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Pentoxifylline Mouthwash: A Novel Approach to Managing Chemotherapy-Induced Oral Mucositis, a Randomized, Double blind, and Placebo-controlled Clinical Trial

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Abstract

Background: Chemotherapy-induced oral mucositis (CIOM) is a prevalent inflammatory condition among cancer patients. Pentoxifylline (PTX), a phosphodiesterase inhibitor with established anti-inflammatory properties, has shown potential in CIOM management. The present study investigated the efficacy and safety of PTX mouthwash as a therapeutic intervention.

Method: A randomized, double-blind, placebo-controlled clinical trial was conducted at Omid Hospital, Isfahan, Iran. Participants diagnosed with CIOM were randomly assigned to receive either PTX mouthwash or placebo for seven days, in addition to standard care. Pain severity was measured using the numerical rating scale. Mucositis severity, xerostomia, and quality of life were assessed via the visual analogue scale and a modified oral mucositis daily questionnaire (OMDQ), respectively, at the baseline and after seven-day follow-ups. Data analysis was conducted using statistical package for the social sciences (SPSS) software, employing a per-protocol approach. $P < 0.05$ was considered to be statistically significant.

Results: Of the participants, 33 in the intervention group and 32 in the control group completed follow-up. There were no statistically significant differences in patients' demographic and clinical characteristics between the groups at the study's outset.

The PTX group demonstrated significant improvements in mucositis grade ($P = 0.02$), pain score ($P = 0.02$), xerostomia ($P = 0.03$), and multiple OMDQ parameters, including overall health status, drinking ability, speech, and oral discomfort in comparison with the placebo group. No significant adverse effects were reported.

Conclusion: The findings suggest that PTX mouthwash may serve as a promising adjunctive therapy for reducing the severity of oral mucositis, alleviating pain, and addressing xerostomia in patients with CIOM, warranting further exploration in larger clinical trials.

Keywords: Oral mucositis, Xerostomia, Pentoxifylline, Chemotherapy, Mouthwash

Introduction

Oral mucositis is a significant condition characterized by erythema, ulceration of the oral mucosa, edema, and acute inflammation, leading to pain and restrictions in oral intake. Chemotherapy-induced oral mucositis (CIOM) is among the most prevalent adverse effects associated with antineoplastic drug administration and radiation therapy.[1] According to a recent report, CIOM affects approximately 20% to 40% of patients with solid tumors undergoing chemotherapy, and as many as 80% of patients with hematologic malignancies receiving high-dose chemotherapy or stem cell transplantation. Furthermore, nearly all patients receiving therapeutic radiation for head and neck cancer may experience this condition. Certain classes of chemotherapeutic agents, particularly antimetabolites, antifolates, purine antagonists, anthracyclines, antitumor antibiotics, and taxanes, are more likely to induce CIOM.[2] The most prominent adverse effects of CIOM include significant pain, disturbances in oral intake, compromised quality of life, an increased risk of infection, and associated economic burdens, all of which can disrupt the course of chemotherapy. CIOM is primarily a complication arising from inflammatory responses, predominantly mediated by nuclear factor Kappa-B (NF-κB).[1-3] This pathway leads to the upregulation of pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1β (IL-1β), adhesion molecules, and cyclooxygenase-2 (COX-2).[3-4]

Various agents, both synthetic and natural, have been explored for the treatment of CIOM, including palifermin, caphosol, actovegin, and kangfuxin.[5-8] Of these options, pretreatment with palifermin during chemotherapy or radiotherapy has demonstrated especially promising outcomes.[5, 9] However, there are numerous reports indicating that both palifermin and caphosol have failed to significantly improve CIOM outcomes.[5, 7] For instance, Wong et al.[7] observed that caphosol did not notably lessen the incidence or duration of severe radiation-induced oral mucositis. Additionally, the gastrointestinal side effects of caphosol, including nausea and an unpleasant taste, were key factors in reducing patient adherence. Pentoxifylline (PTX), a methylxanthine phosphodiesterase inhibitor widely used in the treatment of intermittent claudication, has been investigated for its possible impact on CIOM. Research indicates that PTX suppresses the expression of key inflammatory mediators, including COX-2, TNF-α, IL-1β, and IL-6, which play significant roles in the pathogenesis of oral mucositis (10-12).

Moreover, PTX has been found to reduce levels of C-reactive protein and inducible nitric oxide synthase (iNOS), both recognized as markers of inflammation, underscoring its anti-inflammatory effects.[11, 13, 14] Research involving both animal models

and clinical trials has validated the efficacy of PTX in regulating inflammatory markers.[12, 15-16] Importantly, PTX has demonstrated anti-inflammatory and mucoprotective properties in mouse models of radiation-induced oral mucositis.[12] Furthermore, PTX treatment has proven to be effective in modifying the cellular composition of inflammatory infiltrates in Wistar rat models of oral mucositis.[15] The combination of PTX and vitamin E has also been demonstrated to alleviate the severity and shorten the duration of acute radiotherapy-induced oral mucositis and dysphagia in patients with head and neck cancer. [16] Building on its anti-inflammatory properties, and the compelling evidence from both animal and clinical studies, PTX emerges as a promising candidate for treating CIOM. Nonetheless, the absence of clinical trials specifically assessing the impact of PTX mouthwash on the severity and associated complications of CIOM remains a notable gap. Therefore, the proposed randomized, double-blind, placebo-controlled trial aimed to investigate the effects of PTX mouthwash on CIOM grade, pain intensity, xerostomia, and patients' overall quality of life.

Methods

A prospective, randomized, double-blind, placebo-controlled clinical trial was carried out between September 2020 and September 2022 at the Hematology-Oncology Center of Omid Hospital in Isfahan, Iran. This facility, affiliated with Isfahan University of Medical Sciences, focuses on treating hematological malignancies, solid tumors, and related conditions. The hospital is equipped with cutting-edge medical technologies and staffed by a dedicated healthcare team, and has a capacity of 200 beds.

