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A Comparison of the Effect of Chlorhexidine Mouthwash and Combined Mouthwash (4 drugs) in Preventing and Managing Oral Mucositis in Neutropenic Patients Admitted to the Pediatric Oncology Department: A Randomized Clinical Trial

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Abstract

Background: Given the lack of comprehensive studies comparing the effects of chlorhexidine and combined mouthwashes in preventing oral mucositis in our country, particularly in Yazd province, this study aims to evaluate the effectiveness of combined mouthwash versus chlorhexidine mouthwash in preventing oral mucositis in neutropenic patients.

Materials and Methods: This study was a double-blind randomized controlled trial conducted on children undergoing chemotherapy at Shahid Sadoughi Hospital. Patients were randomly assigned to two groups of 30: one group received combined mouthwash containing diphenhydramine, nystatin, aluminum-magnesium hydroxide, and lidocaine (group 1), while the other group received a 0.2% chlorhexidine mouthwash (group 2). The interventions were administered orally at least twice daily for one month.

Results: The frequency of pain intensity and mucositis in the two groups was similar on the 14th and 28th days (100% of patients were free from pain and mucositis). Additionally, no significant difference was observed between the two groups in terms of pain intensity and frequency of mucositis on the 7th and 21th days ($p > 0.05$). On the 7th day, the frequency of grade 1 mucositis was 3.4% in group 1 and 3.3% in group 2, with no statistically significant difference in the severity of mucositis between the two groups ($p = 0.981$). On the 21th day, the frequency of grade 3 mucositis was 3.4% in group 1 and 0% in group 2; however, there was no statistically significant difference in the severity of mucositis between the two groups on the 21th day ($p = 0.305$).

Conclusion: Although there was no statistical difference in reducing pain severity, mucositis frequency, or mucositis grade between the two groups, chlorhexidine was found to be more effective and satisfactory in practice. Therefore, considering its lower cost, chlorhexidine is recommended as a cost-effective option for the treatment of oral mucositis.

Keywords: Chlorhexidine, Mouthwash, Mucositis, Neutropenia.

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Introduction

In patients undergoing chemotherapy and/or radiotherapy, oral mucositis (OM) is a major acute side effect that impacts the oral cavity (1). The incidence of chemotherapy-induced mucositis is approximately 40% for standard chemotherapy, around 75% for intensive chemotherapy, about 30 to 60% for head and neck radiotherapy, and 90% when radiotherapy is combined with chemotherapy (2). Importantly, the pain caused by oral mucositis from radiotherapy and chemoradiotherapy presents a significant negative impact for patients (3). Symptoms can be severe, often resulting in hospitalization and the need for feeding tubes. These complications severely diminish the quality of life for cancer patients and can lead to more serious issues, such as systemic infections. Oral complications

like mucositis not only cause intense pain and feeding difficulties but also increase the risk of infection and, in extreme cases, sepsis. Additionally, these complications can elevate treatment costs and necessitate hospital stays, sometimes prompting physicians to adjust chemotherapy dosages. This scenario not only heightens morbidity and mortality rates but also undermines optimal treatment (2, 3). Few pharmacological agents or interventions are effective in alleviating the severity of oral mucositis and the pain associated with radiotherapy (3). The effects of various mouthwashes differ based on their mechanisms of action. Chlorhexidine, a potent antiseptic, combats a wide range of microorganisms, including bacteria and some fungi, and is commonly used to prevent and treat oral infections (4). While chlorhexidine primarily serves as an antiseptic, its impact on pain relief or inflammation is less direct. In contrast, a combination mouthwash containing diphenhydramine, nystatin, aluminum-magnesium hydroxide, and lidocaine offers a multifaceted approach. This formulation provides antimicrobial action while also delivering anti-inflammatory, antifungal, and analgesic properties, potentially proving more effective in alleviating symptoms and preventing mucositis (1). Although several combination mouthwash formulations for managing pain from radiotherapy-related oral mucositis have been available for some time (3), there are currently few randomized placebo-controlled trials assessing the efficacy of these preparations, particularly the diphenhydramine- lidocaine-antacid mouthwash. Given the high prevalence of cancer, including acute lymphoblastic leukemia (ALL), in Iran, particularly in Yazd province (5), and considering the use of chemotherapy as the first line of treatment, there is a lack of comprehensive studies on this topic in our country, especially in Yazd province. This study aims to compare the effects of chlorhexidine mouthwash with a combined mouthwash (four drugs) in the prevention and treatment of oral mucositis in neutropenic patients hospitalized in the pediatric oncology department.

