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Systematic Review Exemplar: Preventing Mucositis in Cancer Patients

Karen B Williams, RDH, PhD

Karen B. Williams, RDH, PhD, is a professor and director of the Clinical Research Center at the University of Missouri-Kansas City. She received her certificate in dental hygiene and BS in education at The Ohio State University, her MS in dental hygiene education at the University of Missouri-Kansas City, and PhD in evaluation, measurement and statistics at the University of Kansas. Dr. Williams has been active in clinical dental hygiene for over 35 years and in clinical research for 23 years. Her areas of specialization include research design and statistics, educational methods, dental product efficacy, health outcomes research, and clinical dental hygiene. She is a research consultant for numerous dental manufacturers. Dr. Williams has presented papers and continuing education programs throughout the United States and internationally.

The purpose of *Linking Research to Clinical Practice* is to present evidence-based information to clinical dental hygienists so that they can make informed decisions regarding patient treatment and recommendations. Each issue will feature a different topic area of importance to clinical dental hygienists with A BOTTOM LINE to translate the research findings into clinical application.

Interventions for preventing oral mucositis for patients with cancer receiving treatment Volume (4), 2007.

Worthington, HV; Clarkson, JE; Eden, OB. Cochrane Oral Health Group

Prof Helen Worthington, Coordinating Editor, Cochrane Oral Health Group; School of Dentistry, The University of Manchester, MANDEC, Higher Cambridge Street, Manchester, UK, M15 6FH. E-mail: helen.worthington@manchester.ac.uk. The Cochrane Library, Copyright 2007, The Cochrane Collaboration.

Abstract

Background. Treatment of cancer is increasingly more effective but is associated with short and long term side effects. Oral side effects remain a major source of illness despite the use of a variety of agents to prevent them. One of these side effects is oral mucositis (mouth ulcers).

Objectives. To evaluate the effectiveness of prophylactic agents for oral mucositis in patients with cancer receiving treatment, compared with other potentially active interventions, placebo or no treatment.

Search Strategy. The Cochrane Oral Health Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE were searched. Reference lists from relevant articles were scanned and the authors of eligible studies were contacted to identify trials and obtain additional information. Date of most recent searches: June 2006: CENTRAL (*The Cochrane Library* 2006, Issue 2).

Selection Criteria. Trials were selected if they met the following criteria: design - random allocation of participants; participants - anyone with cancer receiving chemotherapy or radiotherapy treatment for cancer; interventions - agents prescribed to prevent oral mucositis; outcomes - prevention of mucositis, pain, amount of analgesia, dysphagia, systemic infection, length of hospitalisation, cost and patient quality of life.

Data Collection and Analysis. Information regarding methods, participants, interventions and outcome measures and results were independently extracted, in duplicate, by two review authors. Authors were contacted for details of randomisation and withdrawals and a quality assessment was carried out. The Cochrane Collaboration statistical guidelines were followed and risk ratios (RR) calculated using random-effects models.

Main Results. Two hundred and seventy-seven studies were eligible. One hundred and eighty-eight were excluded for various reasons, usually as there was no useable information on mucositis. Of the 89 useable studies all had data for mucositis comprising 7523 randomised patients. Interventions evaluated were: acyclovir, allopurinol mouthrinse, aloe vera, antibiotic pastille or paste, benzydamine, beta carotene, calcium phosphate, camomile, Chinese medicine, chlorhexidine, etoposide, folic acid, glutamine, granulocyte/macrophage colony-stimulating factor (GM-CSF), histamine gel, honey, hydrolytic enzymes, ice chips, iseganan, keratinocyte GF, misonidazole, pilocarpine, pentoxifylline, povidone, prednisone, propantheline anticholinergic, prostaglandin, sucralfate, systemic antibiotic clarithromycin, traumeel, zinc sulphate. Of the 33 interventions included in trials, 12 showed some evidence of a benefit (albeit sometimes weak) for either preventing or reducing the severity of mucositis. Interventions where there was more than one trial in the meta-analysis finding a significant difference when compared with a placebo or no treatment were:

