



The Effect of Oral Care with Chlorhexidine, Vitamin E and Honey on Mucositis in Pediatric Intensive Care Patients: A Randomized Controlled Trial

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ABSTRACT

Purpose: This study was performed to determine the effect of oral care using chlorhexidine, vitamin E and honey on oral mucositis (OM) management in children treated in a pediatric intensive care unit (PICU).

Design and methods: The study was a randomized controlled trial with a parallel design. The study sample was composed of 150 children who were treated in the PICU of a university hospital in Turkey. Children enrolled in the study were randomly divided into six groups based on the oral care solutions used ($n = 25$ in each group). The Demographic Information Form and the World Health Organization Oral Mucositis Index were used for data collection.

Results: The mucositis indices of the children presenting with and without OM upon admission to the PICU were compared on days 1, 3, 6, 9, 12, 15, 18 and 21 and the study found that the mucositis index values of the children treated with vitamin E were significantly lower than in the other groups ($p < 0.05$ for each), while those of the children given chlorhexidine were significantly higher than in the other groups ($p < 0.05$ for each).

Conclusions: At the end of the study, vitamin E was determined to be the most effective agent in OM management, followed by honey as the second most effective agent. Chlorhexidine was found to be less effective in OM management compared to the other two agents. Based on this, vitamin E is recommended for use in oral mucositis-preventive and therapeutic oral care practices.

Practice implications: The results of the present study conducted with PICU patients will be useful in the administration of oral care. These findings are also important for nurses who have the responsibility of oral mucositis management.

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Introduction

Oral Mucositis (OM) is the inflammation and ulceration of oral mucosa (Kobya-Bulut & Guducu-Tufekci, 2016). The duration and severity of this dysfunction have not been completely identified and its course varies based on the patient and the treatment performed (Cubukcu, Baytan, & Gunes, 2006). There are various grading systems for OM and the system recommended by the World Health Organization (WHO) is the most frequently used. Accordingly, OM is accepted as a four-phase dysfunction including an initial inflammatory/vascular phase (Phase I), an epithelial phase (Phase II), an ulcerative/bacteriological

phase (Phase III) and a recovery phase (Phase IV) (Cubukcu, 2005; Cubukcu et al., 2006; WHO, 1979).

The greater variation in immunological responses and resistance in children compared to adults increases the incidence of OM. Patients in the pediatric intensive care unit (PICU) are especially at risk of OM development. Among unconscious pediatric patients, inability to take liquid and food via the oral route, breathing through the mouth and the drying of oral mucosa caused by oxygen treatment may lead to OM development (Cubukcu, 2005). Furthermore, since swallowing reflexes become weakened or are absent in unconscious children, bacteria reproduce within the saliva and accumulate in the mouth. Gram-positive and Gram-negative bacteria cause secondary infection by growing on the mucosa and impairing its structural integrity. Candida and herpes simplex are also among the main sources of infection (Cubukcu et al., 2006). Moreover, migration of these microorganisms to the lungs can result in colonization and infection in those organs (Grap & Munro, 2004). Therefore, the importance of providing regular

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oral care for intensive care patients should be emphasized (Cubukcu et al., 2006; Grap & Munro, 2004).

For the prevention and treatment of OM, it is very important that the substances used in oral care should be effective, safe, easy to administer and without adverse effects (Koby-Bulut & Guducu-Tufekci, 2016). Although there are many options, such as physiological serum, sodium bicarbonate, vitamin E, povidone iodine, benzydamine, glutamine, zinc, growth factor, palifermin, low-power laser treatment and cryotherapy, an effective treatment strategy has not yet been developed (Izgu, 2017; Koby-Bulut & Guducu-Tufekci, 2016). The major cause for this is the use of separate oral care regimens and variations in the efficiency of the agents used for eliminating the symptoms. However, a preventive measure taken or an agent administered may be significantly effective for a specific phase of mucositis, yet may have a detrimental effect in another phase (Cubukcu et al., 2006; Koby-Bulut & Guducu-Tufekci, 2016). Other studies in the literature have shown that chlorhexidine and vitamin E are frequently used in the management of oral mucositis (Azizi, Alirezai, Pedram, & Mafi, 2015; Chaitanya et al., 2017; Cheng, Chang, & Yuen, 2004; Costa, Fernandes, Quinderé, Souza, & Pinto, 2003; El-Housseiny, Saleh, El-Masry, & Allam, 2007; Ferreira et al., 2004; Kishore-Kumar, 2015; Nashwan, 2011; Pereira Pinto et al., 2006; Setiawan, Reniarti, & Oewen, 2006; Wadleigh et al., 1992).

