Original Article

Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer

Mostafa Sarvizadeh, Simin Hemati, Mohsen Meidani[1], Moghtada Ashouri, Mahnaz Roayaei, Armindokht Shahsanai[2]

Departments of Radiation Oncology, [1]Infectious Diseases, and [2]Community Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Oral mucositis is a debilitating side effect of cancer treatment for which there is not much successful treatments at yet. We evaluated the effectiveness of topical morphine compared with a routine mouthwash in managing cancer treatment-induced mucositis.

Materials and Methods: Thirty head and neck cancer patients with severe mucositis (World Health Organization Grade III or IV) were randomized into the morphine and magic mouthwash groups. Patients received morphine sulfate 2% or magic solution (contained magnesium aluminum hydroxide, viscous lidocaine, and diphenhydramine), 10 ml for every 3 h, six times a day, for 6 days. Both groups received same dietary and oral hygiene instructions and care. Mucositis was graded at baseline and every 3 days after treatment. Patients' satisfaction and drug effect maintenance were also evaluated.

Results: Twenty-eight patients (mean age of 49.5 ± 13.2 years, 63.3% female) completed the trial; 15 in the morphine group and 13 in the magic group. There was a decrease in mucositis severity in both of the morphine ($P < 0.001$) and magic ($P = 0.049$) groups. However, at the 6th day, more reduction was observed in mucositis severity in the morphine compared with magic group ($P = 0.045$). Drug effect maintenance was similar between the two groups, but patients in the morphine group were more satisfied by their treatments than those in the magic group ($P = 0.008$).

Conclusions: Topical morphine is more effective and more satisfactory to patients than the magic mouthwash in reducing severity of cancer treatment-induced oral mucositis. More studies with larger sample size and longer follow-up are required in this regard.

Key Words: Head and neck carcinoma, mucositis, pain, topical morphine

Address for correspondence:
Dr. Simin Hemati, Department of Radiation Oncology, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: hemati@med.mui.ac.ir
Received: 25.11.2012, **Accepted:** 26.02.2013

INTRODUCTION

Cancer treatment-induced oral mucositis is a common and serious adverse effect that occurs due to some chemotherapeutic agents, radiotherapy of the head and neck regions, and chemoradiotherapy combined treatments. The incidence and severity is varied among patients and different types of cancer treatment; studies showed an incidence of about 40% with standard chemotherapy, rising to 75% with high-dose chemotherapy, 30-60% with radiation to the head and neck regions, and in up to 90% of those receiving chemoradiotherapy combined treatments.[1] Direct mucosal injury and superimposed bacterial infections are proposed as underlying mechanisms.

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.151254

How to cite this article: Sarvizadeh M, Hemati S, Meidani M, Ashouri M, Roayaei M, Shahsanai A. Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer. Adv Biomed Res 2015;4:44.

Beside cancer treatment dose, individual factors including patient's age, nutritional status, type of malignancy, oral hygiene, and smoking are some of the risk factors associated with development and severity of mucosal injury.[1,2]

Severity of oral mucositis varies from mild mucosal erythema to severe ulceration and infections. Pain, xerostomia, and bleeding are common problems that can result in inability to tolerate food or fluids, for which, parenteral or enteral support may be required in severe cases. Oral mucositis not only can lead to malnutrition and impaired quality of life by limiting the patient's ability to tolerate the treatment but it can also affect cancer treatment outcome and patient's survival. Thus, the morbidity and economic consequences of mucositis are considerable.[2-4]

Various interventions have been investigated for prevention and treatment of oral mucositis. Although some of them were found to have some benefits in preventing or reducing the severity of mucositis, there is no intervention completely successful as yet.[5-7] Considering the role of oral hygiene, professional dental care is recommended to all patients before starting cancer treatment and through the therapy.[6] Despite the postulated role of infection in the pathophysiology of oral mucositis, and several systemic and local antimicrobial agents investigated as preventive/therapeutic measures, systemic reviews and available guidelines are not in favor of improvement by such therapies.[6,8] Low-level laser therapy has been shown as partly effective in preventing development of oral mucositis and significantly effective in reducing pain and severity and duration of symptoms.[6,9] Other recommended therapies with some benefits are cryotherapy and the keratinocyte growth factor-1, palifermin.[6,7] However, such therapies are not widely available and are somehow expensive.

