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ORIGINAL ARTICLE

The effects of a combination oral spray (Mucosamin®) for the prevention of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation: a double blind randomized clinical trial

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Abstract

Purpose Oral mucositis (OM) is a frequent complication of conditioning regimens for hematopoietic stem cell transplantation (HSCT). Damage to the nuclear and non-nuclear materials of the mucosal cells by the production of Reactive Oxygen Species (ROS) and proinflammatory cytokines could result to development and progression of OM. Previous studies have shown the effectiveness of Mucosamin® oral spray in the management of pain and acceleration of OM healing. The aims of the current study were to evaluate prophylactic effects of Mucosamin® oral spray in reducing the incidence and severity of OM in pediatric patients undergoing allogeneic HSCT.

Method The current study was designed as a double-blind, placebo-controlled randomized clinical trial. Sixty patients were enrolled in the study and received placebo or Mucosamin® spray. Patients in both groups used sprays 4 times daily. Product application was begun at the time of initiation of conditioning regimen and was continued for 14 days.

Results Mucosamin® significantly reduced incidence and severity of OM compared to the placebo (*P* values: 0.027 and 0.035, respectively). This product could also decrease OM duration and delay OM onset (*P* values: 0.007 and 0.006, respectively).

Conclusion Mucosamin® could effectively reduce incidence, severity, and duration of OM and delay OM onset in pediatric patients undergoing allogeneic HSCT.

Trial registration The study protocol was registered in the Iranian Registry of Clinical Trials under the registry number IRCT20190917044805N1.

Keywords Oral mucositis · Allogenic hematopoietic transplant · Pediatric · Mucosamin® · Hyaluronic acid

Introduction

Oral mucositis (OM) is one of the frequent and most troublesome complications of high-dose chemotherapy. OM's incidence rate and severity are highly variable in different patients and disease states. The incidence and severity of OM in patients undergoing hematopoietic stem cell transplantation (HSCT), particularly allogeneic HSCT, are relatively high and usually occur in the first 30 days after transplantation [1, 2]. The incidence rate of 30–60% has been reported for high-grade OM; however, nearly all patients may develop OM to some extent [3, 4]. Gender and body mass index (BMI) are two factors whose impact on OM has not been clearly proven. While some papers have reported a higher incidence in girl patients with higher BMI, other studies have reported the opposite results [5, 6]. OM could result in severe acute pain, interfere with oral intake, increase the duration of hospitalization, and result in chronic pain [7, 8]. These complications could negatively affect the quality of life and increase the recovery period [8]. Microbial colonization contributes to ulcerative mucositis

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development and infectious complications of OM, including oral fungal infection, reactivation of herpes simplex virus, and alpha-hemolytic streptococcal bacteremia [9–12].

Pathogenesis of OM consists of damage to the nuclear and non-nuclear materials of the submucosal and mucosal cells leading to the activation of the inflammatory cascade, which is the leading cause of cellular damages. Production of reactive oxygen species (ROS) by damaged tissue and up-regulation of transcription factors and proinflammatory cytokines like nuclear factor-kB (NF-kB), tumor necrosis factor α (TNFα), interleukin 6 (IL-6), and interleukin 1β (IL-1β) are hallmark factors which lead to the inflammatory response [3, 13]. The stimulation of macrophage and matrix metalloproteinase (MMP) by fibronectin are the other factors that may result in mucosal damage and ulceration [13]. These destructive effects on submucosal and mucosal cells begin immediately after the conditioning regimen [13]. However, significant erythema or ulceration may not be noticeable until 4 days after chemotherapy initiation [14].

Conditioning regimens used before stem cell transfusion have a critical role in HSCT procedure since they prevent graft rejection and reduce tumor burden. High dose of chemotherapeutic agents is used in conditioning regimens. These protocols are determined based on the patients and disease-related factors. The main components of the conditioning regimen in HSCT are alkylating, and antimetabolite agents, which are the most common drugs that cause OM development. OM development and its severity are higher in pediatric patients undergoing HSCT who receive busulfan [15].

