

Management of oral mucositis in children

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Abstract. – OBJECTIVE: Children undergoing chemotherapy or hematopoietic stem cell transplantation may suffer from Oral mucositis. Therefore, the aim of this systematic review was to find the protocols which are used in the management of oral mucositis (OM) in children.

MATERIALS AND METHODS: A search was performed to find the related studies. After reading the searched articles, 15 studies were selected for this review.

RESULTS: Good oral care, glutamine, some biological agents, and laser therapy, had a significant effect to reduce the pain sensation and occurrence of oral mucositis in children.

CONCLUSIONS: It has been concluded that there are many types of management, such as oral care and laser therapy, which can be used to reduce the severity of oral mucositis.

Key Words:

Hematopoietic stem cell transplant (HSCT), Mucositis, Laser therapy, Chemotherapy.

Introduction

Leukemia is one of the most common malignancies in children with 30-40% prevalence¹. For the management of acute lymphoblastic leukemia (ALL) high dose of methotrexate in the chemotherapy is used that significantly increase the risk of Oral Mucositis (OM)². Other lines of treatment include hematopoietic stem cell transplant (HSCT) which is the infusion of multipotent stem cells derived from peripheral or cord blood and bone marrow to repair the hematopoietic system. OM is also a side effect of it³.

OM is defined as oropharynx inflammation, which results from the therapy of cancer³. It starts after 2-18 days of the initiation of chemotherapy⁴ and affects almost 80% of children who are undergoing HSCT⁵ and 40% of children who are receiving standard chemotherapy⁶. It is a painful and adverse effect which reduces the quality of life (QoL) of patients and many other problems

in children, i.e., malnutrition due to poor intake⁷. OM also affects speech, nutrient intake, increase or decrease saliva production, ulceration, extend in treatment and delays chemotherapy, affect QoL and hence mortality⁸. The prevalence of OM in children greatly varies and it depends on the treatment of cancer⁹.

Management

The prevention and treatment of OM mainly focused on relief of the symptoms through the applications of antifungal, obtundents, anesthetics, or even placebo combinations¹⁰. There is also clear evidence that good oral health may help to reduce the OM symptoms¹¹. Many treatments and protocols are available for the management of OM, such as sodium bicarbonate, iodine, physiological serum, benzydamine, growth factors, Vitamin E, LPTP (low-power laser therapy), povidone, zinc, glutamine, cryotherapy and palifermin^{12,13}.

Good oral health can significantly reduce the development of OM without an increase in infection and septicemia in the oral cavity¹⁴. Supersaturated calcium phosphate rinse (SCPR) is a natural electrolyte solution containing calcium and phosphate ions that resemble the ionic and pH balance of saliva. It is a naturally present solution which contains calcium and phosphate ions¹⁵. It can reduce the severity of OM by lubricating the oral mucosa in patients who are on hematopoietic stem cell transplantation (HSCT)¹⁵. The topical use of Vitamin E also showed effectiveness in the management of OM^{16,17}.

The severity and incidence of OM can be reduced with the supplementation of glutamine. The use of glutamine is safe and appropriate for the prevention of OM¹⁸. Caphosol is well tolerated in clinical reports without any side effects¹⁵. However, its efficacy has not been replicated in randomized studies, particularly for pediatric patients, there are only a few studies available¹⁹.

Laser therapy is a simple and easy technique that has the following properties: analgesic (630 to 650 nm and 780 to 900 nm), wound healing ($\lambda=632.8$ nm and 780 to 900 nm) and anti-inflammatory (with same wavelengths). These properties are evaluated by experimental, biological and physical studies²². Pieces of evidence^{22,23} show that this therapy has a potential role in the prevention of OM. Low power laser therapy has an effect both in prevention and in reducing the symptoms of oral mucositis in cancer patients²⁴. This therapy is now recommended by the International Association of Oral Oncology/Multinational Association of Supportive Care in Cancer (ISOO/MASCC) for those patients who are receiving transplants or chemotherapy²⁰. The mechanism of laser therapy action is still controversial, but some recent studies have suggested that it can reduce oxidative stress and activate intracellular chromophores directly, therefore, triggering an increase in proliferation of fibroblasts, endothelial cells, pericytes, keratinocytes, osteoblasts with analgesic effects²¹.

The severity of MTX-induced OM results in impairment in the children's quality of life which may lead to delay in treatment^{25,26}. After the infusion of HD-MTX, Leucovorin (LV) is given to minimize the effects of MTX^{27,28}. It has been reported²⁵ that the prevalence of MTX-induced mucositis in children with ALL was 20% even after the treatment of LV.