The study protocol received ethical approval from the Isfahan University of Medical Sciences Ethics Committee (IR.MUI.RESEARCH.REC.1399.391) and was registered with the Iranian Registry of Clinical Trials (ID: IRCT20180722040556N9). All patient data were treated confidential, and exclusively used for research purposes. The study participants provided informed consent and were assured that declining to participate or withdrawing from the study would not impact their treatment protocols.

Mouthwash preparation

PTX, a water-soluble drug with a solubility of approximately 77 mg/ml at 25°C, was supplied by Amin® Pharmaceutical Company in Isfahan, Iran for this study. The PTX mouthwash, formulated at a concentration of 40 mg/ml, and the placebo were both prepared in the Department of Pharmaceutics at Isfahan University. The PTX mouthwash was formulated by dissolving PTX powder in deionized water, adding sodium benzoate at a concentration of 0.5 mg/ml as a preservative, and including glucose syrup, which constituted 100 ml of the total 500 ml solution, to mask the drug's taste and align its flavor with that of the placebo. The placebo was produced using the same method but without PTX. Both formulations were stored in identical 250 ml glass bottles under refrigerated conditions, ensuring no visible differences in color, flavor, or taste between the drug and placebo mouthwashes.

Population

The study population consisted of patients referred to Omid Hospital who met the following inclusion criteria: being 18 years or older; diagnosed with oral mucositis due to chemotherapy or bone marrow transplantation (BMT); presenting with any severity of oral mucositis as classified by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0;[17] having a predicted survival of more than three months;

and lacking any history of oral or salivary gland diseases.

Patients were excluded from the study based on the following criteria: (1) known hypersensitivity to PTX or any excipients in the oral formulation, (2) participation in another clinical trial within the same timeframe, unless at least four weeks had elapsed since the previous study, (3) chronic use of steroids or immunosuppressive medications, (4) any acute or chronic inflammatory or progressive oral disease, and (5) prior history of oral or salivary gland disease.

Concealing and randomization

A total included patients were undergoing blocked randomization using a web-based online random allocation system.[18] The online software facilitated the entry of relevant information, including the number of treatment groups (placebo and PTX), a block size of 8, and the total patient count. Randomized codes were generated, and the anticipated sample size was subsequently divided into two groups: placebo and PTX.

Each enrolled patient was provided with a coded glass container containing either PTX 40 mg/ml mouthwash or a visually identical placebo, to be used as directed. To ensure proper blinding, both formulations were packaged in opaque 500 ml glass containers, with a unique code assigned to each container. The coding was managed via block randomization under the supervision of the study coordinator. The assigned codes were secured by the principal investigator in Sealed, Opaque, Sequentially Numbered Envelopes (SNOSE). These packages contained the group assignments and were only opened once the participant's details were recorded. Neither participants, investigators, physicians, nor statistical analysts had knowledge of the specific codes linked to the patients. Regular monitoring was conducted to ensure strict adherence to the protocol, complemented by periodic audits to confirm the reliability of the concealment process.

Study intervention and data collection

Patients were instructed to gargle with 20 ml of the prescribed mouthwash three times daily for three minutes, starting at the onset of oral mucositis and continuing for seven days. All participants followed a standardized oral mucositis prevention protocol, which included routine oral hygiene measures such as brushing after meals and rinsing the oral cavity. This protocol also incorporated the administration of 20 drops of nystatin every three hours, mouthwashes combining 10 ml of chlorhexidine 0.02% with 10 ml of diluted povidone-iodine every three hours, and prophylactic antifungal and antiviral treatments with fluconazole and acyclovir, respectively.

Demographic parameters, including age, gender, type of underlying cancer, primary severity of mucositis, and pain levels, were documented for all participants in the study. The severity of mucositis was evaluated using the NCI-CTCAE version 4.0, which categorizes mucositis as follows: grade 0 (no mucositis), grade 1 (painless ulcers, erythema, or mild soreness without lesions), grade 2 (painful erythema, edema, or ulcers, but the patient can eat or swallow), grade 3 (painful erythema, edema, or ulcers requiring intravenous hydration), and grade 4 (severe ulceration requiring parenteral or enteral nutritional support).[17, 19]

Pain severity was assessed using a Numerical Rating Scale (NRS) ranging from 0 to 10.[20] The primary outcome measures included the severity of mucositis, pain levels, xerostomia, and patients' quality of life.

Xerostomia was assessed using the Visual Analogue Scale (VAS) xerostomia questionnaire. This tool comprises eight questions addressing challenges in speaking and swallowing, the extent of dryness experienced in the mouth, throat, tongue, and lips, and the sensation of thirst.[19] Quality of

life was assessed using a modified Oral Mucositis Daily Questionnaire (OMDQ). This adjusted version emphasized aspects such as overall health, the intensity of mouth and throat pain, and the functional limitations caused by pain. OMDQ itself is a self-reported instrument specifically designed to measure the severity and daily life impact of oral mucositis symptoms from the patient's perspective. It includes parameters such as: pain severity (self-reported discomfort levels), difficulty in eating and drinking (impact on oral intake), speech impairment (difficulty in speaking due to mucositis), sleep disturbances (disruptions caused by mucositis-related pain), overall quality of life (how mucositis affects daily functioning).The questionnaire is structured for daily assessment, allowing healthcare providers to track mucositis progression and response to treatment.[21, 22]

Patient assessments began prior to the use of the mouthwash and continued daily for seven days. The study conductor, who had received two months of training at the faculty of dentistry under the supervision of an oral and dental disease specialist, was responsible for evaluating the severity of oral mucositis. Assessments were conducted visually, following the criteria outlined in the NCI-CTCAE version 4.[17] In instances of uncertainty, the oral and dental specialist provided guidance through face-to-face examinations.

Questionnaires' validation

Prior to the commencement of the study, the Persian version of OMDQ and VAS questionnaires were prepared through a comprehensive translation and validation process. Intercultural validation was initially deemed unnecessary, as the questionnaires did not include items addressing intercultural differences. Instead, a forward and backward translation methodology was used. An English language expert translated the questionnaire from English to Persian, followed by a back-translation into English by another translator. The back-translated version was then compared to the original questionnaire to verify linguistic accuracy and identify any discrepancies.

