

# Effect of Topical Morphine (Mouthwash) on Oral Pain Due to Chemotherapy- and/or Radiotherapy-Induced Mucositis: A Randomized Double-Blinded Study

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## Abstract

**Purpose:** The objective of the study was to determine if mouthwashes with a morphine-containing solution decrease oral pain associated with radiotherapy- and/or chemotherapy-induced oral mucositis (OM).

**Methods:** Randomized double-blinded crossover study to evaluate the effect of topical oral application of 2% morphine solution in patients suffering from radiotherapy- and/or chemotherapy-induced OM. Participants assigned to either the morphine solution or a placebo mouthwash received one of the solutions days 1–3 and were then switched over to the other treatment for days 4–6.

**Results:** Nine patients were randomized in both groups. All patients (mean age,  $55.1 \pm 3.0$ ) except one had head and neck cancers. Mean intensity of pain associated with mucosal injury (World Health Organization [WHO] mucositis  $\geq 2$ ) was on a 10-point visual analogue scale:  $6.0 \pm 2.7$ ). The analysis of variance (ANOVA) model that included morphine or placebo, day and time of mouthwash, and mouthwash effect shows that 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 (standard deviation [SD]  $\pm 98.2$ ) minutes for morphine. Most other reported symptoms were present at the baseline and were probably associated with the main disease and not secondary to the morphine mouthwash.

**Conclusions:** Our results suggest a possible analgesic effect of topical morphine in line with previous studies. However, more efforts must be made for the adjustment of systemic analgesics and the development of new alternatives to treat locally OM-associated pain.

## Introduction

ORAL MUCOSITIS (OM) is a common side effect of chemotherapy and radiation therapy, with an incidence ranging from 15%–90%.<sup>1–4</sup> Associated pain can frequently lead to the administration of systemic opioid analgesics and artificial nutrition and to the interruption of the treatment protocol.<sup>4–7</sup> For the treatment of pain, the efficiency of systemic opioids is well established, but no unified approach exists for topical treatments.<sup>3,5,8–15</sup> Evidence of the activation of opioid receptors due to inflammatory change in tissue has

led to attempts to explore the potential analgesic effect of opioids peripherally.<sup>16,17</sup> Cerchiatti et al.<sup>18,19</sup> showed in two studies that topical morphine decreased pain induced by mucositis secondary to radiotherapy or chemotherapy treatments. In the first one, 26 patients were enrolled and randomly assigned to “magic” mouthwash or to a morphine mouthwash.<sup>18</sup> The results showed a significant decrease in the duration and intensity of pain in the group with morphine. The second study that analyzed the dose-response relationship (1% and 2%) concluded that a concentration of 2% was more effective.<sup>19</sup>

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We report on a randomized, double-blinded, placebo-controlled, crossover pilot study assessing the analgesic effects of morphine applied topically to painful oral mucositis. We tested the hypothesis that pain alleviation will significantly decrease after morphine mouthwash.

### Patients and Methods

The study was approved by the local Ethic and Research Committee. Patients were included if they were older than 18 years, treated either in a hospitalized or ambulatory setting in the Geneva University Hospitals, received chemotherapy or radiotherapy causing OM and oral pain. The associated mucosal injury needed to be at least of grade 2 (World Health Organization [WHO] grading scale of mucositis) and the patient had to sign a written informed consent.<sup>20</sup> Patients were not included if they presented some risk of swallowing the mouthwash solution (determined before inclusion by a recovery of less than 90% of the 15 mL of water solution used for testing), if they had some cognitive impairment, and if they refused to stop mouthwash with local anesthetic. Fifteen milliliters of morphine 2% (30 mg morphine chlorhydrate) or placebo (quinine diHCl at 50 mg/15 mL to mimic the bitter taste of morphine) were administered regularly 6 times per day. Patients were instructed not to swallow during rinses and to hold mouthwash for 2 minutes. General basic oral care was offered to all the patients. Systemic and rescue analgesic medication was prescribed according to the WHO scale by the physician in charge of the patient. The trial was randomized double-blinded crossover in design. Randomization was done by blocks of 5, using the Latin square method. Patients were treated for 3 days after which they were crossed over to the alternative treatment for the next 3 days.

The principal end point was the mean of the difference of pain alleviation before and 1 hour after mouthwash in the two arms.

Minor end points were the duration of pain relief, the requirement of supplementary systemic analgesics, and the severity of other local symptoms probably related to morphine mouthwash.