Chlorhexidine is a wide-spectrum antimicrobial and antiseptic solution frequently used in oral care which is effective on Gram-positive/negative bacteria and fungi (Cavusoglu, 2007; Ozveren, 2010). However, its taste is unpleasant and it may create a burning sensation in the mouth, and with long-term use, discoloration of the teeth and dysgeusia may develop (Cavusoglu, 2007; Macedo, Morais, Dantas, & Morais, 2015; Ozveren, 2010). Due to the ineffectual outcomes and adverse side effects exhibited by chlorhexidine, its efficacy in OM management has been discussed in recent studies (Cavusoglu, 2007; Koby-Bulut & Guducu-Tufekci, 2016; Macedo et al., 2015).

Vitamin E can be applied topically or systemically since its toxicity is acceptably very low and it is generally well tolerated (El-Housseiny et al., 2007). It is not mutagenic, teratogenic or carcinogenic. Although high systemic doses of vitamin E may increase the tendency for bleeding, there are no data showing such an adverse effect with topical use (Azizi et al., 2015). Previous studies have reported that vitamin E used topically twice a day was effective in OM management (Azizi et al., 2015; Chaitanya et al., 2017; El-Housseiny et al., 2007; Wadleigh et al., 1992).

In recent years, the use of honey, which is among alternative methods used in the treatment of wounds, has attracted the attention of healthcare professionals all over the world (Biglari et al., 2013; Izgu, 2017). Previous studies have reported on the antibacterial properties of honey, especially against antibiotic-resistant bacteria, and its use in the healing of wounds. Honey has proven to be a valuable alternative for the treatment of leg ulcers, surgical injuries, burns and various skin diseases, wound healing in cancer patients and in the treatment of oral infections (Al-Jaouni et al., 2017; Khanal, Baliga, & Uppal, 2010; Lay-flurrie, 2008; Maiti et al., 2012; Raessi et al., 2014; Samdariya, Lewis, Kauser, Ahmed, & Kumar, 2015).

Aim

The present study was conducted in order to determine the effects of three different oral care methods (chlorhexidine, vitamin E and honey) frequently used in the prevention and treatment of OM in children admitted to the PICU.

Methods

Design

The study was conducted as a randomized controlled trial with a parallel design.

Settings and participants

The population of the study was composed of children who were treated in the Pediatric Intensive Care Unit of Duzce University Health Practice and Research Center in Turkey, between September 2016 and November 2017. The PICU is equipped with four beds and has a total nursing staff of six. The sample was divided into two groups which included children with and without OM when admitted to PICU. After power analysis, the sample size was calculated as 75 for each group (with/without OM) with a power of 80%, an error rate of 5% and an effect size of 0.25. The sampling of the study was comprised of a total of 150 children two years of age or older who presented with no obstacles to the treatment (e.g., allergy to honey, diabetes, blood glucose issues) and whose families agreed to their participation in the study.

Three different oral care solutions were used to prevent and treat OM. Children enrolled in the study were randomly divided into six groups based on the oral care solutions used ($n = 25$ in each group). Children were matched for age, sex, degree of OM, disease status and treatment protocol and randomly assigned, via drawing of lots, to the study groups. For ethical reasons, no control group was generated and all groups underwent oral care.

Groups of children with OM admitted to the PICU: Group-1. Patients treated with chlorhexidine, Group-2. Patients treated with vitamin E, Group-3. Patients treated with honey Groups of children without OM admitted to the PICU; Group-4. Patients treated with chlorhexidine, Group-5. Patients treated with vitamin E, Group-6. Patients treated with honey.