A technical committee was convened to evaluate the questionnaire's writing style, clarity, and alignment with the study objectives. This committee comprised a textual critic, two psychologists, two general practitioners, and ten oncologists. After extensive discussion and evaluation, the questionnaire received approval for implementation in the study. Subsequently, a content validity assessment was conducted. A total number of 20 patients from the outpatient department at Omid Hospital completed the questionnaire, and two weeks later, the same patients were asked to complete the questionnaire again. A total of 40 completed questionnaires were analyzed to ensure content validity.

Patients' adherence and adverse drug reaction

The secondary outcome measures included evaluating the efficacy of the PTX mouthwash, assessing any potential adverse effects, and monitoring patient compliance. Adherence was assessed during routine follow-up appointments, noting if patients are following the required protocol. Patients who did not adhere to consuming at least 80% of the total cumulative amount of mouthwash or the identical placebo were considered non-compliant and excluded from the study. Any reported adverse drug reactions were evaluated according to CTCAE version 4 during the follow-up period.[17]

Statistical protocol

Sample size calculation

Drawing from prior studies,[8, 21] the sample size for the present study was calculated using a specific equation to assess variations in a particular parameter under two distinct conditions. The equation used incorporated several variables: N (denoting the required sample size), z_1 (representing the reliability

coefficient at a 95% confidence level), z_2 (indicating the power coefficient corresponding to 80% power), p_1 and p_2 (both set at 50%, reflecting the probability in the two groups), and d (designating the margin of error in the study).

$$N = \frac{(z_1 + z_2)^2[p_1(1 - p_1) + p_2(1 - p_2)]}{d^2}$$

$$N = \frac{(1.96 + 0.84)^2[0.5(0.5) + 0.5(0.5)]}{(0.35)^2}$$

$$\cong 32$$

The estimated sample size for each group was projected to be 32 participants, as outlined in the accompanying flow diagram (Figure 1).

Statistical analyses

To evaluate the normality of data distribution in both the intervention and placebo groups, the Kolmogorov-Smirnov test was employed. For the assessment of dependent quantitative variables such as overall health, mouth and throat soreness, swallowing, drinking, eating, talking, sleeping, xerostomia, and pain, both independent t-tests and paired t-tests were used. These tests were conducted to compare the variables between and within the intervention groups. For measuring internal consistency of considered questionnaires, Cronbach's Alpha reliability tests were used. The analysis was conducted using statistical package for the social sciences (SPSS) software (version 23), employing a per-protocol approach. This methodology ensured that only patients who successfully completed the entire monitoring period were included in the evaluation. A *P*-value of less than 0.05 ($P < 0.05$) was considered to be statistically significant.

Results

A total of 76 patients were screened for eligibility, of which 70 met the inclusion criteria and were randomly assigned to either the PTX or placebo group, with 35 participants in each. During the study, two patients from the intervention group and one from the control group were lost to follow-up due to non-cooperation or modifications in their treatment regimen. Consequently, 33 patients in the intervention group and 32 in the placebo group completed the study (Figure 1). As presented in Table 1, the number of male patients in the intervention and placebo groups were 17 (51.5%) and 16 (50%), respectively. The mean age of the patients was 40.48 ± 10.81 years in the intervention group and 41.79 ± 16.19 years in the placebo group. The most prevalent malignancies in the intervention group were multiple myeloma (24%) and Hodgkin disease (24%), while in the placebo group, multiple myeloma was the most common at 30%. The primary pain scores recorded were 3.94 ± 1.06 for the intervention group and 4.42 ± 1.64 for the placebo group. There were no significant differences between primary pain scores in both comparative groups. As shown in Table 1, there were no statistically significant differences in pain levels across any grade of mucositis as well.

Furthermore, the majority of patients in both groups presented with grade 1 mucositis at the start of the study, with rates of 39% in the intervention group and 42% in the placebo group.

Before implementing the intervention, a comparative analysis of the two groups was performed using the Mann-Whitney test. The results indicated no statistically significant differences ($P > 0.05$) in demographic characteristics and study variables between the groups at the study's outset (Table 1).

As presented in Table 2, mucositis grading showed significant improvement in both the PTX ($P < 0.05$) and placebo ($P = 0.04$) groups after a seven-day follow-up period. However, the mucositis grade was significantly lower in the intervention group compared to the placebo group ($P = 0.02$).

Initial comparisons revealed no statistically significant differences in baseline pain scores between the intervention and placebo groups,

suggesting both groups began the study under similar conditions. However, after a seven-day follow-up, the intervention group—those who received the PTX mouthwash—exhibited a significantly greater reduction in mean pain scores compared with the placebo group.

While both groups showed measurable improvement in pain levels (with $P < 0.01$ indicating high statistical significance), the enhanced relief observed in the PTX group points to the therapeutic potential of this treatment. Notably, participants in the intervention group also required fewer narcotic analgesics by the end of the follow-up period, further reinforcing the effectiveness of PTX mouthwash in managing CIOM. These findings collectively highlight not only the analgesic benefits of PTX but also its role in reducing dependency on stronger, potentially habit-forming pain medications.

Additionally, xerostomia grading improved in both the PTX ($P < 0.05$) and placebo ($P < 0.05$) groups over the seven-day follow-up period, with the intervention group showing a significantly lower xerostomia grade compared with the placebo group ($P = 0.03$). Table 2, Figure 2-4 further illustrates significant improvements in several OMDQ questionnaire indices, including overall health score ($P < 0.05$), drinking difficulty ($P = 0.02$), speech impairment ($P = 0.04$), and overall mouth and throat pain severity ($P = 0.05$) in the intervention group compared with the placebo group. However, no statistically significant differences were observed for mouth and throat pain severity ($P = 0.95$), swallowing difficulty ($P = 0.35$), eating difficulty ($P = 0.06$), and sleep disturbance ($P = 0.63$). Additionally, within-group analyses in both cohorts revealed significant improvements across all items of the OMDQ questionnaire indices following the seven-day follow-up period.

