Original Article

The Effect of Oral-care Program and Mouthwash Use as a Prophylaxis in Minimizing the Incidence of Chemotherapy-Induced Oral Mucositis of Pediatric and Adolescent Cancer Patients

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Abstract

Objectives: The aim was to assess the effect of the oral-care program and Kin® Care mouthwash on the rate and severity of chemotherapy-induced oral mucositis (OM) in pediatric and adolescent cancer patients.

Methods: A randomized clinical trial study was conducted from May 2018 through May 2019. It was held in the Children Cancer Center of Hiwa Oncology and Hematology Hospital and included 48 participants aged 5-17 years who received chemotherapy. They were randomly allocated into either intervention or control groups; 24 patients each. The control group did not receive oral-care protocol intervention except for symptomatic measures. In contrast, the intervention group was provided with oral-care instructions and Kin® Care mouthwash. Clinical evaluations were performed before commencing chemotherapy and then, twice per week, for three consecutive weeks. The World Health Organization Mucositis grading, the visual analog scale, oral hygiene status, and drinking and eating abilities were assessed.

Results: There were no statistically significant differences between the two groups concerning age, gender, and tumor type. The most severe grades of OM (Grade III-IV) among the intervention group were significantly less than the control group (2.1% versus 22.9%). Besides, the use of Kin® Care mouthwash decreased the occurrence of OM into half. The risk ratio of developing OM (Grades II-IV) was 0.51.

Conclusions: Regular oral-care program and Kin® Care solution for children receiving chemotherapy effectively decreases the rate and severity of OM.

Keywords: *Chemotherapy; Oral-care program; Oral mucositis; Kin® Care mouthwash.*

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Introduction

Oral mucositis (OM) is an inflammation of oral cavity mucosa. It is characterized by the presence of erythematous areas that are subsequently combined with ulcerations[1]. Oral mucositis is caused by the destruction of the epithelium of oral mucosa and suppressing its growth secondary to antineoplastic treatment in the form of chemotherapeutic drug substances or radiotherapy[2,3].

The incidence of chemotherapy-induced OM is approximately 40% for adult patients treated with chemotherapy[4]. Although the frequency of OM differs according to the type of cancer and treatment regimen, up to 80% of children receiving chemotherapy will experience some degrees of OM[5]. Children who suffer from hematologic malignancies experience mucositis more frequently than those who suffer from solid tumors[6]. Furthermore, this group of patients is also more likely to be afflicted with more severe forms of OM as compared with patients who suffer from other malignancies[6]. It appears that the prevalence of OM in pediatric patients is higher than that of adults; this may be due to the presence of more rapid cell division in pediatrics[7]. Patients treated with a combination of agents known to cause OM are more likely to suffer more from it[8]. The frequency and severity of OM are fundamentally dependent on the type, duration, and dose of chemotherapy being used[9].

Four to five days after the initiation of chemotherapy, the clinical manifestations of OM, observation of erythematous areas in the oral cavity will occur. After seven to ten days, ulcers start to develop, and then they gradually grow in number and size and tend to merge to form large ulcerated zones[10,11]. The ulcers are generally of scant depth with a necrotic base, and the margins show little inflammatory infiltration[3,10]. These lesions are very painful in such a way that causes difficulties in swallowing and take about two weeks to heal once chemotherapy has been suspended[3,10].

The standard first step of the prevention of OM changes is the implementation of good oral hygiene and the use of an oral-care protocol for all children who are receiving chemotherapy[12]. Several oral-care protocols have been studied in the literature[12]. Besides, dental specialists' consultation is recommended before the induction of chemotherapy, if possible[12].

Different method and treatment agents have been used to prevent chemotherapy-induced OM, including the fundamental oral-care protocol (brushing, flossing, dental visits before and during the treatment and usage of bland mouthwashes), anti-inflammatory, antimicrobial and antiseptic agents, cryotherapy, vitamins, cytokines, immune regulators, and herbal drugs[13,14].

Using a particular oral-care program has a significant impact on decreasing the incidence and severity of oral complications experienced by cancer patients who are receiving chemotherapy[2,5,15,16]

The present study aimed to find out the effect of the oral-care program and using Kin® Care oral solution in decreasing the rate and severity of chemotherapy-induced OM in pediatric cancer patients.

