

Mini Review

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Morphine Mouthwash in Oral Mucositis: A Mini Review

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ABSTRACT

Oral mucositis is a frequent adverse effect of chemotherapy and radiation therapy in cancer patients. The mucositis impacts overall quality of life (QoL) by producing pain with variable intensity leading to difficulty in oral intake, lack of sleep, etc. A multimodal therapy is advocated for management of oral mucositis in cancer patients and includes certain preventive and therapeutic interventions aiming at symptom control. The systemic analgesics are frequently used but may be associated various side effects associated with analgesics including opioid. The use of oral submucosal route for opioids has been advocated in view of existence of peripheral opioid receptors for its analgesic property. We review the literature for use of morphine mouthwash for management of painful oral mucositis.

KEYWORDS: Morphine; Mouthwash; Adverse effects; Mucositis; Cancer.

Cancer patients require multidisciplinary approach including chemotherapy and radiation therapy. Apart from other therapy associated side effects, oral mucositis remains a major concern for patient undergoing chemotherapy and/or radiation therapy.^{1,2} The incidence of mucositis ranges 15-90%.¹⁻⁴ The oral mucositis is associated with chemo-radiation of head and neck cancer primarily. The usual chemotherapeutic drug regimen for patients with unresectable, locally advanced cancer is combination of cisplatin and 5-fluorouracil (5-FU) with concurrent radiation.⁵⁻⁸ The 5-FU-based chemotherapies have more risk of mucositis.⁹⁻¹¹ The mucositis occurrence and its severity remain dose dependent (chemotherapeutic drugs, cumulative radiation exposure).^{8,11} Continuous infusion of chemotherapeutic drugs leads to increased risk of developing mucositis.^{8,12,13} The cancer patients receiving such combination of chemotherapeutic drugs along with radiation therapy remains at risk of painful mucositis which may result in interruptions of subsequent treatment. Thus, such symptom may not only adversely affect quality of life (QoL) but also affect the disease outcome.

The treatment related oral mucositis remains painful with variable intensity and at times severe pain leading to patient distress. It may affect overall QoL with decrease oral intake, painful deglutition, affect sleep and may result in serious clinical complications.^{4,9,11} So such painful oral mucositis requires immediate intervention with various analgesics including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. However, use of NSAIDs requires caution in view of chemotherapy induced hematopoietic suppression and also may not be adequate for control of moderate to severe pain.¹ Thus, need of opioid analgesics is frequently required based on severity of pain of oral mucositis.^{1,2} During the acute mucositis, oral intake remains painful and thus necessitating the intravenous administration of narcotic analgesics. Opioid administration is associated with various side effects commonly include sedation, dizziness, nausea, vomiting, constipation, respiratory depression, physical dependence and tolerance.^{1,3} Therefore, effective use of systemic opioid requires balancing between pain relief and the undesirable side effects. The use of other adjuvant therapy may help in reducing the opioid requirement for optimal pain relief.

The use of topical anesthetics along with oral hygiene is useful for symptom management of painful oral mucositis.¹⁴ Though the robust evidence do not exists, but mucosal coating

agents with analgesic properties have been reported to be effective for management of painful oral mucositis. The opioid analgesics like morphine produces its analgesics effects by binding to opioid receptors in the central nervous system (CNS) and the peripheral terminals of afferent nerves.¹⁵⁻¹⁷ The literature reports *via* various basic and clinical research about the analgesic efficacy of local application of exogenous opioid for management of painful inflammatory conditions.¹⁸⁻²¹ The oral and parenteral analgesic effect of opioid are well established with robust evidence, but no unified approach with concrete evidence exists for topical treatments.^{3,9,22} It has been shown that the opioid receptors exists in peripheral sensory neurons and thus can be activated by topical analgesics resulting pain relief.²³ It has also been reported that oral epithelial cells contain opioid receptors.²⁴ The opioid ligands with a preference for μ -receptors are generally

most potent when applied locally.¹⁵ Morphine has a predictable low absorption through the trans-mucosal route. The sublingual as well as trans-mucosal absorptions of drugs are dependent on both pH level and lipid solubility.^{25,26} Therefore, morphine being less lipophilic (partition coefficient 0.00001) and ionized at the low pH level of the oral cavity (morphine pKa at 37 °C=7.9) is poorly absorbed.^{27,28} Evidence of the activation of opioid receptors due to inflammatory change in tissues has led to the exploration of the potential analgesic effect of opioid peripherally.^{29,30} This suggest that morphine mouthwash would provide optimal analgesia without getting absorbed systemically and thus less adverse effects. The literature supports the effectiveness of morphine mouthwash for treatment of oral mucositis in cancer patients (Table 1). The overall literature suggests that morphine mouthwash (1-2%) provide effective pain relief for 30-120 min-

