



Comparative Study of Morphine Mouthwash and Benzydamine Gargles in Managing Radiation-Induced Oral Mucositis

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Abstract

Background: Oral mucositis is a common and painful side effect of radiotherapy in patients with head and neck cancers. It often leads to difficulty in eating, swallowing, and speaking, affecting the patient's quality of life and treatment compliance.

Aim: To compare the effectiveness of morphine mouthwash with benzydamine gargles in the management of radiation-induced oral mucositis in patients with early oral cavity and oropharyngeal cancers.

Methods: This randomized prospective study included 100 patients who received adjuvant or definitive radiotherapy. Fifty patients were assigned to the morphine group (Group M) and fifty to the benzydamine group (Group B). Patients developed Grade II mucositis during radiotherapy and were then started on their respective mouthwashes. Mucositis was graded according to RTOG criteria, and pain was assessed using the Numeric Rating Pain Scale weekly till completion of radiotherapy.

Results: Both groups were comparable in baseline characteristics. From the third week onward, the morphine group showed a significant reduction in mucositis grade and pain score compared to the benzydamine group ($p < 0.001$). By week 7, the mean mucositis grade and pain score were markedly lower in the morphine group.

Conclusion: Morphine mouthwash was found to be more effective than benzydamine gargles in reducing the severity of radiation-induced mucositis and associated pain. It is a safe, well-tolerated, and cost-effective option that can improve patient comfort and compliance during radiotherapy.

Keywords: Oral mucositis, Morphine mouthwash, Benzydamine, Radiotherapy, Oral cavity cancer, Oropharyngeal cancer and Head and Neck Cancer.

Introduction

Oral mucositis is a frequent, painful, and dose-limiting complication in patients undergoing radiotherapy (RT) and/or chemotherapy (CT), particularly those with oral cavity and oropharyngeal cancers. It manifests initially as erythema and progresses to ulcerative lesions, significantly impairing eating, speaking, and quality of life. Severe mucositis may force interruptions or modifications in treatment, thus potentially compromising oncologic outcomes.[1]

The incidence and severity of oral mucositis vary considerably among patients and across different cancer treatment modalities. Reported rates are approximately 40% with standard chemotherapy, increasing to up to 75% with high-dose chemotherapy, 30–60% with radiotherapy to the head and neck region, and as high as 90% among patients receiving concurrent chemoradiotherapy.[2]

Various interventions have been explored for the prevention and management of oral mucositis in patients undergoing cancer therapy. Although several agents benzydamine hydrochloride, chlorhexidine mouthwash, and topical anaesthetics are used; however, their efficacy remains limited, particularly in patients receiving concurrent chemoradiotherapy. Agents have demonstrated partial efficacy in reducing the incidence or severity of mucositis, no single intervention has yet proven to be completely effective or universally successful in its prevention or treatment. General approaches include effective oral care, dietary modifications, and topical mucosal protectants. The appropriate use of topical anaesthetics and systemic analgesics remains the cornerstone of therapy.[3,4]

Since there is currently no drug that can completely prevent or cure oral mucositis, patient-controlled analgesia with morphine remains the standard approach for managing mucositis-related pain. In addition, patients commonly use topical anaesthetics such as lidocaine, either alone or in combination with other soothing agents, in formulations popularly referred to as “Benzydamine” mouthwashes, to obtain temporary relief from pain and discomfort.[5]

Benzydamine, a non-steroidal anti-inflammatory agent with local analgesic properties, has been studied both prophylactically and therapeutically for radiation- and chemoradiation-induced oral mucositis. Several randomized controlled trials and meta-analyses have shown that benzydamine mouthwash can reduce severity, delay ulceration, reduce pain, and lower incidence of higher-grade mucositis compared to placebo or standard care.[6]

Morphine mouthwash (topical/oral application) has been proposed as a treatment option to alleviate the pain associated with established mucositis. The rationale is that topical opioids may act locally to reduce pain intensity without significant systemic absorption or side effects. Some clinical trials (randomised, double-blinded) have reported that morphine mouthwash reduces pain scores in patients with mucositis from RT and/or CT.

Its efficacy in reducing mucositis grade (i.e. severity of mucosal ulceration) is less well established.[7] Despite these advances, gaps remain. There is limited data directly comparing Benzydamine and Morphine mouthwash in their effects on both mucositis grade trajectory and pain scale over time in a well-matched patient population, especially in early oral cavity and oropharyngeal cancers. Therefore, the present study was designed to compare the effectiveness of Morphine mouthwash versus Benzydamine mouthwash (Control) in the management of oral mucositis among patients with early-stage oral cavity and oropharyngeal cancers undergoing radiotherapy. The objective was to assess their comparative impact on mucositis grade reduction, pain control, and overall patient comfort.

