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Effectiveness of cinnamol and chlorhexidine in treating oral mucositis in cancer patients: A Randomized Clinical Trial

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Abstract

Background: Oral mucositis is a common complication of chemotherapy that significantly reduces patients' quality of life. While chlorhexidine mouthwash has been shown to improve oral mucositis, it can also cause side effects such as dysgeusia. In this context, simpler, plant-based alternatives like cinnamol may offer similar benefits without the associated side effects. This study aimed to compare the effectiveness of cinnamol mouthwash with that of chlorhexidine mouthwash in treating oral mucositis in cancer patients undergoing treatment with doxorubicin.

Methods: This randomized clinical trial included 81 patients with cancer (Breast, ovarian, bladder, lung, and colorectal) from two hospitals in Neyshabur and Sabzevar cities, located in northeastern Iran, in 2023. Participants were allocated to the control (n=27), chlorhexidine (n=27), and cinnamol (n=27) groups using a block randomization method. The control group received 0.9% physiological saline; the chlorhexidine group used chlorhexidine mouthwash, and the cinnamol group used cinnamol mouthwash. Participants were instructed to mix 25 drops of their assigned solution with 50 mL of lukewarm water, gargle for 30 seconds, and then expel the mixture. The intervention was administered twice every 12 hours for 14 days. Data were collected using a demographic questionnaire and the Standard Mucositis Assessment Tool on the first, seventh, and fourteenth days of the intervention. Data analysis was performed using R software version 4.2.2, employing univariate tests and the cumulative link mixed-effects model (CLMM). Results were presented as odds ratios with 95% confidence intervals.

Results: Both cinnamol and chlorhexidine mouthwashes significantly reduced oral mucositis severity compared to the control group. The odds of more severe mucositis in patients using chlorhexidine were 0.0021 times the odds in the control group (OR = 0.0021, $p<0.001$), meaning a lower risk in the chlorhexidine group by a factor of about $1/0.0021 \approx 476$). Also, cinnamol administration significantly diminished the odds of severe mucositis (OR = 0.0005, $p<0.001$) compared to the control. Over time, the protective effects of chlorhexidine (OR = 0.024, $p<0.001$) and cinnamol (OR = 0.269, $p=0.060$) became more pronounced, indicating a progressive healing trajectory.

Conclusion: Cinnamol and chlorhexidine mouthwashes demonstrated significant efficacy in reducing oral mucositis severity, while chlorhexidine effects were more enhanced over time. These insights suggest that both interventions are valuable in managing oral mucositis, offering valuable guidance for nursing practice and patient care.

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Highlights

What is current knowledge?

Chlorhexidine mouthwash is effective in improving oral mucositis, and chlorhexidine is widely used to manage mucositis in cancer patients.

What is new here?

New findings in the present study showed that cinnamol mouthwash, as a non-chemical compound, could have equal and sometimes even better effects than chlorhexidine mouthwash for the treatment of mucositis. Cinnamol is derived from a natural source (i.e., cinnamon), which is approved by the FDA, and offers much fewer side effects than chemical counterparts, so it can be used to manage mucositis in cancer patients.

Introduction

Cancer is one of the most critical challenges for the world's healthcare systems, accounting for the third cause of death in Iran (1). Surgery, radiotherapy, and chemotherapy are common cancer treatments (2), among which chemotherapy is considered the mainstay (3). Doxorubicin is the most common chemotherapy drug used to treat a wide range of cancers (4); however, its complications and adverse effects on non-cancerous cells and non-target tissues lead to the dysfunction of the heart, liver, kidney, and digestive system (5). The most common digestive system-related complication reported is mucositis, which can extend throughout the gastrointestinal tract from the mouth to the rectum (6).

Oral mucositis is an ulcer characterized by multiple cracks in the mouth mucous membrane and occurs on average in 60% of patients undergoing chemotherapy. According to a study conducted in Iran, 79% of patients undergoing chemotherapy develop mucositis (7). This is a painful ulcer causing discomfort during eating, drinking, and

swallowing, reducing the quality of life (8-11). In severe progressive cases, patients will probably have to halt chemotherapy and demand changing the therapeutic regimen, disrupting the cancer treatment process (12).