- Amifostine which provided minimal benefit in preventing mild and moderate mucositis RRs = 0.95 (95% confidence interval (CI) 0.92 to 0.98) and 0.88 (95% CI 0.80 to 0.98);
- Chinese medicine showed a benefit at all three dichotomies of mucositis with RR values of 0.44 (95% CI 0.20 to 0.96), 0.44 (95% CI 0.33 to 0.59) and 0.16 (95% CI 0.07 to 0.35) for increasing levels of mucositis severity;
- Hydrolytic enzymes reduced moderate and severe mucositis with RRs = 0.52 (95% CI 0.36 to 0.74) and 0.17 (95% CI 0.06 to 0.52); and
- Ice chips prevented mucositis at all levels RRs = 0.64 (95% CI 0.50 to 0.82), 0.38 (95% CI 0.23 to 0.62), and 0.24 (95% CI 0.12 to 0.48).

Other interventions showing some benefit with only one study were: benzydamine, calcium phosphate, etoposide bolus, honey, iseganan, oral care, zinc sulphate.

The general reporting of RCTs, especially concealment of randomisation, was poor. However, the assessments of the quality of the randomisation improved when the authors provided additional information.

Authors' Conclusions. Several of the interventions were found to have some benefit at preventing or reducing the severity of mucositis associated with cancer treatment. The strength of the evidence was variable and implications for practice include consideration that benefits may be specific for certain cancer types and treatment. There is a need for well designed and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent.

Commentary

In the past several years, the dental hygiene community has increasingly focused on the importance of evidence-based decision making for improving oral health outcomes in our patient populations. Concomitantly, the scientific community has raised concern about the inherent problem of "publication bias." Publication bias occurs when editorial review boards and journal publishers preferentially publish clinical trials that have significant findings. As a result, studies demonstrating no effect for treatments and interventions are rarely published. Publication bias in an evidence-based world gives a skewed view of the real effect of treatments and can lead clinicians to make inappropriate treatment decisions. In the early 1990's, the Cochrane Collaboration was started with the goal of providing access to "accurate information about the effects of healthcare world wide." The Cochrane Collaboration produces, and makes available, systematic reviews on a variety of health care intervention topics, including oral health. A systematic review is a methodologically sound approach to comprehensively compiling and analyzing all literature on a given topic. It starts with a research question that provides

the focus for planning a search strategy, selecting studies that represent only the highest level of evidence on the topic, and subsequently summarizing the "state of knowledge" based on this best estimate. The systematic review overcomes many of the problems inherent in conducting a literature review in that selection bias, sampling bias, and quality control bias is intentionally controlled. Selection bias is addressed by specifying a very inclusive search strategy for obtaining related studies. The search strategy often includes identification of all search engines that might yield relevant studies, papers presented at meetings, and/or contacting leading researchers in the field to ferret out existence of unpublished data. Studies are selected regardless of language or country of origin, and once the search has identified all possible studies, quality is assured by analyzing studies methodology and choosing for inclusion only those studies that meet rigorous standards of quality. This systematic review is a good example of a systematic review, and was focused on evaluating the effectiveness of various prophylactic agents for preventing or reducing severity of oral mucositis in patients receiving cancer treatment. Overall, it clearly demonstrates that there is no simple means by which mucositis can be prevented nor one-step approach to managing mucositis in cancer patients. Additionally, it shows that certain interventions may be more effective for certain cancer treatments than others.

Treatments for cancer (in particular chemotherapy or radiotherapy) have increased survival rates in patients, but the short-term effects on the mouth, especially with respect to severe mucositis or oral candidiasis, can predispose individuals to pain, difficulty eating, bacteremia, and interruption of cancer treatment. This presents a significant challenge to the oncology team as well as the oral health professionals to know best practice standards that will prevent development of mucositis or candidiasis, or at the very least minimize the severity of these problems. Numerous interventions have been examined and include palliative surface protectants as well as treatments that possess anti-inflammatory and antimicrobial properties. Additionally, studies have assessed numerous outcomes including pain, duration and severity of difficulty eating, infection, delay of treatment, toxicity, quality of life, weight loss, and death.

In this review, the research team was particularly interested in comparing active mucositis preventing interventions with placebo treatments or no treatment as a means to determine the incremental effectiveness of the active treatments. Consistent with systematic review methods, the researchers clearly defined: the types of studies that would be included in their analysis (only randomized clinical trials); what target population studies had to address (patients with cancer receiving chemotherapy or radiotherapy or both); treatments that were intended to have a prophylactic effect for oral mucositis and that were compared to a placebo or no treatment; and studies that had mucositis as a primary outcome. Several other secondary outcomes were evaluated as well, but the primary emphasis was on preventing mucositis. Where there were questions regarding methodology of any of the studies, the researchers attempted to contact the original authors to clarify needed information.