Materials and Methods

Study setting

The present study was randomized prospective comparative analytical study conducted in radiotherapy department, Gujrat Cancer Research Institute (GCRI) Ahmedabad. A total of 100 patients were enrolled, with 50 patients in each arm of the study. The participants were selected from patients attending the Radiotherapy Outpatient Department of our institute. The study was carried out over a period of two years after obtaining approval from the Institutional Ethics Committee, and all ethical principles of voluntary participation, confidentiality, and informed consent were strictly followed.

Patients diagnosed with oral cavity and oropharyngeal cancers in the early stage and planned for postoperative radiotherapy without concurrent chemotherapy were included in the study. Only those with a Karnofsky performance score greater than 70 were considered eligible for participation. Patients were excluded if they had received radiation therapy previously or were undergoing concurrent chemotherapy. Individuals with locally advanced oral cavity or oropharyngeal cancers, as well as those diagnosed with laryngeal, hypopharyngeal, or nasopharyngeal cancers, were not included. Patients who were already on oral morphine therapy at the initiation of radiation treatment or those who had received neoadjuvant chemotherapy were also excluded. Furthermore, patients presenting with distant metastasis at the time of diagnosis were omitted from the study. To minimize confounding factors, individuals with significant comorbid conditions, such as diabetes mellitus, were also excluded.

Intervention

The present study was conducted to compare the effectiveness of morphine gargles with benzydamine gargles in the management of radiation-induced oral mucositis among patients with oral cavity and oropharyngeal cancers undergoing radiotherapy. Patients enrolled in the study were randomly allocated into two groups—Group M (Morphine mouthwash) and Group B (Benzydamine mouthwash)—in an alternate sequence. At the

initiation of radiotherapy, all patients received routine supportive medications along with Betadine gargles from the first day of treatment. The patients were carefully monitored for the development of mucositis. Once Grade II mucositis was observed, participants were divided into two groups: the study group, which received morphine gargles, and the control group, which received benzydamine gargles.

Patients in Group M received morphine mouthwash, which was prepared by dissolving two tablets of morphine sulphate (10 mg each, total 20 mg) in 100 ml of distilled water. Participants were instructed to use 15 ml of this solution six times daily. They were advised to hold the mouthwash in the mouth for approximately five minutes and then spit it out, with strict instructions not to swallow the solution. Patients in Group B followed a similar regimen using benzydamine mouthwash.

Radiation Therapy Planning

Radiation therapy was planned according to individual case requirements. Techniques employed included two-dimensional (2D) conventional radiotherapy, three-dimensional conformal radiotherapy (3D-CRT), or Intensity-Modulated Radiation Therapy (IMRT). The selection of technique depended on tumour site, stage, and institutional protocol.

Clinical Assessment

Following the initiation of the assigned intervention, patients were evaluated on a weekly basis until the completion of radiotherapy. The severity of oral mucositis was graded according to the Radiation Therapy Oncology Group (RTOG) toxicity scale, while pain intensity was assessed using the Numerical Rating Pain Scale (NRPS). At the beginning of radiotherapy, each patient was thoroughly briefed about the pain assessment scale to ensure accurate self-reporting. The weekly evaluations allowed for consistent monitoring of changes in mucositis grade and pain levels, thereby enabling a comparative analysis of the therapeutic efficacy and symptomatic relief provided by morphine and benzydamine gargles throughout the course of radiation therapy.

After completion of treatment, patients were scheduled for regular follow-up visits—every month for the first three months, and every three months thereafter. During each follow-up, patients were evaluated for any side effects of radiotherapy and symptoms of mucositis. A thorough oral cavity examination, including inspection and palpation, was performed, and the neck was palpated to assess nodal status. A CT scan was advised during the third follow-up visit or earlier if any clinical findings suggested recurrence or suspicious lesions. Patients who reported persistent difficulty in swallowing (dysphagia) or voice changes were referred to a speech therapist and were taught swallowing and speech exercises.

In cases where recurrent disease was detected, patients were counselled regarding further management options, which included palliative chemotherapy or salvage surgery as appropriate. If the patient was found to be disease-free after the third follow-up, subsequent follow-ups were continued at three-month intervals to ensure ongoing surveillance and early detection of any recurrence.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline demographic and clinical characteristics of the study population. Comparisons of baseline variables between the two groups were carried out using the Independent Samples t-test for continuous variables and the Chi-square test for categorical variables.