The content validity of the VAS and OMDQ questionnaires was assessed using the intra-class correlation coefficient, yielding coefficients between 0.8 and 1, indicating a reliability and validity exceeding the acceptable threshold.

The administration of PTX mouthwash was evaluated for adverse events during the seven-day follow-up period. As indicated in Table 3 and based on CTCAE Version 4.0,[17] PTX mouthwash management exhibited minimal unfavorable effects compared with the placebo and was well-tolerated. Both groups reported mild gastrointestinal and respiratory disorders, though these effects were not statistically significant.

Discussion

Our study presents compelling evidence supporting PTX mouthwash as an effective and well-tolerated treatment for CIOM. A randomized, double-blind, placebo-controlled trial demonstrated statistically significant improvements in mucositis severity, pain relief, xerostomia, and overall quality of life for patients using PTX compared with a placebo. Given the absence of significant adverse effects, this intervention appears promising for CIOM management and justifies further exploration in larger clinical trials.

The management of CIOM remains a significant challenge, prompting exploration of novel therapeutic approaches. Various drug regimens have been explored for the prevention and treatment of CIOM. Reliable evidence supports the effectiveness of palifermin and cryotherapy in preventing oral mucositis,[23] while reports concerning other medications, such as caphosol, actovegin, and kangfuxin, have been inconsistent.[5-8] For instance, research has shown that palifermin, a recombinant human keratinocyte growth factor, significantly reduces the incidence and severity of oral mucositis in cancer patients undergoing chemotherapy and

radiation therapy. A study by Hamzi et al.,[24] found that palifermin was safe, well-tolerated, and effective in pediatric patients with severe oral mucositis following intensified chemotherapy. Additionally, the National Cancer Institute highlights palifermin as a breakthrough treatment that improves the quality of life for patients experiencing mucositis.[25]

A recent systematic review and meta-analysis demonstrated that oral cryotherapy significantly lowers the risk of developing oral mucositis in patients undergoing chemotherapy and BMT. The study found that cryotherapy reduced mucositis incidence across multiple trials, reinforcing its role as a preventive strategy.[26]

To the best of our knowledge, no prior clinical trial has evaluated the effectiveness of PTX mouthwash in the management of CIOM. Our study is the first investigation of its kind, demonstrating that patients treated with PTX mouthwash experienced a significant reduction in mucositis severity, xerostomia, and pain over a seven-day follow-up period. Additionally, PTX mouthwash significantly improved overall health score, drinking difficulty, speech impairment, and overall mouth and throat pain severity in patients with CIOM, although no significant differences were noted in mouth and throat pain severity, swallowing and eating difficulty, and sleep disturbance.

PTX, a methylxanthine phosphodiesterase inhibitor, has been reported to possess anti-inflammatory properties by suppressing the expression of various inflammatory mediators, including iNOS, COX-2, TNF-α, IL-1β, and IL-6.[10-14] The mechanisms by which PTX prevents and treats oral and mucosal damage have been explored in several studies.[12, 27-28] Lima et al.[29] conducted an animal study, revealing that PTX and thalidomide in short-term experience offers substantial protective effects against 5-Fluorouracil induced oral mucositis, attributed to its anti-inflammatory properties and reduction of TNF-α levels. Similarly, Gruber et al.[12] reported that PTX has anti-inflammatory effects on fractionated radiation-induced oral mucositis, significantly lowering the expression of TNF-α and IL-1β in a mouse tongue model.

In another study by Gruber et al.[27], PTX was shown to have mucoprotective effects, significantly reducing hypoxia and its markers (hypoxia-inducible factor-1α and Glucose transporter-1) in a fractionated radiation model. Furthermore, Yang et al.[30] investigated the protective effects of PTX against radiation-induced apoptosis in serous acinar cells of salivary glands in rats.

Their findings suggest that PTX may help preserve glandular function by reducing cellular damage and enhancing tissue resilience following radiation exposure. This supports its potential therapeutic role in mitigating radiation-induced xerostomia and other oral complications.

The ability of PTX to modulate inflammatory pathways and cellular responses presents a compelling rationale for its efficacy in managing CIOM. By attenuating the effects of pro-inflammatory mediators such as TNF-α and IL-1β, PTX may contribute to a reduction in the inflammatory cascade responsible for mucosal injury. Additionally, its capacity to mitigate hypoxia—an important factor in tissue stress and damage—supports its role in preserving mucosal integrity during chemotherapy.

Another critical aspect of PTX's mechanism is its ability to reduce apoptosis, particularly in oral epithelial cells, which are highly susceptible to chemotherapy-induced cytotoxicity. This mucoprotective effect likely contributes to the observed reduction in mucositis severity and pain, as demonstrated in the present study. Our results suggest that PTX may serve as a therapeutic

agent capable of enhancing epithelial resilience, improving patient comfort, and promoting mucosal healing. Given these promising results, further research is warranted to determine its long-term benefits, optimal dosing strategies, and comparative efficacy against established mucositis treatments.

Several clinical trials have indicated that PTX may be effective in preventing and treating chemotherapy and radiotherapy-induced oral mucositis.[16, 30] Bianco et al.[31] reported that patients with hematologic malignancies undergoing BMT who received PTX at doses of 1200 mg/d, 1600 mg/d, and 2000 mg/d orally from day -10 to day +100 post-transplant experienced significantly less mucositis compared with the placebo group. Consistent with the pain reduction effects noted in our study, Bianco et al.[31] observed that patients receiving PTX treatment experienced a notable reduction in mucositis severity, with fewer cases requiring anesthesia for pain management. Additionally, these patients were able to meet their oral caloric intake requirements earlier than those in the control group, suggesting that PTX may contribute to improved oral function and nutritional status during treatment. These findings further support PTX's potential as a therapeutic agent for managing CIOM and enhancing patient recovery. While Bianco et al.'s study primarily investigated the tolerability of PTX and its role in preventing complications following BMT, our research specifically assessed PTX's therapeutic efficacy in managing CIOM. In contrast to their focus on post-BMT outcomes, our study highlights PTX's ability to alleviate mucositis severity and its associated symptoms, including xerostomia, pain, and overall quality of life. This distinction underscores the broader potential of PTX in supportive oncology care, particularly in enhancing mucosal recovery and improving patient well-being during chemotherapy.

