بسم الله الرحمن الرحيم

In the name of God

Isfahan University of medical science

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

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تقدیم

به پدرم یگانه اسوه ایثار

و مادرم اسوه مهربانی

و همسر بردبارم که در تمام مراحل همراه و یاورم بوده

و ثمره زندگیم: کوثر

با تشکر

از اساتید گرانمایه خانم دکتر سیمین همتی و جناب آقای دکتر عباس گوکی زاده که همواره وجود پرمهرشان را از من دریغ نکردند و در تمام مراحل این امر خطیر پشتیبانم بودند.

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"In the Name of God"

Dear Dr. Simin Hemati

It is my pleasure to inform you as corresponding author and your colleagues *" Dr. Mostafa Sarvizadeh (first author), Dr. Mohsen Meidani, Dr. Moghtada Ashouri , Dr. Mahnaz Roayaei , Dr. Armindokht Shahsanai "* that your manuscript entitled " *Morphine Mouthwash for Management of Oral Mucositis in Patients with Head and Neck Cancer"* has been accepted for publication in the journal of *"Advanced Biomedical Research"*, Vol 2; No 4.

Thank you for submitting your article to this journal. We look forward to receiving your next precious articles.

Best regards,

Shaghayegh Haghjooy Javanmard, MD .PhD

Editor in chief

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Morphine Mouthwash for Management of Oral Mucositis in Patients with Head and Neck Cancer

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Running Title: Topical Morphine for Oral Mucositis

Abstract

Background: Oral mucositis is a debilitating side effects 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 three hours, six times a day, for six days. Both groups received same dietary and oral hygiene instructions and care. Mucositis was graded at baseline and every three 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 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 the magic group ($p=0.008$).

Conclusions: Topical morphine is more effective and more satisfied by 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.

Keywords: mucositis, topical morphine, pain, head and neck carcinoma

INTRODUCTION

Cancer treatment-induced oral mucositis is a common and serious adverse effect that is occurred with 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% to 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. Beside cancer treatment dose, individual factors including patient's age, nutritional status, type of malignancy, oral hygiene, and smoking are some risk factors associated with development and severity of mucosal injury. [2],[1]

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 it can also affect cancer treatment outcome and patient's survival. Thus, the morbidity and economic consequences of mucositis are considerable. [2],[3],[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 at yet. [5],[6],[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. [8],[6] 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],[12],[13],[14] Such therapy has 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 the management of oral mucositis in patients with head and neck cancer.

METHODS

Patients and settings:

This unicenter, double-blinded, randomized, controlled study was conducted between Apr. and Jul. 2011 in Omid Oncology Hospital in Isfahan (Iran). The study population was selected from consecutive head and neck cancer adult patients 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.

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 three hours; six times a day. The morphine solution was prepared by the faculty of pharmacy under supervision of the Food and Drug Organization of the local Medical University. The magic group used a mouthwash contained 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 three 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 six days. Helped with 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 received 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 six to seven 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 to 7 weeks. Some patients were entered into this trial while still under cancer treatment while others have 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 if there was a requirement for parenteral or enteral support. Patients also were asked about if pain/discomfort relived by mouthwash and if so for how long (< 1 h, 1 to 2 h, > 2 h). 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 value of < 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 remained patients (mean age = 49.5±13.2, 63.3% female) who completed the trial were considered for analysis. As presented in Table 1, the two groups were similar in baseline characteristics.

After starting the treatment, a non-significant 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 1 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 satisfied by their treatments than 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 ones 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 more satisfied by patients than the magic mouthwash.

The results of our study were similar to previous ones, albeit some differences in drug dosage and pain 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 four to six days. The study showed significant pain relief by morphine lasting for about 2 h, and also significant placebo effects. Burning sensation by topical morphine caused one patient dropped out in this study. [14] In another controlled study, Cerchietti et al. compared topical morphine 2% with magic mouthwash (both solutions; 15 mL, every three hours, 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 three hours. 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 ten patients with severe oral mucositis, investigators used a high dose of topical morphine; 5mg in 15 mL, every 2 h, keeping in mouth for 5 min. Authors reported good pain relief lasting for 30 to 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) while 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 that highlights a short-lasting effect of this mouthwash. [12],[14] Therefore, further pharmacological trials are needed to find if it is possible to prolonged drug effect maintenance while decreasing the total dose and thus preventing possible side effects.

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Figure Legends

Figure 1: Trend of change in mucositis severity in the two studied groups, p = 0.05

Table 1. Demographic and baseline clinical characteristics of the patients

		Morphine n = 15	Control n = 13	P
Age, Year		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	**< 1h**	8	8	0.479**
	1 to 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

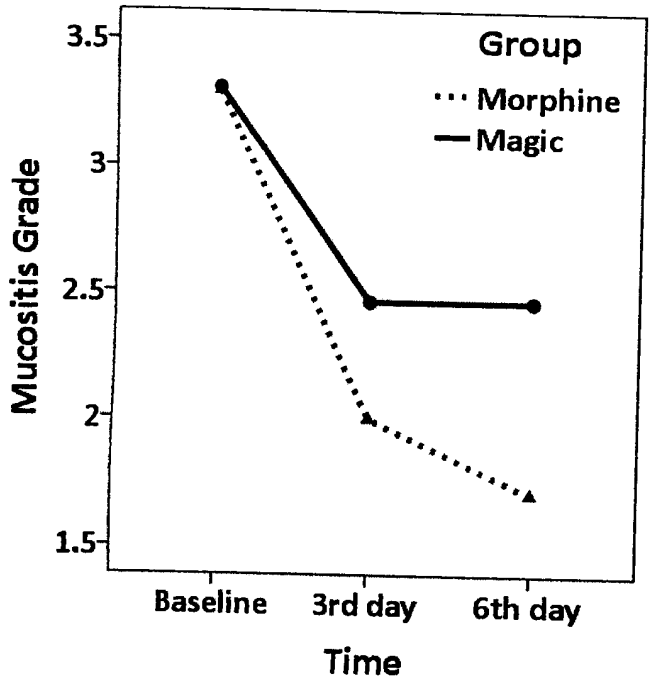

Figure 1: Trend of change in mucositis severity in the two studied groups, p = 0.05