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Investigating the effectiveness of N-Acetyl Cysteine mouthwash in preventing chemotherapy-induced oral mucositis: A randomized, double-blind controlled trial

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Abstract

Objectives: More than 75% of high-risk individuals experience oral mucositis as a side effect of head, neck, and oral radiotherapy and chemotherapy. The chemical N-Acetyl Cysteine (NAC) has substantial antioxidant, anti-inflammatory, and antibacterial properties. The goal of this study was to determine the effectiveness of NAC mouthwash in preventing chemotherapy-induced oral mucositis.

Materials and methods: In the current randomized, double-blind controlled trial, 68 patients were randomly divided into two groups (34 patients in the intervention group and 34 patients in the control group).

The recommended therapeutic dose was 1.25% NAC mouthwash. In this 14-day study, the patients were instructed to use the NAC mouthwash twice daily (15 milliliters each dose). The oral mucosa was evaluated on days 1,7, and 14 following the initiation of chemotherapy and the score was documented based on observation.

Results: On the 7^{th} day, the severity of mucositis was significantly greater in the control group than in the intervention group ($P<0.001$). However, this difference was not significant on day 1 ($P=0.459$) and day 14 ($P=0.999$) of the study. Also on 7^{th} day, the incidence of mucositis was significantly lower in patients receiving N-acetyl cysteine than patients receiving placebo. However, no significant difference was observed on day 1 ($P=0.144$) and day 14 ($P=0.999$) of the study.

Conclusion: According to the results, NAC mouthwash leads to a decrease in the severity of mucositis caused by chemotherapy. It seems that it can be effective as a treatment and preventive medicine for mucositis.

Clinical relevance: According to the findings, NAC mouthwash lessens mucositis severity and may help to prevent its onset.

Keywords: Chemotherapy, Mouthwash, N-Acetyl Cysteine, Oral mucositis

Introduction

The prevalence of cancer, a common and chronic disease, has been rising in recent years (1). Chemotherapy, radiation therapy, and surgery are some of the treatment options for cancer that have been developed thanks to scientific advancements. It is noteworthy that all treatment options have adverse effects as well (2).

More than 75% of high-risk individuals experience oral mucositis, as the side effect of chemotherapy (3). Mucositis, a painful side effect of anticancer medications, is caused by the epithelial mucosa's inflammatory response to chemotherapy's cytotoxic effects (4). The risk factors of chemotherapy-induced oral mucositis can be either patient-dependent or associated with anticancer treatments. Factors such as body mass index, oral hygiene, nutritional condition, smoking, alcohol consumption, genetic, and gender are patient-dependent (5). The pathophysiology of oral mucositis involves various stages starting with initiation phase. During this phase, the DNA of the epithelial cells of the oral mucosa get damaged and produce reactive oxygen species. Followed by that, inflammatory cytokines are upregulated and signaling and amplification of inflammatory cascade occurs. During this stage, NF-κB activates and induces the production and release of pro-inflammatory cytokines, such as TNF- α, IL-1 β, and IL-6 in response to the cellular damages. Also, further non-DNA damages initiate apoptotic pathway and results in disrupting the integrity between the epithelium and submucosa at the basement membrane level. Then, patients experience ulceration and scarring which is extremely painful and finally, the healing process initiates (5, 6).

Several treatment options have been introduced to manage chemotherapy-induced oral mucositis (7). Some of these treatment methods have been approved and suggested by the 2020 Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) clinical guidelines for managing oral mucositis secondary to cancer therapy. Basic oral care is an essential factor in managing oral mucositis. Additionally, the use of anti-inflammatory drugs, and the use of benzydamine mouthwash is

recommended. Photobiomodulation is effective in reducing inflammation and improving tissue regeneration. Cryotherapy also limits the cytotoxic effects of cancer therapy due to its vasoconstrictor property. Growth factors and cytokines play an essential role in preventing and treating oral mucositis. Additionally, other substances such as cover agents, antimicrobial substances, analgesics, anesthetics, fluconazole, and doxepin are introduced as treatments for oral mucositis. Furthermore, natural substances such as vitamins, minerals, and nutritional supplements have been effective in managing oral mucositis (8).

