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Review article

Preventive Modalities for Oral Mucositis: A Literature Review

Bojan Poposki[1], Kiro Ivanovski[1], Ana Pejčić[2,3], Vlatko Kokolanski[1], Ivana Stanković[2]

[1]*Ss. Cyril and Methodius University in Skopje, Faculty of Dentistry, Skopje, North Macedonia*
[2]*University of Niš, Faculty of Medicine, Department of Periodontology and Oral Medicine, Niš, Serbia*
[3]*Clinic of Dental Medicine, Department of Periodontology and Oral Medicine, Niš, Serbia*

SUMMARY

Introduction/Aim. Oral mucositis is an acute, inflammatory, and ulcerative condition of the oral mucosa caused by chemotherapy and/or radiotherapy. Considering the frequency of oral mucositis, its impact on the physical and mental health of patients, as well as the depletion of the economic capacities of an individual and society, the importance of prevention and management of oral mucositis is clearly highlighted. The aim of our study was to determine the modern preventive modalities for oral mucositis.
Literature review. A search of studies indexed in the literature from 2002 to 2022 was conducted using the PubMed database. The search was conducted with the keywords: stomatitis, mucositis, oral mucositis, chemotherapy, radiotherapy, prevention, and oral cancer. There are numerous preventive modalities for oral mucositis, including: patient education, professional oral health care, home hygiene, rinsing solutions, anti-inflammatory agents such as benzydamine, photobiomodulation, cryotherapy, miconazole, liquid mucoadhesive hydrogel, high potency polymerized cross-linked sucralfate, morphine mouthwash solution, growth factors and cytokines, honey, vitamin C, vitamin E, vitamin B2, zinc and glutamine.
Conclusion. The following preventive modalities for oral mucositis stand out as the most significant in the literature: benzydamine, laser therapy according to the specifications available in the literature, cryotherapy, 0.2% morphine mouthwash solution, and orally administered glutamine. The variability in the results indicates the complex nature of this clinical entity and the need for additional research, which will support the existing results and enrich the literature with new preventive modalities.

Keywords: stomatitis, oral mucositis, chemotherapy, radiotherapy, prevention, oral cancer

Corresponding author:
Ivana Stanković
e-mail: ivanaobradovic84@hotmail.com

INTRODUCTION

With the rise of chemotherapy as a therapeutic modality in the 1940s, the number of adverse changes of the oral mucosa, generally referred to as stomatitis, increased significantly. Due to the lack of effective therapeutic methods, as well as preventive guidelines for stomatitis, the quality of life and the prognosis of these patients have continuously worsened (1). In the past, the term "stomatitis", in addition to being used for the changes that occur because of chemotherapy and/or radiotherapy, was also used for many other diseases affecting the oral mucosa. The term "mucositis" i.e., "oral mucositis" began to be used in the 1980s as a more precise term describing lesions resulting from cytotoxic cancer therapy (2). The complex pathogenetic mechanisms of the previously called stomatitis were discovered in 2007, and thus the new term "oral mucositis" was officially adopted, which described the lesions that occur because of the cytotoxic effects of chemo- and/or radiotherapy. In the same year, ICD-9 code 528.0 was assigned to lesions associated with cytotoxic cancer therapy. The ICD-10 code for oral mucositis is K12.3 (3).

Oral mucositis is an acute, inflammatory, and ulcerative condition of the oral mucosa whose incidence during chemotherapy is 40%, and in combination with radiotherapy, the incidence rate reaches a value close to 100% (4, 5). Depending on the intensity of the changes of oral mucositis, there may be a significant decrease in the quality of life of these patients due to disturbance of nutrition and sleep, communication problems, and immense pain (6). In certain cases, patients may lose consciousness because of pain and dehydration, which further necessitates stopping cancer treatment (7).

