J Exp Pathol. 2024;5(1):24-30.

Journal of Experimental Pathology Commentary

Methylene Blue Oral Rinse: An Effective Alternative for the Treatment of Pain in Oral Mucositis during Head and Neck Cancer Treatment

Reuben Horace[1], Sara P. Roldan[2], Carlos J. Roldan[3,4*]

[1]Department of Emergency Medicine, Duke University Medical Center, Durham, NC, USA

[2]Baylor University, Waco, Texas, USA

[3]Department of Pain Medicine, The University of Texas MD Anderson Texas Center, Houston, Texas, USA

[4]Department of Emergency Medicine, McGovern Medical School, Houston, Texas, USA

*Correspondence should be addressed to Carlos J. Roldan, croldan@mdanderson.org

Received date: June 13, 2024, **Accepted date:** August 07, 2024

Citation: Horace R, Roldan SP, Roldan CJ. Methylene Blue Oral Rinse: An Effective Alternative for the Treatment of Pain in Oral Mucositis During Head and Neck Cancer Treatment. J Exp Pathol. 2024;5(1):24-30.

Introduction

While the general population perceives mucositis as soreness and inflammation of the mouth or gut, the cancer patient experiences it as one of the most dreaded and debilitating side effects of therapy. Mucositis can be painful, but especially oral mucositis (OM) stands as a prevalent adverse consequence of cancer treatment impacting the oral, pharyngeal, and esophageal mucosa [1]. The etiology and severity of OM lesions exhibit variability contingent upon the modality of treatment employed. For individuals undergoing chemotherapy, the incidence of OM approximates 40%, with a proportional increase noted in accordance with the chemotherapy agent and the number of therapy cycles [2]. In contrast, patients subjected to radiation therapy (RT) targeting the head and neck region present with an OM incidence exceeding 80%, a figure that may approach 100% among those undergoing modified fractionation and/or concurrent chemotherapy approaches [3]. The clinical spectrum of OM encompasses progressive oral pain, dysphagia, and odynophagia. Concurrently, patients may experience a diminished tolerance for oral intake, precipitating dehydration, sarcopenia, weight loss, and overall debilitation. The concomitant burden of unplanned hospitalizations, necessitating enteral hydration and nutrition via gastric feeding tubes, engenders heightened healthcare costs and jeopardizes the continuity of cancer treatment, compromising the outcome of oncologic patients [4].

Despite the advent of promising preventative strategies, their clinical efficacy remains circumscribed [5]. Attenuation of pain emerges as a paramount objective, holding a pivotal role in cancer treatment. Conventional palliative modalities encompass topical anesthetics, mucosal protective agents, corticosteroids, antihistamine mouthwashes, systemic opioids, non-steroidal anti-inflammatory drugs, and adjuvant analgesics such as gabapentin [6]. Nevertheless, the recurrent recourse to escalating doses of systemic opioids, inclusive of intravenous administration and patient-controlled analgesia devices, persists as a commonplace response to refractory OM pain, notwithstanding adequate safety standards [7]. Drawing upon its structural properties, topical methylene blue solution has garnered attention for its therapeutic utility across diverse cutaneous pain syndromes, such as anal fissures and genital herpes. As an oral rinse, it has demonstrated efficacy in ameliorating pain intensity and reducing opioid requisites vis-à-vis conventional therapy alone for individuals afflicted by oropharyngeal mucositis secondary to various cancer treatments [8]. The analgesic efficacy of methylene blue is attributed to its multifaceted modulation of nociceptive pathways, encompassing peripheral neurolysis, inhibition of nitric oxide synthetase, guanylyl cyclase, and histamine, culminating in an overarching antinociceptive effect [9].

The study in which this narrative review is based on looked to further substantiate the proposition that methylene blue mouthwash represents a viable and safe adjunctive

therapeutic option for mitigating OM-associated pain in patients afflicted by head and neck cancer (HNC) undergoing RT, either as a standalone modality or in conjunction with concurrent chemotherapy.

