JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1475337
J Contemp Med 2024;14(4):180-188

Original Article / Orijinal Araştırma

The Effect of Oral Care Protocols on Mucositis in Pediatric Cancer Patients: A Randomized Controlled Trial

Çocuk Kanser Hastalarında Ağız Bakım Protokollerinin Mukozite Etkisi: Randomize Kontrollü Bir Çalışma

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Abstract

Aim: Standard oral care protocols can reduce the incidence of mucositis. This study aimed to evaluate the effect of the "Oral Care Protocol" containing sodium bicarbonate or saline on mucositis development, degree, and duration in pediatric cancer patients.

Material and Method: This study is a blind, parallel trial design, randomized controlled study. Patients (n=43) who received inpatient chemotherapy treatment for more than three days at the Pediatric Hematology and Oncology Unit were included. The oral care protocol with saline was given to the patients in the control group (n=22), and the oral care protocol with sodium bicarbonate was given to the patients in the study group (n=21). The primary outcome was the development of mucositis. The secondary outcomes were mucositis degree, patient data at the time of mucositis development, and the duration of mucositis. The characteristics of the patients in the study and control groups and the data of patients with and without mucositis were compared with Fisher's exact test, t-test, and chi-square analysis.

Results: No statistically significant difference was found between the study and control groups in terms of mean age, gender, diagnosis, relapse status, treatment stage, risk group, and treatment protocols. Mucositis developed in 18.2% of the patients in the control group and 9.5% of the patients in the study group. No statistically significant difference was found in terms of mucositis development, degree, and duration.

Conclusion: The oral care protocol with sodium bicarbonate can be used to prevent mucositis in pediatric cancer patients. ClinicalTrials.gov Identifier: NCT04586491.

Keywords: Children, cancer, mucositis, oral care, sodium bicarbonate

Öz

Amaç: Standart ağız bakım protokolleri mukozit insidansını azaltabilir. Bu çalışmada, pediatrik kanser hastalarında sodyum bikarbonat veya salin içeren "Ağız Bakım Protokolü"nün mukozit gelişimi, derecesi ve süresi üzerine etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu çalışma kör, paralel deneme tasarımına sahip, randomize kontrollü bir çalışmadır. Çocuk Hematoloji ve Onkoloji Ünitesinde üç günden fazla yatarak kemoterapi tedavisi gören hastalar (n=43) çalışmaya dahil edildi. Kontrol grubundaki hastalara (n=22) salin ile ağız bakım protokolü, çalışma grubundaki hastalara (n=21) ise sodyum bikarbonat ile ağız bakım protokolü verildi. Birincil sonuç mukozit gelişimiydi. İkincil sonuçlar mukozit derecesi, mukozit gelişimi sırasındaki hasta verileri ve mukozitin süresiydi. Çalışma ve kontrol grubundaki hastaların özellikleri ile mukoziti olan ve olmayan hastaların verileri Fisher'in kesin testi, t-testi ve ki-kare analizi ile karşılaştırıldı.

Bulgular: Çalışma ve kontrol grupları arasında yaş ortalaması, cinsiyet, tanı, relaps durumu, tedavi evresi, risk grubu ve tedavi protokolleri açısından istatistiksel olarak anlamlı fark bulunamadı. Kontrol grubundaki hastaların %18,2'sinde, çalışma grubundaki hastaların ise %9,5'inde mukozit gelişti. Mukozit gelişimi, derecesi ve süresi açısından istatistiksel olarak anlamlı fark bulunamadı.

Sonuç: Sodyum bikarbonat içeren ağız bakım protokolü pediatrik kanser hastalarında mukozitin önlenmesinde kullanılabilir. ClinicalTrials.gov Tanımlayıcı: NCT04586491.

Anahtar Kelimeler: Çocuklar, kanser, mukozit, ağız bakımı, sodyum bikarbonat

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Received *(Geliş Tarihi)*: 15.05.2024 **Accepted *(Kabul Tarihi)*:** 27.06.2024