While PTX has shown promise in managing CIOM, some studies have reported conflicting results regarding its efficacy. Verdi et al.[32] conducted a clinical trial evaluating PTX at a dosage of 1600 mg/day in patients with cisplatin and 5-FU-induced mucositis. Their findings indicated that PTX failed to demonstrate a cytoprotective effect and was ineffective in preventing mucositis. However, the study's limited sample size—only 10 participants—raises concerns about the reliability and generalizability of these results.

These discrepancies highlight the need for further large-scale clinical trials to determine PTX's true potential in CIOM management. Factors such as dosage optimization, patient selection, and treatment duration may play a crucial role in its effectiveness. A comparative analysis with other established mucositis treatments could also provide valuable insights into PTX's therapeutic viability.

Sayed et al.[16] conducted a randomized controlled study investigating the effects of PTX and vitamin E on radiotherapy-induced oral mucositis and dysphagia in patients with head and neck cancer. Their findings indicated that while the combination did not significantly reduce the incidence or onset of mucositis and dysphagia, it did shorten their median duration. Additionally, the intervention significantly decreased the incidence of severe (grade 3 and 4) mucositis and dysphagia, suggesting a potential role in mitigating the severity of these conditions.

In contrast, our study specifically examined the therapeutic efficacy of PTX mouthwash in managing CIOM. The results demonstrated a notable reduction in severe mucositis cases, with grade 4 mucositis decreasing from 4 to 1 and grade 3 mucositis from 6 to 2 over seven days. Furthermore, PTX mouthwash significantly improved

drinking ability, reinforcing its potential in alleviating oral discomfort. However, its effects on swallowing and eating difficulties were not statistically significant, raising questions about its effectiveness in addressing dysphagia. These findings highlight the need for further research to determine PTX's broader impact on swallowing function and overall nutritional intake in CIOM patients.

The novelty of this study lies in the evaluation of a PTX mouthwash formulation for CIOM, offering a more targeted approach with potentially reduced systemic toxicity. Unlike systemic PTX administration, the mouthwash formulation minimizes contraindications for patients with recent cerebral or retinal hemorrhage or acute myocardial infarction, making it a potentially safer alternative. Furthermore, our study provides comprehensive assessments of xerostomia, pain, and the progression of oral mucositis treatment—areas that have received limited attention in previous research.

To enhance internal validity, the study was designed as a randomized, double-blind, placebo-controlled clinical trial, with data collection and evaluation performed by a single investigator. In terms of tolerability, PTX mouthwash was well-received, with reported side effects—including nausea, vomiting, cough, and hoarseness—not significantly differing from those observed in the control group.

Despite its promising findings, the present study has certain limitations which include the absence of standardized PTX dosing, a relatively small sample size, and the lack of evaluation of gastrointestinal mucositis. Additionally, confounding factors such as neutropenia, chemotherapy regimen-induced oral mucositis, and individual oral hygiene practices were not accounted for, potentially influencing the outcomes. Nonetheless, given its efficacy in reducing mucositis severity and improving patient symptoms, PTX mouthwash appears to be a safe and effective therapeutic option for CIOM management. Further large-scale studies are warranted to validate these findings, refine dosing strategies, and explore its broader clinical applications.

Our study demonstrates the potential therapeutic benefit of PTX mouthwash in alleviating pain associated with CIOM. Although initial pain scores did not differ significantly between the intervention and placebo groups, the PTX group experienced a markedly greater reduction in mean pain scores following a seven-day treatment period. This suggests that PTX may offer a targeted approach to symptom relief beyond the natural healing process or placebo effect. Importantly, both groups showed statistically significant improvement over time, which aligns with the expected clinical trajectory of CIOM resolution. However, the superior pain control observed in the PTX group, coupled with reduced reliance on narcotic analgesics, is of particular interest. These outcomes suggest not only enhanced symptom management but also a potential role for PTX in reducing the burden of opioid-related side-effects, a critical consideration in oncology care.

Taken together, these findings underscore the clinical utility of PTX mouthwash as a promising, low-cost adjunctive therapy in the multidisciplinary management of oral mucositis in cancer patients. Moreover, the present study opens the door for further investigation into its mechanisms of action in the oral cavity, potentially involving modulation of cytokine release, tissue perfusion, and local immune responses. Additionally, comparative trials with other commonly used mouthwashes or mucosal protectants could help clarify PTX's position in the clinical management of CIOM.

Conclusion

Our study suggest that PTX mouthwash (40 mg/ml), administered daily for seven days, may serve as a promising adjunctive therapy for reducing the severity of oral mucositis, alleviating pain, and addressing xerostomia in patients with CIOM. Additionally, PTX demonstrated notable improvements in quality of life, particularly in overall health perception, drinking ability, speech, and oral discomfort. Despite these promising results, further research is required to determine the optimal PTX dosage and evaluate its efficacy in a larger cohort. Future studies should also consider individual factors, such as oral hygiene practices, to better understand its therapeutic potential and long-term benefits in CIOM management.

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Authors' Contribution
A. D, A. M, A. S, A. R, M. Sh and M.R contributed to the literature review, study design, providing data, writing, and revised manuscript. F. Kh contributed to study design, data gathering, drafting and reviewing the manuscript and also were responsible for patient's oral cavity evaluation and analysis. A. M supervised the whole study. All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest
None declared.

