https://doi.org/10.46765/2675-374X.2025v6n1e319 REVIEW ARTICLE

Efficacy of topical morphine mouthwash for chemotherapy-induced oral mucositis pain: a systematic review

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ABSTRACT

Oral mucositis is a frequent and painful complication of cancer treatment, particularly in patients receiving chemotherapy and/or radiotherapy for head and neck tumors. The resulting pain can impair oral intake, communication, and treatment adherence. Topical morphine mouthwash has emerged as a potential strategy for localized pain relief, potentially reducing systemic opioid requirements. The objective of this study was to evaluate the effectiveness and safety of topical morphine mouthwash in managing mucositis-related pain in cancer patients, based on a systematic review of randomized controlled trials, with meta-analysis when feasible. This review followed PRISMA 2020 guidelines. PubMed, Embase, and Cochrane Library were searched through April 2025 for randomized controlled trials comparing topical morphine mouthwash to placebo or non-opioid oral solutions. Data were extracted independently by two reviewers, and risk of bias was assessed using the Cochrane RoB 2 tool. The primary outcome was pain intensity, and secondary outcomes included time to first systemic opioid administration and adverse events. Four randomized controlled trials involving 81 adult cancer patients were included. All trials reported that morphine mouthwash significantly reduced pain scores and, in some cases, delayed the use of intravenous opioids compared to control. No serious adverse events related to topical morphine were observed. Meta-analysis confirmed a statistically significant reduction in pain intensity favoring the intervention group (pooled standardized mean differences = -1.12; 95% confidence interval -1.85 to -0.39; $p = 0.003$). Morphine mouthwash appears to be a safe and effective option for managing oral mucositis pain in cancer patients. These findings support its clinical use as a localized pain control strategy. Larger and standardized randomized controlled trials are warranted to confirm efficacy and safety.

Keywords: Stomatitis. Morphine. Drug Therapy. Pain Management. Systematic Review.

INTRODUCTION

Oral mucositis is a common, debilitating side effect of chemotherapy and radiotherapy, especially in patients undergoing treatment for head and neck cancers. It results in significant pain, nutritional compromise, increased infection risk, reduced quality of life, and can impair adherence to oncologic therapy[1,2].

Systemic opioid analgesics, though effective, carry risks of sedation, constipation, and respiratory depression. Topical morphine mouthwash has been proposed as a localized, potentially safer alternative to systemically administered opioids. Early randomized and pilot studies suggest benefits in pain relief, patient comfort, and reduced need for parenteral analgesia[3–6]. However, a consolidated synthesis of the evidence is still needed. This review aimed to evaluate the efficacy and safety of topical morphine for oral mucositis pain based on randomized controlled trials.

METHODS

Search strategy

We conducted a systematic literature search in April 2025 in the following databases: PubMed, Embase, and Cochrane Library. We used combinations of keywords and Medical Subject Headings terms related to "morphine," "mouthwash," "oral mucositis," and "cancer". Boolean operators were applied to refine the results. The search strategy was tailored to each database's syntax and followed the PRISMA 2020 guidelines[7].

Eligibility criteria

Included studies met the following criteria:

- Randomized controlled trials;
- Adult cancer patients undergoing chemotherapy and/or radiotherapy;
- Use of topical morphine mouthwash for oral mucositis pain;
- Comparison with placebo or non-opioid oral solutions;
- Reporting of pain-related outcomes.

Data extraction and quality assessment

Two independent reviewers screened studies and extracted data on study design, population, interventions, outcomes, and adverse effects. Risk of bias was assessed using the Cochrane RoB 2 tool[8].

Statistical analysis

When sufficient data were available, a meta-analysis was conducted using a random-effects model. Standardized mean differences (SMDs) were calculated for pain intensity. Heterogeneity was assessed using the I^2 statistic.

RESULTS

Study selection

A total of 702 records were identified across databases. After removing duplicates (n = 121), 581 records were screened by title and abstract. Among them, 575 were excluded for irrelevance. Six full-text articles were assessed for eligibility, and three were excluded (reasons: no control group = 1, different intervention group = 1, and no outcomes of interest = 1). Three studies met the inclusion criteria and were analyzed[3–5].