Recently, natural substances and their derivatives have attracted the attention of researchers in the field of dentistry and have been used to manage several oral infections and oral lesions. Hopefully, their results have shown promising analgesic, antioxidant, anti-inflammatory, antibacterial, and antifungal properties (9-15).

NAC is the N-acetylated form of the amino acid L-cysteine, which is obtained by extracting cysteine from the N-acetylated derivative in the first step of glutathione synthesis (16). Although NAC is not found naturally, cysteine alone is present in various foods such as garlic, yogurt, chicken and turkey (17). In addition to being used as a mucolytic, N-Acetylcysteine (NAC) is commonly used to treat paracetamol overdoses. Its toxicity is rare and has a steady safety profile (18). It is frequently used as a beneficial drug in the treatment of wound inflammation due to its significant antioxidant, anti-inflammatory, and antibacterial potential (19).

NAC acts as an antioxidant primarily by raising intracellular glutathione (GSH) levels, which is crucial for maintaining cellular redox balance. Glutathione, a natural antioxidant, regulates immune function and is considered beneficial in treating various illnesses (20). NAC also reduces inflammatory markers such as TNF-α and interleukins by inhibiting NF-κB activity (21). Additionally, it can prevent trauma progression, tissue damage, and free radical-induced chronic diseases (22).

Oral intake of NAC is safe and well tolerated, with few adverse side effects (23). However, when used excessively, it can lead to dry mouth, nausea, diarrhea, and vomiting (18). NAC has shown relevant therapeutic potential in several experimental investigations (19, 24-26).

Still, very few research has been done on how well it works against different pathological disorders in clinical trials. So, we aimed to research how well NAC mouthwash works to treat chemotherapy-induced oral mucositis. The goal of this study was to determine the effectiveness of NAC mouthwash in preventing chemotherapy-induced oral mucositis, taking into account the antioxidant benefits of this molecule and the lack of research regarding this topic.

Materials and methods

This randomized, double-blind clinical trial was in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Mazandaran University of Medical Sciences and received the ethical code (IR.MAZUMS.REC.1401.181). Furthermore, it was registered to the Iranian Registry of Clinical Trials and received the IRCT code (IRCT20220712055439N1) on 2022/08/03. The patients were entered into the investigation after receiving a sufficient explanation about the study and signing the consent form.

Participants and inclusion criteria

In this study, 68 cancer patients were examined who had been referred to the outpatient ward of the Imam Khomeini Hospital in Sari, Iran, and who had undergone chemotherapy for the first time before undergoing other cancer treatments, such as surgery or radiotherapy. The inclusion criteria were outpatients who were fully alert, had healthy oral mucosa, were not suffering from respiratory illnesses, asthma, diabetes, and autoimmune diseases, had no fever, were not using painkillers (constantly), narcotics, alcohol, cigarettes, antibiotics, or other types of mouthwash and were not receiving any concurrent treatments (27, 28). The exclusion criteria were patient withdrawal from participation at any stage of the research, lack of cooperation or regular return for follow-ups, incidence of any type of oral infection that was diagnosed according to clinical examination and/or laboratory test results, the occurrence of significant adverse events or new medical conditions that made continued attendance medically inappropriate. Additionally, lack of commitment to treatment protocol or concomitant use of prohibited interventions were among the exclusion criteria of the study.

The sample size of the present study was determined according to a study conducted by Al-Kamel et al. (28). In their study, after 14 days of intervention the means of 1.67±0.47 and 2.0±0.49 were obtained in the intervention group and control group, respectively. Considering the significance level (α) of 5% and the test power (1- β) of 80%, and using the formula below, 34 samples were calculated in each group.