Considering the frequency of oral mucositis, its impact on the physical and mental health of patients, as well as the depletion of the economic capacities of an individual and society, the importance of prevention and management of oral mucositis is clearly highlighted (8). Since the literature indicates different preventive modalities for this clinical entity (9-18), the aim of our study was to determine the modern preventive modalities for oral mucositis.

LITERATURE REVIEW

A search of studies indexed in the literature from 2002 to 2022 was conducted using the PubMed database. The search was conducted with the keywords: stomatitis, mucositis, oral mucositis, chemotherapy, radiotherapy, prevention, and oral cancer. The data were grouped according to a frequently used division of preventive modalities for oral mucositis (19-22): 1) Basic oral hygiene; 2) Anti-inflammatory therapy; 3) Photobiomodulation; 4) Cryotherapy; 5) Antimicrobial agents, coating agents, anesthetics, and analgesics; 6) Growth factors and cytokines, and 7) Natural and miscellaneous agents. We used the additional keywords (23) for each of the separate categories: basic oral care, chlorhexidine, patient education, anti-inflammatory agents, laser therapy, LLLT, photobiomodulation, cryotherapy, analgesics, antimicrobials, mucosal coating agents, growth factors, cytokines, natural products, honey, aloe vera, vitamin E, vitamin C, vitamin B, zinc, and glutamine. We included English-language sources that, with appropriate clinical, histological, or molecular data, evaluate the effect of the appropriate preventive agent for oral mucositis.

After searching the literature, a total of 90 sources were used for this study, including: original papers, literature reviews, systematic reviews, clinical studies, randomized controlled studies, and books.

According to the available data, the division of the different preventive modalities we used was initially introduced by the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO), which have a great contribution for the prevention and management of oral mucositis and which, in the period from 2004 to 2021, are constantly researching and renewing clinical guidelines for the prevention and treatment of chemotherapy-induced oral mucositis (19-23).

Basic oral care

When it comes to basic oral care, it is inevitable to mention patient education, professional oral health care, as well as home hygiene and the use of

different solutions for rinsing the oral cavity (24). Several studies evaluating the effect of patient education as a preventive measure for oral mucositis were available in the recent literature (25-28). The studies implement training sessions for self-assessment and maintenance of oral health with professional staff. Three studies (25, 27, 28) found that patient education significantly reduced the frequency and intensity of oral mucositis in patients with head and neck cancer and patients with hematologic-associated cancer, while a comparative study by Schmidt et al. (26) found no benefit from patient education. We believe that patient education is undoubtedly useful and may result in patient benefit despite the diversity of data from the literature.

The impact of professional oral health care in relation to oral mucositis is usually evaluated by evaluating the intensity of oral mucositis and the intensity of pain. In two studies (29, 30), a reduction in the intensity of oral mucositis was registered, while one study (31) registered a reduction in pain as a result of oral mucositis during regular implementation of professional oral health care. Dental evaluation and treatment as indicated prior to cancer therapy are desirable to reduce the risk of local and systemic infections from odontogenic sources.

Considering chlorhexidine as a rinsing solution, the available data was consistent (22, 32, 33) and indicates that chlorhexidine does not have a preventive effect on the occurrence of oral mucositis. However, this does not preclude other indications for chlorhexidine in cancer patients, such as prevention or treatment of oral infections. If chlorhexidine is indicated because of a concomitant oral infection and oral mucositis, it is acceptable to use it because of the oral infection.

Anti-inflammatory agents

When it comes to anti-inflammatory therapy and prevention of oral mucositis, the use of benzydamine solution for rinsing the oral cavity is most often mentioned in the literature. The results of numerous studies investigating the effect of benzydamine on the severity of oral mucositis are summarized in the studies of Ariyawardana et al. (34) and Nicolatou-Gallitis et al. (35) and indicate a significant reduction in the intensity of oral mucositis and pain in patients receiving chemo- and/or radiotherapy. Benzydamine exhibits anti-inflammatory properties by inhibiting the production of pro-inflammatory cytokines such as TNFα and IL-1β (36) which play a key role in the pathogenetic mechanisms of oral mucositis (34, 37).