Therefore, treating or reducing complications caused by oral mucositis can significantly help continue the treatment process (13). Interventions, such as treating oral and dental diseases before chemotherapy, using cryotherapy 30 minutes before chemotherapy, maintaining oral and dental hygiene, using mucosal proliferation, anti-fungal, and anti-inflammatory medications, as well as mouthwashes, are recommended (14,15).

Today, many mouthwashes, such as chlorhexidine, are available in Iran's pharmaceutical market to prevent oral mucositis. Despite its relatively favorable therapeutic effects, chlorhexidine can change the mouth's bacterial flora, tooth color, and the sense of taste, beside causing mouth irritation (16,17). The mentioned side effects considerably reduce patients' adherence to chemical medications of oral mucositis. Thus, using therapeutic methods with fewer complications can increase cancer patients' acceptance of the treatment process (18).

Studies have shown that 84% of Iranian cancer patients prefer using safer alternatives or complementary medicine (CAM), like herbal compounds, to manage complications such as oral mucositis (19). Cinnamol mouthwash is among herbal mouthwashes available in Iranian pharmacopeia (20). The chemical elements of cinnamon are classified by the United States Food and Drug Administration (FDA) as a group of generally low or with no risk medicinal products (21). Cinnamol contains an effective ingredient of cinnamon called eugenol (18), probably responsible for its antimicrobial, antiviral, antioxidant, and anti-inflammatory effects. The mouthwash product is made of cinnamon and clove extract (Agenol), which possesses anti-inflammatory properties and mitigates the redness and inflammation of the oral mucosa (22-24).

Gupta et al. (2015) reported that the compounds in cinnamon mouthwash could reduce dental plaques and improve the mouth and teeth conditions of non-cancer patients (25).

Considering the high prevalence of oral mucositis in patients undergoing chemotherapy (26) and the adverse effects of this complication on patients' well-being and treatment process, it is recommended to seek more safe and effective therapeutic modalities. Besides, cancer patients would prefer using herbal compounds, which have lower costs compared to chemical mouthwashes. Considering the lack of research on the effects of cinnamol mouthwash on oral mucositis among Iranian cancer patients, the current study was conducted to compare the impact of cinnamol with that of chlorhexidine mouthwash on the incidence and severity of oral mucositis in cancer patients treated with doxorubicin.

Methods

This was a three-arm, double-blind, randomized, controlled clinical trial. The study population consisted of patients with breast, ovarian, bladder, lung, or colorectal cancer from two academic medical centers: Hakim Hospital in Neyshabur and Vasei Hospital in Sabzevar, located in northeastern Iran, in 2023.

According to the study of Abedipour et al. (2006) and Ashktorab et al. (2009), the sample size was calculated with a confidence limit of 95% and a test power of 80% (26,27). Given the post-treatment prevalence of 15% for mucositis in the intervention group in Abedipour et al.'s study and 53% in the control group in Ashktorab et al.'s report, and considering a 20% attrition rate, the sample size was calculated as 27 people in each group and a total of 81 participants.

Inclusion criteria were the ability to read and write, receiving doxorubicin (260 mg/m2), and obtaining a minimum score of 1 from the standard mucositis assessment tool.

Patients who visited a cancer specialist during chemotherapy due to oral lesions or mucosa inflammation were examined using the Standard Mucositis Assessment Tool (SMAT) of the World Health Organization (WHO) to confirm oral mucositis, and those who scored 1 were included in the study.

Exclusion criteria encompassed suffering from severe oral and dental problems, having artificial teeth, using dental floss and toothpicks, using other mouthwashes, sensitivity to cinnamol, not following the instructed protocol more than four times, unwillingness to continue participation in the research, and death.

Participants were randomized using a block randomization method and divided into three groups of 27 people using permutation blocks of size 3. Using this random assignment method, 27 people were placed in the cinnamol group, 27 others in the chlorhexidine group, and 27 individuals in the control group. Random allocation of the patients to study groups was performed by a person who was unaware of the group assignments. Also, the patients were unaware of which group they were placed in. For this purpose, random numbers were placed into separate opaque envelopes, with no one being privy to the content of the envelopes before they were opened.