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 * (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

The participants were enrolled consecutively over a six month period from August to December in 2022. Moreover, they were randomly allocated to the intervention (n=34) and control (n=34) groups using block randomization with a block size of four. A random allocation sequence was generated using random allocation software, which produced 17 quadruple blocks. Within each block, participants were assigned in a 1:1 ratio to the two study groups according to the computer-generated random sequence. The allocation sequence was generated before participants' enrollment and was used to ensure balanced group sizes throughout the study. The researchers gave sufficient explanations to the patients before starting the treatment. Patients entered the study after signing the informed consent form. This intervention took 14 days.

Developing the mouthwash

A beaker containing ultra-pure water and 2 grams of sodium saccharin was weighed and then put on a heater stirrer set to 70°C and a specific rotation speed. The container was then filled with 12.5 grams of N-acetyl-cysteine, which was weighed first. The added materials were entirely dissolved as if a fully transparent solution was obtained, while the magnet was rotating and the reaction medium was heated. The next stage involved adding another beaker containing 50 ml of alcohol along with 2 grams of methyl and 200 mg of propyl paraben to the beaker from the previous step. To reduce the irritant effects of alcohol on the oral mucosa, increase the product's viscosity, and modify the flavor, 50 ml of glycerin was then added to the mixture. At 70°C, the remaining ultra-pure water was added and stirring was continued until all components were mixed entirely.

While N-acetyl-cysteine was not included in the formulation, all steps involved in making the placebo mouthwash were analogous to those used to make the mouthwash containing the active ingredient.

Evaluation of mouthwash microbiology

The aim of microbial limit test was to determine total aerobic microbial count (TAMC) and total yeast and mold count (TYMC). Differential microbial test aimed to determine the type of the possible contamination by pathogens, including E. coli, S. aureus, and P. aeruginosa. The aim of preservative challenge test was to evaluate the efficiency of preservative substance added to the formulation.

The culture medium of Cetrimide was used for Pseudomonas aeruginosa, mannitol salt agar (MSA) for Staph aureus, and MacConkey for E-coli to confirm the type of possible microorganisms contaminated the mouthwash (29-31).

Study protocol

In this 14-day study, patients were randomly assigned to two groups: control (34 participants) and intervention (34 participants). Upon enrollment, each participant was given a dark bottle containing mouthwash that had a uniform appearance. These bottles concealed the N-acetylcysteine mouthwash or placebo from the examiner and the patient using special codes, thus the examiner and patients were blinded in the present study. Mouthwash was recommended twice daily (after breakfast, before bed, and after brushing teeth), with the amount of 15 ml for 30 seconds, from the first day of chemotherapy to the fourteenth day.

The patients were informed about supportive therapies, such as consuming lots of water and avoiding spicy or sour meals. Also, they were advised not to rinse their mouth, eat, or drink anything for 30 minutes after using the mouthwash. Also, they were advised not to use any other mouthwash during the study. Patients were instructed to brush their teeth using a soft toothbrush and kids toothpaste, wear dentures only while eating, and rinse their mouth after each meal. During the follow-up sessions the oral mucosa of the patients was examined by a blinded examiner based on the index provided by the world health organization (WHO). According to this index, the results were reported in five categories, including (0= No

mucositis, 1= Erythema, no wound, no blush, no pain, no sensitivity, 2= Erythema, blush, wound, somehow able to eat solid food, 3= Ulcer but fluid diet required, 4= No possibility of feeding) (32). Oral mucositis severity was assessed on day 1, and again on days 7 and 14 after starting chemotherapy.

Data analysis

The descriptive indices, including mean, standard deviation, frequency, and percentage were applied in this investigation. Mann-Whitney test, chi-square test, and generalized estimating equation (GEE) were employed in inferential analysis to compare the severity of mucositis in two groups, the frequency of two qualitative variables, and the simultaneous effect of factors on the severity of mucositis, respectively. The significance level was considered less than 0.05, and statistical analyses were performed using SPSS 22 software.