Oral cryotherapy (OC) is referred to as the cooling of the mouth at the time of chemotherapy infusion. It endorses the vasoconstriction which

causes the reduction in delivery of drugs and results in less toxicity in tissues²⁹. Due to less risk of harm and potential benefits, treatment of OC has been recommended by Sung et al³⁰.

Vitamins, minerals, monounsaturated fatty acids, and phenolic compounds make olive oil healthy³¹. The useful properties of Aloe Vera come from minerals, enzymes, hormones, amino acids, vitamins, phenolic compounds and some other active compounds which are present in Aloe Vera. However, its efficiency as medicinal material has not been proven clinically until now³². Sodium bicarbonate promotes a fresh and clean oral environment by maintaining healthy pH in the oral cavity, hence it lowers the chance of infection³³.

Methodology

Search Strategy

A search of the literature was performed in Embase, PubMed, ScienceDirect and Cochrane. The search was done with the main terms, such as oral mucositis, management of mucositis, prevention of oral mucositis, mucositis in children. The authors also carried out a hand search of references, which are present in review articles and original studies.

Inclusion and Exclusion

The studies in which children aged ≤ 18 years and experiencing Oral mucositis (OM) published

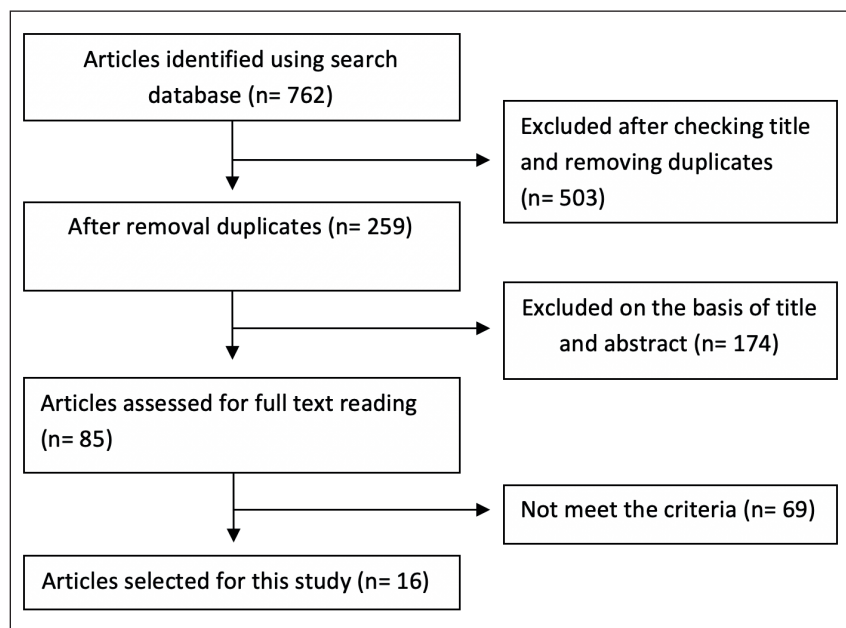


Figure 1. Flow chart.

from 2005 to 2021 were included. Clinical and research works in English were included. Literature reviews, review articles, case reports and non-research studies were excluded. Articles which were not written in English were also excluded.

Extraction and Analysis of Data

After the removal of duplicate articles, 259 studies remained. After the selection of title and abstract by two reviewers, 85 articles were selected for full-text reading. The remaining 85 articles were assessed full text. By this method, 16 studies were identified which were added in this systematic review (Figure 1).

Search Data

From included studies, the following data were obtained: author and year of publication; country;

study design; number and age of patients, the treatment used for mucositis, reason of mucositis and results of treatment.

Results

Sarah et al³⁴ used two oral hygiene regimens ESTB (extra soft toothbrush) and SCPR (supersaturated calcium phosphate rinse) to assess their effect on oral mucositis and observed that the SCPR group reduced mucositis. The effect of chlorhexidine, vitamin and honey was assessed by Sener et al³⁵ in a randomized control trial and observed that the group of children who received the Vitamin E had a lower index of mucositis while the group who received chlorhexidine had a higher index of mucositis than other groups (Table I).

Table I. Efficacy of oral care in the prevention of mucositis.