Materials and Methods

Design of study and procedure

This study is a double-blind randomized controlled trial (RCT) conducted on children undergoing chemotherapy in the pediatric oncology department of Shahid Sadoughi Hospital, Yazd. The participants included neutropenic patients (≤1500 neutrophils per microliter) aged 2 to 18 years receiving chemotherapy. Patients were randomly (using random number table) assigned to two groups of 30: one group received a combined mouthwash containing 25 cc of diphenhydramine, one complete vial of nystatin (100,000 units per milliliter), 25 cc of aluminum-magnesium hydroxide, and 4 drops of 2% lidocaine (group 1), while the other group received a 0.2% chlorhexidine mouthwash (group 2). The interventions were administered orally at least twice daily for one month, with weekly clinical examinations conducted by a pediatric oncology specialist who was unaware of the mouthwash type. The mouthwashes were provided in identical coded containers by a nurse who was also unaware of the contents. A designated individual monitored the ethical conduct of the study.

Sampling Procedure

The sample size was determined using the following formula, assuming a 30% difference in the incidence of mucositis between the two groups, with a significance level of 5% and a power of 80%, resulting in a total of 60 participants being assessed.

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$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 [P_1(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2}$$

Eq. (1)

Inclusion Criteria

1. Patients aged 2 to 18 years.
2. Patients with acute lymphoblastic leukemia (ALL) undergoing chemotherapy with a single protocol (B-cell or T-cell based on the 2022 guidelines).
3. Neutropenia without oral mucositis.

Exclusion Criteria

1. Irregular medication use.
2. Patients who did not return for timely follow-up.
3. Patients experiencing any side effects.

Pain was classified using the Visual Analog Scale (VAS) questionnaire (6). The questions of questionnaire were responded by children.

Degree of Mucositis

According to WHO criteria (7):

• **Grade 0:** No mucositis.

• **Grade 1:** Mild irritation of the oral mucosa accompanied by pain; no visible lesions present; the patient is able to maintain a normal diet

• **Grade 2:** Ulcers are present in the oral mucosa; the patient can still swallow pediatric oncology food. Clinical examinations were conducted by a physician unaware of the mouthwash type.

• **Grade 3:** The patient experiences severe sensitivity when swallowing solid food; a liquid diet is essential.

• **Grade 4:** The patient is unable to swallow; complete intravenous or tube feeding is required.

Fig 1 shows consort flowchart of the effect of chlorhexidine mouthwash and combined mouthwash (4 drugs) in the prevention and treatment of oral mucositis in neutropenic patients.

Statistical Analysis

Data were entered into SPSS software version 23. Frequency distributions were reported as frequency and percentage. The Chi-square test was used for statistical analysis, and the independent t-test was employed to compare quantitative data. A p-value of less than 0.05 was considered statistically significant.

Results

The present study was conducted on 59 children with an average age of 6.13 ± 3.6 years. The frequency distribution of these patients in terms of gender showed that 32 (54.2%) were boys and 27 (45.8%) were girls. Additionally, the frequency of side effects was zero in both groups. The mean duration of hospitalization was 4.45 ± 4.71 days in group 1 and 3.50 ± 0.7 days in group 2 ($p = 0.761$). The comparison of the two groups in terms of pain is shown in Table I. As shown in Table I, the frequency of pain intensity in the two groups was the same on the 14th and 28th days (100% of patients were without pain). Additionally, no significant difference was observed between the two groups in terms of pain intensity on the 7th and 21th days ($p > 0.05$). The comparison of the two groups in terms of mucositis is shown in Table II. As shown in Table II, the frequency of mucositis in the two groups was the same on the 14th and 28th days (100% of patients were without mucositis). Additionally, no significant difference was observed between the two groups in terms of the frequency of mucositis on the 7th and 21th days ($p > 0.05$). Table III shows the comparison of the two groups in terms of severity of grade. As the results show, on the 7th day, the frequency of grade 1 mucositis was 3.4% in group 1 and 3.3% in group 2, with no statistically significant difference in the severity of mucositis between the two groups ($p = 0.981$).