Data were collected using a demographic questionnaire (Gender, marital status, type of cancer, and history of diseases, chronic pain, and smoking). The WHO SMAT (2005) was used to subdivide oral mucositis into five grades (0-4), score 0 for the absence of mucositis, score 1 for pain and redness in the mouth without ulcers, score 2 for ulcers and redness in the mouth, score 3 for sores and redness disallowing the consumption of solid foods, and score 4 representing the most severe mixed condition rendering eating and drinking impossible (28-30).

The validity and reliability of the SMAT were assessed by Ashktorab et al. (2009), reporting validity values > 0.90 (27). In the present study, Cronbach's alpha was calculated to be 0.88. The following solutions were used as mouthwashes: 0.9% physiological saline (Control group), cinnamol mouthwash solution (Isfahan Goldaro Company, Iran), and 0.2% chlorhexidine (Iran Pharmaceutical Company). Cinnamol is a standardized product containing 94-115 mg of eugenol in a 5 mL volume. The ingredients included the hydroalcoholic extract of dried powdered clove buds and flowers (Eugenia caryophyllata L., 2.5 mL), hydroalcoholic extract of dried powdered cinnamon bark (Cinnamomum zeylanicum L., 2 mL), hydroalcoholic extract of dried powdered cardamom fruit (Elettaria cardamomum L., 0.5 mL).

A total of 81 bottles with the same shape, color, and volume (100 mL) were produced under the guidance of a clinical pharmacist and by observing aseptic conditions. The bottles were filled with 90 mL of the solutions and packed.

The participants underwent comprehensive training and were educated, face-to-face, on the provided mouthwashes, oral and dental hygiene, and how to dilute the solutions and perform mouth-washing for 15 minutes. They were instructed to mix 25 drops of physiological serum, cinnamol, and chlorhexidine mouthwashes with 50 mL of lukewarm water, gargle for 30 seconds every 12 hours (Twice a day, for 14 days) after brushing, and then expel. A standard dropper was provided to ensure the equal size of mouthwash solution drops across groups. Receiving feedback confirmed that the participants understood the process. An educational pamphlet was also offered at the end of the educational session. To ensure the secrecy of the type of mouthwash used, the bottles used for all three groups were placed inside the same sealed envelopes so that there was no possibility of identification. Participants were asked to record the date and time of using the mouthwash and provide it to the researcher at the end of the fourteenth day of the intervention. The researcher's contact information was also provided to the patients for any queries or problems. Daily follow-up was conducted using telephone calls to ensure timely and correct use of mouthwash and minimize the likelihood of error.

Data analysis was performed using an intention-to-treat approach, including all participants as originally allocated, regardless of adherence. To ensure blinding, the patients were provided with training by individuals who were unaware of patients' group assignments. All participants were informed about the study design, including the presence of three groups (Cinnamol, Chlorhexidine, and control) and the random allocation process. However, to maintain blinding, the participants were unaware of which specific group they were assigned to. In addition, data were analyzed by an individual who was unaware of group assignments.

The primary outcome of the study was the severity of oral mucositis, as assessed by the WHO Standard Mucositis Assessment Tool (SMAT) on days 1, 7, and 14 after the onset of the intervention. Secondary outcomes included time-related trends in mucositis severity and interaction effects between time and treatment groups.

Statistical analysis

Data were analyzed following the intention-to-treat principle, including all participants as originally assigned regardless of treatment adherence. Descriptive data were reported as mean ± SD for quantitative variables and numbers and percentages for qualitative variables. The differences in characteristics between the three groups were tested using Chi-squared and Fisher's exact test for categorical variables. Baseline SMAT, as an ordinal variable, was compared between groups using the Kruskal-Wallis test.

The primary outcome, mucositis severity (An ordinal variable, 0-4 scale), was analyzed using appropriate ordinal methods. For this, a cumulative link mixed-effects model (CLMM) was applied to assess treatment effects while adjusting for baseline severity and intra-individual variabilities. Baseline SMAT and history of particular diseases were included as covariates in the model. Results were presented as odds ratios along with 95% confidence intervals. Statistical analyses were performed using R software version 4.2.2 for Windows. A two-sided p-value of < 0.05 was considered statistically significant.