Patients and methods

The study was a randomized clinical trial conducted for one year, extended from May 2018 to May 2019. It was held in the Children Cancer Center of Hiwa Oncology and Hematology Hospital/ Sulaimani city. Enrolled in the study were children and adolescents aged 5-17 years old who had received either single (high-dose) or combination of chemotherapy for hematological malignancies or solid tumors. They were also capable of demonstrating tooth brushing and mouth rinsing, as judged by the investigators. The Research Ethical Committee of the Kurdistan Board of Medical Specialties (KBMS) approved the study proposal, and a formal acceptance letter was obtained from the hospital before starting the study. All the patients and their parents were informed about the aim of the study. The patients participated after their parents had signed a consent form.

The study sample size was 48 patients, and they were randomly allocated into either intervention or control groups; 24 patients in each group. In the control group, patients did not receive the oral-care protocol intervention and the importance of oral care. However, they were treated with symptomatic measures according to the routine practice at the hospital when they developed oral lesions. At the same time, the intervention group was provided with oral-care instructions and oral solution (Kin® Care mouthwash, Spain).

The oral-care program was performed as follows:

1- Brushing the teeth with a soft toothbrush and toothpaste.

2- Rinsing the mouth with sodium chloride (0.9%) solution for 30 seconds.

3- Rinsing the mouth with the Kin® Care solution for two minutes (preventing swallowing it and eating anything after applying the mouth rinse for half an hour).

4- Rinsing the mouth with Kin® Care solution (7.5 ml) every six hours and before bedtime with the repetition of the steps mentioned above.

Clinical evaluations were performed before commencing chemotherapy and then, twice per week, for three consecutive weeks (day 1 – day 21) after the initiation of chemotherapy. Then, the highest score for the occurrence and severity of OM was chosen for each patient. The presence of OM was identified on the clinical manifestation of ulcerative lesions in the oral mucosa, and the World Health Organization (WHO) grading system for mucositis[17] was used. It composed of five grades as follows: no subjective or objective evidence of mucositis (Grade 0), pain with or without erythema, but without ulcer (Grade I), erythema and ulceration, and the patient can swallow solid foods (Grade II), erythema and ulceration and the patient can drink liquids but not swallow solid foods (Grade III), and erythema and ulceration and the patient cannot swallow liquids or swallow solid foods (Grade IV)[17]. Moreover, a visual analog scale (VAS) was used for the evaluation of pain, and the status of oral hygiene assessed as good, fair, and poor. Furthermore, the drinking and eating functional ability during the study period were assessed concerning the consistency of eaten food as normal, only soft food, only liquid, or cannot take any think orally.

Statistical Analysis

The "IBM SPSS Statistics version 25" was used to analyze the data, and both descriptive and inferential statistics were utilized. Pearson Chi-Square test was used to determine the significance of associations between the variable pairs. Spearman's correlation was used to calculate the strength of the association between the two variables. The one-way multivariate analysis of variance (one-way MANOVA) was performed. The risk ratio (RR) and Odds ratio (OR) of OM occurrence were also calculated. A p-value of (≤0.05) was considered statistically significant associations.

Results

The studied sample consisted of 31 (64.6%) males and 17 (35.4%) females. The mean ± SD (standard deviation) age of the patients was 9.1 ± 3.9, and most of them (62.5%) aged between 5-9 years. Hematologic neoplasms constituted 83.3%, while solid tumors accounted for 16.7% only. The male: female ratio and the mean age of the patient in the control group were higher than the intervention group (table 1). There were no statistically significant differences between the intervention and the control groups concerning age, gender, and tumor type.

The one-way MANOVA test showed a statistically significant difference between the three dependent variables (i.e., the status of oral hygiene, function, and pain scores) and independent variables of the patients' groups (i.e., intervention and control groups), and the result of the test was as follows: F (3, 44) = 4.38, P-value = 0.009, Wilks' Lambda = 0.77, Partial Eta Squared = 0.23. Besides, we also calculated the RR of developing OM (stages II-IV), which was 0.51 (OR = 0.5, 95% CI: 0.3-0.83), i.e., the use of Kin® Care mouthwash decreased the occurrence of OM into half.

Further analysis showed the total cases having OM (Grade I-IV) were less in the interventional group in comparing to the control group; however, grade II was the most common (37.5%), being equally distributed in both groups. However, grades III and IV were seen more frequently in the control group (11 patients, 22.9%) than in the intervention group (1 patient, 2.1%). Furthermore, grade II-IV in the intervention group (20.9%) was half of those in the control group (41.7%). Statistical analysis showed a highly significant difference (p = 0.005) and association (r = 0.549) of OM grades between the two groups (Table 2 and Figure 1).

Table 3 showed the frequency distribution of the patients' functional abilities of drinking fluids and swallowing foods in both studied groups. 68.8% of the total sampled patients had normal functional abilities, and only minor percentages (8.3%) cannot intake fluid or foods. However, there was a statistically highly significant association (p = 0.005, r = 0.458) of food intake with the groups. Besides, 45.8% of patients who were using Kin® Care solution were able to consume food and drink fluids more comfortably than the control group (22.9%) (Table 3).