Children under two years old could not be included in Groups-3 and -6 (due to the risk of botulism in infants under one year of age) in addition to those allergic to honey (based on parents' statements), diagnosed with diabetes (based on patient files), diagnosed with a blood glucose problem (based on blood glucose follow-up chart in patient files) or children for whom the treatment was not appropriate. Children under two years of age were not included in the study to ensure that the study groups were homogeneous. A preliminary test was performed before the implementation of the study. The data collection tools and applications were applied to five children and their parents not enrolled in the sample in order to evaluate the effectiveness of the data collection tools and applications used in the study.

Data collection tools

Data for the study were collected using the *Demographic Information Form* and the *World Health Organization Oral Mucositis Index*.

Demographic Information Form

This form was prepared by the researchers after a review of the literature and was composed of 15 questions about the child regarding sex, age, disease status, diagnosis and treatment protocol (Cubukcu, 2005; Cubukcu et al., 2006; Koby-Bulut & Guducu-Tufekci, 2016).

World Health Organization Oral Mucositis Index

This classification system is preferred for pediatric patients due to its correspondence to clinical models and its easy application in clinical research. In this system, anatomical changes in the oral mucosa and the severity of the mucositis are scored between «0» and «4» as follows: 0 – no mucositis and normal oral mucosa; 1 – mucositis at a mild level, presence of pain and slightly erythematous areas in mucosa, gums, tongue, or palate; 2 – mucositis at a moderate level, presence of erythema and ulcers smaller than 2 mm, able to perform normal feeding; 3 – severe mucositis, presence of ulcers, deep, painful erythema, only liquid food supported; 4 – mucositis at a life-threatening level, presence of ulcers, erythema, severe pain, and bleeding rendering feeding impossible, necessitating parenteral feeding (Cubukcu, 2005; Patussi, Sassi, Munhoz, Zaninetti, & Schussel, 2014; WHO, 1979).

Implementation stages

Before the study, the researchers met with the parents of the children, who were then told about the study and asked to sign informed consent forms. The characteristics of the children were recorded during the first day of their hospitalization using the *Demographic Information Form*. Mucositis scoring was performed via the *World Health Organization Oral Mucositis Index* by monitoring the condition inside the children's mouths. Index scores were recorded every day from the first day of hospitalization. The mucositis assessment was done by a specialist physician working in the clinic, but who did not know the details of the study groups. The daily OM assessments were carried out in the clinic consistently by the same physician.

Oral care was applied to the children in all groups twice a day (every 12 h). All applications were conducted by the two researchers, one of whom is a clinical nurse. Attention was given to the consistent and accurate use of the substances during treatment procedures and a follow-up chart was prepared. The daily amount of honey was calculated as 1–1.5 g per weight (kg) of the child (Khanal et al., 2010; Kobya-Bulut & Guducu-Tufekci, 2016). For ease of application, the calculated amount of honey was applied into the child's mouth using a tablespoon, dessert spoon or teaspoon. One full tablespoon of honey was administered as 30.96 g, one full dessert spoon as 9.83 g, and one full teaspoon as 3.70 g. Honey was applied to the complete oral mucosa (right and left cheek mucosa, lower and upper palate, bottom and top of the tongue), teeth and lips by the researcher. Conscious patients were asked to keep the honey in the mouth and throat for at least 1 min and to swallow it slowly so as to make contact with the pharyngeal mucosa. The flower honey used in this study was taken from the highlands of Zonguldak Province, located in the Western Black Sea Region of Turkey. An analysis of the honey content was obtained for the assessment and the values were found to be appropriate. Moreover, pollens of eight distinct plant families were detected in the honey sample, showing it to be of high quality in terms of its pollen diversity.