INTRODUCTION

Oral hygiene is one of the applications in which the individual most needs hygienic care. Oral hygiene in children is essential for minimizing the risk of infection and for strong healthy tooth development. Inadequate oral care may cause dry mouth, dental caries, periodontal diseases, bad breath, stomatitis, and mucositis.[1] The pediatric population is one of the patient groups that most need oral care. Oral care is standard practice, especially in pediatric hematology-oncology units to prevent chemotherapy-related mucositis.[2] Oral evaluation helps to determine the frequency of oral care in case of mucositis. Perry et al.[3] stated that the knowledge of pediatric hematology and oncology nurses on oral care, prevention, and management of complications is variable. Nurses need professional oral care training and cooperation. Oral care is one of the most common care practices that pediatric nurses should use in pediatric patients, but it can often be neglected.[4] The development of mucositis can cause both pain and feeding difficulties in patients and greatly affects the comfort of the child and his family. The most important intervention is to prevent the development of mucositis. Quick and relaxing interventions are required during the treatment process. Additionally, in patients who develop severe mucositis, the chemotherapy protocol may need to be interrupted, and the hospitalization period will be prolonged. It is vital to prevent mucositis from developing, as well as preventing it from reaching serious mucositis.[1-4]

The effectiveness of preventive and therapeutic oral care protocols must be evaluated.[5] Chlorhexidine, saline, sodium bicarbonate, benzydamine, sucralfate, granulocyte stimulating factor, low-dose laser therapy, and cryotherapy can be used to prevent mucositis, but none are definitively effective in chemotherapy-associated mucositis.[6-8] In a guideline for children with oral and oropharyngeal mucositis who have received cancer treatment or HSCT (bone marrow transplantation), it is stated that there are weak recommendations regarding the use of low-dose laser therapy, cryotherapy, and keratinocyte growth factor.[9] In a systematic review and meta-analysis study for children with cancer, prophylactic low-dose laser therapy was reported to reduce mucositis.[10] In a systematic review examining interventions in the treatment of oral mucositis in patients undergoing cancer treatment, comparisons of benzydamine HCl versus placebo, sucralfate versus placebo, low-dose laser versus placebo, and the low-dose laser found effective at reducing mucositis. In pain control, patient-controlled analgesia, continuous infusion, and cognitive behavioral therapy can be used. The use of fewer opioids is recommended for patient-controlled analgesia versus continuous infusion. New interventions in the treatment of mucositis and controlled studies evaluating the effectiveness of the interventions are needed.[11] In randomized controlled studies, mouthwash with morphine was found to be effective in reducing pain due to mucositis associated with chemotherapy.[12,13] Nasogastric tube feeding, and total parenteral nutrition (TPN) are recommended in pediatric cancer patients with gastrointestinal mucositis, but oral intake can be continued by preventing the development of mucositis.[14]

In a systematic review, that used dental care, saline, sodium bicarbonate, mixed mouthwashes, and chlorhexidine for managing oral mucositis (OM) in cancer patients, there was insufficient evidence for these products. It is recommended to develop oral care protocols and evaluate their effectiveness.[15] Yarom et al.[16] recommended in favor of zinc and a recommendation against glutamine. The use of benzydamine mouthwash was also recommended.[17] In a review of the use of various agents, an effective agent was not recommended, and they stated that pilocarpine and pentoxifylline were ineffective.[18]

In a study on the effectiveness of sodium bicarbonate in the prevention and management of mucositis, salt and soda, chlorhexidine, and mouthwash were compared, and no difference was found between the groups. The use of soda was suggested for chemotherapy-induced mucositis.[19] In another systematic review, no difference was found when chlorhexidine, sterile water, and NaCl 0.9% were compared, and the use of chlorhexidine mouthwash was not supported.[20] Another study suggested the use of chlorhexidine to reduce oral mucosal damage in children with cancer.[21] In the prevention and treatment of OM, sodium bicarbonate mouthwash is not recommended in any guidelines for children, and there is insufficient and weak evidence, in studies directed at the adult population. However, since it is harmless, sodium bicarbonate can frequently be used in maintaining oral hygiene. The use of sodium bicarbonate in children may not be beneficial, and it is unpleasant and irritating, the saline can be used in children.[15] There are differences in terms of the agents used in oral care in patients initiating chemotherapy. Sodium bicarbonate is a frequently used and easily accessible preparation. However, studies evaluating its effectiveness in the pediatric population are limited.[22]

Bhatt et al.[23] applied a standardized mucositis protocol for the prevention and management of oral mucositis in HSCT patients receiving high-dose chemotherapy. They stated that the standardized oral care protocol is effective in the management of mucositis. Yavuz and Bal Yılmaz[24] found that the planned oral care training given before chemotherapy reduced the degree of mucositis and pain levels in children. In another study, the standard oral care protocol reduced the incidence of mucositis in children with cancer.[25]

Aim

This study was conducted to determine the effects of oral care protocol containing sodium bicarbonate or saline solution in the prevention of oral mucositis (OM), mucositis degree, and duration in children with cancer.