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Moreover, the intensity of mucositis was the same in both groups on the 14th and 28th days, with 100% of patients in grade 0. On the 21th day, the frequency of grade 3 mucositis was 3.4% in group 1 and 0% in group 2; however, there was no statistically significant difference in the severity of mucositis between the two groups on the 21th day (p = 0.305).

Table I: The comparison of the two groups in terms of pain

Group	Day	Without pain N (%)	With pain N (%)	Total N (%)	P-value*
Group 1	7	28 (96.6)	1 (3.4)	29 (100)	**0.981**
Group 2	7	29 (96.7)	1 (3.3)	30 (100)	
Group 1	14	29 (100)	0 (0)	29 (100)	……..
Group 2	14	30 (100)	0 (0)	30 (100)	
Group 1	21	28 (96.6)	1 (3.4)	29 (100)	**0.305**
Group 2	21	30 (100)	0 (0)	30 (100)	
Group 1	28	29 (100)	0 (0)	29 (100)	…….
Group 2	28	30 (100)	0 (0)	30 (100)	

Combined Mouthwash (group 1), Chlorhexidine mouthwash (group 2)
*Chi-Square test

Table II: The comparison of the two groups in terms of mucositis

The Type of drug	Day	Without mucositis N (%)	With mucositis N (%)	Total N (%)	P-value
Group 1	7	28 (96.6)	1 (3.4)	29 (100)	**0.981**
Group 2	7	29 (96.7)	1 (3.3)	30 (100)	
Group 1	14	29 (100)	0 (0)	29 (100)	…
Group 2	14	30 (100)	0 (0)	30 (100)	
Group 1	21	28 (96.6)	1 (3.4)	29 (100)	**0.305**
Group 2	21	30 (100)	0 (0)	30 (100)	
Group 1	28	29 (100)	0 (0)	29 (100)	…
Group 2	28	30 (100)	0 (0)	30 (100)	

Combined Mouthwash (group 1), Chlorhexidine mouthwash (group 2)
*Chi-Square test

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Table III: The comparison of the two groups in terms of severity of grade (mucositis)

The Type of drug	Day	Severity of grade				Total	P-value
		0 N (%)	1 N (%)	2 N (%)	3 N (%)	N (%)	
Group 1	7	28 (96.6)	1 (3.4)	0 (0)	0 (0)	29 (100)	**0.981**
Group 2	7	29 (96.7)	1 (3.3)	0 (0)	0 (0)	30 (100)	
Group 1	14	29 (100)	0 (0)	0 (0)	0 (0)	29 (100)	…
Group 2	14	30 (100)	0 (0)	0 (0)	0 (0)	30 (100)	
Group 1	21	28 (96.6)	0 (0)	0 (0)	1 (3.4)	29 (100)	**0.305**
Group 2	21	30 (100)	0 (0)	0 (0)	0 (0)	30 (100)	
Group 1	28	29 (100)	0 (0)	0 (0)	0 (0)	29 (100)	…
Group 2	28	30 (100)	0 (0)	0 (0)	0 (0)	30 (100)	