Study	Intervention	Study design	Results	Adverse effects	Remarks
Mostafa et al ³¹	30 patients with oral mucositis Grade 3 or 4 received morphine sulfate 2% or magic solution (magnesium aluminum hydroxide, viscous lidocaine, and diphenhydramine), 10 ml for every 3 h, six times a day, for 6 days.	Prospective randomized study	At the 6 th day, more reduction was observed in mucositis severity in the morphine compared with magic group ($p=0.045$). Patients in the morphine group were more satisfied by their treatments than those in the magic group ($p=0.008$).	Nil reported	Topical morphine is more effective and more satisfactory to patients than the magic mouthwash in reducing severity of oral mucositis.
Wayne-Bossert P et al ³²	9 patients with oral mucositis of at least grade II received 15 ml of 2% morphine mouthwash or placebo, 6 times a day, for 4-6 days.	Randomized double-blinded crossover study	Pain alleviation 1 hour after mouthwash was significantly influenced by the gesture of the mouthwash ($p<0.001$) with either morphine or placebo) and almost by the efficiency of morphine ($p=0.020$). Duration of pain relief was 123.7±98.2 min with morphine.	Burning sensation by topical morphine caused one patient to drop out from the study	Authors suggest a possible analgesic effect of topical morphine.
Cerchiotti et al ³³	26 patients were randomly assigned to morphine mouthwash (MO group=14 patients) or magic mouthwash (MG group=12 patients)	Randomize, controlled, parallel comparative study	Duration of severe pain was 3.5 days less in the MO group compared with the MG group ($p= 0.032$). Intensity of oral pain was also lower in the MO group compared with the MG group ($p=0.038$). More patients in the MG group needed supplementary (oral or parenteral) analgesia compared with the MO group ($p=0.019$). There was a significant difference in duration of severe functional impairment ($p=0.017$).	MG group reported nausea (1), loss of taste (3), viscous saliva (2), dry mouth (2) and excessive anesthesia (1) MO group reported dry mouth and a burning sensation in 1 patient.	MO is a simple and effective treatment to decrease the severity and duration of pain and the duration of functional impairment
Saroja S et al ³⁴	10 patients rinsed with 5 mg morphine sulphate in 15 ml of diluent solution every 2 hour and instructed to keep it in mouth for 5 min and then spit it out.	Open label study	Good pain relief lasting for 30-60 min.	Patients reported difficult rinsing initially because of the restricted movement of mouth opening due to trismus.	Oral morphine rinse resulted in effective of pain relief and improved opening of mouth in cancer patients with mucositis.
Nielsen BN et al ³⁵	12 children received oral morphine as atomizer oral spray. The morphine spray was retained in mouth for 10 seconds before spitting.	Prospective observational sequential study.	Pain decreased by 36% after 30 min of topicalization. The serum morphine and its metabolites levels were well below the effective analgesics levels.	None reported	Oral morphine topicalization provides effective pain relief.
Leandro CA et al ³⁶	Conducted in two blocks: dose response and efficacy/safety study. Ten patients received 15 mL of 1-2% morphine oral rinse. Of the 22 patients, serum morphine concentration was estimated in 5 representative patients.	Prospective randomized	Oral rinse with 2% morphine provides better pain relief as compared to 1% (80% vs. 60%, $p=0.024$). No systemically active detectable morphine concentration was observed.	One patient in the 1% group and 2 in the 2% group complained of a local side effect like burning/itching sensation.	Morphine oral rinse provides optimal pain relief without systemic absorption.

Table 1: Reported literature for use of morphine mouthwash for oral mucositis.

utes. Thus, mouthwash may be repeated every 2 hourly along with other components of multimodal management.

To conclude, we suggest that morphine mouthwash may be considered as an effective management strategy as a part of multimodal treatment of oral mucositis in cancer patients receiving chemotherapy and/or radiation therapy. The effective pain relief may be achieved with 10-15 ml of 2% morphine aqueous solution and can be used 2-3 hourly as mouthwash in patients with mucositis pain.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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