A soft capsule containing 100 IU of natural vitamin E was used for the vitamin E application (Azizi et al., 2015; Chaitanya et al., 2017; El-Housseiny et al., 2007). The capsule was broken open by the researcher and the vitamin E was applied to the complete oral mucosa (right and left cheek mucosa, lower and upper palate, bottom and top of the tongue), teeth and lips. The chlorhexidine treatment followed the routine practice used for oral care in PICU patients. In this study, a ready-to-use oral care solution consisting of chlorhexidine gluconate was applied to the complete oral mucosa (right and left cheek mucosa, lower and upper palate, bottom and top of the tongue), teeth and lips via a sponge stick. When the daily amounts were calculated, no cost difference was found among the three agents.

Ethical approval

All procedures performed in this study were in accordance with the 1964 Helsinki declaration institutional and national research committee ethical standards and its later amendments or comparable ethical standards. Written consent was obtained from the Duzce University Ethics Committee for Clinical Research. The parents who agreed to participate after being informed about the study also gave their written consent.

Statistical analyses

Descriptive statistics of all data in the study were calculated as the median (Q2), 1st quartile (Q1), and 3rd quartile (Q3), percentages. Normality assumptions of quantitative variables were assessed by the Shapiro Wilk test. The Kruskal Wallis test (post hoc: Dunn test) was used for the comparisons between groups. The generalized estimating equations (log link, post hoc: LSD test) method was used to compare the measurement values of score variables at different periods between

groups. The Pearson Chi-square and Fisher-Freeman-Halton tests were used for the correlations between categorical variables. Statistical analyses were performed using the SPSS 22 program, with $p < 0.05$ considered as statistically significant.

Results

A total of 49% of the individuals included in the study were females and 51% were males. The median age of the participants was 7.25 years ($Q_1:4$, $Q_3:12$).

General characteristics of groups with OM and evaluation of mucositis improvement

The mean age values of the children admitted to the PICU with developed OM showed that the groups were homogeneous ($p = 0.863$, Table 1). There was no statistically significant difference among the groups in terms of sex ($p = 0.948$, Table 1). Moreover, there was no statistically significant difference among groups for secondary chronic or ischemic disease, oral intake, intubation, amount of oxygen use, swallowing function or for the risk of developing mucositis ($p > 0.05$, Table 1). There was no significant difference among groups for the median value of hospitalization in intensive care ($p = 0.264$, Table 1). For the median mucositis index value that was measured on the first day, no significant difference was found among the groups that had mucositis initially ($p = 0.984$, Table 1).

When mucositis indices measured at different periods were compared based on the groups, it was observed that the difference between groups changed according to the mucositis index values measured at different periods or that the differences between mucositis index values were different in each group ($p < 0.001$, Table 3). At the end of the multiple comparison test, the mucositis index values measured on Days 3, 6, 9, 12, 15, 18 and 21 in Group-1 were significantly higher than the values measured on the corresponding days in Group-2 ($p < 0.05$ for each). The mucositis index values measured on Days 12, 15, 18 and 21 in Group-1 were found to be significantly higher than the values measured on the same days in Group-3 ($p < 0.05$ for each). The mucositis index values measured on Days 3, 6, 9, 12 and 15 in Group-2 were significantly lower than the values measured on corresponding days in Group-3 ($p < 0.05$ for each). Furthermore, the mucositis index values measured on Days 6, 9, 12, 15, 18 and 21 were significantly lower compared to the basal value in Group-1 ($p < 0.01$ for each). The mucositis index value assessed on the first day was significantly higher than the values on all other days in Group-2 ($p < 0.01$ for each). The basal mucositis index values measured in Group-3 were significantly higher than the values measured on Days 6, 9, 12, 15, 18 and 21 ($p < 0.01$ for each, Table 3).

General characteristics of groups without OM and evaluation of mucositis prevention

When median age values of the children without OM admitted to the PICU were examined, it was determined that the groups were also homogeneous ($p = 0.977$, Table 2). No significant difference was found among the groups for sex ($p = 0.948$, Table 2). Moreover, there was no statistically significant difference among the groups for secondary chronic or ischemic disease, oral intake, intubation, amount of oxygen use, swallowing function or the risk of developing mucositis ($p > 0.05$, Table 2). There was no significant difference among groups for the median value of hospitalization in intensive care ($p = 0.062$, Table 2). For the median mucositis index value measured on the first day, there was no significant difference among the groups that did not have mucositis initially ($p = 0.368$, Table 2).