Photobiomodulation

Recent data from the literature support the use of photobiomodulation for the prevention of oral mucositis, especially in bone marrow transplantation, in head and neck radiotherapy (without chemotherapy) and in head and neck radiotherapy in combination with chemotherapy (38). To achieve an optimal therapeutic effect, it is important to precisely follow the recommendations and specific settings of the laser published in the literature, which depend on the reason for therapy, as well as the type of therapy (radiotherapy or a combination of radio- and chemotherapy) (22). Bensadoun and Nair (39) recommend the use of red or infrared LLLT with diode output between 10-100 mW, dose of 2-3 J/cm^2/cm^2 for prophylaxis and 4 J/cm^2 (maximum limit) for therapeutic effect, application on single spot rather than scanning motion.

Cryotherapy

Conventional methods for applying cryotherapy in the oral cavity are the use of cold water or ice, but there are other, newer methods, and commercial devices that are used in daily practice (40). Vasoconstriction caused by low temperatures reduces the transport of cytotoxic drugs to oral tissues and thus prevents secondary complications (41). Additionally, low temperatures reduce metabolic activity in the basal layer, making the epithelium less sensitive to cytotoxic agents (42).

The effects of cryotherapy have been investigated in bone marrow transplant patients (43-48), in patients with 5-FU bolus chemotherapy for solid tumors (49, 50), in patients treated with short-term infusion chemotherapy and short-half-life agents (41), and in patients treated with head and neck radiotherapy (51).

The latest guidelines recommend the use of cryotherapy in two cases: in patients undergoing autologous bone marrow transplantation treated with high doses of melphalan; in patients receiving 5-FU bolus therapy, 30 minutes during the therapy itself (22).

Antimicrobials, coating agents, anesthetics, and analgetics

Candidiasis is a common oral infection in patients with cancer and it can secondarily infect the lesions of oral mucositis, worsening the symptoms and making it difficult for them to epithelize. Therefore, it is theorized that antifungal drugs can prevent oral mucositis (52).

Rao et al. (53) in their study of 181 patients registered a reduced incidence of oral mucositis and oral candidiasis with twice weekly prophylactic administration of fluconazole during chemoradiotherapy in patients with head and neck cancer.

Miconazole is a synthetic imidazole antifungal agent that is often used to treat candidomycotic infections. However, oral medications for topical use, due to dynamics in the oral medium, need to be applied frequently, which makes it difficult for patients to cooperate and adhere to the therapeutic regimen. Therefore, Orvain et al. (54) in their study investigated the new formulation of miconazole, administered as a mucoadhesive buccal tablet, but the research was not aimed at monitoring oral mucositis, but at indirect indicators (hospitalization time, morphine use) of oral mucositis.

The oral mucosa of cancer patients is more susceptible to physiological trauma. For this purpose, coating agents have been created that form a barrier that reduces the irritation of the oral mucosa (52). Several studies of viscous liquid mucoadhesive hydrogel (MAH) are found in the literature (55-57), however, the results of these studies are not sufficient to establish official guidelines for the use of this preparation for the prevention of oral mucositis. Complete prevention and rapid elimination of oral mucositis were registered in McCullough's research (58), which opens new directions for studying the coating agent used in the study—HPPCLS (High-Potency Polymerized Cross-Linked Sucralfate).

From the category of analgesics, the local use of 0.2% morphine mouthwash solution is recommended for the regulation of pain caused by oral mucositis in patients with head and neck cancer treated with chemoradiotherapy (22, 59, 60).

Growth factors and cytokines

Growth factors and cytokines can stimulate the regeneration of oral mucosa cells, preventing oral mucositis and reducing its negative effects (61). The effects of different growth factors and cytokines have been studied in the literature, such as: G-CSF (granulocyte colony-stimulating factor), GM-CSF (granulocyte-macrophage colony-stimulating factor) (62-64), EGF (epidermal growth factor) (65, 66), EPO (erythropoietin) (67), as well as the most frequently mentioned family of growth factors, which give the most favorable results —KGF (keratinocyte growth factors) in the form of palifermin (68-72).