Therapeutic and preventive options for OM are limited. While palifermin is the only approved product for the prevention of OM in patients undergoing HSCT, it is not available in many countries [16]. Local interventions like cryotherapy and oral hygiene measures are routinely undertaken in many centers to prevent OM in autologous and allogeneic HSCT patients [17–19]. Although different medical mouthwashes are under investigation, their effectiveness has not been proved or is somewhat limited [17]. Limited studies have shown the beneficial effects of mucoadhesive agents such as hyaluronic acid in patients with OM, but because these studies are not of strong power, current practice guidelines does not recommend their routine use in this patient population [20].Consequently, they are not used routinely in therapeutic and preventive protocols for OM. Photobiomodulation (PBM) could also significantly prevent OM development and its complication. Major guidelines have recommended PBM for HSCT patients receiving high-dose chemotherapy with or without radiotherapy and patients receiving head and neck radiotherapy and or chemotherapy [17].

Topical application of 0.2% hyaluronic acid has been reported to significantly reduce pain and size of ulcers and prompt healing in patients with recurrent aphthous ulcers, oral ulcers of Behçet's disease, and oral lichen planus [21–23]. It has also been reported that hyaluronic acid application could prevent new ulcers in patients with a history of recurrent aphthous ulcers [21]. On the contrary, the hyaluronic acid application could not reduce the duration of oral intake impairment in patients with oral ulcers in the context of lichen planus [23]. Some limited animal studies have reported beneficial effects of glycine in preventing chemotherapy-induced OM, which is probably through attenuating inflammatory response and free radical production. It has been proposed that topical application of glycine might provide better effects than systemic glycine due to its higher concentration in the site of required action [24].

Mucosamin® (Professional Dietetics S.p.A, Italy) is a topical spray that is one of the under-investigation options for the treatment and prevention of OM. It contains sodium hyaluronate, four amino acids (L-lysine, L-leucine, L-proline, L-glycine), and preservatives. Some studies have evaluated the therapeutic effect of Mucosamin® product on chemotherapy- or radiotherapy-induced oral mucositis [25–28]. They showed the positive effects of this product in reducing pain and severity of mucositis, prompting healing of ulcers, and improving oral intake [25–28]. Only one study investigated the prophylactic effect of Mucosamin® in vitro, and after positive effects were observed, its preventive effect in five patients with a history of OM was evaluated. It was reported that Mucosamin® reduced pain and severity of OM compared to the previous chemotherapy cycles [29].

Since the clinical data about the effects of Mucosamin® for prevention and routine use of this product in OM in HSCT patients do not exist, this clinical trial is defined. In this study, the effects of Mucosamin® in the prevention of OM are investigated in a randomized pilot placebo-controlled double-blind clinical trial to determine the effects of this product in pediatric allogeneic HSCT patients undergoing conditioning chemotherapy.

Methods

Study design

This study was a double-blind, placebo-controlled randomized clinical trial. It was conducted in the pediatric HSCT ward of Shariati hospital, a tertiary teaching center affiliated to Tehran University of Medical Sciences, (TUMS) from February 2020 to August 2021. The study protocol was approved by the ethics committee of TUMS with approval code of IR.TUMS.TIPS.REC.1398.133. Information about the procedure, risks, and benefits of the study was provided for the patients and families before their enrollment. Because the patients were underage, their legal guardians signed an informed consent form before involvement in

the study. The study protocol was also registered in the Iranian Registry of Clinical Trials under the registry number IRCT20190917044805N1.

Study population

All children admitted to Shariati hospital for receiving HSCT were assessed for the eligibility criteria to enroll in the study. Inclusion criteria included 4 to 18 years old and candidate for receiving allogeneic HCST. Patients who were younger than 4 years old were not enrolled in the study because it was presumed that they could not use the product properly and they could not have good adherence to the study protocol. Exclusion criteria were patients with baseline diagnosis of Fanconi anemia and having active OM and sensitivity to the product components.

All patients underwent dental evaluation before admission and received normal saline mouthwash and nystatin oral suspension every 3 h from the beginning of the conditioning regimen. The patients received a conditioning regimen with busulfan/cyclophosphamide (Bu/Cy), except those diagnosed with aplastic anemia. These patients received a conditioning regimen with cyclophosphamide. The HSCT protocol was also consisted of immunosuppressive agents including methotrexate and/or cyclosporine, antifungal prophylaxis with fluconazole, pneumocystis jiroveci, prophylaxis with sulfamethoxazole-trimethoprim, and antiviral prophylaxis with acyclovir or ganciclovir. The details of the conditioning regimen are provided in Tables S1 to S5 of the Supplementary Information file available online.