A complete assessment with the measure of the intensity of pain, the severity of dysphagia, the severity of other local symptoms, and the oral examination were performed on the day of inclusion, day 4, and day 7 by a research nurse. Patients completed a daily diary with the assessment of oral pain intensity with a 10-cm visual analogue scale (VAS) before and 1 hour after each mouthwash. An increase in the current analgesic medication and the need for supplemental doses were documented. A total sample size of a 2×2 crossover design of 14 had 95% power to detect a difference in mean pain score of 2.000 points on the VAS (the difference between an arm morphine mean, of 3.000 and an arm placebo mean, of 1.000) when the common standard deviation was 1.000 and using a two-group *t* test with a 0.050 two-sided significance level.

Unpaired Student's *t* test was used to compare mean scores of the visual analogue scale between the two different arms at specific time points. Mean pain alleviation after mouthwash has been compared using analysis of variance (ANOVA) with a repeated measure design first between both arms, then be-

tween morphine and placebo. A carryover effect was calculated. The study has been registered NCT00613743.

### Results

During the study period (May to October 2007), 20 patients were approached for inclusion. Five patients refused to participate for the following reasons: 3 did not want to take morphine and 2 refused to stop mouthwashes with local anesthetics. Three patients were ineligible because OM WHO grade 2 was not confirmed on oral examination and 1 because he failed the swallow test. The study was closed after 11 patients were included because of the difficulty of finding eligible patients. Finally, 5 patients were randomized to the morphine arm (that received first the morphine solution) and 6 to the placebo arm. One patient in each arm withdrew on day 1 of the study: a patient complained of immediate severe mouth burning sensation after the first mouthwash with morphine and another became afraid to swallow morphine. Mean age ( $\pm$ standard deviation [SD]) of the 9 included patients (males: 2) was  $55.1 \pm 3.0$ . Two patients were hospitalized. Primary cancer site was head/neck ( $n=8$ ) and breast ( $n=1$ ). Mini Mental Status examination score was 30 in all patients. Nine patients received chemotherapy (cisplatin [ $n=8$ ], doxorubicin hydrochloride [ $n=1$ ]); 7 patients radiotherapy. Eight and 1 patients had a mucositis WHO grade 2 and 3, respectively. Severity of dysphagia was: those able to eat solid food ( $n=0$ ), able to eat soft food ( $n=2$ ), able to swallow only liquids ( $n=7$ ), oral alimentation was impossible ( $n=0$ ). One patient was fed by enteral nutrition. Although 6 patients had a pain score higher than 5 on the VAS at the time of inclusion, 9 patients received paracetamol, 5 nonsteroidal anti-inflammatory drugs (NSAIDs), and 3 opioids.

Seven patients took only 4 mouthwashes daily instead of 6. The first ANOVA model that included morphine and placebo arm, day and time of mouthwash, and mouthwash effect shows that pain alleviation 1 hour after mouthwash was significantly influenced by the arm (morphine or placebo;  $p=0.000$ ), the gesture of mouthwash ( $p=0.000$ ), and almost by the day ( $p=0.038$ ). The second ANOVA model that included morphine or placebo, day and time of mouthwash, and mouthwash effect shows that 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 ( $p=0.020$ ). However there was no effect observed between the different mouthwashes on the same day ( $p=0.849$ ) nor between the different days ( $p=0.522$ ).

There was an important sequence effect with a carryover from the period with morphine to the period with placebo ( $p=0.000$ ; Fig. 1). Pain relief lasted respectively (mean  $\pm$  SD)  $124 \pm 98$  minutes for the morphine mouthwash and  $126 \pm 81$  minutes for placebo ( $p > 0.01$ ). Table 1 summarizes the secondary end points. Intensities of symptoms were not statistically different during the 6 days of the study or between the two arms (analysis of variance). Most reported symptoms present at the baseline were probably associated with the main disease and the associated treatments and did not improve during the study time. Severity of dysphagia was similar during the 6 days of the study.

Three patients in the arm that received morphine during the first phase used daily breakthrough doses during all the