The most recent guidelines recommend the use of intravenous KGF-1 for the prevention of oral mucositis in patients with hematologic malignancies who have undergone bone marrow transplantation (22, 73). Current data do not recommend the topical use of GM-CSF for the prevention of oral mucositis in patients with hematological cancer who have undergone bone marrow transplantation (22, 74).

Natural and miscellaneous agents

Honey has often been investigated in medicine, due to its: antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, antitumor, antimutagenic, and regenerative properties (75-79).

Charalambous et al. (76) evaluated and determined the potential effect of a solution of thyme and honey to improve quality of life and improve symptoms in patients with head and neck cancer. According to Khanjani et al. (80), the use of an aqueous solution of honey (in the ratio of honey: water, 1:20) is effective for the prevention and reduction of the intensity of oral mucositis in patients with acute myeloid leukemia. Sener et al. (81) treated patients with oral mucositis with a mixture of honey and vitamin E and found that this solution better controlled oral mucositis than chlorhexidine. According to the latest guidelines (22), honey is recommended for the prevention of oral mucositis in patients with head and neck cancer treated with radiotherapy or chemoradiotherapy, but honey also has a cariogenic effect, so its application must be moderate (82).

The most common form of vitamin E—α-tocopherol has cytoprotective and anti-inflammatory characteristics (83). The efficacy of vitamin E for the prevention and regulation of oral mucositis has been investigated in different tumors/carcinomas, where it has been administered in different forms: solution for gargling and swallowing in hematological patients treated with chemotherapy (84), tablet form, and as an oil in hematological patients and patients

treated with chemotherapy (85), topical use in solid tumors treated with chemotherapy (86, 87) and in the form of a solution for gargling and swallowing in patients with head and neck cancer treated with radiotherapy (88).

Ferreira et al. (89) evaluated the prophylactic efficacy of vitamin C and vitamin B2 on methotrexate-induced gastrointestinal mucositis in an animal model. The authors (89) registered a benefit from the use of vitamin C, but not from the use of vitamin B2. Rasheed et al. (90) examined the concentration of vitamin C in bone marrow transplant patients and registered a more advanced form of mucositis in patients with a lower concentration of vitamin C in the body. Kletzel et al. (91) prescribed vitamin C (2 g per day) in bone marrow transplant patients and detected an improvement in the clinical manifestation of oral mucositis and an improvement in quality of life through a pain-free diet.

In the literature, when it comes to the prevention of oral mucositis, zinc is often mentioned as an important electrolyte for the homeostasis of the body, which is involved in the processes of wound healing and the immune response of the individual (86). Chaitanya et al. (92) found in their research that zinc treatment resulted in a milder clinical presentation of oral mucositis, and vitamin C treatment resulted in less pain in the subjects. In combination, zinc and Vitamin C resulted in milder clinical manifestation, less pain and better taste perception. Other studies also confirm the efficacy of zinc in the prevention of oral mucositis (93-95), however, there are also studies that indicate the absence of efficacy of zinc in the prevention of oral mucositis (96, 97). Due to the diversity of results, there are still no official guidelines for the use of zinc in the prevention of oral mucositis.

Due to the protective effect of saliva, different methods of stimulation of salivary secretion and their effect on the prevention of oral mucositis were investigated in the literature, such as: stimulation with chewing gum (98, 99), electrical stimulation (100) and intravenous application of N-acetyl cysteine (101). There is not enough evidence about the preventive effect of the mentioned methods (98-101) in the prevention of oral mucositis.