Because there is no agent currently available for effectively preventing or treating oral mucositis, patient-controlled analgesia with morphine is still recommended for management of pain.[6] Patients also often used topical anesthetics (lidocaine) alone, or in various combinations known as "magic" or "miracle" mouthwashes for pain relief.[10] However, parenteral opioids are associated with systemic side effects, and local discomfort and numbness affecting the sensation of taste and the gag reflex often limits the use of local anesthetics. Some studies showed benefits from topical-applied morphine in management of oral mucositis.[11-14] Such therapy has its advantages, such as simplicity, low cost, minimal systemic side effects, and better patient's compliance. The beneficial effects of topical morphine for oral mucositis might not be limited to its analgesic effects. Some evidence verified that opioid receptors are expressed on oral epithelial cells and morphine can accelerate the cell migration, which in turn can help to the wound healing process.[15] But the level of evidence is still insufficient to make a general recommendation. Thus, in a double-blinded, randomized controlled trial, we aimed to investigate the efficacy of topical morphine in comparison with a routine therapy (magic mouthwash) in the management of oral mucositis in patients with head and neck cancer.

MATERIALS AND METHODS

Patients and settings

This unicenter, double-blinded, randomized, controlled study was conducted between April and July 2011 in Omid Oncology Hospital in Isfahan (Iran). The study population was selected from consecutive adult patients with head and neck cancer who, as the result of cancer treatment (chemotherapy, radiotherapy, chemoradiotherapy), had severe oral mucositis; grade III or IV of the World Health Organization (WHO) rating of global mucositis.[16] Those with history of severe renal or hepatic insufficiency, collagen-vascular disease, allergic reaction to morphine, current smokers or alcohol users, pregnant women were not included. Calculated sample size per group was 15, considering $\alpha = 0.05$, study power = 90%, and effect size = 2.8.[11] The Ethics Committee of Isfahan University of Medical Sciences approved the study, and written consent was obtained from all patients after full explanation of the study aim and protocol. Also, the trial was registered in *clinicaltrials.gov* (NCT01837446).

Intervention

Patients were randomized into the morphine and magic mouthwash groups by random table numbers. The morphine group used the mouthwash of 2% morphine solution (20 mg morphine sulfate diluted in 100 ml of water), 10 ml every 3 h; six times a day. The morphine solution was prepared by the faculty of pharmacy under the supervision of the Food and Drug Organization of the local Medical University. The magic group used a mouthwash containing a mixture of 240 ml magnesium aluminum hydroxide (Alborz Co., Iran), 25 ml 2% viscous lidocaine (SinaDaru Co., Iran), and 60 ml diphenhydramine (Emad Co., Iran), 10 ml every 3 hours; six times a day. Patients were instructed not to swallow the solution and to hold it for at least two minutes. Total treatment period was 6 days. With the help from a pharmacist colleague, solutions were administered in the same coded bottles and attending physician and patients were unaware about the treatment arms. Both groups received same verbal instructions on oral hygiene

and dietary guidelines. All patients received the same professional oral care if needed; removal of dentures, debridement of necrotic tissues, etc., but they did not receive steroids and/or antimicrobials before inclusion.

Cancer treatment

In our studied patients, chemotherapy alone treatment included cisplatin-based therapy with 21-day intervals for four cycles. In those under radiotherapy, treatment was a total dose of 70 Gy irradiation over 6-7 weeks using two parallel opposed fields to treat the primary tumor, involving lymph nodes, and the relevant areas of lymphatic drainage. Concomitant chemotherapy consisted of weekly cisplatin (30 mg/m^2) for 6-7 weeks. Some patients were entered into this trial while still under cancer treatment, whereas others had just finished the treatment course.

Clinical assessment

Patients were visited by a radiation oncologist who was unaware of the treatment arms at baseline, 3rd day, and 6th day of the intervention. The WHO grading system of mucositis was administered for each patient in which 0 indicated a healed mucositis and no signs or symptoms, 1 indicated mild soreness, but not problem in eating; 2 indicated painful erythema, edema, or ulcers, but able to eat; 3 indicated severe painful erythema, edema, or ulcers and having problem in eating; and 4 indicated whether there was a requirement for parenteral or enteral support. Patients were also asked whether pain/discomfort was relieved by mouthwash, and if so for how long (<1 hour, 1-2 hours, >2 hours). Their satisfaction with treatment was graded as satisfied, tolerable, and intolerable.

Statistical analyses

Data were analyzed using SPSS version 16.0. Baseline characteristics were compared between the two groups using independent sample *t*-test and Chi-square test. Change in the severity of mucositis was evaluated by Friedman test in each group and by Mann–Whitney test between the two groups. A $P < 0.05$ was considered statistically significant.