Placebo preparation

Placebo product contained all components of Mucosamin® spray except sodium hyaluronate and four amino acids. It consisted of purified distilled water and pharmaceutical grades of methylparaben 0.18%W/V, propylparaben 0.02%W/V, lactic acid 0.015%V/V, tetrasodium EDTA 0.01%W/V, and propylene glycol 5%V/V. The placebo spray was prepared by the department of the Pharmaceutical Sciences of the Faculty of Pharmacy of the TUMS. It was delivered in the same container as commercial product of Mucosamin® spray. According to the random number table, all sprays, placebo, and product were marked with unique code. The manufacturer has recommended to store Mucosamin® oral spray between 15 and 30 °C and away from direct sunlight. All participants, physicians, nurses, and investigator who assessed the patient's mucositis were blinded, and only one who prepared the placebo product and marked code on all products was not blinded. Based on the National Health Service recommendation, the placebo products could be stored at room temperature for 28 days [30].

Study groups and procedure

Patients were randomly and equally assigned to intervention and placebo groups. While the former group received Mucosamin® oral spray, the latter group received placebo product. Random number table was used for randomization. Method of randomization was blocked randomization. All patients were requested to administer the product to all mouth surfaces, including the tongue, floor of the mouth, soft palate, buccal mucosa, and labial frenulum, every 6 h. Patients were recommended to administer the product after using other mouthwashes and neither eat nor drink for 30 min after spray application. The investigation of oral spray in both groups started on the day of conditioning chemotherapy administration and was continued for 2 weeks. The investigator asked about the adherence to the study protocol from the parents of the patients; at each visit, adherence to the study protocol was reinforced, and patients with poor adherence were excluded. Stem cell transfusion was performed on day seven. In case the patient developed OM while using products, routine care including IV analgesic, IV hydration, IV nutritional support, investigation of oral cavity for infections, and saline mouthwash was provided, and the patient was asked to use the spray following application of saline mouthwash.

Study outcomes and data collection

The study was designed to evaluate the preventive effects of Mucosamin® spray in reducing the incidence and severity of OM in pediatric patients undergoing allogeneic HSCT. The primary outcomes of the study were to evaluate the difference of mucositis incidence and severity between two groups. Beside these primary outcomes, the effect of Mucosamin® spray on decreasing the duration of OM, delaying the onset of OM, and decreasing the duration of hospitalization and time to engraftment was also evaluated between two groups as the secondary outcomes.

Patients were examined with oral cavity inspection on days 0, 3, 6, 9, 12, 15, 18, and 21 after chemotherapy initiation for detection and recording of OM. The grading of OM severity is done according to the NCI-CTCEA v5 [31], as shown in Table 1. The scale was chosen because of long-term experience in our center, its practicality and feasibility, and its recent date of publication. Other OM evaluation scales like the World Health Organization scale are mainly based on findings in oral mucosa of the patients which does not necessarily result in clinical effects. On the other hand, NCI-CTCEA v5 grade can show the degree of clinical impairment and is not, a significant degree, affected by subjective findings. All of the patients were evaluated by a sole investigator who was blinded and trained by an experienced nurse in grading the OM [32]. In addition, demographic

Table 1 NCI-CTCAE version 5 classification of oral mucositis severity

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Oral mucositis (OM)	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain, interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

data, counts of white blood cells and platelets, hemoglobin levels, and kidney function tests at the time of enrolment were also recorded.

Statistical analysis

SPSS and STATA software was used to statistical analysis. The quantitative continuous data were analyzed by two methods. Two samples independent *t* test was utilized for the data with normal distribution, and the mean and standard deviation (SD) were reported. The rest of the data was analyzed by the Mann–Whitney *U* test and median and interquartile range (IQR). The qualitative data were compared with Pearson's Chi-square test.

Incidence and severity of OM were compared with the survival model of Cox and ordinal regression, respectively. The odds ratio and hazard ratio were reported for this analysis. *P* value was also reported for both qualitative (including gender and baseline diagnosis) and quantitative data. *P* value less than 0.05 was considered as a significant difference between intervention and placebo group.