Results

This study involved 81 participants, divided into the control (n=27), chlorhexidine (n=27), and cinnamol (n=27) groups. Data from all 81 participants were analyzed, as indicated in the CONSORT diagram (Figure 1).

The results showed that 55.56% of the participants were female, with an overall mean age of 55.06 ± 14.48 years (Table 1). Demographic and clinical characteristics showed no statistically significant differences between the groups, except for the history of diseases.

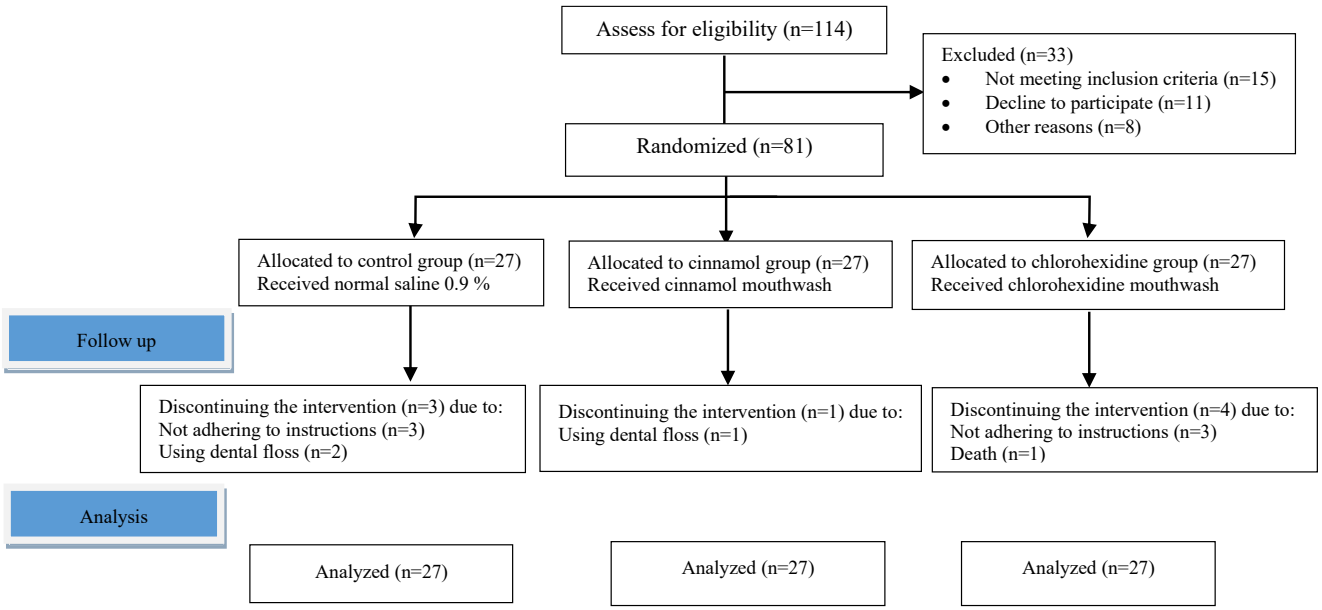

Figure 1. Consort flow diagram of the study

Table 1. Baseline characteristics of participants in the control and intervention groups (n=27 in each group)