The review team made an effort to use a search strategy that effectively included as many research studies as possible, whether they were available from electronic searching (eg, published in professional journals, in clinical trials registers, available from various search engines, etc.), were currently being conducted by researchers in the field, or had been presented at meetings but not published. The research team independently conducted a quality assessment of each article included in the review to ensure that it met sufficient quality standards for inclusion. They reported excellent agreement between reviewers with regard to rating quality of studies for inclusion.

Of the 227 studies that were initially identified in the search process, the researchers determined that 188 of these had critical design or measurement problems that kept them from meeting the rigorous standards for inclusion. Of the remaining 89 studies that did meet these standards, 24 studies were conducted in the United States, 30 were conducted in Europe, and the remaining 35 were performed in 13 different countries. Thus, the studies included in this systematic review provided data from a highly diverse and global population of both adult and pediatric cancer patients. The interventions evaluated were diverse as well and included a variety of medications (acyclovir, amifostine, antibiotics, chlorhexidine, etoposide, pilocarpine), enzymes (allopurinol), anti-inflammatory medications (benzylamine, calcium phosphate), acid buffers (sulcrafate), and natural treatments (beta carotene, aloe vera, chamomile, honey, ice chips, oral hygiene, and Chinese medicine), just to name a few.

There was sufficient evidence to support that some of the treatments were effective in reducing or preventing oral mucositis. Amifostine had some of the best evidence with 11 clinical trials (that included a total of 845 subjects) having a reduction in risk for mucositis compared to placebo or no treatment. Oral proteolytic enzymes also showed fairly strong evidence for reducing severity rather than preventing oral mucositis. Inflammatory mediators, benzylamine and calcium phosphate,

were also found to be significantly more effective than a placebo for preventing mucositis, but both were based on findings from single studies of 36 and 94 patients, respectively.

Of the natural treatments, there was no evidence that aloe vera, beta carotene or chamomile were effective in preventing mucositis, although these products are commonly used as palliative agents to improve patient comfort. However, there was weak evidence that Chinese medicine, comprised of various unidentified herbal concoctions, could reduce the risk for mucositis, and that honey could reduce prevalence of severe mucositis. However, the researchers caution that the strength of this evidence was relatively unreliable, and the herbs used in the Chinese medicine were not specified. Certainly one cannot generalize from this that Chinese medicine on the whole is effective. However, there was relatively good evidence that ice chips may prevent or reduce the severity of mucositis primarily in patients receiving 5-FU as part of their chemotherapy regimen. Additionally, good oral hygiene was found in a single study, to have some preventive benefits in individuals receiving head and neck radiotherapy.

Of interest, trials investigating the effectiveness of topical antimicrobials (9 studies in all) such as chlorhexidine and providone, did not show a consistent effect for preventing mucositis in cancer patients. It is important to note that the researchers state that there was insufficient evidence to substantiate effectiveness, not that there was evidence to show no effect, an important distinction.

This systematic review provides important information for dental hygiene clinicians. Knowing the state of evidence on topics related to oral health allows the dental hygienist to provide more accurate and scientifically relevant information to patients. Cancer patients having treatments that can disrupt the integrity of the oral mucosa need to know that there are options available for them to discuss with their oncologist. Additionally, the dental hygienist is a primary source for information on maintaining optimal home care procedures during cancer treatment.

