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The Effects of Hyaluronic Acid Gel on Oral Mucositis in Children Receiving Chemotherapy

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Abstract

Aim Oral mucositis (OM) is a common side effect of systemic chemotherapy (CT) in cancer patients. The aim of this study was to investigate the effect of hyaluronic acid (HA) gel on OM in children receiving CT.

Material and method A total of 40 pediatric patients aged between 3 and 18 years who were diagnosed with leukemia and treated with CT in the inpatient setting were included. The patients were randomly divided into groups. The HA group (n=20) received HA gel and the control group (n=20) received sodium bicarbonate. The grade of OM was evaluated based on the World Health Organization Common Toxicity Criteria Scale. The pain severity was assessed using the Visual Analog Scale (VAS).

Results Of the patients, 21 (52.5%) were girls and 19 (47.5%) were boys. The mean age was 9.37±5.11 (range, 3 to 18) years. The majority of the patients (77.5%) had a diagnosis of pro-B-cell acute lymphoblastic leukemia (ALL). There was no statistically significant difference in the number of OM lesions and VAS scores between the groups (p>0.05).

Conclusion The study results show that both standard oral care with sodium bicarbonate and HA gel have similar effects on pain relief and regression of OM in pediatric cancer patients undergoing CT. The HA gel is a feasible alternative for the pediatric population.

Keywords Chemotherapy, Childhood leukemia, Hyaluronic acid gel, Oral mucositis, Pediatrics

Introduction

Oral mucositis (OM) is a common side effect of chemotherapy (CT) and radiation therapy (RT), characterized by erythematous and ulcerated oral mucosal lesions (1). It is seen in about 80% of patients receiving high-dose CT and in nearly 100% of patients receiving RT to the head and neck region (2).

Oral mucositis is associated with pain, dysphagia, loss of taste, weight loss, and secondary infections, leading to impaired quality of life (3). It is more common in young individuals than elderly (4). Due to the cytotoxic effects of CT on epithelial basal cell layer, as well as atrophy and tissue ulceration, the reparative and regenerative process of the tissues is reduced. In addition, nearly all CT agents suppress the bone marrow, leading to granulocytopenia and thrombocytopenia and predisposing the patient to infection and bleeding (5). The ulcerated oral epithelium prepares the ground for the entry of microbes into the body, thereby resulting in systemic and local infections. Then, patients become dehydrated and malnourished due to pain. As OM progresses following CT, cellular and molecular alterations occur, leading to breakage of the deoxyribonucleic acid (DNA) helix and release of reactive oxygen species (ROS) into the circulation. The ROS activates transcription factors such as P53 and nuclear factor-kappa B (NF-κB), leading to cellular apoptosis (6). Several factors are involved in these biological processes including the drug dose, drug toxicities, time interval between CT cycles, additional RT, the general condition of the patient, sensitivity of the patient to CT agents, and oral hygiene and dental status of the patient (7).

The management of CT-related side effects includes antimicrobial mouthwash, adhesive mucosal barrier, cryotherapy, and topical analgesics (2). In recent years, keratinocyte growth factor (KGF), low-level laser therapy (LLLT), and hyaluronic acid (HA) have been investigated in the treatment of OM (8).

Sodium Bicarbonate (SB) is a widely used agent for the prevention and treatment of OM, a condition that causes inflammation and ulceration of the mucous membranes in the mouth. It is also used as a cleansing agent due to its ability to dissolve mucus and loosen debris. The benefits of SB use are due to its alkalizing effect, which raises oral pH and prevents the growth of aciduric bacteria. This makes saliva more fluid and prevents the accumulation of detritus. Furthermore, its use is strongly encouraged due to its low cost, patient-friendly application, lack of side effects, and long shelf life (9).

The HA is a natural polysaccharide composed of D-glucuronic acid and N-acetyl-D-glucosamine and is synthesized as a linear polymer. The majority of the cells have a capacity to synthesize HA at a varying extent in the cell cycle. The main function of

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HA appears to be in tissue healing, by activating and modulating inflammatory responses, stimulating cellular proliferation, migration, and angiogenesis, inducing basal keratinocyte proliferation and re-epithelization by reducing collagen deposition and scarring (10). Animal (11, 12) and clinical studies (10, 13, 14) have shown that HA yields favorable results in reducing pain and inducing healing in wound healing and ulcerative aphthous lesions. It is also known that topical hyaluronic acid application may be effective in the symptomatic treatment of oral mucositis observed after CT (15). Although there are not enough studies on human subjects, animal experiments have shown that hyaluronic acid is certainly effective in the treatment of oral mucositis (16). In the present study, we aimed to investigate the effect of HA gel on OM in CT-treated pediatric patients.