Results

Mouthwash microbiology

None of the concentrations and tubes that were examined for the MPN analysis showed any signs of microbial growth; (all were contrasted with the negative control group) and in accordance with the amount of dilutions produced in the prepared sample and the table in the US Pharmacopoeia (USP), a maximum of 30 colonies are present in each milliliter of the product based on USP <61>(31). This number is within the normal range corresponding to the product in this study. The SCDA culture medium yielded an average of 9 colonies throughout the pour plate test, translating to 90 colonies per milliliter of the product. There were also 10 colonies per milliliter of the product in the SDA culture media, or 1 colony on average. In the differential examination of microorganisms, neither a colony in the MacConkey's culture medium, MSA, or Cetrimide's culture media was found, that showed the finished products were free of E. coli, Staph aureus, and Pseudomonas aeruginosa, based on General Chapter 1111 USP Reference (33).

Overall assessment

In this study, 68 patients were evaluated and divided into intervention (n=34) and control (n=34) groups. The study population consisted of patients with lung (6%), breast (35.2%),

colorectal (11.7%), ovarian (6%), leukemia (23.5%), and gastric (17.6%) cancers. All enrolled patients completed the study, and no adverse side effect regarding administering mouthwash was reported. Furthermore, no cases of oral infection were observed in any of the studied groups. Women made up 63.2% of the participants in this study, making them the majority in both the intervention and control groups, with no considerable gender difference between the two groups (P-value=0.801). More details about patients' demographic data are available in Table 1.

Table 1: Demographic information of the cancer patients in N-Acetyl Cysteine and placebo groups[a]

Variable	**Group**		**P-value***
	drug	**Placebo**	
Gender [a]			
Female	21 (61.8)	22 (64.7)	0.801
Male	13 (38.2)	12 (35.3)	
Age (years) [b]	52.88±10.83	49.44±12.44	0.235
Cancer [a] (medication)			
Lung (Carboplatin + Paclitaxel)	2 (5.9)	2 (5.9)	
Breast (Doxorubicin + Endoxan)	9 (26.5)	15 (44.1)	
Ovarian (Carboplatin + Paclitaxel)	3 (8.8)	1 (2.9)	
Leukemia (Cytarabine + Daunorubicin)	7 (20.6)	9 (26.5)	
Colorectal (5-Fluorouracil + Irinotecan)	5 (8.8)	3 (8.8)	0.492
Gastric (5-Fluorouracil + Taxotere)	8 (23.5)	4 (11.8)	

[a] The data are expressed as presented as n (%). [b] The data are expressed as Mean ± SD

* The P-value for data of age is based on t-test and the other P-values are based on Chi-square test.

No complications associated with the use of NAC were noticed during the study. Details on patients' screening, allocation, drop-out and those included for analysis are presented in figure 1.