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Table 1. Baseline clinical and demographic characteristics of patients in intervention and placebo groups (N= 65)

Variables	Intervention group (n = 33)	Placebo group (n = 32)	*P*-value
Age (years) (mean ± SD)	40.48 ± 10.81	41.79 ± 16.19	0.72
Sex n (%) **Male**	17 (51.5%)	16 (50%)	0.05
Baseline malignancies	*P*= 0.46		
Multiple myeloma	8(24%)	10(30%)	0.15
Hodgkin disease	8(24%)	5(15%)	0.45
Acute myeloid leukemia	7(21%)	3(9%)	0.78
Acute lymphocytic leukemia	5(15%)	7(21%)	0.29
Others	5(15%)	8(24%)	0.55
Primary pain scores*(mean ± SD) **Grade 2 mucositis** **Grade 3 mucositis** **Grade 4 mucositis**	3.94 ± 1.06 1.96 ± 1.1 3.54 ± 1.23 5.94 ± 1.85	4.42 ± 1.64 2.72 ± 1.43 3.82 ± 1.74 6.42 ± 1.67	0.08 0.06 0.11 0.09
Overall primary grade of mucositis ** **(mean ± SD)**	1.96 ± 1.10	1.91 ± 1.20	
Grade 0	1 (3%)	2 (6%)	
Grade 1	13 (39%)	14 (42%)	0.3
Grade 2	9 (27%)	7 (21%)	
Grade 3	6 (18%)	5 (15%)	
Grade 4	4 (12%)	5 (15%)	

*Based on Visual Analogue Scale (VAS) questionnaire, ** Based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0; N: Number; SD: Standard deviation

Table 2. Comparison of intervention variables between intervention (n= 33) and placebo (n=32) groups at the baseline and after seven-day follow-ups

Variables	Intervention group (mean ± SD) (n = 33)		Placebo group (mean ± SD) (n = 32)		*P*-value primary Intergroup	*P*-value secondary Intergroup	*P*-value Within Intervention group	*P*-value Within placebo group
	Baseline	7-day follow-ups	Baseline	7-day Follow-ups				
Mucositis grading*	1.96 ± 1.10	1.00 ± 1.000	1.91 ± 1.20	1.52 ± 1.149	0.32	0.02	0.00	0.04
Pain score**	3.94 ± 1.059	1.49 ± 1.340	4.42 ± 1.640	2.30 ± 1.40	0.08	0.02	0.00	0.00
Grade 2 mucositis	1.96 ± 1.1	0.56 ± 0.2	2.72 ± 1.43	1.76 ± 1.7	0.06	0.00	0.02	0.03
Grade 3 mucositis	3.54 ± 1.23	1.55 ± 1.13	3.82 ± 1.74	2.84 ± 1.63	0.11	0.01	0.01	0.05
Grade 4 mucositis	5.94 ± 1.85	2.84 ± 1.45	6.42 ± 1.67	3.94 ± 1.95	0.09	0.00	0.00	0.01
Xerostomia grading***	4.87 ± 1.59	1.48 ± 0.90	4.93 ± 1.78	2.72 ± 1.09	0.87	0.03	0.00	0.00
IV morphine equivalents mg/24h Median (range)	43 (0–135)	15 (1–98)	46 (0–142)	20 (1–110)	0.2	0.04	0.04	0.03
modified Oral Mucositis Daily Questionnaire's (OMDQ) Parameters								
Overall health Score	6.79 ± 1.47	2.55 ± 1.44	6.73 ± 1.58	4.82 ± 1.21	0.6	0.00	0.00	0.01
Mouth and throat pain severity	2.85 ± .97	1.52 ± .97	2.76 ± 0.97	1.42 ± 1.30	0.65	0.94	0.00	0.00
Swallowing difficulty	2.70 ± 1.04	1.15 ± 1.00	2.58 ± 1.03	1.42 ± 1.30	0.57	0.34	0.00	0.00
Drinking difficulty	2.91 ± 1.01	1.15 ± 1.00	2.58 ± 1.00	1.82 ± 1.23	0.23	0.02	0.01	0.03
Eating difficulty	2.94 ± 0.97	1.27 ± 1.04	2.76 ± 0.94	1.79 ± 1.30	0.45	0.06	0.00	0.02
Speech impairment	2.91 ± 1.04	1.09 ± 1.07	2.82 ± 0.95	1.67 ± 1.24	0.76	0.04	0.00	0.00
Sleep disturbance	2.97 ± 0.85	1.55 ± 1.17	3.12 ± 0.1	1.67 ± 1.29	0.48	0.63	0.03	0.05

Overall mouth and throat pain severity	7.06 ± 1.58	2.91 ± 1.51	6.70 ± 1.57	4.30 ± 1.47	0.05	0.00	0.00	0.01

*Based on Visual Analogue Scale (VAS) questionnaire, **Based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0, ***Based on Visual Analogue Scale (VAS) xerostomia; N: Number; SD: Standard deviation; IV: Intravenous; H: Hour; Mg: Milligram

Table 3. Adverse drug reactions in enrolled patients were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (Throughout the investigation, no grade 4 or 5 responses were observed)

Adverse drug reactions	**Intervention group (N = 39) N (%)**	**Placebo group (N = 43) N (%)**	***P*-value**
Nausea	17 (43.6%)	19 (44.2%)	0.409
Grade 1	12	11	
Grade 2	4	8	
Grade 3	1	1	
Vomiting	10 (25.6%)	12 (27.9%)	0.449
Grade 1	7	6	
Grade 2	2	4	
Grade 3	1	1	
Drowsiness	4 (10.3%)	3 (7%)	0.797
Grade 1	2	1	
Grade 2	2	2	
Grade 3	0	0	
Fatigue	6 (15.4%)	4 (9.3%)	0.615
Grade 1	3	3	
Grade 2	3	1	
Grade 3	0	0	
Taste changes	2 (5.1%)	4 (9.3%)	0.336
Grade 1	1	3	
Grade 2	1	1	
Grade 3	0	0	