Material and Methods

Study design and study population

This clinical cross-sectional study was conducted at the Department of Pediatric Hematology and Oncology of a tertiary care center in Van, Turkey, between June 1st, 2019, and June 2nd, 2020. The study included pediatric patients aged 3 to 18 years who were hospitalized with a diagnosis of malignancies, receiving chemotherapy (CT), and capable of cooperating with study procedures. Inclusion criteria required patients to meet these conditions, while exclusion criteria included the presence of other systemic diseases, prior exposure to radiotherapy, or cooperation difficulties.

A total of 59 patients were assessed for eligibility. 11 patients of these patients did not meet the inclusion criteria and were excluded. Among the 48 eligible patients, 43 agreed to participate, while 5 declined. The enrolled participants were randomly divided into two equal groups of 20 patients each, using the envelope randomization method. The remaining three patients discontinued participation during the study period (two from the control group and one from the HA group), leaving 20 patients in each group for final analysis. The study flowchart is shown in Figure 1.

ALLIC BFM (Acute Lymphoblastic Leukemia Berlin-Frankfurt-Münster study group trials) 2009 chemotherapy protocol, an internationally accepted treatment protocol, was applied at the clinic. The protocol is for childhood leukemia and lasts approximately 2.5 years. Both groups received equal or similar doses of CT as per the treatment protocol.

Prior to enrollment, written informed consent was obtained from the parents and/or legal guardians of all participants. The study protocol was approved by the Van Yuzuncu Yil University Faculty of Medicine Clinical Research Ethics Committee (No: 06/03.07.2019) and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

The first group served as the control group. Patients and their caregivers received routine oral hygiene education prior to CT. This included instructions on brushing teeth and the tongue twice daily using a soft-bristled nylon toothbrush and fluoride toothpaste. Patients were advised to avoid foods that remain in the mouth for extended periods. Oral care was performed four times daily after meals using a bicarbonate serum solution (0.9% sodium chloride and 5% sodium bicarbonate). If oral mucositis (OM) developed, the lesions were treated with bicarbonate solution four times a day, regardless of OM severity. In cases of severe pain, topical local anesthetics were permitted.

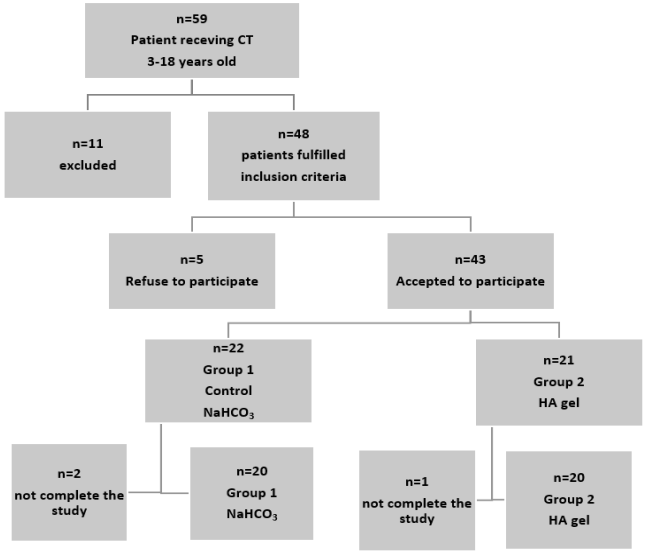

Figure 1: Study flowchart (CT: Chemotherapy, HA: Hyaluronic Acid)

The second group (HA group) also received routine oral hygiene education before CT. Once OM developed, the lesions were treated with high-molecular-weight hyaluronic acid (HA; sodium salt, 600 mg/100 g; Aftamed® protective barrier gel, Aktident, Istanbul, Turkey) four times daily (morning, afternoon, evening after meals, and night) for five to seven days, in accordance with the manufacturer's instructions. The gel was applied directly to the lesions, and patients were instructed to refrain from consuming food or beverages for 30 minutes post-application. Similar to the control group, topical local anesthetics were permitted in cases of severe pain.