Study hypothesis

There is a difference in oral mucositis, OM degree, and duration between groups.

There is a difference in variables in patients with and without mucositis.

MATERIAL AND METHOD

Study design and participants

This study was conducted as a randomized controlled trial with a parallel design. The study participants were composed of children with cancer who received chemotherapy in the Pediatric Hematology and Oncology Unit of a university hospital in Turkey, between October 2019 and February 2020. This trial was approved by the Ethics Committee of the Hospital. It is registered also at the NIH (NCT04586491). This study was guided by the CONSORT checklist.[26]

The sample size was calculated according to Alkhouli et al.'s[27] study using the G*Power software (v. 3.1.9.4). The significant level was set at 0.05 and the statistical power of the study was set at 80%. It estimated that three patients for each group were required to demonstrate an effect size (0.99). The study sample was comprised of 43 children with cancer aged 1-17 years, who received chemotherapy for ≥3 days at inpatient clinics between October 2019 and February 2020, and whose families agreed to their participation in the study (**Figure 1**). Patients excluded who have oral ulceration or mucositis, taking any antiviral or antifungal therapy for OM before enrollment, and at the terminal period. Written informed consent was obtained from children and parents.

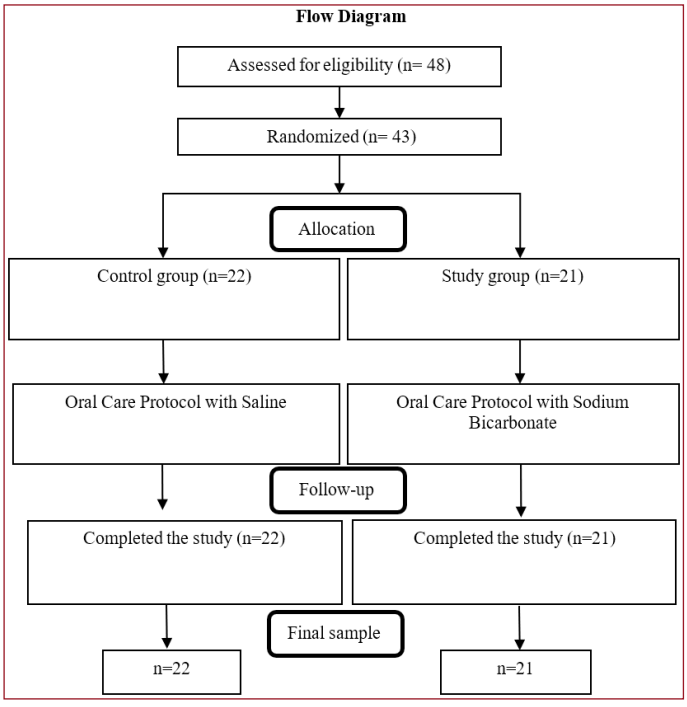

Figure 1. Flow diagram of this study

This trial was blinded and the patients/parents, nurses, and investigators had no idea about the groups. The nurse interns who were not in the study randomly assigned all patients into groups.

Randomization

After the child was included in the sample, he/she was included in the study or control group by stratified randomization method. Randomization was achieved between the study and control groups by stratifying the patients in terms of gender, age, and diagnosis variables. Increasing age and the diagnosis were conditions that prolonged the duration of severe oral mucositis.[28] Therefore, the stratified randomization method was used. In the study, the gender variable was naturally divided into 2 layers, and the age divided into 5 layers as "<1 year, 1-3 years old,> 3-6 years old, 6-12 years old,> 12 years old". The diagnostic variable is divided into 3 layers "Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), and Oncological tumors". In this case, 2×5×3=30 combinations made between variables. According to this randomization method, the possibility of imbalance occurring between the groups is limited.

Study procedure

Informed consent was obtained from parents of children before the study. The nurse interns who were not in the study randomly assigned all patients into groups; study group/ oral care protocol with sodium bicarbonate 8.4% solution, control group/ oral care protocol with saline solution. All patients took standard oral care protocol in the unit.