Author, year	Country	Study design	Number of patients	Age, years	Treatment	Reason of OM	Results
Sarah Mubaraki et al 2020 ³⁴	Saudi Arabia	Prospective	45 in 3 groups (15 in each) Group A = Control Group B = ESTB (extra soft tooth-brush) Group C = SCPR (supersaturated calcium phosphate rinse)	7-10 years	Group = Control Group B = control regimen+used extra-soft toothbrush Group C= control redimen+used supersaturated calcium phosphate rinse	Chemotherapy for the hematopoietic stem cell transplant	The three groups; ontrol, CESTB (extra soft tooth brush) and SCPR (supersaturated calcium phosphate rinse) had no significant difference. However, SCPR group had reduced mucositis as compared to control group and ESTB group
DilekKonuk et al 2019 ³⁵	Turkey	RCT	150 in 6 groups (25 in each group)	Median age 7.25 years	1. Children with OM admitted in in PICU (Pediatric Intensive Care Unit) Group 1 = chlorhexidine Group 2 = Vitamin E Group 3 =Honey 2. Groups of children without OM admitted to PICU Group 4 = chlorhexidine Group 5 = Vitamin E Group 6 = Honey	----	The group of children which received the Vitamin E had lower while the group that received chlorhexidine had a higher index of mucositis than other groups

Table II. Efficacy of glutamine and caphosol in the prevention of mucositis.

Author, year	Study design	Number of patients	Age, years	Treatment	Reason of OM	Results
Nur et al 2020 ³⁶	Randomized trial	48 in two groups. 24 = Glutamine 24 = placebo	1-18 years	Oral glutamine, 400 mg/kg body weight daily	Chemotherapy in Children with Acute Lymphoblastic Leukemia	The occurrence of oral mucositis in glutamine group was 4.2% and in placebo group, it occurred 62.5%. Prevention of oral mucositis was directly linked with glutamine use
Nathaniel et al 2017 ³⁷	Multicentre randomized double-blinded placebo-controlled clinical trial	220	4-21 years	Caphosol in 2 solutions 1. 15 ml phosphate solution 2. 15 ml calcium solution	Myeloablative haematopoietic cell transplantation	It has been reported that mucositis was not reduced in caphosol group vs. placebo. The occurrence of OM in caphosol group was 63% and in placebo group was 68%

In a randomized control trial, Nur et al³⁶ examine the effects of glutamine (400 mg/kg orally) in children. The occurrence of oral mucositis in the glutamine group was 4.2% and in the placebo group it occurred 62.5%. Prevention of oral mucositis was directly linked with glutamine use. Caphosol was used by Nathaniel et al³⁷ to reduce the effect of oral mucositis in children facing myeloablative hematopoietic cell transplantation. It has been reported that mucositis was not reduced in caphosol group vs. placebo. The occurrence of OM in caphosol group was 63% while in the placebo group was 68% (Table II).

Noirit-Esclassan et al³⁸ conducted a prospective non-randomized study on 3 to 18 years old children who were experiencing oral mucositis due to radiotherapy or chemotherapy. Children were treated with Photobiomodulation (PBM) with two wavelengths in combination: 635 and 815 nm. The incorporation of intra and extra-oral application of PBM is feasible. This application is easily tolerated even by young patients. Another perspective and randomized study was carried out by Margherita et al³⁹ in which a diode laser device was used to treat OM which is induced by chemotherapy on children aged between 3-18 years. The results of this treatment showed pain reduction in the PBM group. Class IV laser therapy was used by Maddalena et al⁴⁰ to prevent oral mucosi-

tis in children having hematopoietic stem cell transplantation or chemotherapy. All patients received this laser therapy for 4 consecutive days. Improvement in pain was observed and the issue of oral mucositis was fully solved on the 11th day of follow-up. No apparent side effects were observed. Significant pain reduction in mucositis was reported after 1 to 2 days of therapy. A placebo-controlled randomized study was performed by Kuhn et al⁴¹ to evaluate the effect of low-intensity laser therapy on the prevention of oral mucositis in children. In the laser-treated group, only one patient out of 9 remained with mucal lesion and, in the control group, 9 patients out of 12 had lesions on the 7th day after the diagnosis of OM (Table III).

The effect of leucovorin therapy (LV) to reduce the HD-MTX induced mucositis was evaluated in 6 studies. The study which used a 30 mg/m dose showed that deficiency of folate had more toxic effects⁴². The rate of oral mucositis is 20% with the dose of 15 mg/m² after 42 hours²⁵. The dose of 15 mg/m² showed high prevalence in the first cycle of HD-MTX as compared to the following cycles⁴³. Lower rate of oral mucositis was observed in a therapy group with an LV dose of 10mg/sqm⁴⁴ (Table III).

