Original Article

Could methylene blue be used to manage burning mouth syndrome? A pilot case series

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Abstract – Objective: Burning mouth syndrome is a disabling condition of complex pathophysiology characterized by spontaneous pain felt in the oral mucosa in the absence of evident mucosal lesions which lacks efficient treatments to this day. The purpose of this study was to demonstrate the efficacy of methylene blue in the management of burning mouth syndrome. Methods: The study was conducted at the dental clinic of the Anta Diop University and Newtown dental clinic of Dakar, Senegal. A solution of methylene blue as a mouth-rinse (0.5%) was applied for 5 minutes in five patients satisfying the ICHD-3 diagnostic criteria for burning mouth syndrome. This procedure was repeated every 6 hours 3 times per 24h, during 7 days. Using numeric rating scale, pain severity was assessed as the mean pain felt during the last day of application. Results: After 7 days, the pain was significantly reduced by two-thirds and almost absent at 3 and 6 months follow-up. No secondary effects of the use of methylene blue were observed. Putative mechanisms of action and potential implications for treatment are discussed. Conclusion: Methylene blue is an old compound but a novel topical therapy that could prove beneficial in the management of burning mouth syndrome.

Introduction

Burning mouth syndrome (BMS) is a disabling condition characterized by spontaneous pain felt in the oral mucosa, defined by the International Headache Society (IHS) [1] as ““intraoral burning or dysesthetic sensation, which occurs daily for more than 2 hours and persists for more than 3 months, without clinically obvious causal lesions” (ICHD-3) [1]. As opposed to secondary BMS which has a causal factor [2], primary or idiopathic BMS is of unknown etiology. The prevalence of BMS affects between 0.01% and 3.7% in the adult population but can be much higher in specific patient groups such as menopausal women (12–40%); the average sex-ratio is approximately 1 man for 7 women, depending on the studies [3,4].

The characteristics of BMS have been comprehensively reviewed with focus on its historical [5,6], clinical [2,7], and pathophysiologic [8–12] characteristics. Accumulating evidence suggest that BMS is a neuropathic condition experienced by patients presenting morphological and functional alterations in both the peripheral and central nervous system, detectable at the subclinical level. Although often described as a clinically homogenous entity, BMS might refer to different conditions [9,13–15].

Regarding BMS therapy, several comprehensive reviews and meta-analysis [2,16–23] overall indicate both a lack of satisfactory treatments and a poor level of evidence of the existing studies with few randomized controlled trials (RCTs). Considering the disabling nature of BMS, including alterations of quality of life and social integration [13,24,25], high levels of somatic and psychiatric/psychological comorbidities [26–31], the need for efficient treatment is crucial for patients and a public health issue. To address such an issue, the 2016 Cochrane review [20] suggests designing well controlled RCTs and identifying new therapeutic approaches.

Methylene Blue (MB)

In Senegal, some patients spontaneously use Methylene Blue (MB) to alleviate oral pain, although no recommendation for this indication can be found in the literature. MB is a
cationic heterocyclic aromatic chemical compound (Methylthioninium Chloride) that has been used for more than 130 years in Medicine as a vital dye with very low tissue toxicity [32]. Among its many medical effects such as detoxification, disinfection and positive psychotropic effects [33], it has shown analgesics effects in rheumatology, orthopedics [34,35] and dermatology [35–45] and in experimental pain [46]. Interestingly MB has even shown analgesic effects in both orofacial pain conditions [47,48] and neuropathic pain [40,49] which prompted us to consider it as a possibly viable treatment option for BMS.

The aim of this study was therefore to test the putative analgesic effect of MB mouth-rinses in Burning Mouth Syndrome in an open case study.