Results

Demographic and baseline characteristics

Sixty patients were enrolled in this study and were equally allocated to the intervention or placebo group. Only one patient in the intervention group was excluded from the study after receiving a conditioning regimen because he showed acute sinusitis symptoms, and his transplant was postponed. Eventually, 29 patients in the intervention group and 30 patients in the placebo group completed the study. However, in this study, the gathered data from all sixty patients were analyzed by the intention-to-treat method for final analysis. The Consort flow diagram of this study is provided in Fig. 1.

Table 2 shows the baseline demographic data of the patients. There was no significant difference between the two groups considering these data.

Primary and secondary outcomes of the study

All the patients enrolled in the current study experienced OM, except one of the patients in the intervention group. Grades 4 and 5 of OM were not experienced by any patients in the current study. While the incidence rate of grades 1, 2, and 3 of OM in the placebo group was 97%, 70%, and 50%, it was 73%, 73%, and 37% in the intervention group, respectively. The highest grade of OM (grade3 in current study) was occurred in 15 (50%) patients of placebo group and 12 (37%) patients of intervention group. The

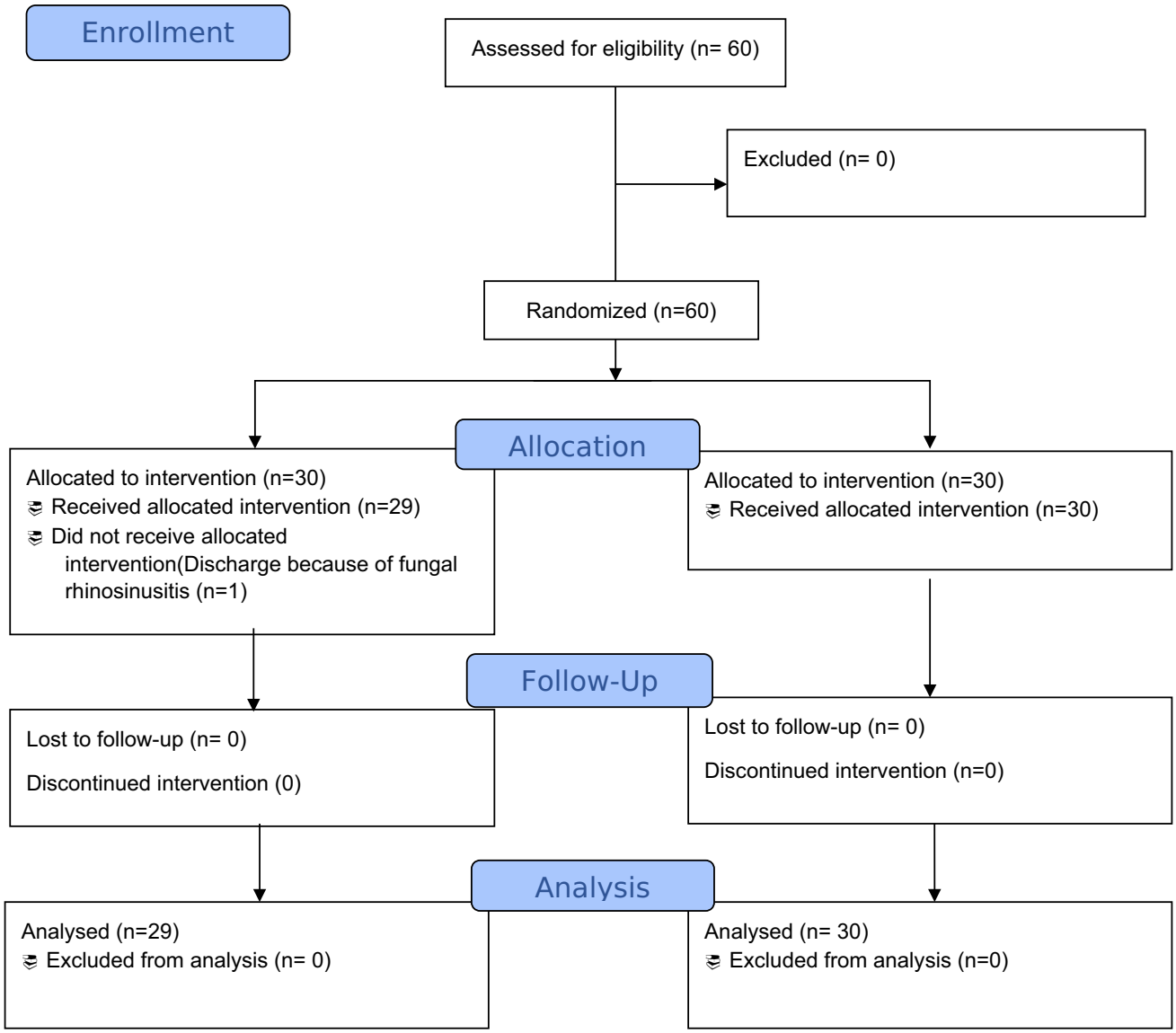

Fig. 1 CONSORT flow diagram of the investigation

Mucosamin® effectively decreased the incidence of OM compared to the placebo (*P* value: 0.027, HR: 0.547, 95%CI: 0.320–0.933), and the possibility of OM occurrence in the intervention group was 45% lower than the placebo group (HR: 0.547, 95%CI: 0.320–0.933). Mucosamin® also significantly reduced the severity of OM (*P* value: 0.035, OR: 0.623, 95%CI: 0.401–0.967), and the possibility of severe OM in the intervention group was 38% lower than the other placebo group (OR: 0.623, 95%CI: 0.401–0.967). Table 3 presents the OM incidence rate in both intervention and control groups. The incidence rates were compared by survival model of Cox regression, and the overall *P* value was reported.