When the mucositis indices measured at different intervals were compared, differences were observed among the groups based on mucositis index values measured at different periods or between the

Table 1
Comparison of clinical and nonclinical characteristics of children initially having oral mucositis.

		Oral care method								p
		With mucositis								
		Chlorhexidine		Vitamin E		Honey		Total		
		n	%	n	%	n	%	n	%	
Sex*	Female	13	34.2	12	31.6	13	34.2	38	100	0.948
	Male	12	32.4	13	35.1	12	32.4	37	100	
Concomitant disease*	Yes	18	32.7	19	34.5	18	32.7	55	100	0.934
	No	7	35.0	6	30.0	7	35.0	20	100	
Oral intake*	Yes	6	30.0	7	35.0	7	35.0	20	100	0.934
	No	19	34.5	18	32.7	18	32.7	55	100	
Intubation*	Yes	6	35.3	6	35.3	5	29.4	17	100	0.927
	No	19	32.8	19	32.8	20	34.5	58	100	
Oxygen use*	Yes	14	33.3	14	33.3	14	33.3	42	100	1.000
	No	11	33.3	11	33.3	11	33.3	33	100	
Amount of oxygen used (hour/day)	<4	0	0.0	2	40.0	3	60.0	5	100	-
	4–8	0	0.0	4	57.1	3	42.9	7	100	
	8–12	1	20.0	4	80.0	0	0.0	5	100	
	12–16	0	0.0	1	50.0	1	50.0	2	100	
	16–20	2	66.7	1	33.3	0	0.0	3	100	
	20–24	10	50.0	3	15.0	7	35.0	20	100	
Swallowing function*	Yes	18	34.6	18	34.6	16	30.8	52	100	0.778
	No	7	30.4	7	30.4	9	39.1	23	100	
Risk of mucositis development*	Yes	21	35.6	19	32.2	19	32.2	59	100	0.728
	No	4	25.0	6	37.5	6	37.5	16	100	
Age & E		7.8 ± 4.5	2–16	8.4 ± 4.5	2–16	8.4 ± 4.5	2–16	8.2 ± 4.5	2–16	0.863
Hospitalization time in PICU \$		13	8–23	11	4.5–15	10	7–16.5	12	6–17	0.264
Day-1 Mucositis index value \$		1	1–1	1	1–1.5	1	1–1.5	1	1–1	0.984

*Pearson Chi-square, &: Average (Minimum-Maximum), \$: Median (1.Quartile-3.Quartile), E: One Way ANOVA, #: Kruskal-Wallis.

mucositis index values in each group ($p = 0.003$, Table 4). At the end of the multiple comparison test, the mucositis index values measured on Days 9, 12 and 15 in Group-4 were found to be higher than the values measured on the same days in Groups-5 and -6 ($p < 0.05$ for each). It was also detected that the index values in Group-4 measured on Days 9, 12 and 15 were significantly higher compared to the basal value ($p < 0.05$ for each, Table 4).

Discussion

The primary duty of patient care falls to nurses and, as the most important members of the team, they are responsible for oral care and the prevention of mucositis. Nurses are required to be informed about the issue and have the ability to provide effective preventive care against mucositis as well as to administer treatment in the event of its

Table 2
Comparison of clinical and nonclinical characteristics of children initially without oral mucositis.

