

Methylene Blue for the Treatment of Oral Mucositis Associated to Cancer Treatment in Pediatrics

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Abstract

Here, we report the use of a methylene blue oral rinse for the treatment of oral mucositis-associated pain. A child receiving chemotherapy for acute lymphoblastic leukemia had progressive decline in clinical condition from uncontrolled oral pain associated with mucositis. Conventional therapy was shown to be ineffective and eventually discontinued. The patient received a methylene oral rinse treatment, which provided good pain control and allowed him to recover successfully completing his chemotherapy. The use of the methylene blue oral rinse can be a safe, inexpensive, and effective treatment for mucositis-related oral pain in the pediatric cancer patient population.

INTRODUCTION

Oral mucositis presents as a sequelae of inflammatory changes in the epithelial and subepithelial cells within the oral, oropharyngeal, and esophageal mucosa and is very prevalent within the cancer population [1]. Not only is it an uncomfortable complication for many patients undergoing chemotherapy, it is also the most common symptom that requires systemic analgesics among cancer patients [2]. Overall, it is estimated that more than 70% of patients have some degree of gastrointestinal mucositis because of its variable presentation and underreporting [3, 4]. Oral mucositis can be painful, causing impaired eating and drinking, which results in dehydration, malnutrition, interruption in therapy, increased risk of infection, longer hospital stays, and increased treatment costs, with an overall reduction in quality of life [5].

More than 40,000 children in the United States undergo treatment for cancer every year [6]. While cancer is considered a rare disease among children and adolescents [7], oral mucositis is not rare; within this population, 40% of children who receive standard-dose chemotherapy, 80% who receive radiation therapy for head and neck cancers, and 75% who undergo bone marrow transplant develop oral mucositis [6].

The current strategies to prevent oral mucositis in the pediatric population include chewing gum, chlorhexidine gluconate, sucralfate, and a preventive oral disease protocol [7]. Similarly, to alleviate the symptoms of oral mucositis, a few pharmacologic agents have been approved, such as oral rinses (e.g. saline solution and sodium bicarbonate rinses), topical anesthetics (e.g. lidocaine and benzocaine), compound mouthwashes (e.g. a “magic mouth rinse” containing diphenhydramine, lidocaine, and combinations of aluminum hydroxide, magnesium hydroxide, and simethicone), and mucosal surface protectants (e.g., hydroxypropyl cellulose gels) [9]. When a step-up approach fails to provide adequate relief, systemic opiate analgesics are warranted.

Recently, methylene blue oral rinse, a non-anesthetic, non-opioid agent, has been used to treat oral mucositis-associated pain in adult patients with cancer [8]. However, the use of this alternative in the pediatric population has not been reported.

RESULTS

A 6-year-old male was receiving intensive chemotherapy for the treatment of refractory acute lymphoblastic leukemia with a regimen consisting of oral 6-mercaptopurine, an intravenous continuous infusion of methotrexate; leucovorin; and an intrathecal combination of methotrexate, cytosine arabinoside, and dexamethasone. On day seven after starting this regimen, the child developed diffuse painful oral sores. Pain was worse when chewing and swallowing, and he gradually stopped eating solids and was barely able to swallow sips of liquids.

His pain was initially managed with an oral hygiene protocol including an oral rinse and swab with alcohol-free 0.2% chlorhexidine four times a day. He was given ice chips and scattered doses of a morphine elixir without meaningful relief. As his clinical condition rapidly deteriorated, he was occasionally lethargic with persistent drooling; at this point, he had a total weight loss of 450 grams.

His physical examination revealed an irritable child with a weak and uncomfortable appearance. He had a blood pressure of 88/54 mmHg, pulse of 148 beats/min, respiratory rate of 24 breaths/min, and a tympanic temperature of 37.3 °Celsius.