Mucosamin® significantly decreased the total duration of OM that was almost 4 days shorter in the intervention group (10.76 ± 4.78 vs 14.11 ± 4.31, *P* value: 0.007). Table 3 shows the duration of OM. Duration of all grades of mucositis are separately compared, and Table 4 shows the details of these comparisons. Duration of grade 1 was significantly lower in the intervention group (*P* value: 0.006). But it was not considerably different for grades 2 and 3 (*P* values: 0.922 and 0.209, respectively). Total days of grades 2 and 3 involvement were not significantly different between two groups (6 [IQR = 6] vs 7.5 [9]; *P* value: 0.34). Mucosamin® also could not decrease the duration of hospital stay effectively (*P* value: 0.59). The details of these analyses are available in Table 4.

Mucosamin® effectively postponed the onset of OM in pediatric HSCT patients. The median onset of OM after starting chemotherapy in patients in the intervention group

Table 2 Demographic information and baseline examinations

Characteristic	Groups	Drug (mean and SD or median and IQR)		Placebo (mean and SD or median and IQR)		*P* value
Number of patients		30		30		N/A
Age (years) mean ± SD		11.87 ± 5.52		13.18 ± 4.42		0.312
Gender (%)		21 male (70%)		22 male (73.33%)		0.774
		9 female (30%)		8 female (26.66%)		
BMI mean ± SD		21.89 ± 7.13		20.15 ± 6.68		0.332
Baseline diagnosis (%)		ALL	21 (70%)	ALL	19 (63.33%)	0.930
		AML	7 (23.33%)	AML	4 (13.33%)	
		Aplastic Anemia	2 (6.66%)	Aplastic Anemia	4 (13.33)	
		Thalassemia	0	Thalassemia	1 (3.33%)	
		MPS	0	MPS	1 (3.33%)	
		MDS	0	MDS	1 (3.33%)	
Baseline WBC count (cells/ml) [median (IQR)]		3800 (2750)		3030 (2880)		0.744
Baseline PLT count(cells/ml) mean ± SD		217,803.57 ± 154,130.32		216,466.66 ± 131,550.89		0.607
Baseline HGB level(g/dl) mean ± SD		11.29 ± 3.15)		10.98 ± 1.86		0.735
Baseline Cr (mg/dl) [median (IQR)]		0.62 (0.3)		0.64 (0.33)		0.202
Baseline BUN (mg/dl) [median (IQR)]		10 (7.5)		9 (4.88)		0.357
Time required for engraftment [median (IQR)]		14(2.5)		14 (4)		0.912

BMI, body mass index; *ALL*, acute lymphoblastic leukemia; *AML*, acute myeloblastic leukemia; *MPS*, mucopolysaccharidosis; *MDS*, myelodysplastic syndromes; *WBC*, white blood cell; *PLT*, platelet; *HGB*, hemoglobin; *Cr*, creatinine; *BUN*, blood urea nitrogen

Table 3 Oral mucositis incidence

Grades	Incidence of different grades-placebo group	Incidence of different grades-intervention group	*P* value	Hazard ratio	Confidence interval
1	97%	73%	0.027	0.547	0.320–0.933
2	70%	73%			
3	50%	37%			
4 and 5	0%	0%			

was 12 days (IQR = 4.5) compared with 6 (IQR = 3) days in the placebo group (*P* value: 0.006). These data are showed in Table 4.