Patients and methods

This pilot study was conducted between May 2019, and December 2019 at the dental clinic of the Anta Diop University and Newtown dental clinic of Dakar, Senegal. A prospective report of 5 consecutive cases of MB treatment for idiopathic BMS was conducted. The study protocol was approved by the Institutional Review Board of the Dental School. Inclusion criteria were age >18 years old, orofacial pain satisfying the ICHD-3 diagnostic criteria for BMS [1] (Tab. I), no impairment in communication. All patients gave oral and written consent to be treated with MB in the absence of other effective treatment options. Each patient also gave his/her informed written consent to participate in the study. Every patient underwent a thorough medical history, extra and intraoral clinical examination. Known contraindications for the use of MB were specifically searched (i.e. glucose-6-phosphate dehydrogenase deficiency, severe renal dysfunction, pregnancy, high risk for serotoninergic syndrome). The risk for bronchial aspiration was assessed and considered minimal/inexistent for patients with normal cognitive status and the ability to perform gargling. Paraclinical tests were performed including oral candida search, ferritin, vitamin B6, B9 and B12 and thyroid hormones levels.

All patients satisfying the inclusion criteria for BMS were proposed MB for the management of their BMS symptoms. A solution of MB diluted to 0.5% in normal saline (100 mL total) was prepared. Patients were instructed to take a mouthful of the solution, hold it in the mouth on the painful sites for 5 minutes, and then gargle and spit. These steps were to be repeated every 6 hours 3 times per 24h, during 7 days. Pain severity was assessed as the mean pain felt during the last day on a 11 point numeric rating scale [NRS] (0 was defined as the absence of pain and 10 the maximal pain imaginable). Pain score was assessed as baseline (D0) before MB application and at three time points (D3, D5 D7) after MB application, and after 3 and 6 months. Patients were also asked to report any unpleasant sensation or adverse effect relating to MB use. Self-evaluated general Quality of Life and Stress/anxiety was noted as Good or Bad and Yes or No. Statistical analyses were performed using GraphPad software. Pain intensity ratings before (D0) and after MB mouthrinse at D7, 3M and 6M use were compared using ANOVA followed by Dunns post-tests. The level of significance was fixed at 0.05.

Results

The sample comprised 5 patients, all women, with a mean age of 58.8 years old (from 53 to 65 years), the characteristics of which are described in Table II. Five patients were diagnosed

| Table I. Diagnostic criteria of the ICHD-3 (2018) for BMS. |
|----------------------------------------------------------|
| A. Oral pain fulfilling criteria B and C                  |
| B. Recurring daily for >2 hours/day for >3 months        |
| C. Pain has both of the following characteristics:        |
| 1. burning quality                                        |
| 2. felt superficially in the oral mucosa                  |
| D. Oral mucosa is of normal appearance and clinical      |
| examination including sensory testing is normal           |
| E. Not better accounted for by another ICHD-3 diagnosis.  |

| Table II. Characteristics of the BMS patients. |
|-----------------------------------------------|
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|-----------|-----------|-----------|-----------|-----------|
| Age (y.o.)| 57        | 53        | 61        | 58        | 65        |
| Quality of pain | Burning | Burning | Burning | Burning | Burning |
| Location | Tongue & Oral mucosa | Tongue & Oral mucosa | Tongue & Oral mucosa | Tongue & Oral mucosa | Tongue & Oral mucosa |
| Duration of symptoms | 10–12 months | >12 months | >48 months | >48 months | >36 months |
| Pain pattern | All day long | All day long | All day long | All day long | All day long |
| Alleviated by eating | Yes | Yes | No | Yes | No |
| Dysgeusia | No | No | Yes | No | Yes |
| Xerostomia | Yes | No | Yes | Yes | Yes |
| Stress/Anxiety | Anxiety | Anxiety | Stress + Anxiety | Stress + Anxiety | Stress + Anxiety |
as primary BMS; Patient 5 had vitamin B9 and B12 deficiency which were corrected by supplementation, with no alleviation of the symptoms, before administration of MB. Two patients also reported dysgeusia. Evolution of the pain score from baseline to Day 7 showed a significant decrease (M = 7.0 ± 0.79 at D0 vs M = 2.0 ± 0.35 at D7; p < 0.05, Wilcoxon) (Fig. 1). No side effect or discomfort was reported. The relief of the pain in patient 5 was accompanied by a slight self-reported amelioration of the dysgeusia. At 3 and 6 month, mean scores of pain were significantly decreased compared to baseline. Means scores ± SEM were respectively 0.2 ± 0.22 and 0.4 ± 0.27; p < 0.05, with no adverse effect (Tabs. III and IV). No staining of the teeth was observed during the course of the study.