The mean ± SD of VAS in the intervention group was 2.3 ± 1.4 and in the control group was 4.3 ± 1.9. The frequency distribution of the pain score severity showed that 62.5% of our patients had minor pain, and few patients had no pain or severe pain (each presented in 6.2%). Also, 43.7% of patients in the intervention group had no or minor discomfort compared to the control group (25%). There was a statistically highly significant association of the degree of pain assessed by VAS with the groups (p = 0.017) (Table 4).

The majority of pediatric and adolescent cancer patients had proper oral hygiene (62.5%). However, those in the intervention group had better oral hygiene (20.8%) than the control group (12.5%). Nevertheless, this difference was statistically insignificant (Table 5). Concerning the history of OM, only a few patients (14.6%) suffered it. Besides, there was no statistically significant association between oral hygiene status during the study period and the history of OM (Table 6).

Discussion

Chemotherapy-induced OM is characterized by inflammatory changes that develop due to the direct or indirect effect of the cytotoxic agents and can be associated with severe ulcerations. The pathogenesis of OM is a complex condition that encompasses multiple phases of inflammatory processes that include the vascular, epithelial, ulcerative, and the recovery phase[18].

Accordingly, the use of multiple drugs and agents has been suggested for this condition. Among the methods tried in this contest is the professional oral hygiene program[16].

The current study involved the topical application of Kin® Care solution with oral care instruction for cancer patients under chemotherapy. Kin® Care solution is a traditional product, and one of its indications is oral mucosa care. Our results indicated that the Kin® Care solution significantly decreases the occurrence and severity of OM. Nevertheless, grade II OM is still observed in almost a similar frequency in both groups. However, severe OM (Grades III and IV) was seen predominantly in the control group.

The combination of Kin® Care solution use with oral care program significantly improves oral mucosa in children received either single (high dose) or a combination of chemotherapy for hematological malignancies or solid tumors. Several studies have been conducted in Hiwa hospital to prevent or treat oral mucositis[19-22]. Two of these studies applied natural products for reducing the severity of oral mucositis[19,20]. One study implemented low-level laser therapy[21], and the other assessed the risk of developing oral mucositis in pediatric and adolescent patients[22]. To the best of our knowledge, the current study represents the first attempts to provide oral care instruction and Kin® Care solution for prophylaxis from oral mucositis after chemotherapy.

Several other studies in the literature had tried to use other products. Al Jaouni et al.[23] used honey and showed that 20% of the patients in their intervention group had developed grade III and IV OM compared to 55% in the control group. Moreover, Rashad et al.[24] used the application of honey to prevent chemotherapy-induced OM. They reported that none of the patients in the intervention group developed grade IV, and only three patients in the intervention group had developed grade III in comparison to the 13 patients in the control group; the latter developed grade III or grade IV mucositis[24]. Also, plain ice cube and flavored ice cubes and Nigella sativa Oil used in other studies showed an effective reduction of OM[25,26]. Furthermore, normal saline (sodium chloride 0.9% solution) in a few studies had shown its effect on the prevention of OM resulting from chemotherapy[27,28].