Glutamine is an amino acid that is present in large quantities in blood plasma and plays a significant role in cell survival under conditions of metabolic stress (102). Studies in the literature evaluating the preventive effect of glutamine on oral mucositis examine it in two different forms: parenterally and per os (103-108). Considering the studies in which there is an absence of evidence of benefit from parenteral administration of glutamine, as well as one study (103) in which a higher mortality rate was recorded in cancer patients who were given parenteral glutamine, there is no support that the parenteral form of this preparation should be used for the prevention of oral mucositis. Several studies show a positive effect of orally (per os) administered glutamine in patients treated with chemo- and chemoradiotherapy (109-112), which is the supported way of using glutamine for the prevention of oral mucositis (22).

CONCLUSION

Through this research and critical evaluation of the available literature related to oral mucositis, we can note that there is considerable variation in the preventive power of different agents. Undoubtedly, patient education and regular consultations with the dentist are important for the prevention of oral mucositis, but we can single out the following agents and preventive modalities as equally important: benzydamine, laser therapy according to the specifications available in the literature, cryotherapy, 0.2% morphine mouthwash solution, and orally administered glutamine.

The variability in the results indicates the complex nature of this clinical entity and the need for additional research, which will not only support the results of previous research but also enrich the literature with new possibilities for the prevention of this complication caused by chemo- and/or radiotherapy.

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Review article

Preventivni prisupi oralnim mukozitima: pregled literature

Bojan Poposki[1], Kiro Ivanovski[1], Ana Pejčić[2,3], Vlatko Kokolanski[1], Ivana Stanković[2]

[1]*Univerzitet u Skoplju „Sveti Kiril i Metodij", Stomatološki fakultet, Skoplje, Republika Severna Makedonija*
[2]*Univerzitet u Nišu, Medicinski fakultet, Katedra za parodontologiju i oralnu medicinu, Niš, Srbija*
[3]*Klinika za dentalnu medicinu Niš, Služba za parodontologiju i oralnu medicinu, Niš, Srbija*

SAŽETAK

Uvod/Cilj. Oralni mukozitis predstavlja akutno, inflamatorno i ulcerozno stanje oralne sluzokože, koje je uzrokovano hemioterapijom i/ili radioterapijom. S obzirom na učestalost oralnih mukozitisa, njihov uticaj na fizičko i mentalno zdravlje pacijenata, kao i crpljenje ekonomskih kapaciteta pojedinaca i društva, jasno je naglašen načaj prevencije i lečenja mukozitisa. Cilj našeg istraživanja bio je da se utvrde savremeni modaliteti u prevenciji oralnih mukozita.

Pregled literature. Pretraživanje indeksiranih studija od 2002. do 2022. godine sprovedeno je korišićenjem *PubMed* baze podataka. Pretraga je vršena prema ključnim rečima: stomatitis, mukozitis, oralni mukozitis, hemioterapija, radioterapija, prevencija i oralni karcinom. Postoje brojni preventivni modaliteti za oralni mukozit, koji uključuju: edukaciju pacijenata, profesionalnu oralnu zdravstvenu zaštitu, kućnu higijenu, rastvore za ispiranje usta, antiinflamatorna sredstva kao što su benzidiamin, fotobiomodulaciju, krioterapiju, mikonazol, tečni mukoadhezivni hidrogel, polimerizovani visokopotentni umreženi sukralfat, rastvor morfijuma za ispiranje usta, faktore rasta i citokine, med, vitamin C, vitamin E, vitamin B2, cink i glutamin.

Zaključak. U literaturi se kao najznačajniji izdvajaju sledeći modaliteti prevencije oralnih mukozita: benzidiamin, terapija laserom prema uputstvima dostupnim u literaturi, krioterapija, 0,2% rastvor tečnosti za ispiranje usta na bazi morfijuma i oralno primenjeni glutamin. Varijabilnost u rezultatima ukazuje na kompleksnu prirodu ovog kliničkog entiteta i potrebu za dodatnim istraživanjima koja će potkrepiti već postojeće rezultate i obogatiti literaturu novim preventivnim pristupima.

Ključne reči: **stomatitis, oralni mukozitis, hemioterapija, radioterapija, prevencija, oralni kancer**