Assessment and follow-up

Both groups were followed for five and seven days and on Days 0, 1, 2, 3, 4, 5, 6, 7, and 11 according to the World Health Organization (WHO) Common Toxicity Criteria Scale (12). The pain severity was assessed using the Visual Analog Scale (VAS). Recurrence, grade of OM, and VAS scores were recorded, and the same treatment protocol was applied according to the group allocation. All patients were followed for OM, until CT was discontinued.

OM scoring

The OM grading was performed by the same team including a pediatric hematologist and a pediatrician based on the WHO Common Toxicity Criteria Scale. The lesions were classified as Grade 0 = absent; Grade 1 = pain and erythema; Grade 2 = erythema and ulcers with no difficulty in swallowing solid food; Grade 3 = ulcers requiring only liquid diet; and Grade 4 = requiring parenteral and enteral nutrition support. Oral examination and OM scoring were performed on Days 1, 2, 3, 4, 5, 6, 7, and 11, starting from the day of laser treatment. The dentist performing the laser and the pediatrician were excluded from OM grading.

Pain scoring

The VAS is a useful tool which has been widely utilized all over the world (17). In this study, it was also used to evaluate pain status of the patients at the same timepoints with OM grading. The score ranges from 0 (no pain) to 10 (worst pain). Using the VAS, the patients were asked to mark their pain intensity between 0 and 10 (Figure 2).

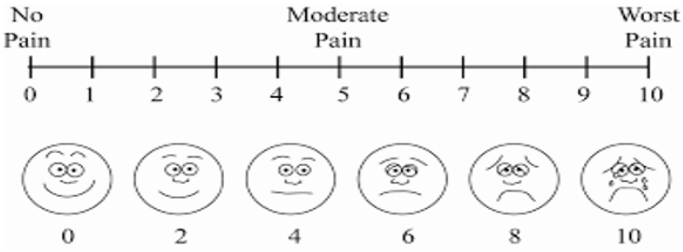

Figure 2: Visual Analog Scale for children

Statistical analysis

The effect size according to the difference in the OM measurements of the control and HA groups on the 11th day compared to the 0th day; 1.038 and post hoc power is 89.24%.

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) version 2020 software (NCSS LLC, Kaysville, UT, USA). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. The normality of distribution was checked using the Kolmogorov-Smirnov test. The Mann-Whitney U test was performed to compare non-normally distributed quantitative variables between the groups. The Pearson chi-square, Fisher exact, and Fisher-Freeman-Halton exact tests were used to compare qualitative variables between the groups. The Friedman test was used for the intra-group analysis of the non-normally distributed quantitative variables. A p value of <0.05 was considered statistically significant.

Results

A total of 40 patients were included in the study. Of these patients, 21 (52.5%) were girls and 19 (47.5%) were boys. The mean age was 9.37±5.11 (range, 3 to 18) years. There was no statistically significant difference in the age and sex between the groups (p>0.05).

Thirty-one patients (77.5%) were diagnosed with pro-B-cell acute lymphoblastic leukemia (ALL), one (2.5%) with T-cell ALL, one (2.5%) with Hodgkin lymphoma, three (7.5%) with acute megakaryoblastic leukemia (AML)-M7, and four (10%) with Burkitt lymphoma. The mean number of CT sessions was 5±1 (range, 2 to 8). There was no statistically significant difference in the distribution of diagnosis and number of CT sessions between the groups (p>0.05) (Figure 3).

The mean number of OM lesions was 3.77±2.04 (range, 1 to 9), indicating a statistically significant difference between the groups (p=0.014 and p<0.05, respectively). The number of OM lesions was statistically significantly higher in the HA group (p<0.05). Oral mucositis mostly affected the buccal mucosa in 20 (50%), sublingual mucosa in 17 (42.5%), palatal mucosa in 24 (60%), lips in nine (22.5%), and oral mucosa in 13 patients (32.5%). There was no statistically significant difference in the distribution of affected areas between the groups (p>0.05) (Table 1).