Oral care protocol

- Oral care training for the child and family
- Daily evaluation of the inside of the mouth with the World Health Organization (WHO) Oral Mucositis Grading Scale
- Oral care 4 times a day if oral grade 0, 6 times a day if grade 1, 8 times a day if grade 2, 12 times a day if grade 3, and 24 times a day if grade 4
- Mouthwash with saline (control group) or sodium bicarbonate 8.4% solution (study group) according to the oral care times
- If the patient is unable to mouthwash (<3-4 years), wipe the inside of the mouth with saline (control group) or sodium bicarbonate 8.4% solution (study group) with a sterile sponge
- Brushing teeth with a soft toothbrush (<3-4 years) if platelet value was >50000 mm³
- If the platelet value was <50000 mm³, wipe the inside of the mouth with a sterile sponge soaked with saline (control group) or sodium bicarbonate solution (study group).
- If grade ≥ 1 or 2 mucositis developed and is accompanied by pain, it included mouthwash with saline containing morphine (1cc of morphine is mixed into 19 cc of saline, and the patient is allowed to mouthwash with saline containing 5cc of morphine 4 times a day).
- If grade ≥ 1 mucositis developed, the patients were fed via nasogastric tube.

In the control group, the saline solutions in 500 cc bottles were stored in patient rooms. In the study group, 1 ampoule (10 cc) of 8.4% sodium bicarbonate was added to 500 cc saline solution and stored in the patient rooms. The solutions were renewed every two days. The use of glutamine and mycostatin is recommended for every patient in the unit. However, it is not the standard approach. Patients may not use it at their own discretion.

Outcomes

The primary outcome was the development of mucositis. The secondary outcomes were mucositis degree, patient data at the time of mucositis development, and the duration of mucositis. During hospitalization, the development status of mucositis and its degree was followed by the WHO Oral Mucositis Grading Scale. If the child with mucositis was older than 8 years old, the ChIMES and Wong-Baker Faces Pain Rating Scale were also applied for the mucositis-related pain. The patient's data about mucositis, the OM duration time, and medical records were recorded in the Mucositis Follow-up Form.

Study Instruments

Socio-Demographic Data Collection Form: It consisted of questions about sociodemographic and treatment-related characteristics of the children; age, gender, socioeconomic level, diagnosis, date of diagnosis, relapse status, treatment stage, diagnosis risk classification, chemotherapy cure, and chemotherapy drugs.[2,12,13,19,27]

The Mucositis Follow-up Form: It included the presence of daily mucositis, duration of mucositis, the use of glutamine and Mycostatin, the chemotherapy drugs on the day of mucositis, the number of neutrophils and thrombocytes on the day of mucositis, and the use of analgesic and morphine mouthwash due to mucositis.

The World Health Organization Mucositis Scale: It is based on the ability to eat and drink. WHO mucositis scores are 0 (no symptoms), 1 (oral pain) erythema-no change in oral intake, 2 (oral erythema and ulcers, solid diet tolerable- soft foods only), 3 (oral ulcers, liquid diet only), 4 (oral feeding impossible). High scores for the WHO mucositis scale indicated severe mucositis. (29) In the clinic where the study was carried out, patients were routinely evaluated with this tool every day.

International Child Mucositis Rating Scale (ChIMES): ChIMES was developed by Tomlinson et al.[30] It evaluates oral mucositis and mucositis-related findings in pediatric oncology patients between 8 and 18 years. ChIMES include the severity of oral pain, the effect of pain on swallowing, eating, drinking, pain relief status, and reason. It consists of six items to evaluate the presence/absence of oral ulcers. Each item of ChIMES 1, 2, 3, and 4 are evaluated with the lowest 0, the highest 5 points; Item 5 is evaluated with the lowest 0, the highest 2 points; Item 6 is evaluated with the lowest 0 and the highest 1 point. When all items are answered, the minimum score obtained from the scale is "0", and the maximum score is "23". The higher the total score obtained from the scale indicates the severity of the mucositis grade. Turkish validity and reliability study of ChIMES is done.[31] The Cronbach's alpha coefficient was 0.91. This scale was used in this study in children with > 0 Grade OM.

Wong-Baker Faces Pain Rating Scale (WB-FACES): It is used to measure pain intensity.[32] Mucositis-related pain is evaluated with the 0-10 WB-FACES in children with OM. It was used in this study in children with > 0 Grade OM.

Ethics

The procedures complied with ethical guidelines and received the Ethics Committee of Dokuz Eylül University (3481GOA 2019/03-55). Written informed consent was obtained from children and parents.

Data analysis

Numbers, percentages, and averages are used to evaluate demographic data. Kolmogorov Smirnov test was used to determine if data was molded by a normal distribution. Mann Whitney U test and Chi-Square analysis were used to compare mucositis development status, degree, and duration in the study and control groups. Mann Whitney U test, Fisher's exact test, and Chi-Square analysis were used to evaluate patients with and without mucositis in terms of some variables. The research data were analyzed using SPSS (23.0). The p-value accepted as statistically significant <.05.

