The effectiveness of strategies for preventing and treating chemotherapy and radiation induced oral mucositis in patients with cancer

Kowanko I, Long L, Hodgkinson B, Evans D

Authors' objectives
To summarise the best available evidence on prevention and treatment strategies for oral mucositis resulting from radiotherapy and/or chemotherapy for cancer in adults.

Searching
Eight different databases (CINAHL, MEDLINE, Currents Contents, EMBASE, PsycLIT, Cochrane Library, Cancerlit, Iowa drug information service) were searched and dates are reported. Reference lists of identified studies and review papers were checked. Unpublished studies were sought using 3 databases (Dissertation Abstracts International, Index to Theses: GB & Ireland, Proceedings First) for theses and conference proceedings. Authors were not contacted for missing information, nor were foreign language papers translated.

Study selection
Study designs of evaluations included in the review
Randomised or quasi-randomised controlled trials were considered. In the absence of such trials, other types of research were considered. Only articles which met certain quality standards were included.

Specific interventions included in the review
All interventions aimed at preventing or treating oral mucositis resulting from radiotherapy and/or chemotherapy for any cancer were considered in this review.

Specific interventions included: oral care protocols, interventions which reduce the mucosal toxicity of chemotherapy drugs (allopurinol, cryotherapy), mouthwashes with mixed actions (chamomile, benzydamine hydrochloride, corticosteroids), immunomodulatory agents (colony stimulating factors, immunoglobin), topical anaesthetics (dyclonine hydrochloride, diphenhydramine, lignocaine and related compounds), antiseptics (chlorhexidine, povidone iodine, hydrogen peroxide), topical antimicrobial agents (nystatin, clotrimazole, other combinations of topical agents including antifungals, PTA lozenges), systemic antifungals (fluconazole), antiviral agents (acyclovir), mucosal barriers and coating agents (sucralfate, other mucosal barriers), cytoprotectants (beta-carotene, vitamin E, azelastine hydrochloride, prostaglandin E, oxpentifylline), mucosal cell stimulants (low energy laser, silver nitrate, glutamine, psychotherapy) and analgesics (opioids).

Participants included in the review
Adult patients with, or at risk of developing, oral mucositis resulting from radiotherapy and/or chemotherapy for any cancer were included. Studies involving children, or patients with, or at risk of, oral mucositis from other causes were excluded.

Outcomes assessed in the review
Outcome measures included prevalence and severity of mucositis, oral pain, oral infection, and patients’ perception of effectiveness.

How were decisions on the relevance of primary studies made?
Two reviewers assessed all identified articles on the basis of abstract or title. Where doubt existed the full article was retrieved.

Assessment of study quality
Assessment of quality was limited to experimental studies. Methodological quality was assessed using a checklist developed by The Joanna Briggs Institute for Evidence Based Nursing and Midwifery (JBIEBNM), based on the work of the Centre for Reviews and Dissemination.
of the Cochrane Collaboration, and the NHS Centre for Reviews and Dissemination at the University of York. The checklist included items on randomisation, concealment of allocation, participant and outcome assessor blinding, withdrawals, identical treatments apart from intervention, baseline comparability, identical measurements, reliability of outcome measures and appropriate statistical analysis (Articles scoring 5 or more yes-scores were included).

Uncontrolled pilot studies or observational studies were summarised in narrative form with appropriate qualifying statements. Two reviewers independently assessed all articles, and disagreements were resolved by discussion with a third reviewer.

Data extraction
Outcome data were extracted using a data extraction tool developed and pilot tested by JBEIBNM. The tool is reported in an Appendix.

Methods of synthesis
How were the studies combined?
The bulk of this review consists of a narrative synthesis of the literature, supplemented with tables of numerical data from individual studies which have been combined in meta-analyses where possible. Peto odds ratios (for categorical data) or standardised mean differences (for continuous data) and their 95% confidence intervals (CIs) were calculated for studies which presented sufficient data.

How were differences between studies investigated?
Heterogeneity between studies was investigated using the standard chi-square test.

Results of the review
Fifty-five articles were of acceptable methodological quality for inclusion, a further 46 papers of lower quality were included in the narrative summary where no better evidence on a topic existed.

Oral care protocols (n=4 controlled trials): At present, there is no convincing experimental evidence that any oral care protocols are effective in preventing or reducing mucositis.

Interventions which reduce the mucosal toxicity of chemotherapy drugs: The use of allopurinol mouthwash (n=3 controlled trials) is supported to prevent mucositis resulting from 5-fluorouracil, although there was significant heterogeneity between studies (SMD=-0.40 (95% CI: -0.76,-0.04)). Cryotherapy (n=2 high quality trials) is a cheap and effective method of minimising mucositis, but patients may develop an aversion to the ice as a result of concurrent nausea from the chemotherapy.