		Oral care methods								p
		Without mucositis								
		Chlorhexidine		Vitamin E		Honey		Total		
		n	%	n	%	n	%	n	%	
Sex*	Female	11	31.4	12	34.3	12	34.3	35	100	0.948
	Male	14	35.0	13	32.5	13	32.5	40	100	
Concomitant disease*	Yes	17	31.5	18	33.3	19	35.2	54	100	0.820
	No	8	38.1	7	33.3	6	28.6	21	100	
Oral intake*	Yes	6	28.6	8	38.1	7	33.3	21	100	0.820
	No	19	35.2	17	31.5	18	33.3	54	100	
Intubation*	Yes	6	33.3	6	33.3	6	33.3	18	100	1.000
	No	19	33.3	19	33.3	19	33.3	57	100	
Oxygen use*	Yes	14	32.6	15	34.9	14	32.6	43	100	0.947
	No	11	34.4	10	31.3	11	34.4	32	100	
Amount of oxygen used (hour/day)	<4	0	0.0	4	36.4	7	63.6	11	100	-
	4–8	5	26.3	6	31.6	8	42.1	19	100	
	8–12	2	50.0	0	0.0	2	50.0	4	100	
	12–16	3	37.5	4	50.0	1	12.5	8	100	
	16–20	0	0.0	3	100.0	0	0.0	3	100	
	20–24	4	57.1	1	14.3	2	28.6	7	100	
Swallowing function*	Yes	16	36.4	16	36.4	12	27.3	44	100	0.415
	No	9	29.0	9	29.0	13	41.9	31	100	
Risk for mucositis development**	Yes	20	31.3	21	32.8	23	35.9	64	100	0.602
	No	5	45.5	4	36.4	2	18.2	11	100	
Age \$		7	(4.5–12.5)	7	(3.5–12.5)	8	(3.25–14)	7	(3.5–13)	0.977
Hospitalization time in PICU \$		7	(4–12)	4.5	3–9	9	5.5–12	7	4–12	0.062
Day-1 assessment \$		0	(0–0)	0	(0–0)	0	(0–0)	0	(0–0)	0.368

*Pearson Chi-square, **Fisher Freeman Halton, \$: Median (1st Quartile-3rd Quartile), #: Kruskal-Wallis.

development (Citlak & Kapucu, 2015). Although OM management is an important part of nursing care, the literature shows that there is no universally accepted approach for it (Cavusoglu, 2007; Citlak & Kapucu, 2015; Izgu, 2017; Kobya-Bulut & Guducu-Tufekci, 2016). In their comprehensive study, Gholizadeh, Sheykhabahaei, and Sadrzadeh-Afshar (2016) searched for the terms “oral mucositis” and “new treatments of mucositis” from 1998 to 2015 on Pubmed, Medline, Ovid, Science Direct and Google. Unfortunately, no single method was determined to be capable of preventing or treating OM in an efficient way (Gholizadeh et al., 2016). Previous research has been limited to studies using oncology patients who had undergone chemotherapy and radiotherapy. In addition, no study to date has compared three distinct methods of oral care.

This study was performed to determine the effect of oral care using chlorhexidine, vitamin E and honey for OM management of children treated in the PICU. Based on the results of the study, it was observed that the most effective agent in OM management was vitamin E, followed by honey. Chlorhexidine was found to be the least effective agent (Tables 3 and 4).

Vitamin E is the most important antioxidant molecule found in humans and it is fat soluble (Altiner, Atalay, & Bilal, 2017; Ongel, 2006). Since inflammation leads to the formation of free radicals, this vitamin is needed to increase antioxidant deposits within the body for OM management (Cavusoglu, 2007). According to the literature, vitamin E prevents tissue damage, contributes to cell regeneration, generates an epithelization effect on the mucosa, repairs the skin, protects cells from oxidative damage, strengthens the immune system, increases leukocyte production and decreases oxidative damage in specialized tissues such as blood vessels (Altiner et al., 2017; Ongel, 2006).

At the end of this study, the mucositis index values of the children treated with vitamin E were found to be significantly lower than those of the other groups (p < 0.05 for each). Similar results have been found in previous studies that investigated the effectiveness of vitamin E. The study by El-Housseiny et al. (2007) performed on pediatric patients undergoing chemotherapy reported that 100 mg of topical vitamin E applied two times a day was found to be an effective preventive measure in the treatment of OM induced by chemotherapy (El-Housseiny et al., 2007). In the randomized controlled study by Ferreira et al. (2004) conducted with patients undergoing head-neck radiotherapy, patients were asked to dissolve 400 mg of vitamin E in their mouths and to swallow after keeping it inside the oral cavity for 5 min. At the end of the study, it was reported that the vitamin E decreased the severity of OM (Ferreira et al., 2004). Vitamin E was also determined to have positive effects on OM management in other studies (Azizi et al., 2015; Chaitanya et al., 2017; Wadleigh et al., 1992).