RESULTS

Sample characteristics

There were no statistically significant differences in terms of gender, age, diagnosis, relapse status, the time between the date of diagnosis and study inclusion, and neutrophil and platelet values at the time of inclusion in the study and control groups (p > .05) (**Table 1**).

Mucositis Development, grade, and duration

Mucositis developed in 18.2% (n=4) of the patients in the control group and 9.5% (n=2) of the patients in the study group. Three patients with mucositis in the control group were in Grade 1, and one patient was in Grade 2. Two patients with mucositis in the study group were Grade 1. Mucositis duration followed in patients with mucositis, and the mucositis of the patients in the control group recovered in 0.8±2.5 days and the study group in 0.1±0.6 days (**Table 2**).

Table 1. Patient demographics

	Control Group / Oral Care Protocol with Saline (n=22)	Study Group / Oral Care Protocol with Sodium Bicarbonate (n=21)	
Gender	n (%)	n (%)	
Girl Boy	6 (27.3) 16 (72.7)	11 (52.4) 10 (47.6)	X2= 2.833 p= .092
Age (years) M±SD	7.2±4.6	8.4±5.4	U=208.500 p= .583
Age group n (%)			
≤6 7-12 13-18	11 (50.0) 7 (31.8) 4 (18.2)	9 (42.8) 6 (28.6) 6 (28.6)	X2= .654 p= .721
Diagnosis			
ALL or AML Oncological tumors	9 (40.9) 13 (59.1)	5 (23.8) 16 (76.2)	X2= 1.431 p= .232
Relapse status			
Yes No	4 (18.2) 18 (81.8)	5 (23.8) 16 (76.2)	X2= .206 p= .650
The time between diagnosis and inclusion in the study (month)			
<6 month >6 month	12 (54.5) 10 (45.5)	13 (61.9) 8 (38.1)	X2= .239 p= .625
Neutrophil value			
<500/µl >500-1,000/µl >1,000 µl	7 (31.8) 7 (31.8) 8 (36.4)	6 (28.6) 6 (28.6) 9 (42.8)	X2= .190 p= .910
Platelet value			
<50000 mm³ >50000 mm³	16 (72.7) 6 (27.3)	17 (81.0) 4 (19.0)	X2= .407 p= .523

ALL= Acute Lymphoblastic Leukemia, AML= Acute Myeloid Leukemia

Table 2: Mucositis development, degree, and duration according to the groups

	Control Group (n=22)	Study Group (n=21)	
Mucositis development	n (%)	n (%)	
Yes No	4 (18.2) 18 (81.8)	2 (9.5) 19 (90.5)	X2= .671 p= .413
Mucositis grade			
Grade 1 Grade 2	3 (13.6) 1 (4.5)	2 (9.5) -	-
Mucositis duration (day)	M±SD 0.8±2.5	M±SD 0.1±0.6	U=209.500 p= .386

Characteristics of Patients with and without Mucositis

Of the patients with mucositis, 66.7% (n=4) were male, and 50% (n=3) were between the ages of 1-6 years. There was no difference between patients with and without mucositis in terms of age group, average age, and gender ($p > .05$).

Of the patients with mucositis 50% were diagnosed with ALL (n=3) and 50% (n=3) were diagnosed with oncological tumors. A difference was found between patients with and without mucositis in terms of diagnosis ($p < .05$). While mucositis did not develop in any patients with AML, mucositis developed in 3 of 7 patients with ALL, and 3 of 27 patients with oncological tumors. There was no difference in terms of the average number of chemotherapy cycles and relapse status of patients with and without mucositis.

When the risk classification of patients with mucositis is examined, it is seen that 66.7% (n=4) of them are at standard risk. Of the patients with mucositis, 66.7% (n=4) were in the consolidation treatment, and 33.3% (n=2) were in maintenance treatment. When the time between diagnosis and including date of the study of patients with mucositis was examined, 50% (n=3) had been receiving chemotherapy for more than 6 months. There was no difference in risk classification, treatment stage, and mean time between diagnosis and including the date of the study in patients with and without mucositis ($p < .05$).