The progression and severity of oral mucositis within each group over time were analysed using the Friedman test, while intergroup comparisons of mucositis grades and pain scores were performed using the Mann–Whitney U test, as the data were non-parametric. All statistical tests were two-tailed, and a p-value less than 0.05 ($p < 0.05$) was considered statistically significant. Results were presented as mean \pm standard deviation (SD) where applicable.

Results

This study included a total of 100 patients diagnosed with early-stage oral cavity and oropharyngeal cancers who received adjuvant or definitive radiotherapy between July 2019 and 2021, in accordance with the predefined inclusion and exclusion criteria. Among these, 50 patients were randomized into the study group, who received morphine mouthwash following the development of Grade II mucositis, while the remaining 50 patients were assigned to the control group, who received benzydamine gargles after developing Grade II mucositis. Both groups were monitored throughout the course of radiotherapy to evaluate the severity of mucositis and pain intensity, enabling a comparative assessment of the efficacy and tolerability of the two treatment modalities.

In our study, Table 1 presents the demographic and baseline clinical characteristics of patients in both groups. The mean age of participants was comparable between the two groups (47.64 ± 11.56 years in Group B and 47.39 ± 9.74 years in Group M; $p = 0.978$). The gender distribution was also similar, with males predominating in both groups ($p = 0.577$). The majority of patients had Grade 2 histology, and the distribution of tumour stage (I and II) was comparable between groups ($p = 1.000$). All patients developed Grade II mucositis before the initiation of mouthwash treatment. Regarding radiation treatment fields, most patients received conformal radiotherapy, with a comparable proportion of bilateral and single-field treatments in both groups ($p = 0.151$).

Overall, there were no statistically significant differences in baseline characteristics between the two groups, indicating that they were well-matched for comparison. (TABLE 1)

CHARACTERISTICS	GROUP B (N 50)	GROUP M (N 50)	P VALUE
Mean age	47.64±11.56	47.39±9.74	0.978 (NS)
Gender			0.577 (NS)
Female	9	6	
Male	41	44	
Histological Grade			0.502 (NS)
Grade 1	12	16	
Grade 2	38	34	
Stage Distribution			1.000 (NS)
I	3	2	
II	47	48	
Mucositis Grade			
II	50	50	
Radiation treatment fields			0.151(NS)
Bilateral	13	7	
Single	9	16	
Conformal	28	27	

Data are presented as mean ±SD or n (%), NS: Non-Significant

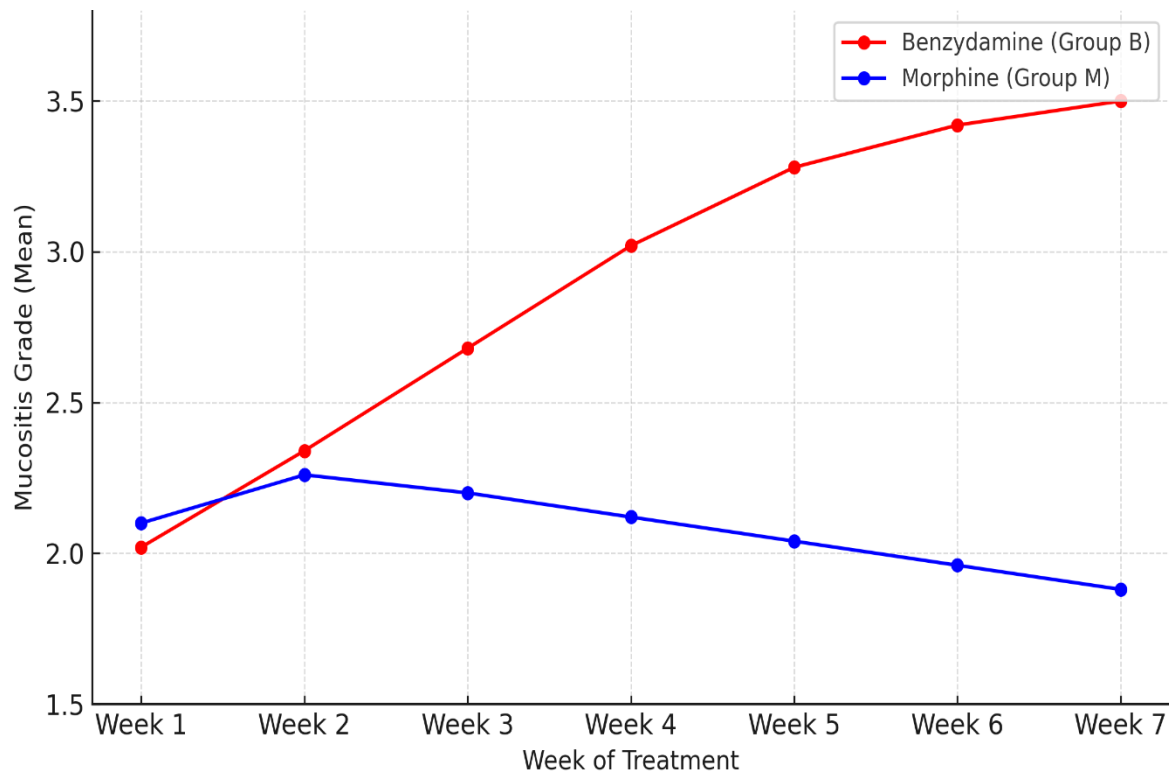
Table 1: Demographic and Baseline Clinical Characteristics of the Patients