On the other hand, in the study by Sung et al. (2007), vitamin E was not found to be effective in OM management among the pediatric patients using chemotherapeutic medications including doxorubicin. In that randomized controlled study, children in the experimental group

Table 3
Mucositis index values at each period for children with oral mucositis initially.

Period	Oral care methods											
	With mucositis											
	Chlorhexidine (Group-1)				Vitamin E (Group-2)				Honey (Group-3)			
	n	Q2	Q1	Q3	n	Q2	Q1	Q3	n	Q2	Q1	Q3
p1	25	2	1	2	25	2	1	2	25	2	1	2
p3	25	2	1	2	25	1	0	1	25	2	1	2
p6	24	1	1	2	22	0	0	0	25	1	1	1
p9	20	1	1	1	16	0	0	0	21	1	0	1
p12	17	1	1	1	13	0	0	0	14	0.5	0	1
p15	13	1	1	1	11	0	0	0	8	0.5	0	1
p18	9	1	1	1	7	0	0	0	7	0	0	1
p21	7	1	0	1	5	0	0	0	5	0	0	0

Q2: Median, Q1: 1st Quartile, Q3: 3rd Quartile.

Table 4
Mucositis index values at each period for children without oral mucositis initially.

Period	Oral care methods											
	Without mucositis											
	Chlorhexidine (Group-4)				Vitamin E (Group-5)				Honey (Group-6)			
	n	Q2	Q1	Q3	n	Q2	Q1	Q3	n	Q2	Q1	Q3
p1	25	0	0	0	25	0	0	0	25	0	0	0
p3	25	0	0	1	25	0	0	0	25	0	0	0
p6	20	0	0	1	18	0	0	0	25	0	0	0
p9	14	1	0	1	12	0	0	0	17	0	0	0
p12	8	1	0.5	2	7	0	0	0	13	0	0	0
p15	5	1	0	1	5	0	0	0	5	0	0	0
p18	2	0.5	0	1	2	0	0	0	2	1	0	2
p21	1	0	0	0	1	0	0	0	1	0	0	0

Q2: Median, Q1: 1st Quartile, Q3: 3rd Quartile.

were given 2 ml of vitamin E topically once a day for two weeks and a placebo solution that was indistinguishable in color, odor and taste was given in the control group. It was concluded that the topical vitamin E did not decrease the severity of OM caused by doxorubicin (Sung et al., 2007).

Another finding in the present study was the determination that the most effective agent following vitamin E in OM management was honey. Honey has ideal antimicrobial features, a low pH and high osmolarity. Glucose produces non-cytotoxic hydrogen peroxide at a high level via an oxidase enzyme. Honey decreases prostaglandin levels, increases nitric oxide concentration in lesions and exhibits anti-inflammatory and antioxidant characteristics (Nagi, Patil, Rakesh, Jain, & Sahu, 2018). There are many case reports showing the effect of honey on the acceleration of the healing process in acute and chronic wounds (Biglari et al., 2013; Dunford, Cooper, Molan, & White, 2000; Lay-flurrie, 2008). Honey is also known to decrease mucosal irritation due to its tissue repairing, wound healing and therapeutic properties in the treatment of various gum and intraoral infections (Nagi et al., 2018; Raessi et al., 2014; Samdariya et al., 2015).

Studies regarding the use of honey in mucositis management have shown positive outcomes. In one recent study, in addition to routine care, patients with head or neck cancer were asked to rinse their mouths with 20 ml of honey three times a day and then to swallow it. At the end of the study, it was reported that this application alleviated their OM pain (Samdariya et al., 2015). Another study found that a mixture of honey and coffee (300 g of honey and 20 g of instant coffee) was effective in the treatment of OM (Raessi et al., 2014). Other findings of studies examining the effectiveness of honey in OM management showed that honey decreased the severity of OM (Al-Jaouni et al., 2017; Amanat, Ahmed, Kazmi, & Aziz, 2017; Charalambous et al., 2018; Khanal et al., 2010; Kobya-Bulut & Guducu-Tufekci, 2016; Maiti et al., 2012; Rao et al., 2017).