Statistical analysis

Summary statistics, including the mean, standard deviation, median, and range, were provided for continuous variables such as age, NRS, and OF, and frequency counts and percentages are provided for categorical variables such as gender. The chi-square test was used to evaluate the association between categorical variables. The Wilcoxon signed-rank test was used to evaluate the change in pain scores from before to after treatment. The Wilcoxon rank sum test was used to evaluate the difference in continuous variables. A boxplot was generated as a visual aid to show the changes of continuous variable between patient groups.

Participants and therapeutic agent

This study included patients of any age, sex, HNC diagnosis, and stage of disease. All patients were receiving radiation therapy alone, or in combination treatment modalities. Completion of the follow-up was defined as an adequate medical records documentation from the initial use of MBOR to its discontinuation. The therapeutic mix was a dilution at 0.05% in water or normal saline solution, provided by institutional compounding pharmacy.

Outcome measures

The study measured patient-self reported numerical rating scale (NRS) scores for oral pain using a scale from 0 (no pain) to 10 (worst possible pain). It also measured changes in oral function burden (OFB) based on an assessment tool on a 7-point scale from 0 (normal) to 6 (total inability to eat, swallow, or talk, with each category scored as unable = 2, difficult = 1, and able = 0 and summed). Both the NRS and OFB scores were tabulated before starting MBOR, immediately after the first use, and until pain control was achieved (**Table 1**). Information was obtained from the medical records. Notes from patients' diaries were frequently documented on the medical encounters.

Discussion

Although uncontrolled oral pain is the final pathway to failed therapy in OM, current efforts seem to focus on the prevention and correction of the histological damage. Overall, the use of

Table 1. Patient demographic characteristics (n=58).

Variable	Category	Frequency	Percentage
Gender	*Female*	*19*	*33%*
	Male	*39*	*67%*
Cancer	*SCC of the tongue*	*26*	*45%*
	SCC of the tonsil	*14*	*24%*
	SCC of the oral mucosa	*3*	*5%*
	SCC of the nose	*2*	*3%*
	SCC of the gums	*2*	*3%*
	SCC of the larynx	*1*	*2%*
	SCC of the mandible	*1*	*2%*
	SCC of the orbit	*1*	*2%*
	Adenocarcinoma of the salivary gland	*2*	*3%*
	Adenocarcinoma of the sinus	*2*	*3%*
	Adenocarcinoma of the tongue	*3*	*5%*
	Adenocarcinoma of the palate	*1*	*2%*
Therapy	*Chemotherapy and radiation*	*23*	*40%*
	Surgery, chemotherapy, and radiation	*15*	*26%*
	Surgery and radiation	*13*	*22%*
	Radiation alone	*7*	*12%*

non-opioid systemic analgesics in this population is of limited use due to factors such thrombocytopenia, neutropenia, inability to use the oral route, renal and liver failure, presence of other comorbidities and polypharmacy, which can preclude the use of non-steroidal anti-inflammatory drugs and acetaminophen. Despite common side effects and well documented risk, the mainstay of managing pain in OM has usually relied on the use of opioid analgesics, frequently, using a patient-controlled analgesia device. Methylene blue oral rinse (MBOR) is emerging as a safe, effective, inexpensive, and widely available alternative which has been studied in clinical trials and reported in observational studies such as the one currently described. This study included patients of any age, sex, head and neck cancer diagnosis, stage of disease, as well as any combination of modalities for cancer treatment. All patients had uncontrolled pain from OM despite conventional treatment including, coating and anesthetic agents in oral rinses and systemic analgesics of all kinds.

Procedures

Patients are instructed to swish and gargle the MBOR mix every 6 hours until pain control is achieved (**Figure 1**). Detailed instructions are given about safety, toxicity, side effects, and precautions. Patients are advised to keep a diary of pain levels before and after oral rinsing, and medications used and their effect on their ability to eat and talk. Since MBOR is not commercially available, it must be mixed at a compounding pharmacy.