### Discussion

The main result of this study is a significant long term decrease in the pain score for the 5 BMS patients tested for MB. Pain was completely relieved in 4 patients. These results are encouraging considering the lack of efficacy and side effects of available treatments and the low cost and safety of MB. Nevertheless, in the absence of a placebo-controlled group comparison, the proportion of placebo-mediated therapeutic effect cannot be properly assessed. A randomized controlled trial is under preparation to address this critical issue.

### Using MB for pain therapy

MB is approved by the US Food and Drug Administration (FDA) for methemoglobinemia, prevention of urinary tract infections in elderly patients, and intraoperative visualization of nerves, nerve tissues, and endocrine glands as well as of pathologic fistulae [32]. MB is used either as a topical or an injectable agent, intradermally or intravenously. Since the first reports of its positive effects in the treatment of neuritic and rheumatic diseases, it has been used in dermatology for the

![Fig. 1. Time course of the pain self-reported on a numeric rating scale at baseline (D0) and after 3, 5 and 7 days (D3, D5, D7).](image-url)
Table IV. Characteristics of the BMS patients 6 months after MB treatment. VAS = Visual Analogic Scale (VAS). USF/SSF = Unstimulated and Stimulated Salivary Flow.

|                          | Patient 1 | Patient 2 | Patient 3 | Patient 4                                  | Patient 5                                  |
|--------------------------|-----------|-----------|-----------|-------------------------------------------|-------------------------------------------|
| Quality of pain          | No pain   | No pain   | No pain   | Slight burning pain relieved during mealtimes | Slight burning, relieved during mealtimes  |
| VAS Pain score           | 0         | 0         | 0         | 1                                         | 1                                         |
| Teeth coloration         | No        | No        | No        | No                                        | No                                        |
| Dysguesia                | No        | No        | No        | No                                        | Slight metallic taste                      |
| Xerostomia               | No        | No        | Yes, at waking time, SF normal | Moderate stress related to family problems and the burning pain | Stress related to the persistent burning pain |
| Stress/Anxiety           | No        | No        | No        | Moderate but clearly improved since MB treatment | Moderate but clearly improved since MB treatment |
| Quality of life          | Good      | Good      | Good      | Moderate but clearly improved since MB treatment | Moderate but clearly improved since MB treatment |

Orofacial pain

To the best of our knowledge, only two studies have documented the analgesic effects of MB in specific orofacial pain conditions. Aghanohosseini et al. (2006) in an open study of 13 patients with Oral Lichen Planus (OLP) lesions found a significant reduction in VAS scores before and after MB [47]. However in this study MB was given in combination with laser irradiation which makes difficult to attribute solely the effects to MB. No attempt to characterize the mechanisms involved in the pain relief was done although it can be supposed that it involved an anti-inflammatory effect, as OLP is a chronic inflammatory mucocutaneous disease. These results were reinforced by those of Sadaksharam et al. 2012 who observed a reduction in the size of OLP lesions although no assessment of pain was reported [53]. In another inflammatory painful oral condition i.e. oral mucositis following irradiation, Roldan et al. [48] reported a series of 5 consecutive patients with intractable pain associated with oral mucositis. The use of 0.5% methylene blue as mouth rinse resulted in a sustained analgesia over 3 weeks i.e. reduction of pain VAS score from 7.2 to 0.8, with a concomitant significant decrease of opioid use. If inflammatory mechanisms are clearly involved in oral mucositis, neuropathic mechanisms can also participate in its pathophysiology [54]. Since BMS is now recognized as a complex condition with neuropathic alterations [9], the analgesics effects observed in our study echo the pain relief obtained in a small double-blind, prospective, randomized controlled study of intravenous MB in patients with different types of neuropathic pain [49].