Variables	Groups			Total N (%)	P-value
	Control group N (%)	Chlorhexidine group N (%)	Cinnamol group N (%)		
Gender					
Male	13 (48.15)	9 (33.33)	14 (51.85)	36 (44.44)	0.350 C
Female	14 (51.85)	18 (66.67)	13 (48.15)	45 (55.56)	
Marital status					
Married	19 (70.37)	24 (88.89)	25 (92.59)	68 (83.95)	0.133 F
Single	5 (18.52)	1 (3.70)	2 (7.41)	8 (9.88)	
Widowed or divorced	3 (11.11)	2 (7.41)	0 (0.00)	5 (6.17)	
Type of cancer					
Breast	10 (37.04)	12 (44.44)	12 (48.00)	34 (43.04)	
Gastric	5 (18.52)	6 (22.22)	4 (16.00)	15 (18.99)	
Colon	3 (11.11)	0 (00.00)	2 (8.00)	5 (6.33)	0.445 F
Esophageal	3 (11.11)	1 (3.70)	3 (12.00)	7 (8.86)	
Small intestine	0 (00.00)	4 (14.81)	1 (4.00)	5 (6.33)	
Other	6 (22.22)	4 (14.81)	3 (12.00)	13 (16.46)	
History of diseases					
Yes	23 (85.19)	8 (29.63)	12 (66.67)	43 (59.72)	< 0.001 C
No	4 (14.81)	19 (70.37)	6 (33.33)	29 (40.28)	
History of chronic pains					
Yes	11 (47.83)	14 (51.85)	14 (51.85)	39 (50.65)	0.949 C
No	12 (52.17)	13 (48.15)	13 (48.15)	38 (49.35)	
History of smoking					
Yes	9 (33.33)	4 (14.81)	9 (33.33)	22 (27.16)	0.210 C
No	18 (66.67)	23 (85.19)	18 (66.67)	59 (72.84)	
Baseline SMAT	4 (3-4) *	4 (3-4)	3 (3-4)	4 (3-4)	0.122 K

* Median (Interquartile range); F: Fisher-Freeman-Halton test; K: Kruskal-Wallis test; C: Chi-square test

Figure 2 illustrates box plots showing the distribution of mucositis severity scores at two time points post-intervention (i.e., Time 1 and Time 2), including the median, interquartile range (IQR), and potential outliers. As shown in Figure 2, at Time 1 post-intervention, the cinnamol group maintained a median mucositis severity score of 1, while both the chlorhexidine and control groups exhibited median scores of 3. By Time 2, the difference between the groups became more pronounced as the cinnamol group showed a substantial improvement (Median score dropping to 0, indicating complete or near-complete healing); the chlorhexidine group also showed a marked reduction, with the median score descending from 3 to 1. In contrast, the control group showed minimal change, retaining a median score of 3 at both time points.

These distinct patterns underscore the varying effectiveness of the interventions, with cinnamol demonstrating the most significant reduction in mucositis severity over time. Figure 3 provides a comprehensive view of mucositis scores of the patients in different groups and at different time points.

Effectiveness of mouthwashes on mucositis severity

To statistically evaluate how the mouthwashes and time influenced mucositis severity, we used a specialized statistical model called a cumulative link mixed-effects model (CLMM). Accounting for the ordinal nature of mucositis severity, the analysis employed proportional odds models suitable for longitudinal ordinal data. This advanced analysis allowed us to compensate for baseline differences in mucositis severity between groups and the fact that we measured each patient's progress multiple times, giving us a more accurate picture of therapeutic effects. We also presumed significant intra-individual variations in mucositis healing (Random intercept for patient variance = 15.86, SD= 3.982), which our model successfully accounted for.

Effect of time on the severity of mucositis

Our findings showed a general reduction in mucositis severity over time across all groups (OR = 0.43, 95% CI: 0.182 – 1.037, p=0.060). However, this overall effect was not statistically significant at the 0.05 level.

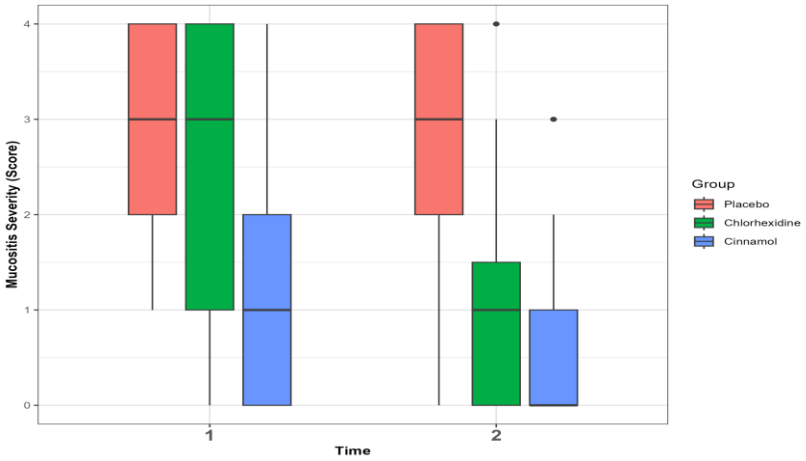

Figure 2. Severity of mucositis over time in different treatment groups: median and interquartile Range