Discussion

To the best of our knowledge, this is the first placebo-controlled, double-blind, randomized clinical trial to evaluate the preventive effects of Mucosamin® on OM in pediatric HSCT patients. Based on the results, the Mucosamin® significantly reduces incidence, severity, and duration of OM. It also delays the onset of OM in pediatric HSCT patients. The onset of OM development was significantly delayed in patients who received Mucosamin®. The exact cellular mechanism of this effects requires further study, though enhanced cell survival and proliferation has been reported in cells exposed to hyaluronic acid which is considered the main part of Mucosamin® oral spray[33, 34]. This effect could also have played a role in prevention of development

Table 4 Comparing duration of grades, total duration of oral mucositis (OM), and duration of hospitalization

Finding	Groups	Intervention group (median and IQR)	Placebo group (median and IQR)	*P* value
Grade1 duration		3 (7.5)	9 (3)	0.006
Grade2 duration		6 (3)	6 (6)	0.922
Grade3 duration		0 (3)	3 (3)	0.209
Total duration of grades 2 and 3		6 (6)	7.5 (9)	0.34
OM onset		12 (4.5)	6 (3)	0.006
OM duration		9 (4.5)	15 (6)	0.007
Duration of hospitalization		32 (12)	31 (14)	0.591

of severe forms of OM. Other components of the product could have also played a role in prevention of development of severe forms of OM and shortening the duration of mild forms. Cell regenerative effects have been reported with l-leucine in both in vivo and in vitro conditions, enhanced cell growth has been reported with l-lysine, enhanced cell proliferation has been reported with glycine, and protection against oxidative stress has been reported with proline [35–38]. These regenerative effects, alongside proliferative effects, could have resulted in decreased incidence of severe forms and duration of milder forms. Decreased duration of milder forms of OM could have eventually translated into decreased duration of OM in general. The exact mechanism of effect requires careful pathologic examination.

The overall combined incidence of OM in the patients enrolled in this study was 98%, and the grade 3 of OM occurred in 43% of the patients. These findings are in line with the results of previous studies. The incidence rate of OM in pediatric HSCT patients has been reported as 43–97% [39]. Moreover, in an adult population of HSCT patients who had received conditioning regimen based on busulfan/cyclophosphamide (Bu/Cy), the incidence rate of all grades of OM and development of severe forms were reported about 100% and 40%, respectively. It is worth noting that the conditioning regimen in most patients in the present study was similar to the conditioning regimen of Vokurka et al.'s research [40]. The average duration of involvement with OM in the current research and the Vokurka et al. is approximately the same, 11 and 12 days, respectively.

Kuwatsuka et al. reported the incidence rate of severe OM (grade 2 or higher) about 50% in adult patients who received conditioning regimens based on Bu/Cy [41]. The incidence rate of grade 2 or higher OM in our study was approximately 70%. It is unclear whether age is an independent risk factor for higher incidence and/or severity of OM in cancer patients or not. Some studies reported more incidence and severity in pediatric patients, and others revealed opposite results. In contrast to the adult population in the Kuwatsuku et al. study, we recruited pediatric patients which can explain the different results. Moreover, the types of cancer could be another risk factor for developing OM [5]. Most of the children in our study have a diagnosis of ALL, which is a different population than AML diagnosis in most patients in the Kuwatsuku et al. study. It has been reported that high levels of inflammatory cytokines might result in higher levels of OM development in patients with acute leukemias. It also has been reported that baseline diagnosis might act as a risk factor for OM and the effect might be significantly greater for acute leukemias [42, 43]. However, no study has reported higher prevalence of OM in a special type of leukemia. Our results, compared to previous findings, indicate that incidence of OM might be higher in some patients with selected baseline diagnosis such as ALL. Further prospective studies are required to exactly report the difference in OM incidence in patients with different baseline diagnosis who undergo HSCT.