Tovo et al⁴⁵ reported the effect of oral cryotherapy (OC) to prevent oral mucositis induced by HSCT (hematopoietic stem cell transplantation). The result showed that prevalence and pain of

Table III. Prevention of oral mucositis in cancer patients with Laser therapy.

Author, year	Country	Study design	Number of patients	Age of patients	Treatment	Cause of oral mucositis	Results
Noirrit-Esclassan et al 2019 ³⁸	France	Prospective, nonrandomized, single-center study	22	3-18 years	Photobiomodulation (PBM) with a combination of two wavelengths (635 and 815 nm).	Chemotherapy and/or radiotherapy	The incorporation of intra and extra-oral application of PBM is feasible. This application is easily tolerated even by young patients
Margherita et al 2017 ³⁹	Italy	Randomized, prospective	101 in 2 groups Group A: PBM = 51 Group B: Placebo = 50	3-18 years	Group A = diode laser device for 4 consecutive days 660 and 970 nm wavelength Group B = same modality but without laser emission	Chemotherapy induced OM	All the children had OM which is induced by chemotherapy. The results of this treatment showed pain reduction in PBM group
Maddalena et al 2014 ⁴⁰	Italy	Prospective	18	10-17 years	Class IV laser therapy for 4 days consecutively	Chemotherapy and/or haematopoietic stem cell transplantation,	Improvement in pain was observed and the issue of oral mucositis was fully solved at 11 th day of follow-up. No apparent side effects were observed. Significant pain reduction in mucositis was reported after 1 to 2 days of therapy
Kuhn et al 2009 ⁴¹	Porto Alegre	Placebo-controlled randomized trial	21 in 2 groups Laser group = 9 Placebo group = 12	Mean age = 8.2	Low-intensity laser therapy (LLT) = GaAlAs, Wavelength 830 nm power: 100 mW dose: 4 J/cm ² . Placebo group received sham treatment.	Chemotherapy or hematopoietic stem-cell transplantation	In laser treated group only one patient out of 9 remained with mucal lesion and in control group, 9 patients out of 12 had lesions on 7 th day after diagnosis of OM

mucositis did not decrease by the treatment of OC (Table IV).

The efficacy of biological agents in the management of OM was evaluated by Muaaz et al⁴⁶ in a randomized control trial. 36 children were divided into 3 groups. Group A received Aloe Vera, Group B and C were given Olive oil and sodium bicarbonate, respectively. Use of Aloe Vera and olive oil showed a significant difference

in OM (p -value was 0.007, 0.002) respectively as compared to sodium bicarbonate which did not exhibit any difference (p -value 0.414) (Table V).

Discussion

The most frequent problem that children face due to HSCT is oral mucositis (OM)⁴⁷. As a result,

Table IV. Effect of leucovorin rescue therapy on methotrexate-induced oral mucositis.

Author, year	Country	Study design	Number of patients	Age, years	Treatment	Results
Moulik et al 2016 ⁴²	India	Prospective	21	8.4	30 mg/m ² iv at 24 h+4 × 15 mg/m ² at 12 h intervals	Shown that deficiency of folate had more toxic effects
Den Hoed et al 2015 ²⁵	Netherlands	Prospective	134	5.3	15 mg/m ² after 42 h every 6 hours	Rate of oral mucositis is 20%
Zhang et al 2014 ⁴³	China	Prospective	136	TT: 5.3 TC/CC: 4.9	15 mg/m ² at 36, 42 and 48 hours	15 mg/m ² showed high prevalence in first cycle of HD-MTX as compared to following cycles
Pauley et al 2013 ⁴⁴	USA	RCT	LR: 233 SR/HR: 252	LR: 4.0 SR/HR: 8.3	LR: 10 mg/m ² iv and SR/HR: 15 mg/m ² iv after 42 h, every 6 h 5 times	Lower rate of oral mucositis was observed in therapy group with LV dose of 10 mg/m ²
Kapoor et al 2012 ⁶⁵	India	Retrospective	41	6.0	30 mg/m ² iv 42 h after iv MTX+15 mg/m ² orally at 48, 54, 60 and 66 hours	Prevalence of mucositis was 12% in the first cycle and 3%, 6% and 0% in cycle 2, 3 and 4 respectively
Xu et al 2007 ⁶⁶	China	Prospective	121	10.3	SR: 15 mg/m ² at 36 hours HR: 30 mg/m ² at 36 hours SR + HR: 15 mg/m ² 4-7× every 6 hours	Rate of oral mucositis is 0%

there is a need to investigate various protocols and regimens to minimize the severity and prevalence of oral mucositis in those children.