RESULTS

Patient and treatment characteristics

During the study period, 30 patients were included into the trial. Unfortunately, 2 patients from the magic mouthwash group (a 78-year-old male and a 58-year-old female with grade 4 mucositis) died before the second or third assessment. Thus, data of the remaining patients (mean age = 49.5 ± 13.2, 63.3% female) who completed the trial were considered for analysis [Figure 1]. As presented in Table 1, the two groups were similar in baseline characteristics.

After starting the treatment, a nonsignificant difference was observed in mucositis severity at the 3rd day in favor of morphine ($P = 0.161$). At the 6th day, there was a significantly more reduction in mucositis severity in patients who received morphine compared with magic solution ($P = 0.045$) [Table 2]. Trend of change in mucositis severity is also presented in Figure 2, and Freidman test showed a decrease in mucositis severity in both of the morphine ($P < 0.001$) and magic ($P = 0.049$) groups.

Regarding other outcome variables, drug effect maintenance was not different between the two groups, but patients in the morphine group were more

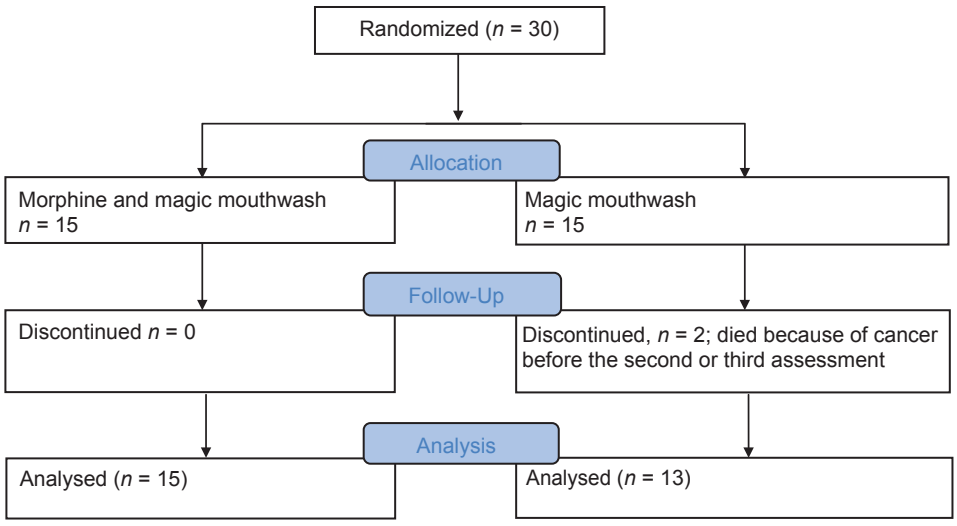

Figure 1: Patients flow diagram

Table 1: Demographic and baseline clinical characteristics of the patients

	Morphine *n*=15	Control *n*=13	*P*
Age, years	47.5±14.6	52.1±11.0	0.357*
Gender, male/female	5/10	5/8	0.544**
Treatment			
Radiotherapy	5	3	0.309**
Chemotherapy	8	5	
Chemoradiotherapy	2	5	
Mucositis grade, III/VI	11/4	9/4	0.569**

Data are presented as mean±SD or *n* (%), *Independent *t* test, **Chi-square test

Table 2: Comparison of clinical outcomes between the two groups after intervention

	Morphine *n*=15	Control *n*=13	*P*
3rd day score	2.00±0.70	2.46±1.05	0.161*
6th day score	1.71±0.60	2.46±1.26	0.045*
Drug effect maintenance			
< 1 h	8	8	0.479**
1-2 h	7	5	
Satisfaction			
Satisfied	8	7	0.008*
Tolerable	6	4	
Intolerable	1	2	
Serum therapy	0	1 (7.6%)	0.433

Data are presented as mean±SD or *n* (%), *Mann-Whitney test, **Chi-square test

satisfied by their treatments than those in the magic group ($P = 0.008$). Also, one patient in the magic group still required serum therapy because of persistent severe mucositis [Table 2]. Adverse effects were almost mild including oral burning/itching during oral rinse. Only one patient in the morphine and two in the magic group reported intolerable taste of the mouthwash.