The Bottom Line

Recent statistics estimate that approximately 1 400 000 people in the United States will be diagnosed with cancer each year. While this number is daunting, the trend in 5-year survival rates for all races gives a reason for optimism. Improvements in cancer treatments have increased 5-year survival rates from 51% in the mid 1970s to approximately 65%, currently. Certainly dental hygienists play an important role in helping identify the 60 000 new cases of oral cancer; however, they play another important role in providing preventive counseling for patients receiving chemotherapy or radiotherapy to the head and neck region. The sheer volume of literature on effectiveness of various interventions for preventing or reducing oral mucositis in this large population makes it virtually impossible for dental hygienists to remain abreast of the most current information. This systematic review, undertaken by the Cochrane Collaboration, provides an analysis of best evidence on treatments that either prevent or reduce severity of mucositis. Knowing that success of mucositis prevention varies depending on cancer therapy will encourage dental hygienists to empower patients to have meaningful conversations with their oncologists about mucositis prevention. Several findings from this review provide guidance for best practices in dental hygiene. Certainly, the evidence that good oral hygiene can be effective in preventing mucositis in individuals having radiotherapy supports the need for effective preventive education for our patients with head and neck cancers. This should be a standard practice irrespective of cancer therapy. Moreover, dental hygienists must be knowledgeable about effectiveness as well as limitations of various treatments. Individuals with mucositis from chemotherapy and radiotherapy are often desperate for relief, making them susceptible to product claims that may not be supported with clinical evidence. The dental team plays an important role in providing sound advice based on scientific, not anecdotal, evidence.

Dental hygienists who possess knowledge about simple natural treatments that are helpful in preventing or reducing severity of mucositis (ice chips for individuals receiving 5 FU as part of their chemotherapy regimen or uncontaminated honey for reducing severity of mucositis) can encourage patients to discuss options with their oncologists. Just as well, they need to know that common treatments such as aloe vera, chamomile, beta carotene, or sucralfate do not have sufficient scientific evidence as effective interventions to recommend these to cancer patients for preventing or reducing mucositis. While they may have a palliative role for improving patient comfort, this should not be confused with being effective treatments for mucositis. Additionally, the dental hygienist can play an important role in helping establish best practices in the dental office by developing guidelines for cancer patients as to how to have meaningful conversations with the oncology team about mucositis prevention.

The researchers who conducted this systematic review for the Cochrane Collaboration comprehensively and meticulously analyzed the 89 best studies in order to determine what is the best evidence on treatments that prevent or reduce severity of oral mucositis for patients receiving chemotherapy or head and neck radiotherapy. Systematic reviews are an important source for scientific evidence in that they provide an objective and global overview of the strength of scientific evidence for various health interventions and outcomes. The Cochrane Collaboration Oral Health Group has produced more than 50 systematic reviews on topics broadly defined as prevention, treatment, and rehabilitation of oral, dental, and craniofacial diseases and disorders. Topics of interest to dental hygienists range from managing oral complications of cancer treatment, fluoride for caries, behavioral interventions to improve patient outcomes in periodontal patients, pit and fissure sealants versus fluoride varnish for preventing dental caries, etc. (<http://www.ohg.cochrane.org/reviews.html#reviews>)

Summary

The sheer volume of literature on topics relevant to dental hygienists can make it difficult to provide patients with best professional advice. Systematic reviews offer a means by which dental hygienists can access best evidence and utilize it in their day-to-day practices. This systematic review provides an example of how a large body of seemingly diverse studies can be distilled into usable information that can inform practice standards. Dental hygiene clinicians will inevitably be in a position to provide counseling to cancer patients or their family members on preventing or reducing the severity of mucositis. The large body of literature and numerous interventions that have been proposed for mucositis makes it difficult for the average clinician to know what treatments yield the best outcomes. This systematic review is a rich source of information as the researchers have methodologically searched, dissected, analyzed, and distilled the most important findings from a wide body of evidence. While there are numerous treatments available for mucositis, only a few have sufficient scientific evidence at this point to make solid recommendations to patients. Clinicians need to counsel their patients to discuss options with the oncology team in advance of therapy in order to limit negative effects on the oral cavity. The systematic review made the following conclusions that suggest that certain treatments may differentially impact mucositis from different cancer treatments:

- Oral care may be effective, primarily with individuals receiving head and neck radiotherapy.
- Amifostine (Ethyol® an injectable amino thiol free radical scavenger) has some benefit in preventing mucositis and in reducing severity of mild mucositis.
- Benzylamine (available as a generic) with anti-inflammatory, analgesic, and antimicrobial properties, has some benefit in preventing mucositis.
- Hydrolytic enzymes reduce the severity of mild to moderate mucositis in patients receiving treatment for head and neck cancers.
- Ice chips may cause local vasoconstriction and limit the oral toxic effect of certain chemotherapeutic drugs, in particular 5-FU.
- Honey may have antibacterial and wound healing properties that can reduce severity of mucositis.