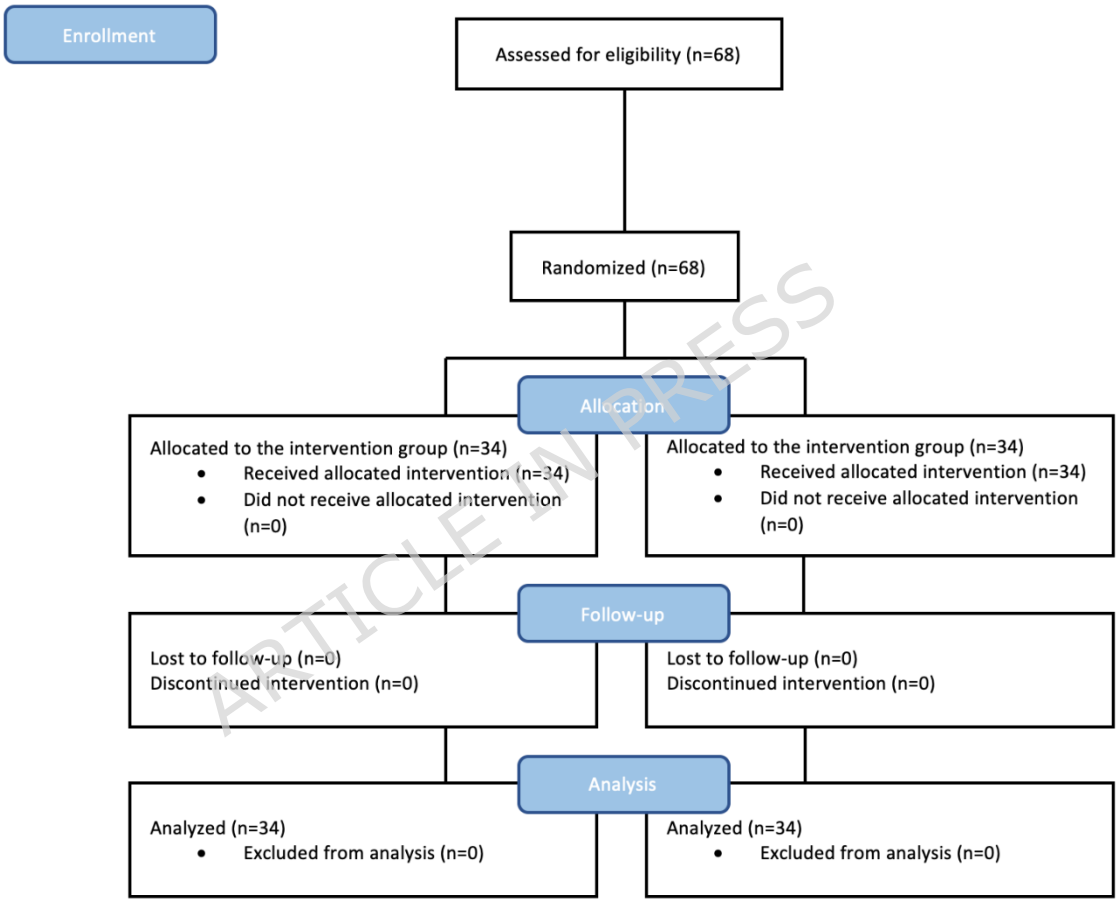

Figure 1: CONSORT flowchart

Except for one patient, almost all patients experienced a reduction in mucositis symptoms after the first week. On day 14, the improvement trend was upward, and in some patients, the oral mucosa was completely healed.

The average age in the intervention group (52.88±10.83) was higher than the control group (49.44±12.44) and this difference was not significant (p-value=0.235).

Clinical findings

According to the inclusion criteria of the study, all enrolled participants had healthy oral mucosa and the same oral mucosal health at the beginning of the study. The following table presents and compares the descriptive data on mucositis intensity for the two intervention and control groups on the research days. Table 2 demonstrates that the severity of mucositis was significantly higher in the control group than in the intervention group on the 7th day.

Table 2: Comparison of the oral mucositis grade in N-Acetyl Cysteine and placebo groups during follow-up [a]

Grade	Day 1		Day 7		Day 14	
	drug	**Placebo**	**drug**	**Placebo**	**drug**	**Placebo**
0	29 (85.3)	24 (70.6)	26 (76.5)	17 (50.0)	33 (97.1)	33 (97.1)
1	3 (8.8)	7 (20.6)	7 (20.6)	3 (8.8)	0	1 (2.9)
2	1 (2.9)	2 (5.9)	0	7 (20.6)	0	0
3	1 (2.9)	1 (2.9)	0	6 (17.6)	0	0
4	0	0	1 (2.9)	1 (2.9)	1 (2.9)	0
P value*	0.459		**<0.001**		0.999	

[a] All data are presented as n (%)

* Fisher's exact test

A significant difference was found in the incidence of mucositis between N-Acetyl Cysteine and placebo groups in the first follow-up (P<0.001) but not in the second follow-up (P=0.999) (Table 3).

