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REVIEW ARTICLE

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Antimicrobials, mucosal coating agents, anesthetics, analgesics, and nutritional supplements for alimentary tract mucositis

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Abstract This review focuses on the value of several groups of agents for the prevention and treatment of mucositis. The review refers to alimentary mucositis as a generalized term that includes oral mucositis and gastrointestinal mucositis. This paper is part of the systematic review made by the mucositis study group which operates in the Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). Several new guidelines are suggested in this review as an update to the primary systematic review that was published by the same group in 2004.

Keywords Mucositis · Antimicrobials · Coating agents · Anesthetics · Analgesics · Nutritional supplement

Introduction

Research activity and publication of results in the arena of cancer therapy-induced alimentary tract mucositis has increased considerably in recent years. We attribute this increase to several factors: 1) mucositis is a prominent cause of patient discomfort during cancer therapy; 2) with successful results in the palliation of other complications, mucositis became one of the primary dose-limiting factors; 3) aggressive cytotoxic therapies increased the severity of side effects to mucous membranes; and 4) efforts made by the Multinational Association of Supportive Care in Cancer (MASCC) and other organizations have increased awareness in the medical community regarding the morbidity and economic consequences of mucositis. As a result, a reassessment of the evidence became necessary in the relatively short time since our group has completed the first such study in 2002 [1–3].

Another reason for the current examination of data is that now we have recognized the pediatric population as a unique subgroup of patients with regards to presenting features, compliance issues, challenges of evaluation, and long term effects of cancer therapies. Extrapolation of adult data to children may lead to false assumptions and would thus be inappropriate. Unfortunately, few articles have addressed this population specifically; we grouped these articles separately.

Materials and methods

We reviewed 55 articles that matched the diverse topics listed in the title, 21 of which were original studies directly related to our areas of interest. Each article was analyzed by at least two panelists and then discussed within the whole group. We reached unanimous consensus in all ratings and conclusions that are presented in the following paragraphs. Articles were grouped by topic, patient population (adults or children), mode of administration, etiology for mucositis (chemotherapy or radiation therapy), and whether the agent studied was aimed at preventing or treating mucositis.

Topical antimicrobials management of oral mucositis in adults: a. chemotherapy and b. radiation therapy

Guideline:

a. No guideline possible; level of evidence: III; grade of recommendation: C, conflicting data. We continue to recommend against the use of chlorhexidine for the treatment of chemotherapy-induced oral mucositis.
b. The panel recommends against use of antibiotic lozenges for the prevention of radiation therapy-induced oral mucositis; level of evidence: II; grade of recommendation: B.

The oral microbiota often has been a suspect in the pathogenesis of mucositis [3]. However, no convincing evidence has been published to make this case. A number of studies used various methods of reduction of the oral microbial burden [2]. Most interventions reached either inconclusive or conflicting results. Recently, Luglie et al. studied chlorhexidine gluconate (CHX) efficacy in preventing chemotherapy-induced oral mucositis [6]. In this case-control study of low power, the authors found decreased incidence of mucositis in CHX patients. Neither bacterial loads, nor immune parameters were presented or introduced in calculations. Conversely, Vokurka et al. examined the preventive effects of povidone-iodine and found no difference in any of the variables between the treatment group and a control group that used normal saline [7]. These results were in contrast to previously published data [8]. We did not consider this evidence sufficient to warrant a modification in the previous guidelines, which were, thus, left unchanged.

Two randomized, controlled studies tested oral lozenges of polymixin, tobramycin, and amphoteracin B (PTA) [9], or bacitracin, clotrimazole, and gentamicin (BCG) [10], respectively. Both studies reported no significant improvement in either incidence or severity of radiation therapy-induced mucositis. Even though some conflicting data exist, the scientific level of these new studies moved the panel to issue a recommendation against the use of antibiotic lozenges for radiation-induced mucositis.

Topical antimicrobials prevention of chemotherapy-induced oral mucositis in children

Guideline:

No guideline possible, insufficient evidence; level of evidence: III; grade of recommendation: B.