Clinical efficacy

The findings of this study underscored the safety and efficacy of 0.05% MBOR in OM pain associated with RT or combined chemotherapy and RT for HNC. Notably, the substantial reduction in mean NRS pain scores post-MBOR administration (mean reduction of 5.53; P<0.0001) attests to its analgesic potency, surpassing that of conventional rinses and systemic analgesics (**Figure 2**). Furthermore, objective assessment via OFB scores revealed a noteworthy mean reduction (mean reduction of -3.03; P<0.0001), further corroborating its clinical efficacy (**Figure 3**).

Therapeutic percutaneous feeding tube utilization

While the clinical indications for percutaneous endoscopic gastrostomy (PEG) tubes are multifactorial, their necessity signifies the magnitude of RT or chemo-RT toxicity [10]. Published data has shown that as many as 60% to 70% of patients receiving treatment with RT for advanced HNC will benefit from a feeding tube at some point during their treatment [11]. Notably, in this study a subset of patients previously reliant on PEG tubes, transitioned to oral feedings following MBOR-induced pain alleviation. Additionally, the low proportion of patients necessitating PEG tube insertion despite MBOR usage underscores its potential to mitigate severe malnourishment (**Figure 4**).

Topical mechanism of methylene blue

Methylene blue's topical analgesic properties have been harnessed across various tegument pain syndromes [12], attributed to its inhibition of peripheral axons, antioxidant, and anti-inflammatory effects [13]. Mechanistically, when utilized as an oral rinse, methylene blue is postulated to denature nociceptive nerve endings within OM lesions, inhibit the nitric oxide inflammatory pathway, and block N-methyl-D-aspartate receptors [14-16].

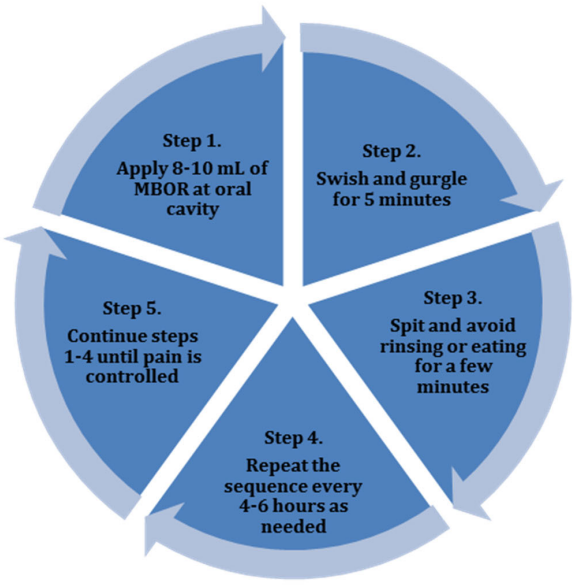

Figure 1. step by step to the use of MBOR.