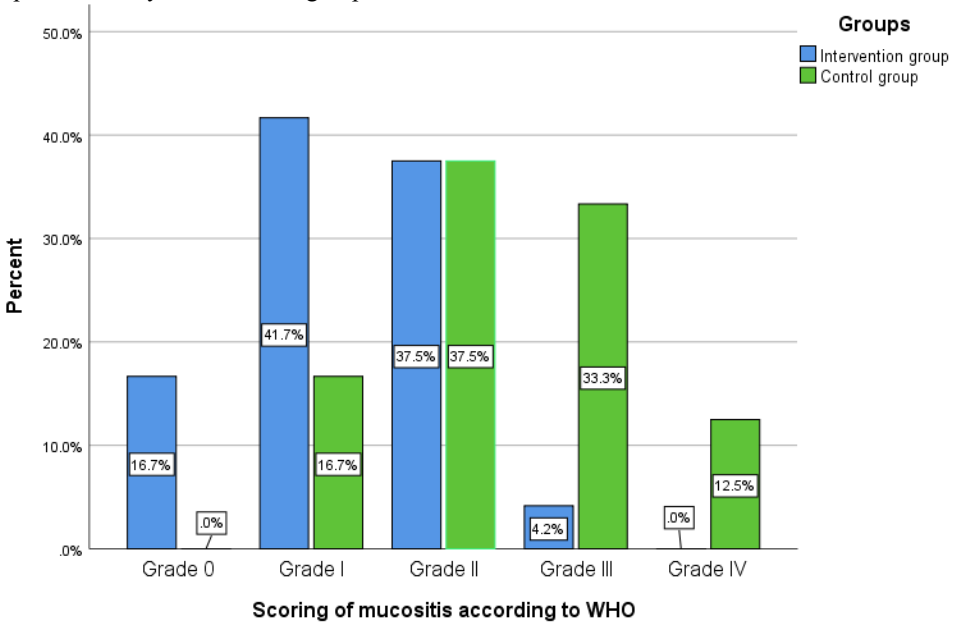

Figure 1: Distribution of OM grades among the study groups (the percentages were calculated according to the total number of patients in each group, i.e., 24).

Table 1: Studied parameters of pediatric patients.

Parameters				Frequency (%)	p-value*
Gender	Total M:F ratio = 1.8:1	Male		31 (64.6)	—
		Female		17 (35.4)	
	Intervention group M:F ratio = 1.2:1	Male		13 (54.2)	0.131
		Female		11 (45.8)	
	Control group M:F = 3:1	Male		18 (75)	
		Female		6 (25)	
Age group (year)	Total Mean ±SD = 9.1±3.9 range; 5-17	5-9		30 (62.5)	—
		10-14		10 (20.8)	
		15-17		8 (16.7)	
	Intervention group Mean ±SD = 8.9±4 range; 5-16	5-9		15 (62.5)	1.0
		10-14		5 (20.8)	
		15-17		4 (16.7)	
	Control group Mean ±SD = 9.4±3.9 range; 5-17	5-9		15 (62.5)	
		10-14		5 (20.8)	
		15-17		4 (16.7)	
Types of neoplasm	Hematological (No.=40, 83.3%)	ALL	Intervention group	9 (18.8)	0.406
			Control group	8 (16.7)	
		Non-Hodgkin lymphoma	Intervention group	3 (6.3)	
			Control group	3 (6.3)	
		AML	Intervention group	2 (4.2)	
			Control group	3 (6.3)	
		Burkitt's lymphoma	Intervention group	3 (6.3)	
			Control group	0 (0)	
		Brain tumor	Intervention group	0 (0)	
			Control group	1 (2.1)	
		Other types	Intervention group	3 (6.3)	
			Control group	5 (10.4)	
	Solid Tumors (No = 8, 16.7%)	Rhabdomyo-sarcoma	Intervention group	1 (2.1)	
			Control group	1 (2.1)	
		Ewing sarcoma	Intervention group	0 (0)	
			Control group	2 (4.2)	
		Neuroblastoma	Intervention group	1 (2.1)	
			Control group	0 (0)	
		Osteosarcoma	Intervention group	1 (2.1)	
			Control group	0 (0)	
		Other types	Intervention group	1 (2.1)	
			Control group	1 (2.1)	

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia.

Table 2: Frequency and percentage distribution of the highest WHO scoring for the clinical grades of mucositis in association with types of patients' management.

Grade	Intervention group	Control group	Total	p-value* (r)
	No. (%)	No. (%)	No. (%)	
0	4 (8.3)	0 (0)	4 (8.3)	0.005 (0.549)
I	10 (20.8)	4 (8.3)	14 (29.2)	
II	9 (18.8)	9 (18.8)	18 (37.5)	
III	1 (2.1)	8 (16.7)	9(18.8)	
IV	0 (0)	3 (6.2)	3 (6.2)	
Total	24 (50)	24 (50)	48(100)	

Table 3: Association of drinking fluids and swallowing of foods in association with the types of patients' management.

Drinking and swallowing of foods	Intervention group	Control group	Total	p-value* (r)
	No. (%)	No. (%)	No. (%)	
Normal	22 (45.8)	11 (22.9)	33 (68.8)	0.005 (0.458)
Only soft foods	0 (0)	8 (16.7)	8 (16.7)	
Only liquids	1 (2.1)	2(4.2)	3 (6.2)	
No foods or liquids	1 (2.1)	3 (6.2)	4 (8.3)	
Total	24 (50)	24 (50)	48(100)	

Table 4: Association of the degrees of pain in association with the types of patients' management.

Pain scoring	Intervention group	Control group	Total	p-value* (r)
	No. (%)	No. (%)	No. (%)	
(0) No	3(6.2)	0 (0)	3(6.2)	0.017 (0.49)
(1-3) Minor	18 (37.5)	12 (25)	30 (62.5)	
(4-6) Moderate	3 (6.2)	9 (18.8)	12 (25)	
(7-10) Severe	0 (0)	3 (6.2)	3 (6.2)	
Total	24 (50)	24 (50)	48(100)	

Table 5: Association of oral hygiene status with the types of patients' management.