Combined Mouthwash (group 1), Chlorhexidine mouthwash (group 2)
*Chi-Square test

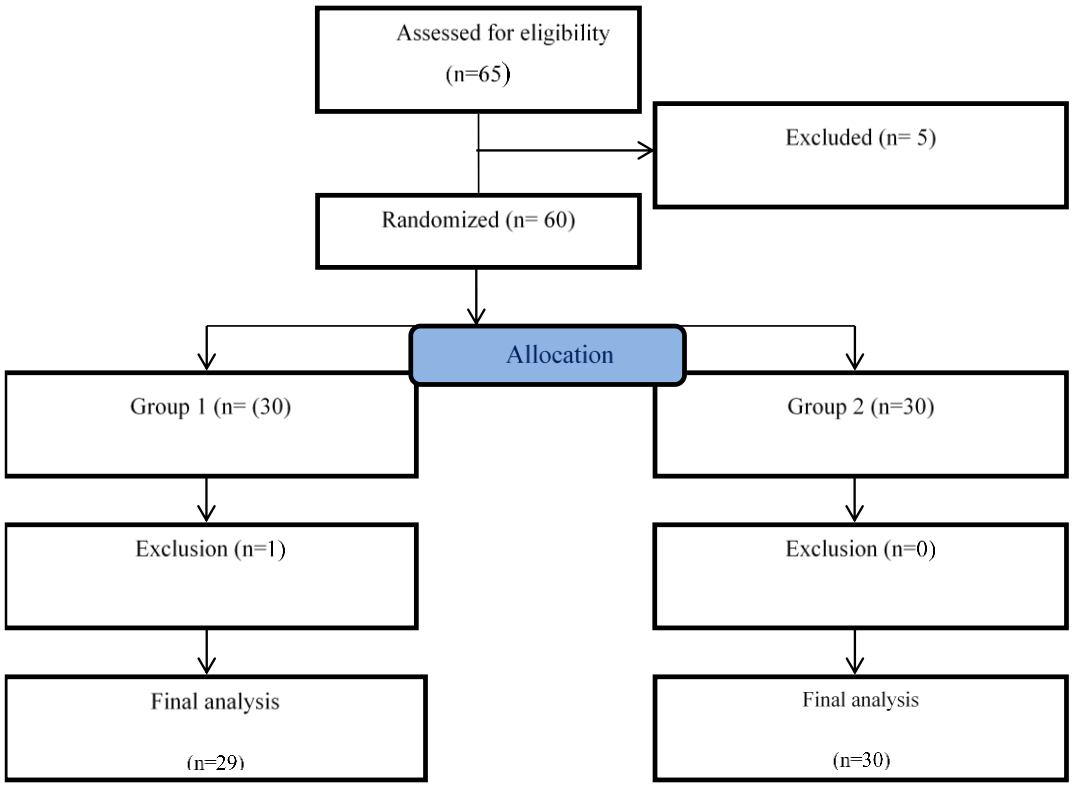

Figure 1. Consort flowchat

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Discussion

Oral mucositis is a significant complication of cancer treatment. Various interventions for the prevention and treatment of oral mucositis have been explored, but none have proven completely successful. This study aimed to investigate the effects of chlorhexidine mouthwash and a combination mouthwash (containing four drugs) on the prevention and treatment of oral mucositis in hospitalized neutropenic patients, with no differences noted in their length of stay. Pain frequency assessments in the two groups showed that on the 14th and 28th days, none of the patients in either group reported pain. Additionally, comparisons of pain severity on the 7th and 21th days indicated no statistically significant difference between the two groups. However, on the 21th day, 3.4% of individuals in the four-drug combination group (diphenhydramine, nystatin, aluminum-magnesium hydroxide, and lidocaine) reported pain, while none in the chlorhexidine group experienced pain. Sio et al., studied the effects of a combination mouthwash containing diphenhydramine, lidocaine, aluminum-magnesium hydroxide (an antacid), doxepin (25 mg/5 ml water) on oral mucositis treatment compared to a placebo. They observed that pain scores in both groups four hours after using either mouthwash decreased compared to the control group (3). Torhal et al., examined the efficacy of a mouthwash in reducing discomfort caused by mucositis in chemotherapy patients.

Their mouthwash consisted of three drugs (lidocaine, diphenhydramine, and sodium bicarbonate in normal saline), and patient responses were reported using a self-assessment scale. The results showed that this three-drug mouthwash effectively relieved pain in patients with chemotherapy-induced mucositis, which aligns with our study's findings (8). Limeira et al., investigated and compared chlorhexidine and a combination drug (including nystatin, dexamethasone, diphenhydramine, morphine, lidocaine, B vitamins, and normal saline) against placebo in reducing oral mucositis in a rat model. They observed significant clinical improvements in both intervention groups compared to the placebo group. Furthermore, comparison between the two intervention groups indicated that the combination drug was more effective than chlorhexidine, regarding clinical and histological parameters. In contrast, our study found no statistical difference between the two groups, possibly due to the more extensive components of the combination drug in their study (1). Samiraninezhad et al., studied the effect of mouthwash on pain levels in patients, following them for 14 days. The control group received aluminum-magnesium hydroxide and diphenhydramine, while another group was treated with doxepin, and a third and fourth groups received chitosan nanogel and doxepin / chitosan nano-gel. Results showed that the group treated with doxepin and chitosan nano-gel significantly reduced pain compared to the control group three days post-treatment. Therefore, these results suggest that innovative treatments may be more effective than traditional therapies (9). The comparison of the frequency of mucositis in the two study groups revealed that the frequency of mucositis on the 14th and 28th days was the same. Moreover, no statistically significant difference was seen between the groups on the 7th and 21th days. Dodd et al. conducted a study comparing the effects of three mouthwashes (salt and soda solution, chlorhexidine, and a magic mouthwash containing lidocaine, Benadryl, and Maalox) on patients with mucositis, following them for 12 days. At the end of the 12th day, no statistically significant