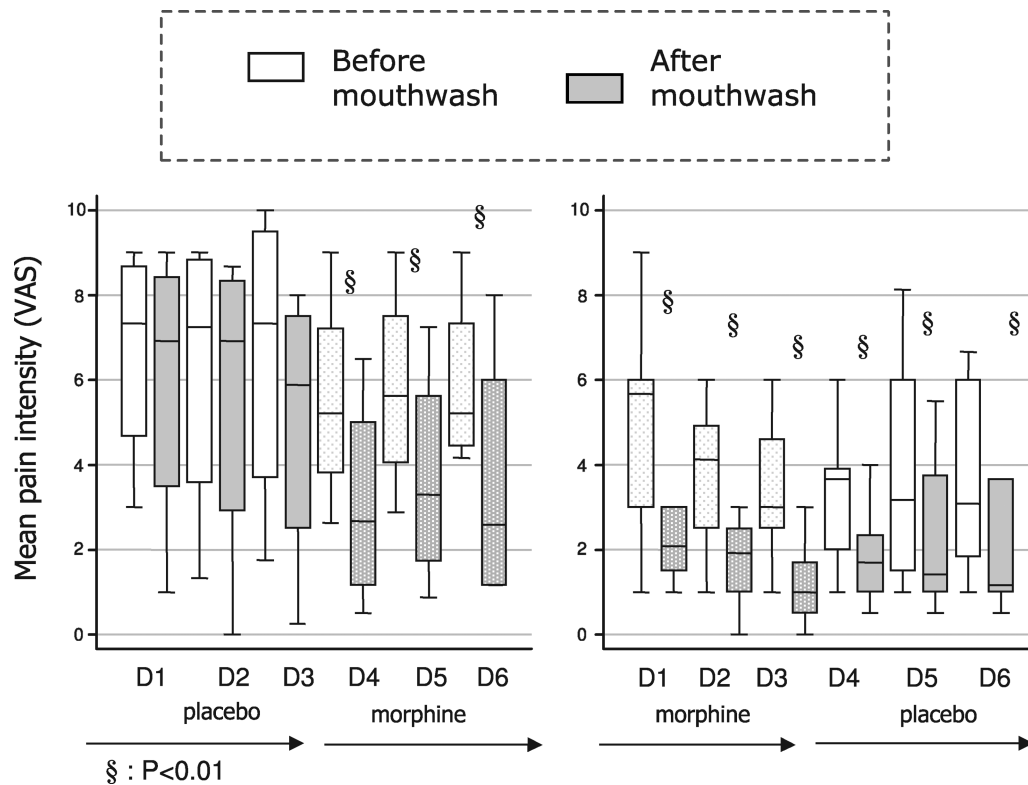


FIG. 1. Mean intensity measured before and after mouthwash.

study time: one took acetaminophen and two patients were treated with oral morphine. There was no difference in the patients' use of around the clock analgesia and the use of rescue medication during the two periods. No systematic adverse effects appeared specifically attributable to morphine. No patients developed microbiological infection during the study period. No one inadvertently swallowed the solution.

**Discussion**

Our results suggest a possible analgesic effect of topical morphine in line with previous studies.<sup>18,19</sup> However, completion of the study was hampered by the difficulty of finding enough eligible patients. It was a challenge to identify ambulatory or hospitalized patients in different settings, with normal cognitive function, who were reliably not swallowing the solution.

The probable carryover effect, preclude any comparison between morphine and placebo, as patients that received morphine during the first period had also a statistically significant increase in pain alleviation during the second period of the study with placebo. It might be that patients receiving morphine initially later had greater likelihood for expectation of efficacy to render the placebo useful as well. Another putative explanation could be related to the fact that peripherally acting opioids modulate the proliferation of inflammatory cells and modify the time course of the intensity of pain.<sup>21</sup> However, in contrary to Cerchietti we could not demonstrate a discernible pattern on average pain rating during the day and between the days, highlighting a short-lasting effect of mouthwash.<sup>19</sup>

This short-lasting effect of local morphine administered by mouthwash also differs from the report of good analgesic peripheral effects of local opioid applied in painful skin ulcers of malignant and not malignant origin.<sup>16,17,22-26</sup>

TABLE 1. SECONDARY END POINTS AT DAY 1, DAY 4, AND DAY 7

	Placebo-morphine (n=5)				Morphine-placebo (n=4)				p	p
	Day 1	Day 4	Day 7	p	Day 1	Day 4	Day 7	p		
Pain (VAS 0-10)	6.8 ± 3.4	3.9 ± 2.0	6.5 ± 1.3	0.438	5.4 ± 2.3	4.2 ± 2.3	4.4 ± 3.0	0.342	0.294	
Nausea (VAS 0-10)	2.5 ± 5.0	1.0 ± 2.0	4.8 ± 5.5	0.543	0.0 ± 0.0	1.8 ± 4.0	0.6 ± 1.3	0.275	0.191	
Mouth dryness (VAS 0-10)	6.1 ± 4.3	5.8 ± 4.3	5.5 ± 4.2	0.665	6.4 ± 1.1	6.6 ± 1.3	3.0 ± 2.8	0.754	0.712	
Lost of taste (VAS 0-10)	8.0 ± 2.8	6.6 ± 2.6	8.0 ± 2.8	0.224	6.4 ± 2.9	5.0 ± 3.3	2.2 ± 2.0	0.265	0.101	

VAS, visual analogue scale.

In conclusion effort must be made for the adjustment of systemic analgesics and new alternatives have to be developed to treat local pain associated with OM.

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### Author Disclosure Statement

No competing financial interests exist.

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