Another finding of the present study was that chlorhexidine was less effective than the other agents in OM management. Chlorhexidine is commonly used in the treatment of mucositis, but its effectiveness is controversial and there is insufficient data to support its use. Studies on the effect of chlorhexidine on OM have yielded varying results. The study by Macedo et al. (2015) found that chlorhexidine gluconate did not eliminate OM lesions completely but that it decreased the level of pain and discomfort. In addition, it was suggested that other medications could provide better results compared to chlorhexidine and that more advanced studies were needed to better explain these effects (Macedo et al., 2015). Choi and Kim (2012) compared chlorhexidine and sodium bicarbonate in the treatment of OM and observed that the patients who applied sodium bicarbonate exhibited better results (Choi & Kim, 2012). In the study by Mehdipour, Taghavi-Zenoz, Asvadi-Kermani, and Hosseinpour (2011), zinc sulfate and chlorhexidine were compared and findings showed that at the 2–3 week early assessment, better results were obtained in the study group using zinc

sulfate (Mehdipour et al., 2011). Other studies have also indicated that chlorhexidine was not effective in OM management (Cabrera-Jaime et al., 2018; Cardona, Balouch, Abdul, Sedghizadeh, & Enciso, 2017; Madan-Kumar, Sequeira, Shenoy, & Shetty, 2008; Potting, Uitterhoeve, Op-Reimer, & Van-Achterberg, 2006; Roopashri, Jayanthi, & Guruprasad, 2011).

In contrast, some studies have shown that by adhering to tissue surfaces, chlorhexidine was effective in the prevention and treatment of OM. Setiawan et al. (2006) compared the effects of chlorhexidine and povidone iodine on OM and concluded that chlorhexidine gluconate was more effective in the healing of oral mucositis compared to povidone iodine (Setiawan et al., 2006). In similar studies performed by Costa et al. (2003) and Pereira Pinto et al. (2006), children in the study group that used chlorhexidine were compared to children in a control group and a significant decrease in the incidence of OM and ulceration was found among the children who used chlorhexidine (Costa et al., 2003; Pereira Pinto et al., 2006). Other studies have also demonstrated the positive effects of chlorhexidine (Cheng et al., 2004; Kishore-Kumar, 2015; Nashwan, 2011).

Practice implications

Patients in the PICU are at risk of developing OM. Oral mucositis treatment is an important part of nursing care; however, no agent has been shown to be completely effective for this condition. Findings in this study determined vitamin E to be the most effective agent and honey the second most effective agent in OM management. Chlorhexidine was observed to be less effective in OM management compared to the other agents. The results of the present study conducted with PICU patients will be useful in the administration of oral care. These findings are also important for nurses who have the responsibility of OM management.

Limitations

The results of this study were limited to the effects of oral care administered to children admitted to the PICU using chlorhexidine, vitamin E and honey for OM management.

Conclusion

To date, no agent has been shown to be completely effective in the treatment of OM and there is no accepted standard treatment. The results of the present study conducted with PICU patients showed that the most effective agent in OM management was vitamin E and the second most effective agent was honey. Chlorhexidine was found to be less effective in OM management compared to the other agents.

Accordingly, the use of vitamin E is recommended for oral care applications to prevent and treat oral mucositis. In addition, honey, which is a natural nutrient, can be safely used as an oral care method to treat children in the PICU who are not diabetic nor allergic to honey. However, honey should not be given to infants less than one year of age due to the risk of botulism.

CRedit authorship contribution statement

Dilek Konuk Sener: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Meryem Aydin:** Funding acquisition, Project administration, Resources, Visualization. **Sengul Cangur:** Formal analysis. **Evren Guven:** Data curation.

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Conflicts of interest

None.

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