In present study, Table 2 summarizes the weekly comparison of mucositis grade and pain score between the two groups after intervention. During the initial weeks (Week 1 and Week 2), there was no significant difference between the groups in either mucositis grade or pain score ($p > 0.05$). However, from Week 3 onward, patients in the morphine group (Group M) showed a significant reduction in both mucositis severity and pain intensity compared to the benzydamine group (Group B) ($p < 0.05$). By the end of treatment (Week 7), the mean mucositis grade decreased to 1.88 ± 0.40 in the morphine group versus 3.50 ± 0.64 in the benzydamine group, while the mean pain score was 3.22 ± 0.76 in Group M compared to 5.10 ± 1.05 in Group B, both showing highly significant differences ($p < 0.001$). Overall, morphine mouthwash demonstrated superior efficacy in reducing both mucositis severity and pain compared to benzydamine. (TABLE 2)

The graph shows that mucositis severity increased steadily in the benzydamine group, while it decreased over time in the morphine group. Overall, morphine mouthwash was more effective in controlling mucositis during radiotherapy. (Graph 1)

WEEK	MUCOSITIS GRADE (MEAN ± SD)		P value	PAIN SCALE (MEAN ± SD)		P value
	BENZYDAMINE (GROUP B)	MORPHINE (GROUP M)		BENZYDAMINE (GROUP B)	MORPHINE (GROUP M)	
WEEK 1	2.02 ± 0.48	2.10 ± 0.44	0.624 (NS)	1.64±0.48	1.68±0.59	0.711
WEEK 2	2.34 ± 0.52	2.26 ± 0.47	0.542 (NS)	3.44± 0.5	2.74±0.53	<0.001**
WEEK 3	2.68 ± 0.56	2.20 ± 0.50	0.041 *	4.04±0.53	3.42±0.69	<0.001**
WEEK 4	3.02 ± 0.60	2.12 ± 0.48	0.008 **	5.6±0.61	4.02±0.55	<0.001**
WEEK 5	3.28 ± 0.58	2.04 ± 0.45	0.002 **	5.94±0.59	3.62±0.6	<0.001**
WEEK 6	3.42 ± 0.62	1.96 ± 0.42	< 0.001 **	5.44±0.73	3±0.81	<0.001**
WEEK 7	3.50 ± 0.64	1.88 ± 0.40	< 0.001 **	5.1±1.05	3.22±0.76	<0.001**

Table 2: Comparison of Clinical Outcomes between the Two Groups After Intervention

Comparison of mucositis grade between Benzydamine and Morphine mouth wash**Discussion**

Oral mucositis is one of the most common and distressing complications of radiotherapy in patients with head and neck cancers. It significantly affects patient compliance, nutritional status, and overall quality of life. The present study compared the effectiveness of morphine mouthwash and benzydamine gargles in the management of radiation-induced oral mucositis and associated pain in patients with oral cavity and oropharyngeal cancers. morphine mouthwash was found to be more effective than benzydamine gargles in reducing both the severity of mucositis and the associated pain.

In our Study, Morphine mouthwash showed a significant reduction in mucositis severity and pain intensity from the third week onward. The mean mucositis grade and pain score were consistently lower in the morphine group across all subsequent weeks. These findings are consistent with previous studies, Cerchietti et al. (2002)[8] first demonstrated that topical morphine solution reduced oral mucositis pain in head and neck cancer patients, improving swallowing and oral intake without systemic opioid side effects. Similarly, other study Vayne-Bossert et al. (2010)[7] also observed that topical morphine rinse significantly reduced mucositis-associated pain compared to placebo, with good tolerability and patient satisfaction.