N: Number

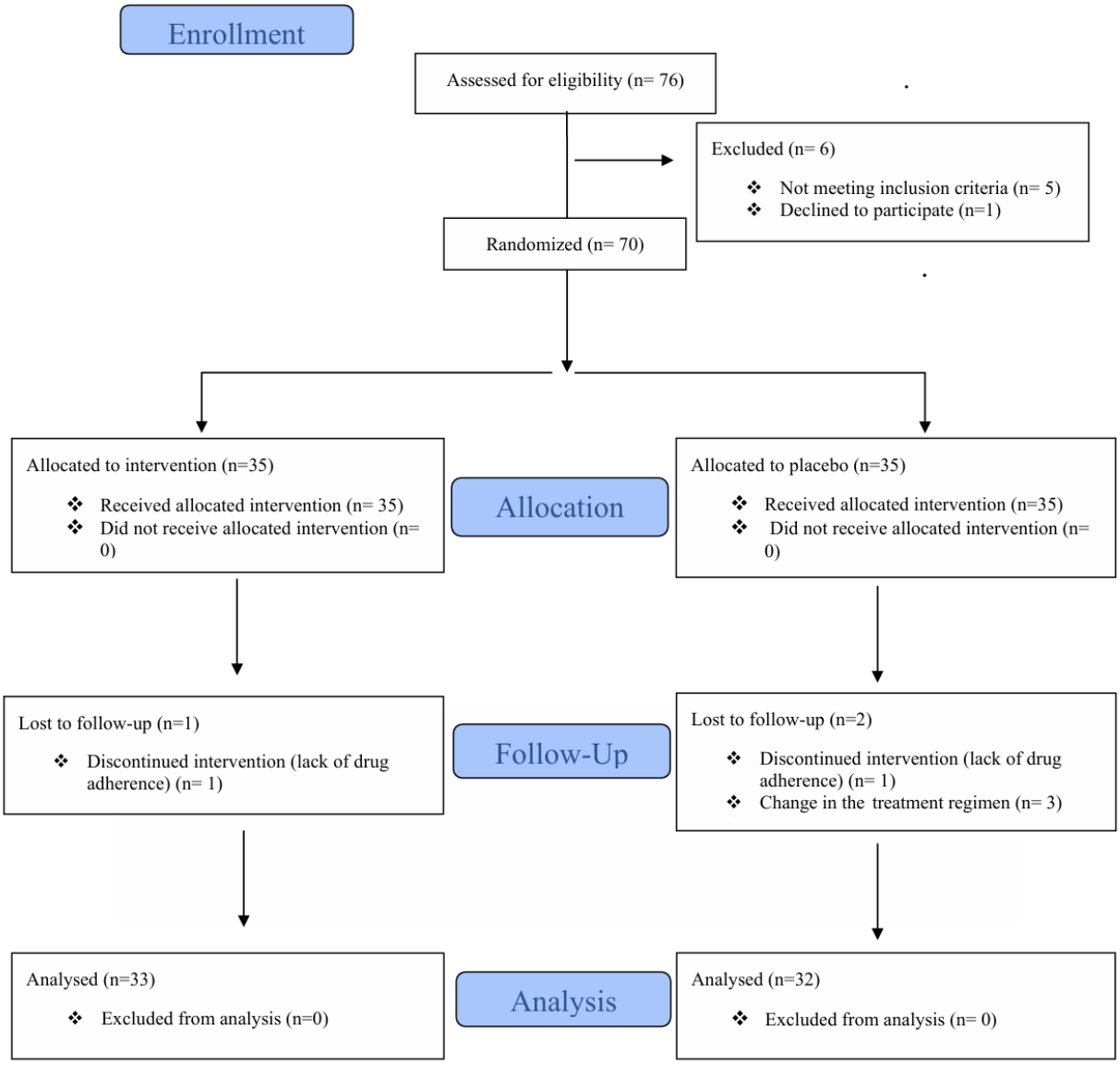
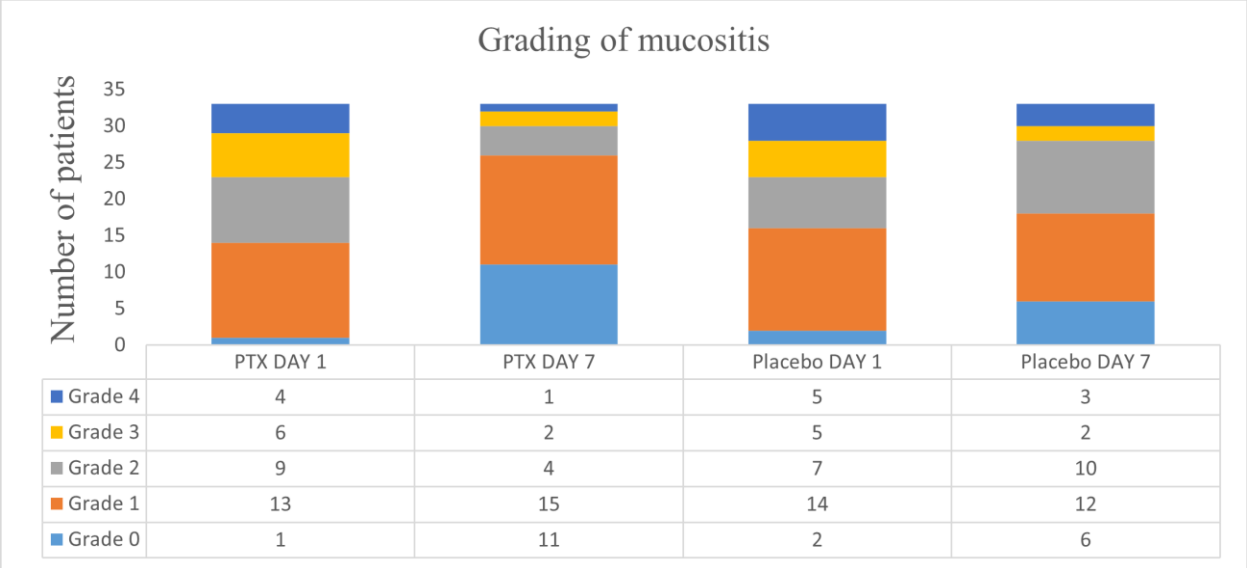


Figure 1. This figure shows the consort flow diagram of the study progress through the phases of a parallel randomized trial of two groups.
N: Number



	PTX DAY 1	PTX DAY 7	Placebo DAY 1	Placebo DAY 7
Grade 4	4	1	5	3
Grade 3	6	2	5	2
Grade 2	9	4	7	10
Grade 1	13	15	14	12
Grade 0	1	11	2	6