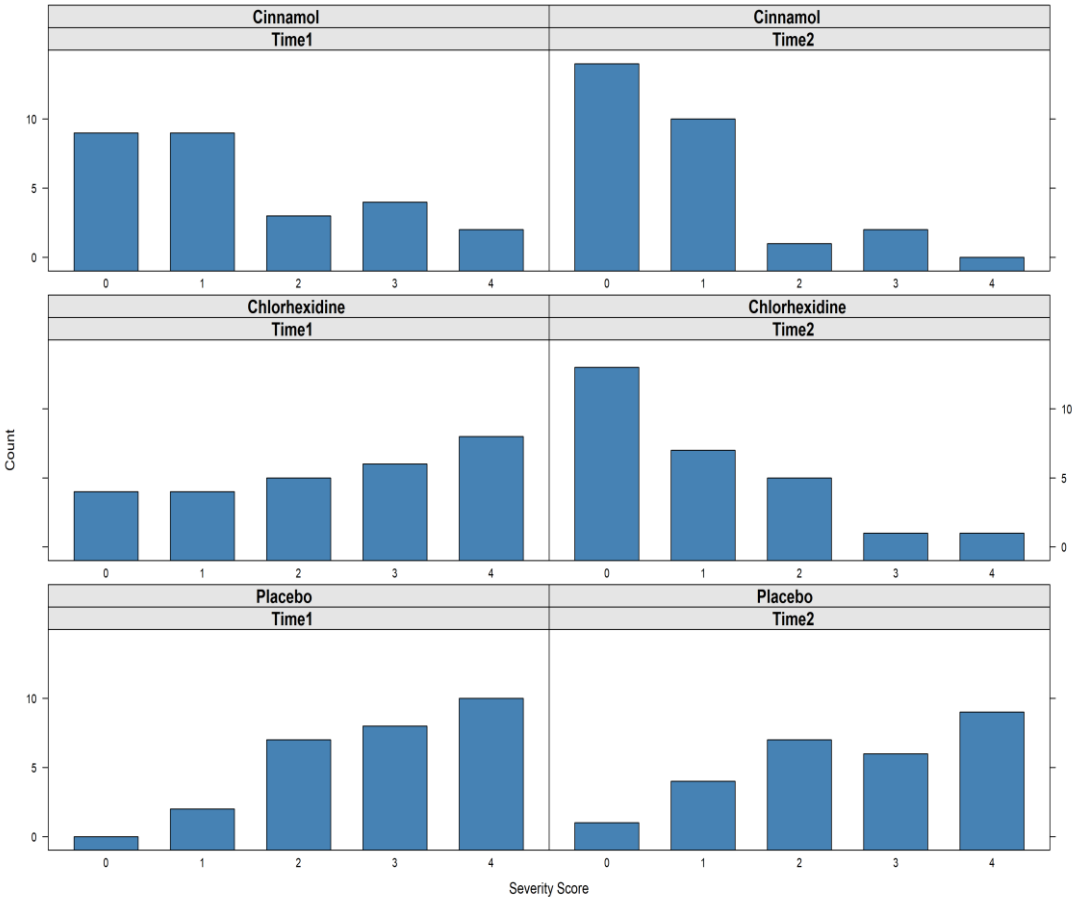

Figure 3. Distribution of mucositis severity scores across study groups at two time points

Overall therapeutic effectiveness of mouthwashes

Beyond the overall time trend, our analysis clearly demonstrated that both cinnamol and chlorhexidine mouthwashes significantly reduced mucositis severity compared to the control group, even after adjusting for differences in the baseline mucositis severity.