The mechanism behind the local effect of morphine lies in its interaction with peripheral opioid receptors present on sensory nerve endings in the inflamed mucosa. Radiation-induced mucosal injury upregulates these receptors, allowing morphine to act locally to reduce nociceptive signalling and inflammation. This localized action explains the pain relief without systemic opioid-related adverse effects, as morphine was used topically and not swallowed.[9]

In contrast, benzydamine, a non-steroidal anti-inflammatory agent, exerts its effect through inhibition of pro-inflammatory cytokines and stabilization of cell membranes. Although it has been recommended for prophylaxis and treatment of mild mucositis. Similar results were found in studies (Epstein JB et al study., 2001)[6] and (Rao et al., 2013)[10]. Its effectiveness decreases in higher-grade mucositis or when mucosal ulceration is already established. In our study, since both groups started intervention after development of grade II mucositis, benzydamine gargles were less effective in controlling pain and severity progression compared to morphine.

In present study, patients using morphine mouthwash reported better tolerance and compliance. No significant adverse effects were reported, suggesting the safety of topical morphine use in oral mucositis. Our study results showed that both morphine and benzydamine mouthwashes are effective in reducing mucositis severity; however, topical morphine was more effective and results were more satisfactory to patients than the benzydamine mouthwash.

Conclusion

Radiation-induced oral mucositis remains a major challenge in the management of patients with head and neck cancers, often leading to significant pain, difficulty in swallowing, and interruptions in radiotherapy. In this study, topical morphine mouthwash proved to be more effective than benzydamine mouthwash in reducing both the severity of mucositis and associated pain. Patients using morphine mouthwash showed faster recovery of oral mucosa, better pain control, and improved tolerance to radiotherapy without noticeable systemic side effects.

The findings suggest that morphine mouthwash is a simple, safe, cost-effective, and well-tolerated option for managing radiation-induced oral mucositis. Its use can improve patient comfort, maintain nutritional intake, and help complete planned radiation schedules without interruption. Further large-scale, multicentric, and blinded studies are recommended to validate these results and to establish standardized preparation, dosing, and administration protocols for routine clinical use.

References

1. Sankar V, Xu Y. Oral Complications from Oropharyngeal Cancer Therapy. *Cancers*. 2023; 15(18):4548. <https://doi.org/10.3390/cancers15184548>
2. Naidu MU, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy induced and/or radiation therapy induced oral mucositis– complicating the treatment of cancer. *Neoplasia* 2004; 6:423 31.
3. Barasch A, Elad S, Altman A, Damato K, Epstein J. Antimicrobials, mucosal coating agents, anaesthetics, analgesics, and nutritional supplements for alimentary tract mucositis. *Support Care Cancer* 2006; 14:528 32.
4. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber Durlacher JE, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; 109:820 31.
5. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, Epstein J, et al.; Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology. Clinical practice guidelines for the prevention and treatment of cancer therapy induced oral and gastrointestinal mucositis. *Cancer* 2004;100 Suppl 9:2026 46.
6. Epstein JB, Silverman S Jr, Paggiarino DA, Crockett S, Schubert MM, Senzer NN, Lockhart PB, Gallagher MJ, Peterson DE, Leveque FG. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Cancer*. 2001 Aug 15;92(4):875-85.
7. Vayne-Bossert P, Escher M, de Vautibault CG, Dulguerov P, Allal A, Desmeules J, Herrmann FR, Pautex S. Effect of topical morphine (mouthwash) on oral pain due to chemotherapy- and/or radiotherapy-induced mucositis: a randomized double-blinded study. *J Palliat Med*. 2010 Feb;13(2):125-8. doi: 10.1089/jpm.2009.0195. PMID: 19827964.
8. Cerchietti LC, Navigante AH, Körte MW, Cohen AM, Quiroga PN, Villaamil EC, et al. Potential utility of topical morphine for mucositis-related pain: A pilot study. *J Pain Symptom Manage*. 2002;24(5):547–552.
9. Stein C, Schäfer M, Machelska H. Attacking pain at its source: new perspectives on opioids. *Nat Med*. 2003;9(8):1003–1008.
10. Rao KV, et al. Efficacy of benzydamine hydrochloride mouthwash in prevention and treatment of radiation-induced oral mucositis. *Indian J Palliat Care*. 2013;19(3):190–195.



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