The two studies reviewed in this paper have addressed the use of topical antimicrobials in pediatric populations treated with high-dose chemotherapy [11, 12]. Both studies used CHX prophylactically and reported lower incidence of oral mucositis when compared to benzydamine and saline rinse, respectively. Unfortunately, both studies were small (34 and 14 patients, respectively) and not blinded. Additionally, it is unclear why CHX would work differently in children than adults, where generally negative results have been described [2].

Topical mucosal coating agents (sucralfate) treatment of oral mucositis in adults: a. chemotherapy and b. radiotherapy

Guideline:

a. No guideline possible for chemotherapy-induced oral mucositis treatment; level of evidence: II; grade of recommendation: C.
b. Due to its lack of efficacy, the panel recommends against the use of sucralfate for the treatment of radiotherapy-induced oral mucositis; level of evidence: II; grade of recommendation: A.

Due to its proven ability to bind to ulcerated epithelium, sucralfate has been postulated to offer palliation and protection to mucositis sufferers. However, results of multiple studies failed to substantiate this hypothesis [2]. Both new articles reviewed in this (randomized, controlled studies) described no difference between micronized and regular sucralfate rinses, respectively, and placebo [14, 15]. Previous data on the use of sucralfate in chemotherapy-induced mucositis include some positive results, which have not been confirmed [2]. However, data on radiation-induced mucositis treatment were consistent and allowed us to recommend against the use of sucralfate in that group of patients.

Topical anesthetic treatment of alimentary mucositis in adults: a. chemotherapy and b. radiation therapy

Guideline:

a. No guideline possible; level of evidence: III; grade of recommendation: C, conflicting data.
b. No guideline possible; level of evidence: V; grade of recommendation: D, insufficient evidence.

Topical anesthesia is an obvious choice for palliation of mucositis pain. Theoretically, it is appealing as medication could be applied at the site of nociception with minimal systemic consequences. Thus, this therapeutic method has been in broad use, albeit without much effort for scientific validation [2]. Agents used most commonly include anesthetic amides and esters (such as lidocaine and benzocaine), either alone or in various combinations often known as “magic” or “miracle” rinses [1]. Limita-

tions of the method include local discomfort and numbness affecting the sensation of taste and the gag reflex.

Two new articles were reviewed on this topic [4, 5], of which one presented no new findings. The second of these publications described the successful topical use of the general anesthetic ketamine in a case report; this was the first such publication, so further study of ketamine is necessary before any conclusions can be reached [5]. Thus, no changes to the previously published guidelines were made.

Topical analgesics for radiation-induced oral mucositis

Guideline:

No guideline possible for the use of topical morphine sulfate or topical fentanyl, insufficient evidence; level of evidence: II; grade of recommendation: D.

With the discovery of opiate receptors in peripheral tissues and upregulation of these receptors during inflammation, topical narcotic administration had scientific justification. We reviewed publications of the initial trials of topical opiate application in patients with oral mucositis. A cohort study compared pain in 14 patients treated with a morphine oral rinse to 12 "miracle" rinse-treated historic controls [17]. The authors described a significant decrease in duration and intensity of mucositis pain in the experimental group. The results of this small cohort trial require further validation before a recommendation can be considered.

A randomized, controlled, blinded study crossed 14 patients between four pain control protocols: two were different formulations of a fentanyl lozenge and the other two were respective formulations of placebo [18]. While this small study aimed to test the tolerability of the lozenges in mucositis patients, the authors found no difference in pain control between the fentanyl and placebo formulations, which they ascribe to insufficient doses of active drug.

One additional question that remains regarding this strategy of pain control in mucositis is how much of the drug actually penetrates through the ulcerated mucosa and into the blood circulation. In particular, fentanyl, which is very liposoluble, may cloud results with mostly central effects after topical application. None of the studies we reviewed tested this possibility.

Systemic analgesics for chemotherapy-induced alimentary mucositis in adults

Guideline:

No guideline possible for transdermal fentanyl use in chemotherapy-induced oral mucositis, conflicting evidence; level of evidence: III; grade of recommendation: C.

While our previous recommendation for use of patient-controlled analgesia with morphine sulfate remains unchanged [1], more recent studies of various opiates/opioids have shown mixed results. One such study of transdermal fentanyl at 25 and 50 μg/h described no better pain control in the active groups than in the group receiving no treatment [15].