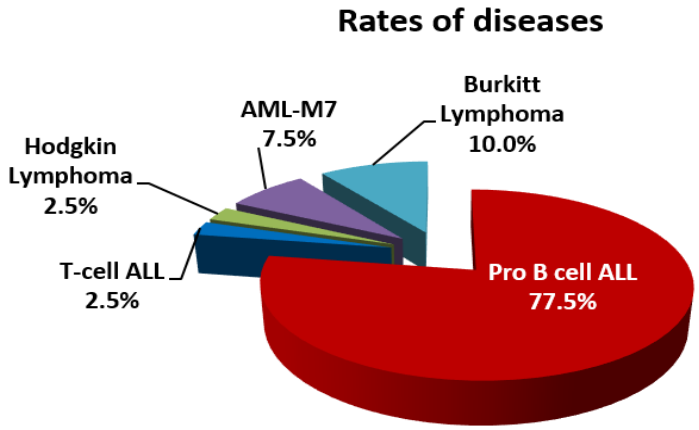

Figure 3: Distribution of diseases of children included in the study (AML: Acute Megakaryoblastic Leukemia; ALL: Acute Lymphoblastic Leukemia)

The number of OM lesions was the highest on Day 0 in both groups with a gradual decrease toward Day 11. The number of OM lesions was higher in the HA group than the control group on Days 0, 1, 2, 3, 4, and 7, while this number was reduced on Day 11. However, there was no statistically significant difference in the number of OM lesions on Days 0, 1, 2, 3, 4, 7, and 11 between the groups (p>0.05) (Figure 4).

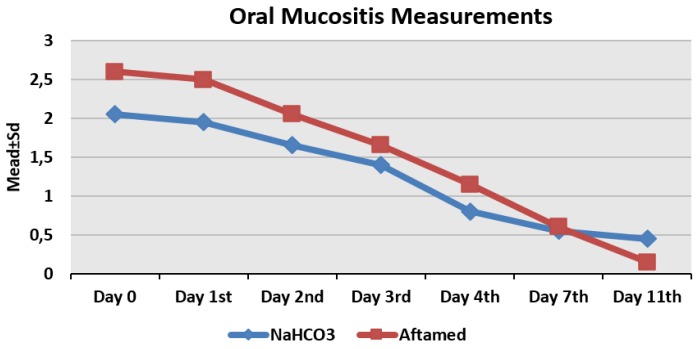

Figure 4: Distribution of oral mucositis measurements (Sd: Standard deviation)

According to the VAS pain scores, the highest score was observed on Day 0 with a gradual decrease toward Day 11. There was no statistically significant difference in the mean VAS scores on Days 0, 1, 2, 3, 4, 7, and 11 between the groups (p>0.05) (Table 2).

Table 1: Distribution of intraoral regions with oral mucositis

Regions with oral mucositis	n (%)
Buccal region	20 (50.0)
Sublingual region	17 (42.5)
Palatal region	24 (60.0)
Labial region	9 (22.5)
Other	13 (32.5)

Oral mucositis has been observed affecting multiple regions in a single patient.

Table 2: Comparison of VAS scores in the groups on days 1, 2, 3, 4, 7, and 11

VAS		$NaHCO_3$	Aftamed	p*
VAS day 0	Mean ± Sd	7.30 ± 1.62	7.20 ± 1.64	0.816
	Median (min - max)	8 (4 - 10)	7 (4 - 10)	
VAS day 1st	Mean ± Sd	7.10 ± 1.65	7.20 ± 1.64	0.907
	Median (min - max)	8 (4 - 10)	7 (4 - 10)	
VAS day 2nd	Mean ± Sd	6.20 ± 1.82	6.00 ± 1.94	0.831
	Median (min - max)	6 (2 - 10)	6 (2 - 8)	
VAS day 3rd	Mean ± Sd	5.00 ± 1.65	5.00 ± 1.90	1.000
	Median (min - max)	5 (2 - 8)	5 (2 - 8)	
VAS day 4th	Mean ± Sd	3.30 ± 2.53	3.60 ± 2 .11	0.685
	Median (min - max)	4 (0 - 8)	4 (0 - 6)	
VAS day 7th	Mean ± Sd	2.50 ± 2 .58	2.35 ± 2.03	0.978
	Median (min - max)	2 (0 - 8)	2 (0 - 6)	

VAS: Visual Analog Scale, Sd: Standard Deviation, Min: Minimum, Max: Maximum
p: Probability value*

Discussion

Oral mucositis is one of the most frequent complications of CT and RT. Despite a vast body of research on this topic in the literature, there is no completely effective treatment or prevention method for OM. The majority of studies have aimed to decrease the frequency and severity of OM rather than to prevent it. In the present study, we compared two methods which are commonly used in the clinical practice in pediatric patients receiving CT. The study's results showed that HA gel was as effective as sodium bicarbonate in reducing pain and the number of OM.

Although there are several studies showing a direct correlation between the frequency of OM and the number of CT sessions, some authors have reported the opposite (18, 19). In the current study, both groups received an equal or similar number of CT sessions to prevent controversial outcomes.