The active ingredients of Mucosamin® are sodium hyaluronate, L-lysine, L-leucine, L-proline, and L-glycine. Sodium hyaluronate is a mucoadhesive polymer that acts as a physical barrier against the oral ulcers. Some limited studies have shown positive prophylactic effects of applying 0.2% topical hyaluronic acid on oral lesions such as recurrent aphthous and lichen planus-related oral lesions [21, 23]. In these investigations, using topical hyaluronic acid promoted the healing rate and reduced the incidence rate of oral lesions. Findings of present research also showed that Mucosamin®, which contains sodium hyaluronate, significantly reduces the incidence, severity, and duration of OM in pediatric HSCT patients.

Production of ROS and running inflammatory cascade plays the main role in OM development and progression [13]. An animal study showed that systemic glycine supplementation could reduce the severity of chemotherapy-induced oral mucositis in hamsters. Positive effects of glycine might be due to reduction in oxidative stress that is due to decreased lipid peroxidation and free radical production in mucosal cells [24]. Glycine is one of the components of Mucosamin® spray. The topical application of this spray delivers a high concentration of glycine to mucosal cells, which could have benefits in decreasing OM severity and duration.

The therapeutic effect of Mucosamin® on chemotherapy-induced OM in HSCT patients has been evaluated in two case control studies [26, 27]. Both studies showed that Mucosamin® effectively reduced severity and duration of OM involvement; therefore, it could reduce pain in these patients. According to these studies, it seems that Mucosamin® was more effective in patients with more severe form of OM. Although both of them concluded in HSCT patients, they did not evaluate preventive effects of this product and they did not enroll children.

Two studies evaluated the effect of Mucosamin® on radiotherapy-induced OM in patients with oral cancers. Colella et al. investigation's results showed the positive effect of Mucosamin® in reducing the pain, decreasing the incidence, prompting healing of ulcers, and improving the oral intake [25]. Although it had interesting results, its open-labeled nature, limited sample size, and different baseline diagnosis of the patients were the significant limitations of that study. The results of a recent study are in line with previous study [28]. This investigation confirmed the effects of the product in reducing the severity of radiotherapy-induced OM and decreased OM duration in these patients.

Cirillo et al. evaluated the prophylactic effects of Mucosamin® in a very limited number of patients receiving chemotherapy and/or radiotherapy [29]. Results of the study done

on 5 patients showed that Mucosamin® effectively reduces the pain and severity of OM and accelerates the healing of lesions.

This study had some limitation. The study population was only pediatric patients who were undergoing allogenic HSCT, and because such a study has not been done previously, the sample size was predicted for a pilot investigation. However, results of the study, which show significant effects with the product, confirm that the sample size has been adequate. Future studies need to examine the effects of the product on larger populations, autologous HSCT, and adult patients. We only evaluated the prophylactic effects of the product in this study, so patients used the product 7 days before and 7 days after HSCT, and they were evaluated for 21 days, which is the duration when the highest incidence of OM is expected. Continuing the use of the product for a longer period of time might provide further beneficial effects. Continuing patient evaluation process even after discharge from the hospital may also further elucidate the effects of the product in reducing the long-term complications of HSCT such as xerostomia.

Conclusion

The present study showed that preventive application of Mucosamin oral spray, which contains sodium hyaluronate and four amino acids (L-lysine, L-leucine, L-proline, L-glycine), could have positive effects on reducing the incidence and severity of OM in pediatric patients undergoing HSCT. Prophylactic application of this product can also decrease the duration of OM, mainly because of decreased duration of grade 1 OM and prevention of higher grades of OM, and promote healing and delay its onset.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-022-07231-y.

Author contribution All authors of this original article have directly participated in the process of investigation. The first draft of the manuscript was written by Dr. Marzieh Shahrabi and Dr. Mohammad Solduzian, and all authors commented on previous versions of the manuscript. Eventually all authors read and approved the final version submitted.

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Declarations

Ethics approval The study protocol was approved by the ethics committee of TUMS with approval code of IR.TUMS.TIPS.REC.1398.133. Approval date: 2019/11/28.

Consent to participate Written informed consent was obtained from legal guardians before study enrollment.

Competing interests The authors declare no competing interests.

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