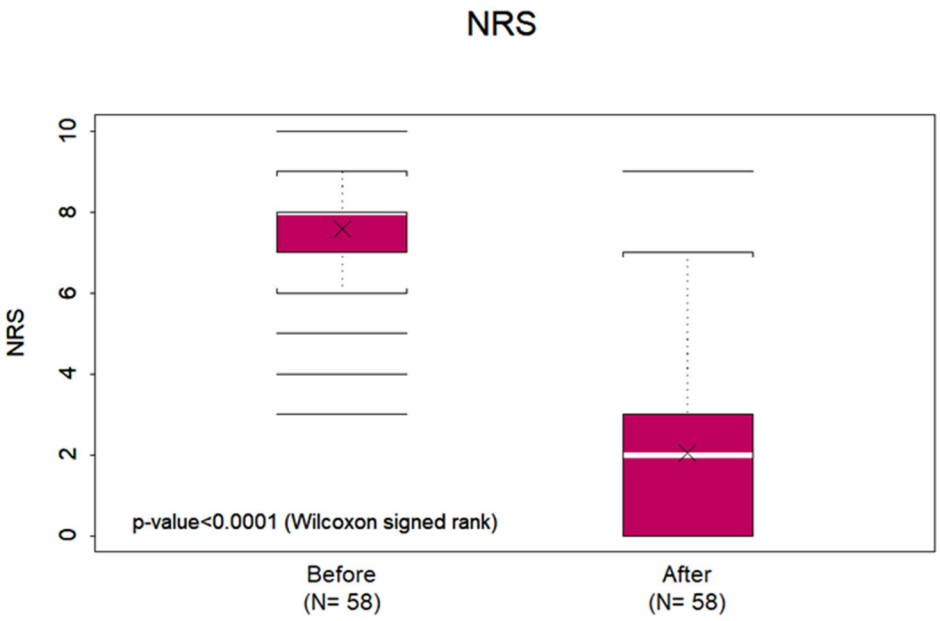

Figure 2. Numerical rating scale (NRS) pain scores before and after treatment with methylene blue oral rinse. The graph shows the mean (X inside the bar); median (white bar inside the box); interquartile range (entire box); 75th percentile + 1.5 interquartile range or maximum value, whichever is smaller (top bracket at the end of the vertical dotted line); 25th percentile – 1 interquartile range or minimum value, whichever is larger (bottom bracket at the end of the vertical dotted line); and outliers (horizontal lines beyond the end of the vertical dotted lines) of the pain scores before (left) and after (right) treatment with methylene blue oral rinse. The pain reduction was significantly different from zero according to the Wilcoxon signed rank test (*P*<0.0001).

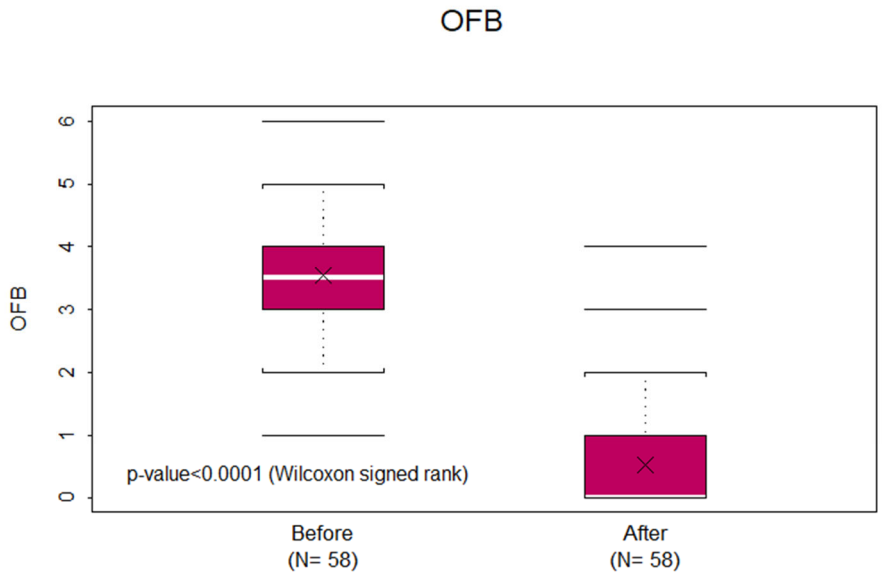

Figure 3. Oral function burden (OFB) scores before and after treatment. The graph shows the mean (X inside the bar); median (white bar inside the box); interquartile range (entire box); 75th percentile + 1.5 interquartile range or maximum value, whichever is smaller (top bracket at the end of the vertical dotted line); 25th percentile – 1 interquartile range or minimum value, whichever is larger (bottom bracket at the end of the vertical dotted line); and outliers (horizontal lines beyond the end of the vertical dotted lines) of oral functioning scores before (left) and after (right) treatment with methylene blue oral rinse. The oral functioning score reduction was significantly different from zero according to the Wilcoxon signed-rank test (P<0.0001).