When the chemotherapies received by the patients were examined, of the patients with mucositis 33.3% (n=2) were taking etoposide, 83.3% (n=5) were taking doxorubicin, 33.3% (n=2) were taking vincristine, and 16.7% (n=1) were taking dexamethasone. Two of 6 patients were receiving etoposide and 1 of 6 patients were receiving dexamethasone, and a difference was found between the use of etoposide and dexamethasone in patients with and without mucositis ($p <.05$).

All patients with mucositis were using glutamine and Mycostatin. A difference was found in terms of glutamine and Mycostatin use in patients with and without mucositis ($p < .05$) (**Table 3**).

The patient's data at the time of mucositis

Of these patients with mucositis, 33.3% had agranulocytosis (ANC < 200/µl) (n=2), 33.3% had moderate neutropenia (ANC: 200-500/µl; n=2) and 33.3% had mild neutropenia (ANC: 500-1,000/µl; n=2). Platelet counts of all patients with mucositis were between 20,000 and 50,000mm³. All patients (n=6) with mucositis were fed by a nasogastric catheter. Morphine mouthwash was applied to five patients with mucositis (83.3%); regular analgesics were administered to four patients with mucositis (66.7%). Three of the patients with mucositis were in the younger age group, so the pain levels associated with mucositis could not be evaluated, and the mean pain score of three patients in the 7-12 age group evaluated by WB-FACES was 6.3±0.5 (min: 6, max: 7) (**Table 4**). The OM and pain associated with mucositis in these three patients were also evaluated with the ChIMES. The intensity of the oral pain was 2.0±0.0 (min: 2 max: 2). The effect of pain on swallowing was 1.6±0.5 (min: 1 max: 2), on eating was 2.0±0.0 (min: 2 max: 2), on drinking was 1.6±0.5 (min: 1 max: 2). Taking painkillers was 1.6±0.5 (min: 1 max: 2), and presence/absence of oral ulcer was 1.6±0.5 (min: 1 max: 2). The mean total score of the ChIMES was 10.6±2.3 (min: 8 max: 12).

Table 3: Comparison of Patients with and without Mucositis

	Patients with mucositis (n=6)	Patients without mucositis (n=37)	
	n (%)	n (%)	
Gender			
Girl	2 (33.3)	15 (40.5)	p=1.000**
Boy	4 (66.7)	22 (59.5)	
Age group			
1-6	3 (50.0)	10 (27.0)	p=1.000**
7-18	3 (50.0)	17 (73.0)	
Age (years) M±SD	6.3±3.7	8.0±5.2	U=94.000 p= .572
Diagnosis n (%)			
ALL or AML	3 (50.0)	11 (21.7)	p=.373**
Oncological tumors	3 (50.0)	26 (70.3)	
Relapse status			
Yes	1 (16.7)	8 (21.6)	p=1.000**
No	5 (83.3)	29 (78.4)	
Total chemotherapy cycle M±SD	5.8±5.1	4.9±5.6	U=97.500 p= .644
Risk Categories n (%)			
Standard-risk group	4 (66.7)	24 (64.9)	p=1.000**
Medium or High-risk group	2 (33.3)	13 (35.1)	
Treatment stage			
Induction or Consolidation	4 (66.7)	21 (56.8)	p=1.000**
Maintenance	2 (33.3)	16 (43.2)	
The time between diagnosis and inclusion in the study (month)			
<6 month	3 (50.0)	22 (59.5)	p= .683**
>6 month	3 (50.0)	15 (40.5)	
Chemotherapy used when the mucositis develops*			
Etoposide (yes/no)	2 (33.3) / 4 (66.7)	/ 37 (100.0)	X2=12.935 p= .000
Doxorubicin (yes/no)	5 (83.3) / 1 (16.7)	21 (56.8) / 16 (43.2)	X2=1.525 p= .217
Vincristine (yes/no)	2 (33.3) / 4 (66.7)	8 (21.6) / 29 (78.4)	X2=.397 p= .529
Dexamethasone (yes/no)	1 (16.7) / 5 (83.3)	/ 37 (100.0)	X2=6.313 p= .012
Glutamine use			
Yes/no	6 (100.0) / -	10 (27.0) / 27 (73.0)	X2=11.767 p= .001
Mycostatin use			
Yes/no	6 (100.0) / -	19 (51.4) / 18 (48.6)	X2=5.021 p= .025

*Most patients use more than one chemotherapy. **Fisher's exact test.