In children with hematological problems, it has been observed that trauma from toothbrush leads to ulceration and uncontrolled bleeding⁴⁸. The American Academy of Pediatric Dentistry

recommended cleaning the teeth by nylon brush 2-3 times daily to reduce the risk of OM severity during the hematological changes⁴⁹.

SCPR (supersaturated calcium phosphate rinse) was found as an effective tool to reduce oral Mucositis⁵⁰. The study included in this systematic review has comparable results by Ambard et al⁵¹

Table V. Effect of Oral Cryotherapy (OC) in prevention of mucositis.

Author, year	Country	Study design	Number of patients	Age, years	Treatment	Reason of OM	Results
Tove et al ⁴⁵ 2020	Sweden	RCT	49 in 2 groups OC Group = 26 Control Group = 23	4-17 years old	OC group cooled their mouths by rinsing with cold water or sucking on ice popsicles and chips at the chemotherapy infusions	Hematopoietic stem cell transplantation (HSCT).	The result showed that prevalence and pain of mucositis did not decrease by the treatment of OC

Table VI. Effect of biological agents in management of oral mucositis.

Author, year	Country	Study design	Number of patients	Age, years	Treatment	Reason of OM	Results
Muaaz et al 2021 ⁴⁶	New Zealand	RCT	36 in three groups (12 in each) Group A = Aloe Vera, Group B = Olive Oil Group C = sodium bicarbonate	6-9 years	Group 1 = Aloe Vera, Group 2 = Olive Oil Group 3 = sodium bicarbonate	Chemotherapy	Use of aloe vera and olive oil showed significant difference in OM (<i>p</i> -value was 0.007, 0.002) respectively as compared to sodium bicarbonate which did not exhibit any difference (<i>p</i> -value 0.414)

who observed no significant difference in patients who were treated with SCPR and in the control group.

Vitamin E has the ability to prevent tissue damage, repairs skin, contributes to the regeneration of cell, gives cell protection from oxidative damage, produce a mucosal epithelization effect, enhance the production of leukocytes, gives strength to the immune system, and reduce oxidative damage in specialized tissues, i.e., blood vessels^{52,53}. Lower Mucositis index was found in those children who used vitamin E topically compared to other groups^{16,17,54,55}.

The severity of chemotherapy-induced OM can be reduced by the supplementation of glutamine by repairing the damage of the cell¹⁸. It has been reported that the most commonly used drugs in pediatric cancer are NSAIDs and codeine⁵⁶. Even though opioid analgesics were widely used, it cannot reduce the severity of OM which led to many problems, such as impaired conscience, constipation and dry mouth. PBM treatment had high tolerance as compared to control⁵⁷.

Most of the studies which used LLLT (low-intensity laser therapy) for cancer patients mainly focused on the prevention of OM. Barasch et al⁵⁸ used laser prophylactically in 20 cancer patients. They were given laser either in the left or right midline, the contralateral side was considered as control. On the laser-treated side, the pain of OM was lower significantly ($p < 0.05$)⁵⁸. Oral cryotherapy (OC) was used for 13 children, but no compliance was reported⁵⁹.

The biological agents used in the included study were chosen as they are easily available, cost-effective, natural and not evaluated in previous studies. They also have different properties that prevent mucositis. Olive oil has an essential phenolic compound, oleocanthal, that reduces the free radical formation. Ultimately it inhibits the increase of mucositis pathogenesis⁶⁰. Olive oil may reduce the OM severity as it has anti-inflammatory properties⁶¹. It is also efficient for the prevention of chemotherapy-induced oral mucositis⁶².

There is no significant difference between olive oil and aloe vera treatment and nor between sodium bicarbonate and aloe vera. However, the treatment of olive oil had more effect compared to sodium carbonate. Other studies^{63,64} also reported the same results.

Conclusions

Many different protocols were used to treat oral mucositis and reduce its effects. The results of the studies w included in this systematic review showed that management, such as laser therapy, some oral care regimens, the use of biological agents, i.e., olive oil and aloe vera, treatment of glutamine had a significant effect on the reduction of OM severity, while some protocols such as OC and use of caphosol did not affect the prevention of OM. Further clinical trials and research studies are required to investigate the

management methods for the prevention of oral mucositis in children.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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