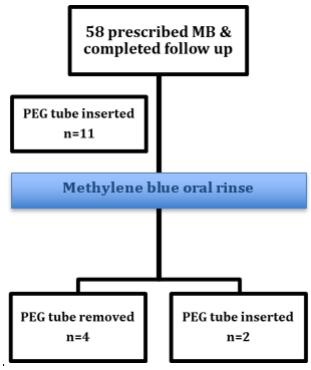

Figure 4. Effect of MBOR on PEG tube placements.

Safety profile of MBOR

During the reported study few patients reported mild and transient adverse events. Three of them experienced oral burning sensation during their first treatment. One patient discontinued use of the mix because of the pharmacy's compounding cost (**Table 3**).

MBOR is emerging as a safe, effective, inexpensive, and widely available alternative, which has been studied in clinical trials and reported in observational studies. Despite concerns surrounding ionization effects on radiated tissue [17], when topically applied and in such low concentrations, an ionization effect had not been reported and was not a concern to the participating radiation oncologists on the reported study.

MBOR's topical application at low concentrations presents negligible systemic absorption and minimal risk of pharmacologic interactions or toxicity. If ingested, MB has rapid absorption which can reach peak plasma concentration in less than 2 hours [18]. Fortunately, the plasma concentration is calculated to be 100-fold less than an equivalent dose if intravenously administrated [19]. Therefore, based on the pharmacokinetics of methylene blue, it is projected that if ingested at diluted concentrations, the plasma levels of methylene blue can reach negligible levels and therefore present a low risk from pharmacologic interactions or systemic toxicity. If swallowed, patients might observe transient greenish discoloration of the feces and urine until clearance is accomplished. Although, broncho aspiration of MBOR has not been reported. Due to the clinical complexity of some patients with HNC, a speech pathologist recommendation must be followed.

Advantages and disadvantages of MBOR

Distinct from other topical agents, MBOR lacks local anesthesia properties, thus preserving gag reflex and taste sensation. Moreover, its potential for cumulative analgesic effect distinguishes it from short-acting oral rinses. However, its inability to access compromised mucosa in the esophagus and larynx poses limitations to its efficacy (**Table 2**).

Table 2. Advantages and disadvantages of MBOR as compared to conventional oral rinses.

Advantages	**Disadvantages**
No adverse events reported	*Transient burning sensation (4.6%)*
No systemic effect	*Transient blue discoloration of mouth and teeth*
Rapid onset of analgesic effect	*Requires direct contact with mucosa sores*
Longer duration of analgesic effect	*Permanent stain of clothes and fabrics*
Accumulative analgesic effect	*No commercial availability*
No anesthetic effect	*Compounding needed*
Does not inhibit gag reflex	*Inability to access esophagus and larynx*
Does not affect the perception of taste	
Widely available	
Low cost	

Table 3. Reported events.

Events (n=9)	Category	Frequency count	Percentage
	Inappropriate use	1	2%
	Burning sensation during use	3	5%
	Location of lesion hard to reach with rinse	1	2%
	Discontinued after 1 dose unknown reason	1	2%
	Discontinued after 2 doses unknown reason	1	2%
	Discontinued due to cost	1	2%
	Discontinued due to stain and messiness	1	2%

Limitations

The study listed inadequacies in data acquisition that could not be addressed owing to the retrospective nature of the study. The discrepancy in the size of the comparison groups and the inability to address patient compliance.

Conclusion

Our narrative advocates for the integration of MBOR as a safe, efficacious, and cost-effective adjunctive therapy for refractory OM pain during RT for HNC. Its accessibility, low-risk profile, and potential to reduce opioid utilization and PEG tube dependency underscore its clinical utility. Large prospective randomized controlled trials are warranted to fully delineate and better evaluate MBOR efficacy.

References

1. Chaveli-López B, Bagán-Sebastián JV. Treatment of oral mucositis due to chemotherapy. J Clin Exp Dent. 2016; 8(2):e201-09.