Using the chlorhexidine mouthwash dramatically reduced the odds of developing more severe mucositis. The odds of experiencing more severe mucositis in patients using chlorhexidine were 0.002 times that in the control group (OR = 0.002, 95% CI: 0.00007–0.06020, p<0.001). In other words, patients in the control group had approximately 500 times higher odds of developing severe mucositis compared to those receiving chlorhexidine. This represents an exceptionally large effect size, underscoring a substantial clinical benefit for chlorhexidine treatment. Cinnamol use was associated with a significant reduction in mucositis severity (OR = 0.0005, 95% CI: 0.00001–0.01903, p<0.001) compared to the control group. However, the accuracy of this estimate requires further validation due to the wide range of respective confidence intervals (Table 2).

Our analysis also confirmed that the baseline severity of mucositis was a strong predictor of improvement and healing (OR = 8.55, 95% CI: 1.03- 70.94, p-value=0.047). Including this baseline measure in our model was important to accurately evaluate the effectiveness of mouthwashes.

Table 2. Estimation of fixed effects of oral mucositis severity predictors with a linear mixed effects model

Parameters	Estimate	OR	95% CI	P-value
Time	-0.835	0.434	0.182-1.037	0.06
Group (Chlorhexidine)	-6.159	0.002	0.00007-0.0602	< 0.001
Group (Cinnamol)	-7.657	0.0005	0.00001-0.0190	< 0.001
Baseline SMAT	2.146	8.552	1.031-70.937	0.047
Time * Group (Chlorhexidine)	-3.739	0.024	0.004-0.141	< 0.001
Time * Group (Cinnamol)	-1.313	0.269	0.068-1.059	0.06

Mouthwash type vs. time interaction

The interaction between the type of mouthwash and time was evaluated to check whether the effect of mouthwashes on mucositis severity could be distinctly modified over time.

In the chlorhexidine group, the effects of the mouthwash on mucositis severity became significantly more pronounced as the time progressed from Time 1 to Time 2 (OR = 0.024, 95% CI: 0.004 – 0.141, p<0.001).

In the cinnamol group, while mouthwash use reduced mucositis severity over time compared to the control group (OR = 0.269, 95% CI: 0.068 – 1.059), this trend was statistically insignificant (p-value=0.06), meaning that the observed improvement could be either weak or due to chance.

Discussion

In this study, we compared the therapeutic effects of cinnamol and chlorhexidine mouthwashes on oral mucositis in cancer patients undergoing chemotherapy with doxorubicin, an agent known to commonly cause oral mucositis as a side effect. Our primary goal was to explore whether the herbal cinnamol could perform similarly to, or better than, chlorhexidine (A chemical agent) in terms of effectiveness and safety. Our findings clearly demonstrated that both cinnamol and chlorhexidine mouthwashes significantly reduced oral mucositis severity compared to the control group. This improvement was remarkable and persisted even after adjusting for initial differences in mucositis severity, which was a significant factor influencing the course of healing according to our analysis.

The substantial effectiveness of both mouthwashes in reducing mucositis severity aligned with the findings of several prior studies. For instance, Sethi et al. (2019) found that both cinnamon extract and chlorhexidine comparably reduced oral microbial load, with no statistically significant difference between them (31). Similarly, the observations of Hashemi et al. (2018) and Gupta et al. (2015) were consistent with our findings, emphasizing the comparable effects of these two mouthwashes in various oral conditions (32,25). Abedipour et al. (2006) and Cabrera et al. (2018) also reported similar efficacy between different mouthwashes and chlorhexidine in treating mucositis and other oral lesions (26,33). These consistent findings reinforce the broad therapeutic potential of herbal and antiseptic mouthwashes in oral care.

While a general declining trend was noticed in mucositis severity over time, this trend was not statistically significant in all groups. The significant time-mouthwash interaction observed in the chlorhexidine group reflected the growing impact of this mouthwash on mucositis severity over the study period (From Time 1 to Time 2), indicating an accelerating healing trajectory. In the cinnamol group; however, the time-mouthwash interaction was not statistically significant. This observation might be due to the low median score in this group at Time 1, leaving less "room" for marked improvements as the time progressed compared to the chlorhexidine group, where the condition was more severe at the baseline. Nonetheless, patients receiving cinnamol progressed toward complete healing, advocating for sustained and potent therapeutic effects.