The authors observed a significant decrease in pain scores compared with the control group, and 3 of the 6 patients with dynamic mechanical allodynia showed an improvement in tactile allodynia after MB treatment. More recently, Zhao et al. 2018 investigated the effect of MB injection for post-herpetic neuralgia (PHN) and evidenced a significant reduction in VAS score associated with a reduction of plasmatic levels of IL-6, TNF-α and cortisol [40].

As this study did not seek to elucidate the underlying mechanisms of the observed analgesic effects, we can only speculate as to the mechanisms involved. Many of the several biological properties of MB rely on its ability to form a redox couple with leucomethylene blue functioning as a reversible oxidation reduction system or electron donor-acceptor couple in presence of NADPH, O₂ and iron containing compounds [49,55–57]. Animal studies as well as human studies have evidenced several relevant mechanisms [32,56,58], among them: the inhibition of both constitutive and inducible NOS (Nitric Oxide Synthase) resulting in decreased production of the proinflammatory NO and concomitant inhibition of guanylate cyclase; inhibition of arachidonic acid metabolism; deactivation of xanthine oxidase; MB is also a powerful antioxidant which prevents the mitochondrial production of oxygen free radicals, enhances cellular oxygen consumption and reduces mitochondrial superoxide and reactive free radical production, thereby providing neuronal protection [37,51]. MB might reduce peripheral nociceptive nerve fiber density in painful areas [37,41,43], inactivate microglia which is a well-known player in neuropathic pain, antagonize N-methyl-D-aspartate receptor. MB has a broad range of targets encompassing multiple neurotransmitter systems, ion channels, and enzymes involved in various neurophysiological functions. In addition MB inhibits monoamine oxidase (MAO) which breaks down catecholamines, resulting in positive anxiolytic and antidepressant effects [59,60]. This effect led to the development of the phenothiazine neuroleptic family.
Toxicity/adverse effects of MB

Toxicity is low and adverse reactions of MB injections (epidural, intravenous or intradermal) are rare [37,38,61–63] and mainly consist of a green or blue urine discoloration [64] although more severe incidents have been reported [65]. However intrathecal injection of MB can cause severe neurotoxic effects [55,66]. MB i.v. must also be given with caution to patients with a history of glucose-6-phosphate dehydrogenase deficiency [67] and those with severe renal impairment since MB has a renal elimination. MB is teratogenic and should not be used in pregnant patients [68]. In addition, there is a risk of serotonin syndrome when MB is injected in patients treated with inhibitors of the reuptake of serotonin such as selective serotonin reuptake inhibitors, tricyclic antidepressants, other monoamine oxidase inhibitors (MAOIs), serotonin–norepinephrine reuptake inhibitors, triptans, and ergot alkaloids [69].

All these effects have been reported after injections. To the best of our knowledge, no adverse effect has been reported with topical use. It is also noteworthy that BM is used in taste research to label the tongue for taste bud counting and no adverse effect, neither pain nor dysgeusia, has been reported [70–72].

Limits of the study

The first limitations of the study are the low sample size and the design of the study which do not allow a high level of evidence (such as the evaluation of non-specific placebo effect). Second MB analgesic effects have only been tested on the short term. Placebo and Hawthorne effects might also affect the results, although a study showed no significant placebo effect of topically administrated medication in BMS patients [73].

Conclusion

Methylene blue is an old compound but a novel topical therapy that could prove beneficial in the management of BMS. Larger studies, with a prospective double-blind randomized placebo-controlled design, are warranted to assess the long-term efficacy, side effects, and complications of oral methylene blue rinse in patients with mucosal pain.

