head and neck cancer.</td>
<td>36</td>
</tr>
<tr>
<td>Figure 6.</td>
<td>Incidence of severe mucositis in patients administered aloe vera vs placebo during radiotherapy with or without chemotherapy for head and neck cancer.</td>
<td>39</td>
</tr>
<tr>
<td>Figure 7.</td>
<td>Incidence of severe mucositis in patients treated with subcutaneous G-CSF vs placebo during radiotherapy for head and neck cancer.</td>
<td>48</td>
</tr>
<tr>
<td>Figure 8a.</td>
<td>Incidence of severe oral mucositis in patients treated with honey vs nothing during radiotherapy for head and neck cancer.</td>
<td>52</td>
</tr>
<tr>
<td>Figure 8b.</td>
<td>Incidence of any mucositis in patients treated with honey vs nothing during radiotherapy for head and neck cancer.</td>
<td>52</td>
</tr>
<tr>
<td>Figure 8c.</td>
<td>Incidence of radiation treatment interruption in patients treated with honey vs nothing during radiotherapy for head and neck cancer.</td>
<td>53</td>
</tr>
<tr>
<td>Figure 9.</td>
<td>Incidence of severe mucositis in patients treated with radiation for head and neck cancer in the morning vs the afternoon.</td>
<td>58</td>
</tr>
<tr>
<td>Figure 10.</td>
<td>Incidence of severe mucositis in patients treated with pilocarpine vs placebo during radiotherapy for head and neck cancer.</td>
<td>61</td>
</tr>
<tr>
<td>Figure 11.</td>
<td>Severity of oral mucositis in patients treated with provodine-iodine vs water during radiotherapy with or without chemotherapy for head and neck cancer.</td>
<td>63</td>
</tr>
<tr>
<td>Figure 12.</td>
<td>Incidence of any oral mucositis in patients treated with PTA paste vs placebo during radiotherapy for head and neck cancer.</td>
<td>65</td>
</tr>
<tr>
<td>Figure 13a.</td>
<td>Incidence of severe oral mucositis in patients treated with sucralfate vs placebo during radiotherapy for head and neck cancer.</td>
<td>70</td>
</tr>
</tbody>
</table>
Figure 13b. Incidence of oral mucositis in patients treated with sucralfate vs placebo during radiotherapy for head and neck cancer.

Figure 13c. Severity of oral mucositis in patients treated with sucralfate vs placebo during radiotherapy for head and neck cancer.

Figure 14a. Incidence of severe mucositis in patients treated with Wobe-Mugo E vs nothing during radiotherapy for head and neck cancer.

Figure 14b. Incidence of any mucositis in patients treated with Wobe-Mugo E vs nothing during radiotherapy for head and neck cancer.

Figure 15. Incidence of severe mucositis in patients treated with zinc capsules vs placebo capsules during radiotherapy with or without chemotherapy for head and neck cancer.
Exegesis
Oral mucositis is a common and costly consequence of cancer treatment that currently lacks adequate intervention options. Patients treated for head and neck malignancies are at particularly high risk of severe mucositis, which significantly impedes delivery of therapy and consequently results in poorer outcomes in this population. As such, the quantitative objective of this review was to identify the effectiveness of agents and devices for oral mucositis prevention in newly diagnosed adult head & neck cancer patients being treated with radiotherapy with or without chemotherapy. The methodological framework developed by the Joanna Briggs Institute was followed to conduct the review. The quantitative component of the review considered any randomised controlled trials. In the absence of RCTs other research designs, such as non-randomised controlled trials and before and after studies, were considered for inclusion in a narrative summary to enable the identification of current best evidence. Databases were searched for published and non-published studies. A total of 202 studies were retrieved for review, with 81 studies excluded after reading the full article for clearly not meeting the inclusion criteria of the review. Two reviewers independently assessed 123 studies for methodological quality, excluding 51 for a range of reasons including failure to present baseline data, and use of intervention for mucositis treatment rather than prophylaxis. In the final 72 studies, 13 interventions provided sufficient evidence to be combined in meta-analyses. Only 8 interventions provided weak evidence of benefit to prevent oral mucositis in head and neck cancer patients treated with radiotherapy, with or without chemotherapy, including amifostine (intravenous administration), aloe vera, G-CSF, honey, sucralfate, morning radiotherapy, providone-iodine and Wobe-Mugos E. Honey was the only intervention to significantly reduce severe mucositis during radiotherapy in all studies, indicating that this is a promising agent deserving further investigation. The remaining interventions had either too few studies conducted or conflicting results to make conclusions regarding effectiveness. A lack of studies which examined the same intervention and inconsistency in reporting of outcomes prevented
aggregation of study results into statistical meta-analysis for most interventions. Furthermore, a general need for additional well designed, adequately powered studies of interventions contributed to the lack of evidence. Future mucositis intervention studies require appropriate placebo controls and double blinding to increase the level of evidence available for the few promising interventions identified.
Declaration

I declare that this thesis is a record of original work and contains no material which has been accepted for the award of any other academic degree or diploma in any university or other tertiary institution, 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 that the digital version of my thesis be made available on the web, via the University's digital resource repository, the Library catalogue, the Australasian Digital Thesis Program (ADTP) and also through web search engines, unless permission has been granted to restrict access for a period of time.

Dr Joanne Bowen
Acknowledgements

I would like to thank my supervisors Dr Craig Lockwood and Emeritus Professor Judy Lumby for their expert guidance during preparation of this thesis and throughout my candidature.

I also acknowledge the generous support of the National Health and Medical Research Council funding received during my candidature.

Finally, I would like to acknowledge the invaluable support received from The University of Adelaide and Joanna Briggs Institute Staff.