In terms of mechanism of action, the bioactive ingredients of cinnamol can possibly ameliorate chemotherapy-induced oxidative damage in non-cancerous tissues (34,35) and enhance the antioxidant capacity of oral tissues and salivary glands, reducing inflammation by decreasing prostaglandin E2 production and interleukin-1β levels (36). Additionally, proanthocyanins in cinnamon play a vital role in the healing of oral inflammatory lesions by modulating pro-inflammatory cytokines like IL-6 and IL-8 (37). As oral mucositis progresses through inflammatory, ulcerative, and bacteriological phases (13), cinnamaldehyde and eugenol in cinnamol mouthwash may decelerate the progression of the inflammatory phase to bacterial infections by reducing oral microbial load (38), thereby accelerating lesion recovery (37,39).

In contrast to our findings, Diaz et al. (2015) asserted that chlorhexidine mouthwash could not improve mucositis (40). This discrepancy might stem from methodological differences, possibly related to the smaller sample size of the recent study compared to ours. Similarly, Harman et al. (2019) reported that chlorhexidine had the least effectiveness among three mouthwashes in preventing and treating chemotherapy-induced mucositis (41). This difference could be due to variations in intervention protocols or the co-administration of other solutions.

A key strength of our research was the direct comparison of the effectiveness of an herbal mouthwash (Cinnamol) with a chemical standard alternative (Chlorhexidine) in treating mucositis, addressing a critical gap in nursing and clinical practice. The relatively adequate sample size and daily phone follow-ups further reinforced the validity of our data. The noteworthy limitations included the possibility that some participants might not had used their mouthwash as precisely as scheduled despite daily follow-ups. Furthermore, using other essential oils as a placebo was not feasible due to potential allergic reactions or complications, leading us to use normal saline as the control. It should be noted that potential confounding factors, such as the type of chemotherapy regimen (Chemotherapy alone or combined with radiotherapy), drug dosage, duration of disease and treatment, and cancer stage, were not assessed or controlled in this study. Nonetheless, variables like cancer type and history of chronic pain or illnesses were assessed, showing no significant impact on outcomes. It is recommended to control potential confounders as much as possible in future research.

Conclusion

This study provided evidence regarding the effectiveness of both cinnamol and chlorhexidine mouthwashes in managing oral mucositis in cancer patients. After adjusting for baseline between-patient differences, our findings demonstrated that both mouthwashes could reduce mucositis severity; however, cinnamol mouthwash showed stronger effectiveness over time, evidenced by complete healing in some patients at the end of the study. Chlorhexidine also yielded substantial clinical effectiveness, which was more pronounced over time. These results suggest the equal and, in some cases, superior effectiveness an herbal mouthwash like cinnamol compared to a widely used chemical mouthwash like chlorhexidine. Although chlorhexidine mouthwash is the recommended treatment for oral mucositis in patients undergoing cancer therapy, the excellent safety of cinnamol mouthwash compared

to chlorhexidine is a significant advantage of the former. Given cinnamon's herbal nature and a possibly better safety profile, our findings have important implications for nursing practice and patient treatment choices. Herbal mouthwashes can enhance patient comfort, accelerate healing time, and potentially improve the quality of life of individuals suffering from this painful condition. Further comprehensive studies with larger sample sizes and more rigorous control of confounding variables are needed to fully investigate the potential of cinnamol mouthwash to replace chlorhexidine.

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Ethical statement

This study was registered at the Iranian Registry for Clinical Trials under the code IRCT20211020052820N1 and received ethical approval (IR.NUMS.REC.1400.03) from the Ethics Committee of Neyshabur University of Medical Sciences. All ethical guidelines pertaining to human research were adhered to, including obtaining written informed consent, maintaining the confidentiality of participants' information, and guaranteeing the right to withdraw from the study. This research followed the ethical principles outlined in the Declaration of Helsinki, as an international guideline for medical research.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

M.S: Study concept and Design, H. R: Data acquisition, M. RN: Critical revision of the manuscript for important intellectual content, M. MH: Technical, and material support, F. KH: Analysis and Interpretation of data, and Statistical analysis, M.G.G: Material support, M.H: Administrative support, Study supervision.

Data availability statement

Data will be available upon reasonable request, subjected to review by the research team and consideration of data confidentiality.

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