2. 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 Sep-Oct;6(5):423-31.

3. Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. Frontiers in Oncology. 2017 May 22;7:89.

4. Elting LS, Keefe DM, Sonis ST, Garden AS, Spijkervet FK, Barasch A, et al. Burden of Illness Head and Neck Writing Committee. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. Cancer. 2008 Nov 15;113(10):2704-13.

5. Lee CT, Galloway TJ. Pathogenesis and Amelioration of Radiation-Induced Oral Mucositis. Curr Treat Options Oncol. 2022 Mar;23(3):311-24.

6. Milazzo-Kiedaisch CA, Itano J, Dutta PR. Role of Gabapentin in Managing Mucositis Pain in Patients Undergoing Radiation Therapy to the Head and Neck. Clin J Oncol Nurs. 2016 Dec 1;20(6):623-8.

7. Alfieri S, Ripamonti CI, Marceglia S, Orlandi E, Iacovelli NA, Granata R, et al. Temporal course and predictive factors of analgesic opioid requirement for chemoradiation-induced oral mucositis in oropharyngeal cancer. Head Neck. 2016 Apr;38 Suppl 1:E1521-7.

8. Roldan CJ, Chung M, Feng L, Bruera E. Methylene Blue for the Treatment of Intractable Pain from Oral Mucositis Related to Cancer Treatment: An Uncontrolled Cohort. J Natl Compr Canc Netw. 2021 Jan 4;19(5):521-7.

9. Salman AE, Salman MA, Saricaoglu F, Akinci SB, Aypar Ü. Pain on injection of propofol: a comparison of methylene blue and lidocaine. J Clin Anesth. 2011 Jun;23(4):270-4.

10. Beadle BM, Liao KP, Giordano SH, Garden AS, Hutcheson KA, Lai SY, et al. Reduced feeding tube duration with intensity-modulated radiation therapy for head and neck cancer: A Surveillance, Epidemiology, and End Results-Medicare Analysis. Cancer. 2017 Jan 1;123(2):283-93.

11. Bhayani MK, Hutcheson KA, Barringer DA, Lisec A, Alvarez CP, Roberts DB, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. Head Neck. 2013 Nov;35(11):1634-40.

12. Chang TW, Fiumara N, Weinstein L. Letter: Methylene blue and light therapy for herpes simplex. Arch Dermatol. 1975;111(2):265-6.

13. Faber P, Ronald A, Millar BW. Methylthioninium chloride: pharmacology and clinical applications with special emphasis on nitric oxide mediated vasodilatory shock during cardiopulmonary bypass. Anaesthesia. 2005;60(6):575-87.

14. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9(8):807-19.

15. Mentes BB, Akin M, Leventoglu S, Gultekin FA, Oguz M. Intradermal methylene blue injection for the treatment of

intractable idiopathic pruritus ani: results of 30 cases. Tech Coloproctol. 2004 Mar;8(1):11-4.

16. Tan KY, Seow-Choen F. Methylene blue injection reduces pain after lateral anal sphincterotomy. Tech Coloproctol. 2007;11(1):68-9.

17. Roldan CJ, Huh B, Song J, Nieto Y, Osei J, Chai T, et al. Methylene blue for intractable pain from oral mucositis related to cancer treatment: a randomized phase 2 clinical trial. BMC Med. 2022 Nov 3;20(1):377.

18. Rengelshausen J, Burhenne J, Fröhlich M, Tayrouz Y, Singh SK, Riedel KD, et al. Pharmacokinetic interaction of chloroquine and methylene blue combination against malaria. Eur J Clin Pharmacol. 2004 Dec;60(10):709-15.

19. Walter-Sack I, Rengelshausen J, Oberwittler H, Burhenne J, Mueller O, Meissner P, et al. High absolute bioavailability of methylene blue given as an aqueous oral formulation. Eur J Clin Pharmacol. 2009 Feb;65(2):179-89.