Table 3: Comparison of the incidence of mucositis in intervention and placebo groups during follow-ups [a]

Group	Day 1	Day 7	Day 14
Drug	5 (14.7)	8 (23.5)	1 (2.9)

Placebo	10 (29.4)	17 (50)	1 (3.0)
P value [b]	0.144	**0.024**	0.999

[a] All data are presented as n (%), which refers to the patients with no evidence of oral mucositis

[b] Chi-square test

Discussion

This study investigated the effectiveness of N-Acetyl Cysteine mouthwash in preventing the occurrence of oral mucositis caused by chemotherapy and its effects on the severity of mucositis. The results of the study showed that the severity of mucositis in the intervention group on the 7th day was significantly different from the control group ($P<0.05$). The severity of mucositis in the intervention group was reported to be 0.34 units lower than that of the control group. The present study was the first study to investigate the effect of NAC mouthwash on chemotherapy-induced mucositis, and due to the lack of studies, it was not possible to compare the results with other studies.

Oral mucositis is a disabling and painful condition caused by dose-related toxicity of antineoplastic drugs. The inflammatory response of the epithelial mucosa to the cytotoxic effects of chemotherapy leads to mucositis, which is painful and has no definitive treatment (4).

Although several interventions and guidelines are available to prevent mucositis, their efficacy is unknown (34).

N-Acetyl Cysteine (NAC) is assumed to be effective in the treatment of chemotherapy-induced mucositis. In addition to being used as a mucolytic combination, N-Acetyl Cysteine (NAC) is a medication frequently used to treat paracetamol overdoses (21).

Numerous investigations into NAC's antioxidant, anti-inflammatory, and antimicrobial properties concluded that it can be used as an adjuvant agent in the treatment of wounds (19, 24, 35, 36). The real effect of NAC as an antioxidant originates from its capacity to enhance the intracellular concentration of glutathione (GSH), the most essential biothiol responsible for cellular redox imbalance (18). Glutathione is a natural antioxidant that is

effective in the majority of immune system functions and has been suggested as a treatment for several illnesses (37). As an anti-inflammatory compound, NAC can reduce the levels of tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6 and IL-1β) by suppressing the action of nuclear factor kappa B (NF-κB) (38, 39). NAC prevents the activity of free radicals that cause chronic diseases, tissue damage, and trauma progression (39).

The goal of this study is to investigate the effectiveness of NAC in preventing chemotherapy-induced oral mucositis. Previous research focused on the effect of NAC on tissue repair in human and animal studies, and the general consensus was that this substance has a positive impact on damaged tissue.

In 2017, a study investigated NAC as a proposed treatment for aphthous and aphthous-like lesions in animal samples; this study stated that due to the antioxidant and anti-inflammatory properties of NAC, it could be used systemically or topically in the form of powder, paste, tablets or mouthwash to treat active lesions of recurrent aphthous stomatitis or to prevent frequent recurrence of lesions (19). Examining the effectiveness of NAC mucoadhesive tablets on recurrent aphthous stomatitis lesions in a clinical trial study by Ghorbani et al. indicated a reduction in the pain intensity and the inflammatory halo diameter, which confirms the anti-inflammatory and wound healing properties of this substance (25).

Also, a study demonstrated that NAC can significantly reduce oxygen reactions by increasing the amount of intracellular glutathione and reducing the depolarization of the mitochondrial membrane, in combination with vitamin E, E+A, and essential fatty acids, and are effective in disorders such as Premature delivery, chronic bronchitis, toxicity caused by acetaminophen, liver cancer, Alzheimer's and Parkinson's (17).