Figure 2. This figure shows the comparison of mucositis grading between intervention (n= 33) and placebo (n=32) groups at the baseline and after seven-day follow-ups.
N: Number

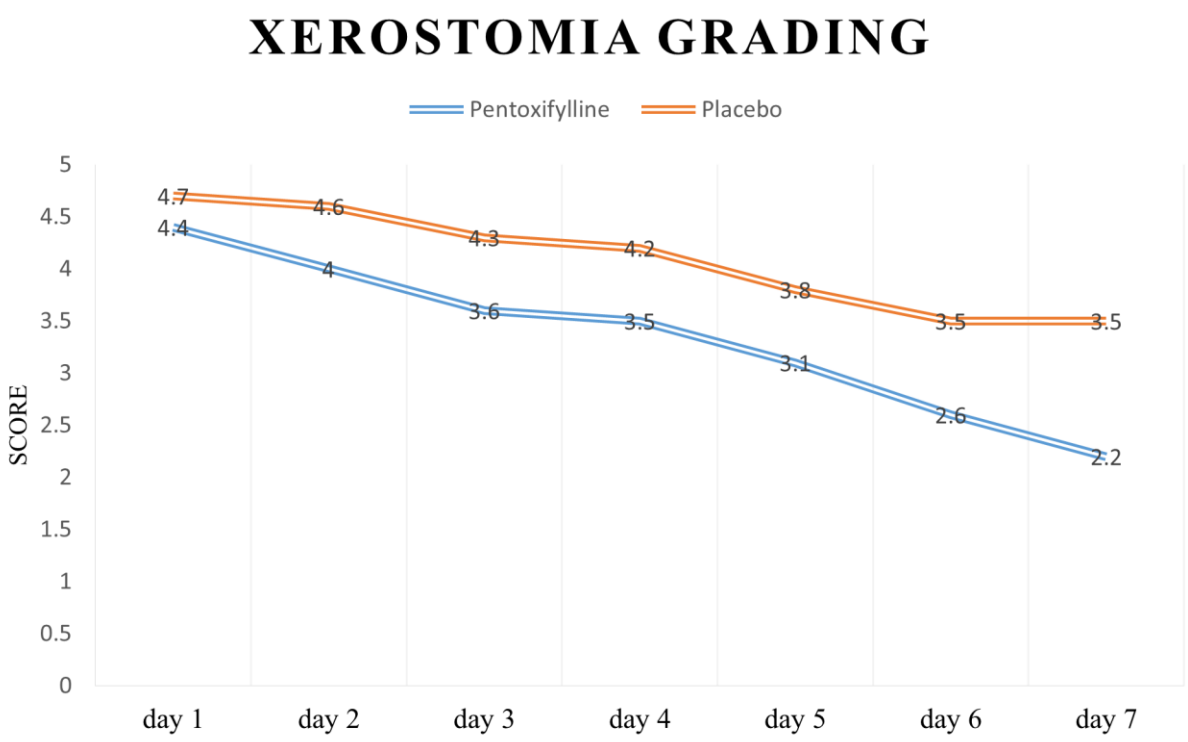


Figure 3. This figure shows the efficacy of pentoxifylline in improving xerostomia grading between intervention (n= 33) and placebo (n=32) groups at the baseline and after seven-day follow-ups.

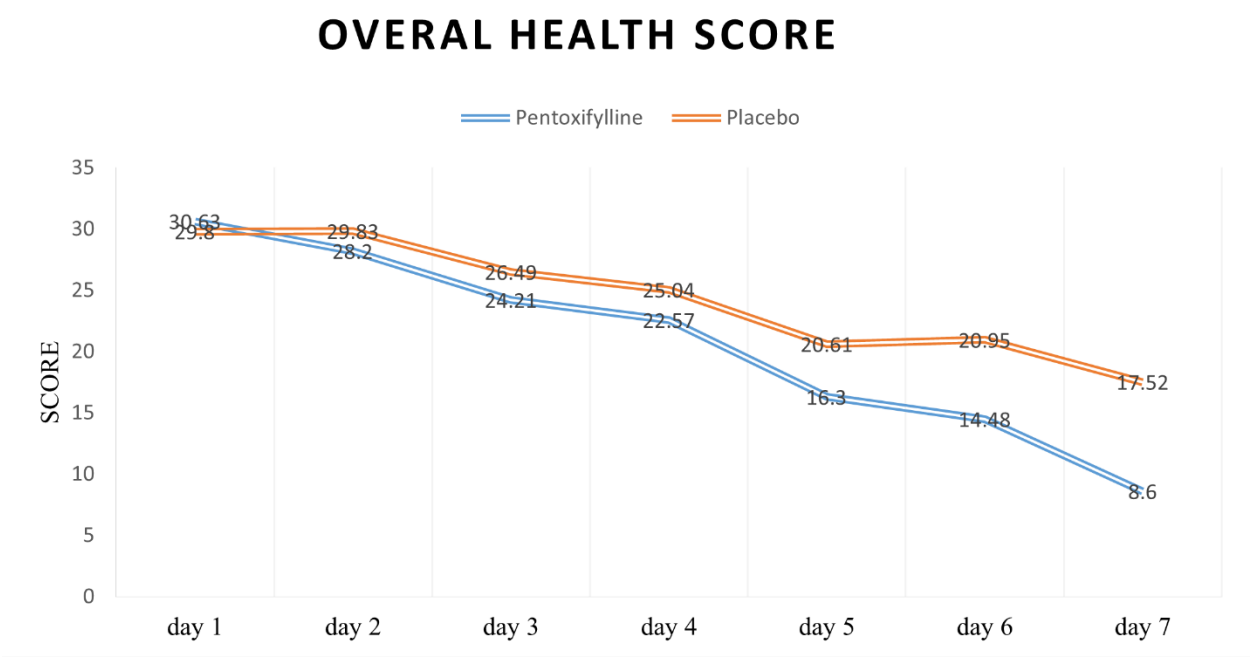


Figure 4. This figure shows the efficacy of pentoxifylline in improving overall health score between intervention (n= 33) and placebo (n=32) groups at the baseline and after seven-day follow-ups.