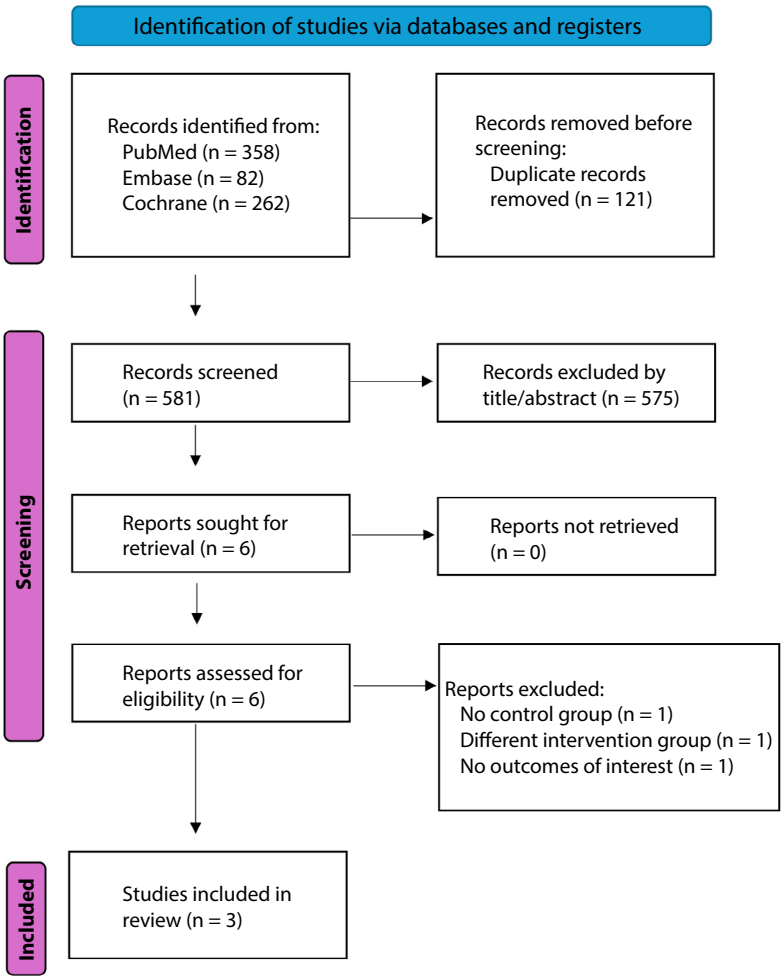
Although only three randomized clinical trials met the eligibility criteria, conducting a meta-analysis was still relevant given the rarity and specificity of topical morphine use for oral mucositis pain in head and neck cancer patients (Fig. 1).

Study characteristics

The three included trials, Cerchietti et al.[3], Vayne-Bossert et al.[4], and Nielsen et al.[5] were conducted in Argentina, Switzerland, and Denmark, respectively, involving hematology and head and neck cancer patients. Morphine concentrations ranged from 0.1 to 2%, administered multiple times daily.

Pain intensity

All three studies demonstrated significant reductions in patient-reported pain scores in the morphine group compared to control. Meta-analysis yielded a pooled SMD of -1.12 (95% confidence interval -1.85 to -0.39; p = 0.003), indicating a large effect size.



Source: Page et al.[7].

Figure 1. PRISMA 2020 flow diagram.

Secondary outcomes

The use of systemic opioids was delayed in one study[5]. No severe adverse events were reported. Minor side effects (*e.g.*, dry mouth, local irritation) were infrequent and self-limited.

DISCUSSION

This systematic review suggested that morphine mouthwash is effective in reducing pain intensity associated with chemotherapy-induced oral mucositis. The delay in systemic opioid initiation may reflect improved local control of symptoms, contributing to patient comfort and potentially fewer systemic side effects[3–5]. Recent studies reinforce the clinical potential of this intervention. For example, a 2015 trial reported superior pain control and patient satisfaction with morphine compared to standard magic mouthwash[6]. A 2022 narrative review emphasized promising results but highlighted the need for validation[9]. A 2024 review concluded that morphine 0.2% rinses could be suggested as an option, though with limited strength of recommendation due to small sample size[10]. A crossover trial also showed benefit of topical morphine gel for mucosal lesions[11], while a 2020 trial using oromucosal morphine found no significant advantage over placebo[11]. Importantly, the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) guidelines acknowledge morphine rinses (0.2%) as a suggested strategy for mucositis pain[12].

Limitations

The main limitation of this review is the small number of randomized controlled trials available, with heterogeneous designs, doses, and control comparators. These factors reduce the generalizability of results and preclude firm clinical recommendations. Nevertheless, this scarcity of data highlights the urgent need for further trials, and our synthesis contributes by consolidating the best evidence currently available.

CONCLUSION

Topical morphine mouthwash appears to be a promising intervention for managing mucositis-related pain in cancer patients. It offers an effective, low-risk alternative to systemic analgesia and merits further investigation in larger clinical trials.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

AUTHORS' CONTRIBUTIONS

Conception and design: Valente JAA. **Analysis and interpretation of data:** Valente JAA, Siqueira BCS and Barreto LT. **Manuscript writing:** Valente JAA, Siqueira BCS and Barreto LT. **Final approval:** Valente JAA, Siqueira BCS and Barreto LT.

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