According to research done in 2016 by Mao et al. on the effects of NAC on wound healing, this compound can promote cell proliferation and increase MnSOD (manganese superoxide dismutase) activity to improve the healing of both human and animal wounds (26).

Another study investigated the mechanism of the NAC effect in the healing process of burn wounds and found that the concentration of NAC was effective in increasing glutathione levels, the activity of living cells for wound healing, and the ability of CCD-966SK cells to

migrate. It was also found that significant epithelialization occurred with 3% NAC. As a result, NAC might be considered a promising medicine with great potential to improve wound healing (36).

A high dose of this substance administered systemically can effectively stop alveolar bone resorption, as shown by NAC's ability to reduce the alveolar bone loss induced by periodontitis in rats (24). The studies mentioned above demonstrated that NAC protects cells from oxygen reactions that cause internal destruction of epithelial cells and cell death by increasing intracellular glutathione levels and reducing mitochondrial membrane depolarization, and by increasing the activity of living cells, inducing epithelialization, and enhancing the ability of CCD-966SK cells to migrate in the wound area. The healing of wounds can be promoted by all of the products above. It should be noted that the concentration of NAC used affects its effectiveness.

In the current investigation, the intervention group's mucositis severity was less severe than the control group's on some study days, and this difference was significant. It seems that NAC is effective in preventing or alleviating the severity of mucositis. This effect may be associated with the anti-inflammatory and wound-healing properties of this compound.

Arbabi-Kalati et al. (2012) studied the impact of zinc sulfate tablets on chemotherapy-induced mucositis. Zinc sulfate can reduce the severity of patients' complaints, dry mouth, and mucositis, according to the findings of this study, which involved systemically administering tablets to patients (27). In the present investigation, we used the topical form of NAC as a mouthwash on oral mucositis to reduce the risk of systemic adverse effects in addition to the maintenance of probable favorable benefits in preventing and reducing the severity of mucositis. However, the present study had several limitations that are worth mentioning to improve future studies. In this study, outpatients were used for greater homogeneity. Therefore, it may not be possible to generalize the obtained results to hospitalized patients. Another limitation was that the evaluated parameters were limited to the intensity of mucositis based on clinical examination, and other clinical parameters or patient’s experience, such as pain, dysphagia, or quality of life were not evaluated. Lack of

commitment of patients to follow study protocols despite follow-ups and telephone calls with patients or their family members could be another limitation of the present study.

Conclusions

The outcomes of this study show that NAC mouthwash reduced the severity of mucositis in the intervention group. The intervention group's mucositis severity was lower than that of the control group on follow-up days. Neither 10 patients in the control group nor 17 in the intervention group displayed any mucositis-related symptoms, suggesting that NAC may be helpful in the prevention of mucositis. Further studies with larger sample sizes are required to confirm the efficacy of NAC mouthwash.

Ethical approval and consent to participate

The present study was conducted according to declaration of Helsinki and obtained the ethical code (IR.MAZUMS.REC.1401.181) from the ethics committee of Mazandaran University of Medical Sciences. Furthermore, it was registered to the Iranian Registry of Clinical Trials, and the IRCT code was obtained on 2022/08/03 (IRCT20220712055439N1). The patients were entered into the investigation after receiving a sufficient explanation about the study and signing the consent form.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Author contributions

Anahita Ghorbani and Tahereh Molania: Conceptualization, Methodology, Supervision; Majid Saeedi: Methodology and Validation; Abolfazl Hosseinnataj: Software and Formal analysis; Reza Negarandeh: Methodology and Data curation; Anahita Lotfizadeh: Investigation, Writing original draft, Writing-review and editing; Seyed Muhammad Mehdi Ghaffari Hamedani, Ehsan Zaboli: Project administration, Validation, and Visualization; AmirHossein Tasfie: Data curation and writing original draft; Ali Jafari: Investigation, Writing-review and editing; Mohammad Pendarnezhad and Seyyed Mohammad Hassan Hashemi: Investigation and Visualization.

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