Table 4. Descriptive Characteristics of Patients with Mucositis

Patient no	Study/ Control group	Age	Gender	Diagnosis	Chemotherapies when the mucositis developed	WHO mucositis grade	Neutrophil (µl)/ Platelet (mm³)	WB-FACES Score	Use of analgesics	Use of Morphine mouthwash	Mucositis duration (day)
P12	S	9	F	Solid tumor	Etoposide-Doxorubicin	1	300/36000	6	no	yes	3
P21	C	11	M	ALL	Dexamethasone-Vincristine	1	800/32000	6	yes	yes	1
P22	C	3	F	ALL	Doxorubicin	1	1300/22500	-	yes	yes	11
P25	C	9	M	Solid tumor	Etoposide-Doxorubicin-Vincristine	2	440/34000	7	yes	yes	2
P26	C	2	M	ALL	Doxorubicin	1	100/32000	-	yes	yes	5
P36	S	4	M	Solid tumor	Doxorubicin	1	200/49000	-	no	no	1

DISCUSSION

The effectiveness of oral protocol containing saline or sodium bicarbonate on the development of mucositis, mucositis degree, and healing time was evaluated in this study. The mucositis developed in 18.2% (n=4) of the patients with an oral protocol containing saline. Although there was no statistical difference, mucositis developed more in the group that used the saline-containing oral care protocol than in the group that used the sodium bicarbonate-containing oral care protocol. Basic oral care in children with cancer usually includes oral care education, regular tooth brushing, and the use of oral saline solutions.[9] None of the mouth rinses such as chlorhexidine, normal saline, sodium bicarbonate, and benzydamine had shown to be effective in preventing chemotherapy-induced OM in children.[6] In a study comparing Aloe-Vera and sodium bicarbonate in children with

ALL (n=22), no statistically significant difference was found in the frequency of OM in the 1st, 5th, 6th, and 8th weeks of the study.[33] However, studies on the pediatric cancer population evaluating the effectiveness of sodium bicarbonate are quite limited.[34,35] There is insufficient evidence for the use of chlorhexidine in children with OM, prophylactic use of 0.12% chlorhexidine gluconate can reduce the frequency of OM.[36] It is seen that the incidence of OM decreased in studies in which regular oral care and training were applied, and standard oral care protocols were used.[22-24]

There was no difference in terms of mucositis degree in this study. Grade 2 mucositis developed in one patient in the control group. The fact that two patients with mucositis in the oral care protocol containing sodium bicarbonate group were grade 1 suggested that sodium bicarbonate might be effective in preventing the increase of mucositis degree. Alkhouli et al.[33] found a statistically significant difference in the occurrence of different OM degrees between groups. Patients in the sodium bicarbonate group began OM sooner than the aloe vera group.[33] In a study comparing propolis and placebo in children with severe OM, 42% of patients had OM in the propolis group, and 48% of patients had OM in the placebo group. Almost half of the patients suffered from severe OM, propolis cannot be recommended for severe OM treatment.[37] In a study using an oral care protocol that includes regular brushing with a soft brush and fluoridated toothpaste and the use of a 0.2% alcohol-free chlorhexidine mouthwash after brushing, children with grade 4 OM were 88% less likely to use the oral care protocol than children with grade 1 OM.[38] The absence of severe OM was pleasing in our study. It showed that our standard oral care protocol is effective in preventing severe OM. Complementary alternative therapies are frequently used in studies, but the content and frequency of the basic oral care approach are often not mentioned in these studies.[33,37]

Although there was no difference in terms of recovery time in this study, we observed that the number of days with OM was low in both groups. In only one patient in the control group, OM continued for 11 days. In Hurrell et al.'s[38] study, the duration of OM was 7 days. In the study of Bhatt et al.[23] their standardized mucositis protocol reduced the incidence and duration of mucositis. Future studies should aim at reducing the grade and duration of OM as well as preventing the development of mucositis.

Pain management is also important for these patients. Oral cryotherapy cannot reduce the incidence of severe OM and oral pain in these patients.[39] Therapeutic LLLT can reduce the severity of oral mucositis and oral pain.[10] Management of OM-related pain should also be addressed in studies. In our study, OM-related pain was also evaluated. The Wong-Baker Faces Pain Scale can be used to evaluate the pain in the mouth due to mucositis.[40] The ChIMES is one of the scales that can be used to evaluate mucositis in children with cancer.[30] In Hurrell et al.'s study,[38] the ChIMES pain score showed an increase in the likelihood of severe OM and the use of CHX mouthwash. In our study, the pain scores of only three patients with mucositis were evaluated due to age group, and mouthwash with morphine was used for pain management. There are no self-report scales for the assessment of OM or OM-related pain in the younger age group such as 3-6 years. Validated screening and assessment tools are especially important for these pediatric patients. Clinical assessment of OM should be a routine care component for children receiving treatment for cancer. Children of different age groups were included in the study. Pain management associated with mucositis should be carried out considering the age group.