He avoided examination of his oral cavity, but a limited view revealed thick saliva, scalloping (i.e. imprints of the teeth on the tongue), coating of the mucosa of sublingual area and the soft palate and scattered compromised oral mucosa of the cheeks. There was evidence of painful erythematous plaques with localized spots of mucosa ulceration (Figure 1). The patient's mucositis was considered grade four on the World-Health-Organization classification and grade six on the Children's International-Mucositis Evaluation-Scale. The remainder of the physical findings were consistent with dehydration. Blood tests showed a white cell count of 8,800 cells/mL, hemoglobin of 9.7 g/dL, and hematocrit of 29.3%. Urine analysis revealed specific gravity of 1.035, his lactic acid level was 2.8 mmol/L. The remainder of the blood test, chemistry, and hepatic function panels were normal.

A trial of methylene blue 0.05% diluted in normal saline solution was provided. The child was instructed to take sips of 3-5 mL of this mixture, hold it in his mouth for 5 minutes, and then spit out the mixture. This mixture was judiciously provided every 4 hours. As the child became more comfortable with the protocol, he was able to hold the methylene blue mixture in his mouth for 5 minutes before spitting it out. After the first dose, drooling was no longer evident. After the second dose, he was eager and able to drink fluids, subsequently he no longer received morphine after three doses. The patient rapidly progressed from being able to eat a soft to a solid diet and was discharged home on day seven after admission. The only adverse effect observed was transient blue discoloration of his mouth and asymptomatic faint greenish discoloration of his feces and urine, likely from unintentional swallowing of the treatment mixture.

DISCUSSION

This new finding of methylene blue as an effective treatment for chemotherapy-induced oral mucositis in a pediatric patient outlines a potential alternative analgesic therapy for this common adverse event of cancer therapy, not explored before on this age population.

Methylene blue is a monoamine oxidase, nitric oxide synthase, and guanylate cyclase inhibitor [9]. When methylene blue and dye with biologic substrates are combined, they react with nucleic acids and damage proteins and lipid membranes of organisms [10]. It is not well understood how these properties translate to its analgesic properties, but there are several clinical and *in vitro* findings of methylene blue's action on both peripheral and central neural pathways [9]. Methylene blue has the unique property of temporarily ablating nerve endings, which has been useful in the treatment of intractable pruritus ani [11]. In patients with open lumbar discectomy, its anti-inflammatory mechanism has been shown to reduce lower back pain after surgery [12]. Deng et al. found that an injection of methylene blue within the disc for discogenic back pain led to decreased pain scores at 3 and 6 months ($p < 0.05$) [13]. Our report now adds to the literature on the therapeutic usefulness of topical methylene blue.

Methylene blue comes in several different formulations, including intravenous and tablet, and was most recently used in conjunction with photodynamic therapy. Its diverse methods of administration make it a

prime anti-nociceptive agent for many types of patients and pain complaints. Unlike other therapies for oral mucositis-related pain that include the use of local anesthetics, this oral rinse formulation uses only methylene blue and normal saline. Without the sensation-dulling effect of local anesthetics, a patient's sensation of taste can be preserved and therefore encouraging oral intake. For the pediatric population, this is paramount, as oral mucositis can lead to rapid weight loss and poor nutritional status.

When used systemically (e.g. oral or parenteral) methylene blue is not risk-free. Patients who are taking monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, or serotonin and norepinephrine reuptake inhibitors are advised to use methylene blue with caution, given the increased risk of life-threatening serotonin syndrome [14] [15]. In addition, when given as an oral capsule may cause nausea, upset stomach, diarrhea, vomiting, or bladder irritation [16]. Despite its potential risk when used systemically, methylene blue appears to be safe and well tolerated in its oral rinse or topical formulation.

CONCLUSION

Methylene blue provided an alternative, opioid-sparing option for a pediatric patient with oral mucositis-related pain. We hope that these findings will continue to transform the analgesic algorithm for the treatment and management of oral mucositis.

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