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difference was found between these groups, regarding signs and symptoms. They also recommended the salt and soda solution due to its lower cost (10). Epstein et al. studied the effectiveness of different mouthwashes (chlorhexidine, nystatin, and saline solution) in preventing oral complications in 86 leukemia patients undergoing chemotherapy or bone marrow transplantation. The study found no difference in the incidence of oral sores or mucositis among the treatment groups (11), which aligns with our study's results. The comparison of mucositis grade frequency between the two study groups showed no statistically significant difference between the groups on the 7th and 21th days. Kuk et al. assessed the effectiveness of a magic mouthwash (containing diphenhydramine, dexamethasone, and nystatin) combined with sucralfate, compared to benzydamine hydrochloride, in alleviating the severity of mucositis symptoms induced by cisplatin chemotherapy. No statistically significant difference in mucositis grades was observed between the two groups (12). Therefore, it appears that the combination of magic mouthwash and sucralfate does not outperform benzydamine hydrochloride for the preventive treatment of oral mucositis, aligning with the results of our study. Barker et al. also examined the effectiveness of diphenhydramine syrup and kaolin-pectin in reducing the severity of radiation-induced mucositis. Each group used one of the mouthwashes four times a day, and the results showed no statistically significant difference in mucositis grade (13). These findings are consistent with our study results. Savizadeh et al., conducted a study comparing the efficacy of topical morphine and magic mouthwash in treating oral mucositis, reporting that both morphine and magic mouthwash effectively reduce the severity of cancer treatment-induced oral mucositis, but morphine was found to be more effective and satisfactory than magic mouthwash (14). Turhal et al. studied the effectiveness of mouthwash; including, lidocaine, diphenhydramine, and sodium bicarbonate in saline solution in patients with chemotherapy-induced oral mucositis and the results showed that the three-drug mouthwash was effective in reducing mucositis severity or symptomatic relief (8). However, this study presented only pre- and post-intervention results and did not compare this intervention with others. Additionally, no side effects were observed in either group in the present study. Another study also examined the side effects of chlorhexidine in treating oral mucositis and found no serious side effects, which aligns with our findings. According to the researchers, the only observed side effects were tooth staining and changes in taste perception, which were not considered significant (15). Magic mouthwash is a multi-drug combination with various components used to reduce the pain and inflammation of oral mucositis, especially in patients undergoing chemotherapy or radiation therapy. These mouthwashes contain different compounds, each with a specific mechanism of action. Diphenhydramine, a first-generation antihistamine, has significant sedative effects and cholinergic blockade. Lidocaine provides temporary pain relief from minor injuries by inhibiting the initiation and transmission of nerve signals, while also decreasing sodium ion permeability in nerve cell membranes (1). Nystatin is crucial in treating fungal infections (16-20), such as candidiasis (1). In cases of oral mucositis, using a nystatin solution is recommended for both prevention and treatment.

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Conclusion

The result of this study indicated that although there was no statistical difference in reducing pain severity, mucositis frequency, or mucositis grade between the two groups, chlorhexidine proved to be more effective and satisfactory. Moreover, both groups did not experience side effects. Therefore, considering its lower cost, chlorhexidine is recommended as a cost-effective option for the treatment of oral mucositis.

Ethical Considerations

This study was approved by the Ethics Committee of Shahid Sadoughi University (IR.SSU.MEDICINE.REC.1403.036) and the Iranian registry clinical trial (IRCT20180209038673N8).

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Authors' Contributions

MT, RE, conceived and planned the study. M.Y contributed to the sample preparation. M.T contributed to the analysis and interpretation of the results. MT, RE, and, M.Y wrote the primary draft of the manuscript. All the authors had a critical review of the final draft of the manuscript and accepted it.

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Conflict of Interest

None

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