Conflicts of interests: The authors declare that they have no conflicts of interest in relation to the publication of this article.

References

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.
2. Scala A, Checchi L, Montecucchi M, Marinì I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 2003;14: 275–291.
3. Jääskeläinen SK, Woda A. Burning mouth syndrome. Cephalalgia 2017;37:627–647.
4. Kohorst JJ, Bruce AJ, Torgerson RR, Schenck LA, Davis MDP. The prevalence of burning mouth syndrome: a population-based study. Br J Dermatol 2015;172:1654–1656.
5. Grushka M, Sessle BJ. Burning mouth syndrome. Dent Clin North Am 1991;35:171–184.
6. Périer J-M. History of Burning Mouth Syndrome (1800-1950): a review. Oral Dis 2018.
7. Grushka M. Clinical features of burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:30–36.
8. Forssell H, Jääskeläinen S, List T, Svensson P, Baad-Hansen L. An update on pathophysiological mechanisms related to idiopathic orofacial pain conditions with implications for management. J Oral Rehabil 2014.
9. Jääskeläinen SK. Pathophysiology of primary burning mouth syndrome. Clin Neurophysiol 2012;123:71–77.
10. Kolika-Faloma M, Jääskeläinen SK, Laine MA, Teerijoki-Oksa T, Sandell M, Forssell H. Pathophysiology of primary burning mouth syndrome with special focus on taste dysfunction: a review. Oral Dis 2015;21:937–948.
11. Lauria G. Small fibre neuropathies. Curr Opin Neurol 2005;18: 591–597.
12. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome).
13. Braud A, Boucher Y. The relationship between the clinical features of idiopathic burning mouth syndrome and self-perceived quality of life. J Oral Sci 2016;58:475–481.
14. Laméry PJ, Lewis MA. Oral medicine in practice: burning mouth syndrome. Br Dent J 1989;167:197–200.
15. Penza P, Majorana A, Lombardi R, Camozzi F, Bonadeo S, Sapelli P, et al. “Burning tongue” and “burning tip”: the diagnostic challenge of the burning mouth syndrome. Clin J Pain 2010;26:528–532.
16. Häggman-Henrikson B, Alstergren P, Davidson T, Högestätt ED, Östlund P, Tranaeus S, et al. Pharmacological treatment of orofacial pain — health technology assessment including a systematic review with network meta-analysis. J Oral Rehabil 2017;44:800–826.
17. Imamura Y, Shinozaki T, Okada-Ogawa A, Noma N, Shinoda M, Iwata K, et al. An updated review on pathophysiology and management of burning mouth syndrome with endocrinological, psychological and neuropathic perspectives. J Oral Rehabil 2019;46:574–587.
18. Kim Y, Yoo T, Han P, Liu Y, Inman JC. A pragmatic evidence-based clinical management algorithm for burning mouth syndrome. J Clin Exp Dent 2018;10:e321–e326.
19. Liu YF, Kim Y, Yoo T, Han P, Inman JC. Burning mouth syndrome: a systematic review of treatments. Oral Dis 2017.
20. McMillan R, Forssell H, Buchanan JA, Glenny A-M., Weldon JC, Zakrzewska JM. Interventions for treating burning mouth syndrome. Cochrane Database Syst Rev 2016;11:CD002779.
21. Ritchie A, Kramer JM. Recent advances in the etiology and treatment of burning mouth syndrome. J Dent Res 2018: 22034518782462.
22. de Souza IF, Mármora BC, Rados PV, Visioli F. Treatment modalities for burning mouth syndrome: a systematic review. Clin Oral Investig 2018;22:1893–905.
23. Zakrzewska JM, Forsell H, Glenny AM. Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev 2005;CD002779.

24. Lamey P-J., Freeman R, Eddie S-A., Pankhurst C, Rees T. Vulnerability and presenting symptoms in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:48–54.