Until now, several methods have been described for the prevention and treatment of OM. Topical HA application has been shown to be an effective method with rapid symptomatic relief for oral ulcers including recurrent aphthous stomatitis (20), which was the basis of the hypothesis that HA could be an effective method for the treatment of OM. In their study, Shahrabi et al. (15) reported that HA was significantly more effective than placebo for the management of pain. Similarly, in this study, the highest score was observed on Day 0, followed by a gradual decrease toward Day 11 in patients receiving HA gel, which is consistent with findings reported in the literature.

According to the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines, basic oral hygiene methods are effective in the management of OM (1). Sodium bicarbonate ($NaHCO_3$) is one of the most common mouthwash agents used in the basic oral hygiene. The MASCC/ISOO guidelines state that there is no recommendation for the use of sodium bicarbonate in the management of OM due to the lack of strong evidence; however, it is advised to be used as one of the oral hygiene protocols for the prevention of OM. In a systematic review, McGuire et al. (21) reported that sodium bicarbonate was a beneficial and harmless method for both oral hygiene maintenance and patient comfort. Several studies have demonstrated that sodium bicarbonate rinse is beneficial and free from serious side effects; however, children may complain about its unpleasant taste (17). Of note, previous studies have reported no significant difference in the effectiveness of sodium bicarbonate and other mouthwashes in reducing OM symptoms (22). In a randomized clinical study, Saxen et al. (23) found no significant difference in the VAS scores between diclofenac sodium and HA gel applications.

Currently, high-molecular-weight HA is commercially available in various formulations (e.g., sprays, gels, and mouthwashes) and concentrations (0.2%, 0.8%, 2.5%, and 3%) (14, 23, 24). Several studies showing the effectiveness of HA in the management of OM have suggested that HA enhances the healing process and reduces the number of OM lesions (15, 25). In a randomized clinical study, Yıldırım et al. (26) evaluated the effect of two different HA concentrations (0.2% versus 0.8%) on postoperative pain and wound healing of palatal donor sites after free gingival graft surgery. They reported that the mean VAS score was improved with the 0.2% HA concentration. In the present study, we used Aftamed® protective barrier gel at 0.6% concentration; however, there is still a need for further studies comparing 0.2% and 0.6% HA concentrations to draw more reliable conclusions on this subject.

Nonetheless, there are some limitations to this study. First, this study's population consisted of pediatric patients and the application of HA gel was difficult to apply for the parents and/or caregivers. As NAHCO3 is liquid and is used as a mouthwash, it can exert positive effects on OM sites located in the throat and adjacently to the tongue root which are invisible, yielding similar results to HA. Further studies comparing HA gel and mouthwash formulations of HA would provide valuable information on this issue.

We believe that one of the reasons for the absence of a significant difference among the methods we compared is the varied application techniques. It is important to note that, due to the gargling form of sodium bicarbonate, it may be effective in the oropharynx; however, it should not be overlooked that HA can only be applied in the oral cavity. The fact that sodium was used as a mouthwash and HA was used as a gel during the study is the limitation of this study.

Conclusion

Oral mucositis is one of the most frequent complications of CT and RT. Despite a vast body of research on this topic in the literature, there is no completely effective treatment or prevention method for OM. The majority of studies have aimed to decrease the frequency and severity of OM rather than to prevent it. In the present study, we compared two methods which are commonly used in the clinical practice in pediatric patients receiving CT. The study's results showed that HA gel was as effective as sodium bicarbonate in reducing pain and the number of OM.

Declarations

Ethics Committee Approval: *The study protocol was approved by the Van Yuzuncu Yil University Faculty of Medicine Clinical Research Ethics Committee (No: 06/03.07.2019)*

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: *Conception/Design of Study- S.K.T., Y.R.M., G.A., K.K., M.B.B.; Data Acquisition- G.A., K.K.; Data Analysis/Interpretation- S.K.T., Y.R.M., M.B.B.; Drafting Manuscript- S.K.T., Y.R.M., G.A., K.K., M.B.B.; Critical Revision of Manuscript- S.K.T., Y.R.M., G.A., K.K., M.B.B.; Final Approval and Accountability- S.K.T., Y.R.M., K.K.; Material and Technical Support- S.K.T., Y.R.M., G.A., K.K., M.B.B.; Supervision- S.K.T., M.B.B.*

Conflict of Interest: *Authors declared no conflict of interest.*

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