In this study, patients with mucositis were using glutamine and Mycostatin. Glutamine can be used to promote mucosal healing during cancer treatment[41] and prevent OM in children with ALL.[42] The keratinocyte growth factor,[9] low-level laser therapy,[43,44] or palifermin can also be used for children with severe mucositis.[45] Honey and olive oil are effective as a preventative and therapeutic measure for OM.[27,46] Probiotics are also effective in reducing OM.[47]

Mucositis developed in 3 of the 7 ALL patients included in the study. OM is more common in children with ALL due to the intensity of treatment.[38] OM management should be given more importance, especially in hematological cancers. Most of the patients with OM were receiving chemotherapy for more than six months. In this study, mucositis developed in two patients on maintenance therapy. Mucositis can develop at any stage of chemotherapy treatment. Therefore, oral care should never be neglected, and a supportive and prophylactic approach should be maintained. Of the six patients with mucositis, two were receiving etoposide and one was receiving dexamethasone. The chemotherapeutic agents are mostly related to severe OM and the interruption in chemotherapy, especially the alkylating agents and antimetabolites.[48] This study revealed that the effective variables in the development of mucositis are diagnosis, risk group, chemotherapy, glutamine, and Mycostatin use. In a study, the presence of HSV, thrombocyte count, Candida spp. found to be associated with an increased degree of mucositis in children and adolescents receiving ALL induction therapy.[49]

The present study had some limitations. There was no age limitation in this study, the younger patients could consider that mucositis was more common in the younger age group. Although stratified randomization was achieved, the patient population is quite large. Only children with leukemia could be studied. If the use of Mycostatin and glutamine were the standard approach in all patients, the effect of the oral care protocol containing saline, or sodium bicarbonate could be more clearly demonstrated. WB-FACES and ChIMES were evaluated in patients with mucositis. However, before the development of OM patients could be evaluated daily with ChIMES.

Implications

The standardized oral care protocols are effective in the management of mucositis. Chlorhexidine, saline, sodium bicarbonate, benzydamine, sucralfate, granulocyte stimulating factor, low-dose laser therapy, and cryotherapy can be used to prevent oral mucositis in children with cancer. In the prevention of OM, mouthwash with sodium bicarbonate is not recommended in any guidelines for children. There is insufficient and weak evidence for sodium bicarbonate mouthwash, studies directed at the adult population mostly. In this study, mucositis developed less in patients who applied oral care protocol with sodium bicarbonate. The mouthwash with sodium bicarbonate can be used in children with cancer. It is recommended to conduct studies in which the standard approach to preventing mucositis is clearly stated, in younger age groups, in cases of ALL. Studies using comparative products should be conducted in pediatric hematology-oncology units where sodium bicarbonate or other agents are used as the standard approach.

CONCLUSION

Mucositis developed in 18.2% of the patients in the control group and 9.5% of the patients in the study group. Less mucositis developed in the patients with the oral care protocol containing sodium bicarbonate. There was no difference in terms of mucositis degree and recovery time in this study. Mucositis developed in 3 of the 7 ALL patients included in the study. The standard oral care protocol was used in this study, which deals with the development of mucositis and the recovery period in 43 children treated with chemotherapy. The oral care protocol containing sodium bicarbonate mouthwash was found to be more effective in preventing the development of mucositis in pediatric cancer patients.

The prevention and treatment of OM are difficult, with several methods and pharmacologic agents tested. Standardized oral care protocols are effective in the management of OM. Accordingly, the standard oral care protocol applied in this study, and the efficacy of mouthwash with saline and sodium bicarbonate evaluated, which is frequently used, but there is inadequate evidence in the pediatric population. Prophylactic use of mouthwash with sodium bicarbonate can be recommended in the pediatric cancer population. The incidence and duration of mucositis and mucositis-related pain can be evaluated in younger pediatric patients receiving high-dose chemotherapy with ALL.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dokuz Eylül University Ethics Committee (Decision No: 3481GOA 2019/03-55).

Informed Consent: Written informed consent was obtained from children and parents.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgment: The authors are grateful for the kind cooperation of pediatric oncology patients, pediatric oncology/hematology nursing staffs, and intern nurses.

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