25. Oghil I, List T, John M, Larsson P. Prevalence and oral health-related quality of life of self-reported orofacial conditions in Sweden. Oral Dis 2017;23:233–240.

26. Tan KY, Seow-Choen F. Methylene blue injection reduces pain after anal diathermy haemorrhoidectomy. Colorectal Dis 2014;16:299–307.

27. Mentes BB, Akin M, Leventoglu S, Gultekin FA, Oguz M. Intradiscal methylene blue injection for the treatment of intractable idiopathic pruritus ani: a case-control study. J Pain Res 2015;8:199–206.

28. Adamo D, Schiavone V, Aria M, Leuci S, Ruoppo E, Dell’Aversana G, et al. Sleep disturbance in patients with burning mouth syndrome: a case-control study. J Orofac Pain 2013;27:304–313.

29. Maillet X, Calbacho V, Torres P, Gremeau-Richard C, Dallel R. Co-injection of pain medications and somatosensory sensitivity in burning mouth syndrome: a systematic review. PLoS One 2016;11:313.

30. van der Ploeg HM, van der Wal N, Eijkman MA, van der Waal I. Psychological aspects of patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:203–208.

31. Galli F, Lodì G, Sardella A, Vegni E. Role of psychological factors in burning mouth syndrome: a systematic review and meta-analysis. Cephalalgia 2017;37:265–77.

32. Mignogna MD, Pollio A, Fortuna G, Leuci S, Ruoppo E, Adamo D, et al. Unexplained somatic comorbidities in patients with burning mouth syndrome: a controlled clinical study. J Orofac Pain 2011;25:131–140.

33. Meissel X, Calbacho V, Torres P, Gremeau-Richard C, Dallel R. Co-occurrence of pain symptoms and somatosensory sensitivity in burning mouth syndrome: a systematic review. PLoS One 2016;11:313.

34. van der Ploeg HM, van der Wal N, Eijkman MA, van der Waal I. Psychological aspects of patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1987;63:664–668.

35. Schirmer RH, Adler H, Pickhardt M, Mandelkow E. Lest we forget you—methylene blue. Neurobiol Aging 2011;32:2325.e7–16.

36. Baldo CF, Silva LM, Arcencio L, Albuquerque AAS, Celotto AC, et al. A multicenter randomized controlled trial on the efficacy of intradiscal methylene blue injection for chronic discogenic low back pain: the IMBI study. PainTargets 2016;15:1181–1187.

37. Farouk R, Lee PW. Intradiscal methylene blue injection for the treatment of intractable idiopathic pruritus ani. Br J Surg 1997;84:670.

38. Mentes BB, Akin M, Leventoglu S, Gultekin FA, Oguz M. Intradiscal methylene blue injection for the treatment of intractable idiopathic pruritus ani: results of 30 cases. Tech Coloproctol 2004;8:11–14.

39. Poles M, List T, John M, Larsson P. Prevalence and oral health-related quality of life of self-reported orofacial conditions in Sweden. Oral Dis 2017;23:233–240.

40. Zhao P, Mei L, Wang W. Clinical study of ultrasound-guided methylene blue thoracic paravertebral nerve block for the treatment of postherpetic neuralgia. Turk Neurosurg 2018.

41. Eusebio E, Graham J, Mody N. Treatment of intractable pruritus ani. Diseases of the Colon Rectum 1990;33 770–772.

42. Aversana G, Fashtami LA, Fatheh M, Djavid GE. Methylene blue injection for the treatment of refractory pruritus ani. Am J Proctol Gastroenterol Colon Rectal Surg 1979;30:34–36.

43. Wolloch Y, Dintsman M. A simple and effective method of treatment for intractable pruritus ani. Am J Proctol Gastroenterol Colon Rectal Surg 1979;30:34–36.

44. Frankenburg FR, Baldessarini RJ. Neuroprotection by methylene blue: a case report. Med Oral Patol Oral Cir Bucal 2006;11:E126–E129.