DISCUSSION

Opioid receptors are expressed on peripheral sensory neurons that can be activated by topical analgesics and result in pain relief.[17] Also, opioids can modulate cell proliferation and survival by stimulating cell migration, and thus can facilitate wound healing process.[15] With these effects and assuming advantages of topical therapy over systemic analgesics, we aimed to investigate the efficacy of topical morphine and compared it with a routine topical therapy, magic mouthwash, in the management of oral mucositis in patients with head and neck cancer. The results of our study showed that both morphine and magic mouthwashes are effective in reducing mucositis severity; however, topical morphine was more effective and results were more satisfactory to patients than the magic mouthwash.

The results of our study were similar to previous ones, albeit some differences in drug dosage and pain

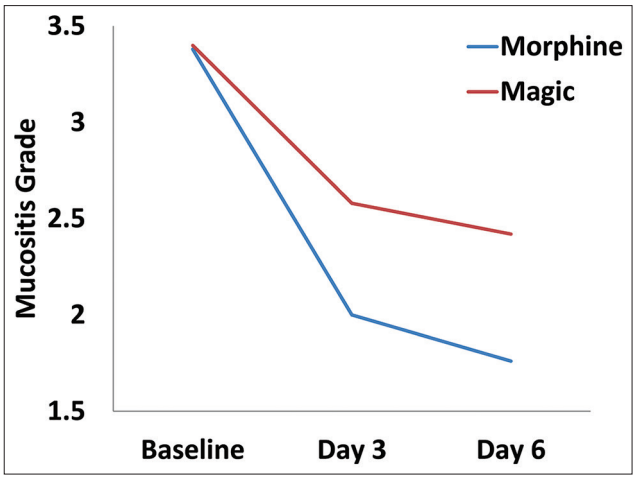

Figure 2: Trend of change in mucositis severity in the two studied groups, $F = 4.28$, $P = 0.05$

relief maintenance. In one small placebo-controlled trial, 9 patients with oral mucositis of at least grade II received 15 ml of 2% morphine mouthwash or placebo, six times a day, for 4-6 days. The study showed significant pain relief by morphine lasting for about 2 hours, and also significant placebo effects. Burning sensation by topical morphine caused one patient to drop out from the study.[14] In another controlled study, Cerchietti *et al*., compared topical morphine 2% with magic mouthwash (both solutions; 15 ml, every 3 h, six times a day) in 26 patients with chemoradiotherapy-induced mucositis of at least grade II. Authors found that topical morphine resulted in more reduction in duration and intensity of pain and also duration of functional impairment compared with magic mouthwash. Also, local side effects were more frequent in magic (41.6%) than morphine (7.1%) mouthwash.[11]

To find a dose-response effect of topical morphine, Cerchietti *et al*., studied topical morphine 2% versus the 1% solution on 10 patients with chemoradiotherapy-induced oral mucositis and found that the 2% solution results in about 20% more reduction in pain than the 1% solution. The authors then tested the 2% solution on 22 patients and results showed time to good/complete pain relief as about 30 min and pain relief maintenance as more than 3 h. Authors also measured serum concentrations of morphine in selected patients and found no active detectable concentrations of morphine. Reported side effects were mild and included burning/itching sensation.[12] In another open-label study on 10 patients with severe oral mucositis, investigators used a high dose of topical morphine; 5 mg in 15 ml, every 2 h, keeping in mouth for 5 m. Authors reported good pain relief lasting for 30-60 min and with minimal side effects. In this study, patients reported difficult

rinsing initially because of the restricted movement of mouth opening due to trismus, which shows that mucositis should be promptly treated so patients can better tolerate topical treatments.[18] Another small dose-finding study in children with oral mucositis, Nielsen *et al*., found significant reduction in pain by topical morphine (0.025-0.400 mg/kg), whereas it has no specific dose-response effects.[19] According to these studies, more investigations are needed to find the most effective while safe dose for topical morphine. Also, according to our results and most of the previous studies, pain relief with topical morphine lasted not more than 2 h, which highlights a short-lasting effect of this mouthwash.[12,14] Therefore, further pharmacological trials are needed to find whether it is possible to prolong drug effect maintenance while decreasing the total dose, and thus preventing possible side effects.

Some studies have shown that chronic morphine treatment results in a delay in cell migration after wounding and also a decrease in bacterial clearance, and thus delays wound closure.[20] Although some other studies indicated beneficial effects of topical opioids on wound healing process[15] and pain relief by topical morphine can decrease the need for systemic use of opioids, some other reports indicated detrimental effects of topical morphine on wound healing.[21] Therefore, further trials are needed to find effects of topical morphine on wound healing process in oral mucositis.