Status of oral hygiene	Intervention group	Control group	Total	p-value* (r)
	No. (%)	No. (%)	No. (%)	
Good	10 (20.8)	6 (12.5)	16 (33.3)	0.21 (0.22)
Fair	14 (29.2)	16 (33.3)	30 (62.5)	
Poor	0 (0)	2 (4.2)	2 (4.2)	
Total	24 (50)	24 (50)	48(100)	

Table 6: Association of oral hygiene status with the history of OM.

Status of oral hygiene	History of oral mucositis		p-value* (r)
	Yes	No	
	No. (%)	No. (%)	
Good	1 (2.1)	15 (31.2)	0.37 (-0.133)
Fair	6 (12.5)	24 (50)	
Poor	0 (0)	2 (4.2)	
Total	7 (14.6)	41 (85.4)	

Many articles in this era reported a reduction in the frequency of OM following oral rinsing with chlorhexidine; the results on its effectiveness had not been decisive due to differences in the underlying disease[28]. Even though using chlorhexidine rinse has led to poor acceptance and compliance in adult patients, although it does not have any systemic hazardous adverse effect, it can lead to reversible discoloration of teeth and mucous membranes with astringent taste if used for a long period[29].

After 21 days of post-chemotherapy, most of our participating pediatric and adolescent cancer patients had normal drinking and swallowing abilities, minor pain, and fair oral hygiene. This improvement is because the number of children who used the Kin® Care solution and got improvement was near twice those in the control group. They were able to consume solid food and drink fluids more comfortably and live without or with minor discomfort. The manifestation of oral ulcerative lesions was substantially lower in pediatric patients receiving the oral-care protocol and Kin® Care solution.

It has been recognized that maintenance of the normal oral function and reduction of pain is essential during cancer treatment and is crucial for the oncologic cure[20]. The results of the present study aligned with other studies in which they demonstrated reducing the severity of OM associated with decreasing the burden of cancer[19,21,30].

Atrophies, erythema, and ulcerative lesions are the predominant clinical characteristics of OM[5]. However, a breakdown in the epithelial integrity has more clinical significance in terms of patient morbidity, potential microbial, and systemic infections when compared with epithelial atrophy or erythema. Besides, mucosal redness is often a subjective finding; whereas, an ulcerative lesion is a more objectively defined clinical feature[31]. Hence, the OM scoring included all these clinical changes besides the functional ability to direct the doctor in providing proper management. In our study, the frequency of registered OM (Grade I-IV) in the intervention group was 41.7%, which is nearly similar to that reported by Cheng et al.[30] (42%), but less than the findings of other studies (52% [32], 80% [31], 65% [33,34], and 71%[35].

It is generally agreed that good preventive oral-care is an essential adjunct to the management of OM[36]. Professional oral hygiene can lower the possibility of developing OM in patients receiving a high dose of chemotherapy[37]. The results of this study have supported the benefits of using an oral-care protocol to reduce the rate and severity of OM in pediatric patients who are receiving chemotherapy. Still, the proper oral hygiene observed in the intervention group was slightly better, although insignificantly, than in the control group. The beneficial effects of the oral-care protocol can be explained by reducing oral microflora colonization interacting with oral tissues that may retard the development of OM. This finding was in tune with previous studies, which reported that poor oral hygiene is associated with an increased risk of developing severe OM[22,30]. Moreover, mucositis guidelines from the Multinational Association for Supportive Care in Cancer/International Society of Oral Oncology recommended regular oral care with brushing, flossing, bland rinses, and moisturizers[38].

The present study showed that the RR of developing OM (Grade II-IV) in the intervention group was reduced substantially. This finding is interesting as long as the presence of ulcers provides a portal site of entry for many infectious organisms within the mucosal lining, especially in neutropenic cancer patients. Moreover, the importance of OM as a risk factor for sepsis was also well established[20].

Finally, the history of OM did not associate with oral hygiene during the study period. This result is plausible because OM is a multifactorial process and the genetic diversity in susceptibility to OM. Additionally, OM could be underestimated since patients evaluated by oncologists rather than a specialized dentist.

Depending on the obtained improved clinical conditions of the children, the professionals at Hiwa Oncology and Hematology Hospital started to implement the use of our recommended program as routine.

Conclusions

The oral-care program, combined with Kin® Care mouthwash, offers promise in reducing OM for pediatric cancer patients receiving chemotherapy.

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