45. Milazzo-Kiedaisch CA, Itano J, Dutta PR. The novel role of gabapentin in managing mucositis pain in patients undergoing radiation therapy to the head and neck. Clin J Oncol Nurs 2016;20:623–628.

46. Wainwright M, Crossley KB. Methylene Blue — a therapeutic dye for all seasons? J Chemother 2002;14:431–443.

47. Milascu C. Chronic pain patient and anaesthesia. Rom J Anaesth Intensive Care 2019;26:59–66.

48. Oz M, Lorke DE, Hasan M, Petroianu GA. Cellular and molecular actions of methylene blue in cerebral global ischemic injury induced blood-brain barrier disruption and brain pathology: a review. CNS Neurol Disord Drug Targets 2016;15:1181–1187.

49. Milascu A. Chronic pain patient and anaesthesia. Rom J Anaesth Intensive Care 2019;26:59–66.
60. Harvey BH, Duvenhage I, Viljoen F, Scheepers N, Malan SF, Wegener G, et al. Role of monoamine oxidase, nitric oxide synthase and regional brain monoamines in the antidepressant-like effects of methylene blue and selected structural analogues. Biochem Pharmacol 2010;80:1580–1591.

61. Akazawa M, Wu Y-H, Liu W-M. Allergy-like reactions to methylene blue following laparoscopic chromopertubation: a systematic review of the literature. Eur J Obstet Gynecol Reprod Biol 2019;238:58–62.

62. Farrokhi MR, Yazdanpanah H, Gholami M, Farrokhi F, Mesbahi AR. Pain and functional improvement effects of methylene blue injection on the soft tissue around fusion site after traumatic thoracolumbar fixation: A double-blind, randomized placebo-controlled study. Clin Neurol Neurosurg 2016;150:6–12.

63. Warrick BJ, Tataru AP, Smolinske S. A systematic analysis of methylene blue for drug-induced shock. Clin Toxicol (Phila) 2016;54:547–555.

64. Cvetković BR, Cvetković VR, Rosić ZV, Milenković D. Late methylene blue appearance in urine after local treatment of cutaneous fistula in hip osteomyelitis as a first sign of renal failure. Acta Chirurgica Iugoslavica 2008;55:117–120.

65. Paszyńska E, Dmitrzak-Weglarz M, Roszak M, Boucher Y, Dutkiewicz A, Tyszkiwicz-Nwafor M, et al. Salivary opiorphin levels in anorexia nervosa: a case control study. World J Biol Psychiatry 2018;1:1–18.

66. Sharr MM, Weller RO, Brice JG. Spinal cord necrosis after intrathecal injection of methylene blue. J Neurol Neurosurg Psychiatry 1978;41:384–386.

67. Youngster I, Arcavi L, Schechmaster R, Akayzen Y, Popliski H, Shimonov J, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. Drug Saf 2010;33:713–726.

68. Cragan JD. Teratogen update: methylene blue. Teratology 1999;60:42–48.

69. Ramsay RR, Dunford C, Gillman PK. Methylene blue and serotonin toxicity: inhibition of monoamine oxidase A (MAO A) confirms a theoretical prediction. Br J Pharmacol 2007;152:946–951.

70. Bartoshuk LM, Duffy VB, Miller IJ. PTC/PROP tasting: anatomy, psychophysics, and sex effects. Physiol Behav 1994;56:1165–1171.

71. Kullaa-Mikkonen A, Koponen A, Seilonen A. Quantitative study of human fungiform papillae and taste buds: variation with aging and in different morphological forms of the tongue. Gerodontics 1987;3:131–135.

72. Miller IJ, Reedy FE. Variations in human taste bud density and taste intensity perception. Physiol Behav 1990;47:1213–1219.

73. Gremveau-Richard C, Woda A, Navez ML, Attal N, Bouhassira D, Gagnieu MC, et al. Topical clonazepam in stomatodynia: a randomised placebo-controlled study. Pain 2004;108:51–57.