Mouthwashes with mixed actions: There is no evidence to support the use of chamomile mouthwash (n=1 RCT) to prevent chemotherapy-induced mucositis. There is good evidence that benzydamine hydrochloride mouthwash (n=7 RCTs) is effective in ameliorating the symptoms of radiation-induced mucositis in patients with head and neck cancer. There is limited evidence in favour of corticosteroid mouthwash (no RCTs).

Immunomodulatory agents: One RCT indicated no significant effect of GM-CSF (Granulocyte-macrophage colony stimulating factor) and another small RCT indicated a beneficial effect of G-CSF (Granulocyte colony stimulating factor). Immunoglobin was reported to minimise mucositis in a clinical report and a controlled trial showed statistically significant reductions in mucositis extent and severity was unclear.

Topical anaesthetics: Their effectiveness has either not been evaluated, or the quality of studies was too poor for inclusion.

Antiseptics: This review does not support the use of chlorhexidine (n=9 RCTs) to prevent mucositis. The use of povidone iodine was supported in one uncontrolled study. There is no evidence supporting the use of hydrogen peroxide mouthwash (n=2 RCTs) to prevent radiation-induced mucositis.
Topical antimicrobial agents: Two RCTs showed a lack of effectiveness of combination mouthwashes containing nystatin on mucositis score, there was significant heterogeneity between the two studies. For clotrimazole and other combinations of topical agents including antifungals no studies were found that met the methodological quality criteria for the review. As yet there is no evidence relating to the efficacy of PTA lozenges in chemotherapy-treated patients.

Systemic antifungals: No conclusions about the effectiveness of prophylactic systemic fluconazole can be made.

Antiviral agents: It appears that prophylactic acyclovir (n=2 RCTs) may have some value in reducing oral lesions due to Herpes in susceptible patients, but that the majority of mucositis lesions do not involve a virus and therefore are not affected by this agent.

Mucosal barriers and coating agents: The evidence does not support the use of sucralfate (n=7 RCTs) to prevent or ameliorate mucositis in cancer patients. No comments can be made about the efficacy of other mucosal barriers. Cytoprotectants: More research is required to investigate the effectiveness of beta-carotene. Vitamin E (n=2 RCTs) had no significant effect on the duration of mucositis. Azelastine hydrochloride (n=1 RCT) significantly reduced the duration and severity of mucositis. The evidence does not support the use of prostaglandin E (n=3 RCTs) to prevent chemotherapy-induced mucositis, nor the use of oxpentifylline (n=1 RCT with cross-over design) to prevent mucositis in chemotherapy-patients.

Mucosal cell stimulants: Low energy laser (n=1 RCT) is of benefit in ameliorating the symptoms of mucositis in bone marrow transplant patients, but more research is required for non-transplanted cancer patients. Silver nitrate (n=2 RCTs) is of questionable value in preventing radiation-induced mucositis. There is limited evidence that glutamine (n=1 RCT) may be useful in reducing mucositis severity, but further research is required.

Psychotherapy (n=2 controlled trials) may be useful to minimise perceived oral pain, but does not affect objective mucositis ratings. Further research is required.

Analgesics (n=3 RCTs): The evidence indicates that morphine administration controlled by the patient is safe and effective for managing oral mucositis pain in cancer patients undergoing in bone marrow transplantation, and that a pharmacokinetically based system warrants further investigation.

Authors' conclusions
For most strategies reviewed there is insufficient evidence to draw any conclusions regarding their effectiveness. In these cases, pending further research, the cheapest and simplest interventions are suggested. There are some interventions which are supported by this review, although the majority of these are based on very few studies.

CRD commentary
This is a well-performed review on prevention and treatment strategies for oral mucositis resulting from radiotherapy and/or chemotherapy for cancer in adults.

The review question was clear, although the inclusion criteria seem very broad.

The search strategy is good. Inclusion and exclusion of studies and methodological quality assessment were performed in an appropriate way. It was not reported how many reviewers were involved in the data extraction process.

Results were described in a narrative way and where appropriate results were pooled. Differences between studies were investigated by means of a chi-square analysis; however, the results of the chi-square test were not presented. The conclusions of the review seem to follow from the evidence presented.

Implications of the review for practice and research
For most strategies further research is required.
Bibliographic details

Indexing Status
Subject indexing assigned by CRD

MeSH
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.