There are some limitations to our study. The sample size of our study was not large enough to provide an appropriate randomization, to detect minimal differences between the two groups, and to find factors associated with better response to the studied topical therapies. Our patients were heterogeneous regarding cancer treatments, though it seems that cancer treatment type might not have direct effects on this treatment response. The study period was also short and it was better to follow the patients for a longer period to find long-term benefits or harms of such therapy.

CONCLUSION

Morphine and magic mouthwashes are effective in reducing severity of cancer treatment induced oral mucositis in patients with head and neck cancer; however, topical morphine is more effective and results were more satisfactory to patients than the magic mouthwash. More studies with larger sample size and longer follow-up are required before recommending topical morphine as a routine in the management of oral mucositis.

ACKNOWLEDGEMENTS

This study was supported by Vice Chancellor for Research of Isfahan University of Medical Sciences. We are grateful to physicians and personnel of Omid Oncology Hospital who helped us in conducting this study. Also we are thankful to Dr. Ali Gholamrezaei who helped us in data analysis and editing this report.

REFERENCES

1. 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.
2. Sonis ST. Oral mucositis. Anticancer Drugs 2011;22:607-12.
3. Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, *et al.* Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 2001;19:2201-5.
4. Gabriel DA, Shea T, Olajida O, Serody JS, Comeau T. The effect of oral mucositis on morbidity and mortality in bone marrow transplant. Semin Oncol 2003;30 (6 Suppl 18):76-83.
5. Barasch A, Elad S, Altman A, Damato K, Epstein J. Antimicrobials, mucosal coating agents, anesthetics, analgesics, and nutritional supplements for alimentary tract mucositis. Support Care Cancer 2006;14:528-32.
6. 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.
7. Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, *et al.* Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 2011;CD000978.
8. Donnelly JP, Bellm LA, Epstein JB, Sonis ST, Symonds RP. Antimicrobial therapy to prevent or treat oral mucositis. Lancet Infect Dis 2003;3:405-12.
9. Bjordal JM, Bensadoun RJ, Tunèr J, Frigo L, Gjerde K, Lopes-Martins RA. A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. Support Care Cancer 2011;19:1069-77.
10. 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.
11. Cerchietti LC, Navigante AH, Bonomi MR, Zaderajko MA, Menéndez PR, Pogany CE, *et al.* Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. Cancer 2002;95:2230-6.
12. Cerchietti LC, Navigante AH, Körte MW, Cohen AM, Quiroga PN, Villaamil EC, *et al.* Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: A pilot study. Pain 2003;105:265-73.
13. Cerchietti L. Morphine mouthwashes for painful mucositis. Support Care Cancer 2007;15:115-6.
14. Vayne-Bossert P, Escher M, de Vautibault CG, Dulguerov P, Allal A, Desmeules J, *et al.* 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;13:125-8.
15. Charbaji N, Schäfer-Korting M, Küchler S. Morphine stimulates cell migration of oral epithelial cells by delta-opioid receptor activation. PLoS One 2012;7:e42616.
16. World Health Organization. WHO handbook for reporting results for cancer treatment. Geneva, Switzerland: World Health Organization; 1979. Available from: http://www.whqlibdoc.who.int/offset/WHO_OFFSET_48.pdf [Last cited on 2012 Nov 06].
17. LeBon B, Zeppetella G, Higginson IJ. Effectiveness of topical administration of opioids in palliative care: A systematic review. J Pain Symptom Manage 2009;37:913-7.
18. Saroja G, Devi PS, Namrata R. Oral morphine solution as an oral rinse or

mouth gargle for mucositis pain. Indian J Palliat Care 2010;16:54-5.
19. Nielsen BN, Aagaard G, Henneberg SW, Schmiegelow K, Hansen SH, Romsing J. Topical morphine for oral mucositis in children: Dose finding and absorption. J Pain Symptom Manage 2012;44:117-23.
20. Martin JL, Koodie L, Krishnan AG, Charboneau R, Barke RA, Roy S. Chronic morphine administration delays wound healing by inhibiting immune cell recruitment to the wound site. Am J Pathol 2010;176:786-99.
21. Rook JM, Hasan W, McCarson KE. Morphine-induced early delays in wound closure: Involvement of sensory neuropeptides and modification of neurokinin receptor expression. Biochem Pharmacol 2009;77:1747-55.

Source of Support: Isfahan University of Medical Sciences, **Conflict of Interest:** None declared.