Systemic analgesics for chemotherapy-induced alimentary mucositis in children

Guideline:

No guideline possible for opiate rotation in pediatric patients with cancer and/or chemotherapy-induced pain; level of evidence: V; grade of recommendation: D.

Opioid rotation at equivalent doses was used in pediatric patients to avoid increased side effects. In the article by Drake et al., this method appeared to work well with the exception of changes to fentanyl [16]. More studies, particularly in children, are needed to establish both the role of fentanyl and opioid rotation in cancer analgesia.

Systemic nutritional supplements in prevention of chemotherapy-induced alimentary mucositis

Guideline:

a. In view of the serious side effects described, the panel suggests against usage of parenteral alanyl glutamine in cancer patients; level of evidence: II; grade of recommendation: C.
b. No guideline possible for use of antioxidant mixtures containing ursodeoxycholic acid, follinic acid, and vitamin E, insufficient evidence.

Glutamine is an amino acid necessary for cell mitosis. Numerous trials have tested the effects of supplementation with glutamine on the prevention and/or treatment of mucositis [2]. Patient populations typically consisted of colorectal cancer patients treated with 5-florouracil-containing protocols. Some studies found decreased pain and severity of oral lesions, while others reported no such effect.

A recent abstract indicated the potential value of topical L-glutamine given via a novel delivery system [19]. As the complete data have not been published, this report has not been considered in the formulation of the guideline. Another study randomized 40 bone marrow transplantation patients in a double-blind fashion to receive either intravenous alanyl-glutamine dipeptide or placebo [20]. Results of this rigorously performed trial indicated worse oral mucositis in the treatment group, but a decreased lower

gastro-intestinal tract mucositis, as measured by episodes of diarrhea. More worrisome, patients in the treatment group had higher numbers of relapse of their malignancy and a non-significant increase in the number of deaths at 2 years. The seriousness of these findings prompted the panel to suggest against the use of parenteral alanyl-glutamine in cancer patients.

Previous reports on antioxidant supplements described some limited success in reducing severity, but not the incidence of oral mucositis [2]. These studies were small and not randomized. Recently, another cohort study tested the effects of a combination of ursodeoxycholic acid, follinic acid, and vitamin E in 37 pediatric cancer patients in the bone marrow transplantation unit [21]. The authors reported a decrease in both incidence and severity of oral mucositis in the treated cohort when compared to a historic control group. Hopefully, these preliminary data will lead to a well-designed, larger study of the effects of antioxidants on mucositis. One other important question remaining is whether antioxidants may impart similar protection to the malignant cells.

Changes in graft versus hot disease (GVHD) prophylaxis for prevention of mucositis

Guideline:

No guideline possible, insufficient evidence; level of evidence: II; grade of recommendation: D.

Immune modulation for the prevention of GVHD in allogeneic bone marrow transplant patients typically starts during the engraftment period. Methotrexate, a mucotoxic medication, is one of the most common drugs used for this purpose. As such, it may contribute to the high prevalence and severity of mucositis usually seen in this group of patients. Both studies reviewed in this paper tested the hypothesis that replacing methotrexate with less mucotoxic regimens will reduce chemotherapy-induced mucositis [22, 23]. One study was randomized and controlled [22], while the other was a cohort trial; both reported decreased incidence and/or severity of oral mucositis. In the former study, mucositis results were so impressive that the authors stopped enrollment early and made the experimental treatment available to all patients. Unfortunately, the same study showed an increase in acute GVHD and relapse in the treatment group. Albeit not statistically significant, these increases may have been conclusive if the study enrolled all of the originally proposed patients. Thus, while replacement of methotrexate may indeed reduce mucositis, more evidence is needed regarding the efficacy of the replacement agents in terms of final outcomes.

New agents of potential interest

Two recent publications described the effect of curcumin on chemotherapy- and radiation-induced mucositis in animal models [24, 25]. Both studies reported significant reduction in incidence and severity of mucositis in curcumin pre-treated animals. The agent was administered orally as a supplement or added to diet and was tolerated without any significant side effects or sequelae. The mechanism of action for curcumin appears to be inhibition of nuclear factor-kappa B, which is associated with a decrease in inflammatory cytokine production and caspase-induced apoptosis. These results are promising, and we are anxiously awaiting the results of human trials.

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