

# Novel management of methylene blue extravasation: A case report and review of literature

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## ABSTRACT

Methylene blue is a highly irritant drug and has been used intraoperatively. Its accidental extravasation can lead to tissue necrosis. In this report, a unique management is described, and the patient recovered without any morbidity.

**Key words:** Accidental drug extravasation, liposuction, methylene blue extravasation

## INTRODUCTION

Methylene blue (MB) has been widely used for a number of medical and surgical indications. Common surgical indications include sentinel lymph node biopsy, identification of gastro-intestinal anastomosis leakages and iatrogenic ureterovesical injuries, etc. Despite MB's long history of use, few adverse events of an accidental extravasation have been reported. We present a case of MB extravasation and its management by the early liposuction. On literature search, we did not find any similar report of use of liposuction in such a situation.

## CASE REPORT

A 79-year-old female, 72 kg, American Society of Anesthesiologists physical status 2, belonging to black race (Fitzpatrick class 5), was diagnosed of having ascending colon carcinoma, along with subcutaneous chest and abdominal nodules. She was scheduled for laparoscopic

right hemi-colectomy under general anesthesia (GA). On the day of surgery, the patient reported to the operating room having a 20G cannula on the right hand. She received GA with endotracheal intubation. After induction of GA, an additional 18G intravenous (IV) cannula was inserted on the dorsum of the right hand (close to the wrist joint) after multiple attempts and was attached to an infusion pump delivering Lactated Ringer's (LR) solution at 400 ml/h. It was a difficult IV cannulation as she was an old lady with dark skin color in addition to having fragile, tortuous veins, most of which were previously pricked due to a couple days' worth of preoperative IV infusions. For surgery, the surgical team positioned the patient, tucked both of her upper limbs alongside the body and started the operation. Surgical dissection was difficult due to multiple adhesions and a suspicion of tumor invasion into the right kidney. Totally, 2 h into the operation, the surgeon suspected a right ureteric injury and requested to administer IV MB for localization. 1% w/v sterile MB injection, 1 mg/kg (diluted in 20 ml of LR solution) infused manually over 10 min through 18G IV cannula on the left hand dorsum (which was continuously infusing IV fluids through an infusion pump) without any significant resistance. After the administration of the MB, the previous infusion was started again at the same rate through the infusion pump. After about 30 min of the MB injection, the surgeon decided to convert the procedure to open exploratory laparotomy due to surgical difficulties. The position of the patient was changed again for the open procedure, and both upper limbs were abducted and kept on the side arm supports

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of the operating table. At this moment, we noted blue discoloration and swelling on the dorsum of the left hand along with blisters, which were extending upward beyond the wrist and measured about 10 cm × 10 cm [Figure 1]. There was minimal swelling of the digits also. The capillary circulation of the digits was well preserved, and capillary refill time was <2 s. The surgeon was notified about the incident. We attempted removal of the extravasated fluid through the cannula by aspiration with a syringe, but only 2-3 ml fluid could be retrieved and therefore the IV cannula was removed. Urgent consultation with a plastic surgeon was sought, who planned immediate liposuction of the swelling. Liposuction without infiltration of tumescence fluid was carried out straightaway, and about 50 ml of the blue colored fluid was retrieved from the swelling and the hand was dressed and immobilized by a splint. Surgical procedure (hemicolecotomy) went uneventful, and the patient was shifted to a high dependency unit after the operation. On 1<sup>st</sup> postoperative day, the hand swelling had reduced significantly (with no vascular impairment), and there was only the loss of superficial skin (epidermis). Patient stayed in the hospital for 10 days and during this period, the plastic surgeons reviewed her on a daily basis. On subsequent visits to the clinic, it was found that she had complete healing of the skin damage with no need for skin grafting and had no neurological dysfunction of the hand.

## DISCUSSION

Incidence of inadvertent ureteral injuries during laparotomy is about 0.007-1.8%. Although these are uncommon, the identification of such injuries is often delayed with an average time to detection ranging from 5.3 to 180 days.<sup>[1]</sup> The intraoperative detection of such injuries can reduce morbidity and treatment expenses. Intraoperative detection of ureteric injuries can be facilitated by IV or intra-ureteric injection of indigo carmine or MB. Extravasation of



**Figure 1:** Methylene blue extravasation

blue-tinged urine helps to confirm the nature and location of the injury.<sup>[2-4]</sup> Our patient developed skin necrosis following extravasation of MB used for the identification of suspected iatrogenic ureteric injury. Extravasation is the inadvertent leakage of injection into the subcutaneous or perivascular tissues. Approximately 10-30% of patients receiving IV MB experience this complication.<sup>[5]</sup> A number of mechanisms can result in the injection escaping the vein, e.g., the puncturing of vein wall either by a catheter or needle, obstructed infusion flow (blood can cause back pressure, leading to infusion escaping from the puncture site); or an inflammatory reaction in the vein can lead to retraction of the capillary endothelial cells and leakage of the infusing fluid. Mechanisms of tissue damage include vasomotor effects, pH disturbances, high osmolality and chemical reactions.<sup>[6]</sup>

Methylene blue is thought to inhibit the nitric oxide — mediated cyclic guanosine monophosphate (cGMP) pathway, which is responsible for smooth muscle relaxation and vasodilation. MB may cause vasoconstriction of arterioles and tissue ischemia when used as a concentrated solution. Consequently, when cGMP is inhibited, cyclic adenosine monophosphate is released, which is the downstream target of noradrenergic receptors, thus permitting  $\alpha$ -adrenergic receptor activation, causing vasoconstriction and subsequently tissue infarction.<sup>[7,8]</sup> Moreover, chemical properties of MB may lead to cytotoxicity. Additionally, MB is oxidized to formaldehyde and other deaminized oxide radicals.<sup>[9]</sup> Buildup of these products in the subcutaneous tissue, coupled with decreased blood flow, may lead to direct injury as well as macrophage-mediated inflammatory injury.<sup>[10]</sup> Moreover, MB 1% w/v solution has a pH of 3.0-4.5, further adding to the drug's potential cytotoxic effect.<sup>[11]</sup> Though the manufacturer recommends slow IV administration, there is no strict recommendation by them regarding its administration through a central vein, Dumbarton *et al.* preferred the central vein route.<sup>[12]</sup> Contrarily, MB has been administered safely through peripheral IV routes as boluses or short-term infusions and on occasion, for long-term infusions (44-120 h), with no reported administration site changes.<sup>[13]</sup>

There are a number of reports of cutaneous adverse effects after subcutaneous MB injections. In one report, authors described skin ulceration 5 weeks after injection of 2 ml of MB 1% solution, for the pelvic lymphatic tracing into the foot of a man with stage II vesicle cancer.<sup>[14]</sup> MB has also been used widely, to identify sentinel lymph nodes for staging procedures in breast cancer though a retrospective review of 24 patients showed that, when it was injected intradermally (3-5 ml of 1% solution), 3 patients developed skin erythema, 1 developed ulceration, and 1 developed

full thickness necrosis.<sup>[10]</sup> Bleicher *et al.* noticed the inflammation resembling cellulitis in 5.9-9.8% of 78 women in whom MB was injected intradermally.<sup>[15]</sup> Though none of these patients developed skin necrosis, the cellulitis was followed by deep fat necrosis.

The degree and the severity of the tissue necrosis are directly proportional to the concentration and volume of the extravasated MB.<sup>[16]</sup> Our patient received a 7 ml (70) mg of MB 1% diluted in 20 ml via peripheral IV catheter. After 30 min of administration, its extravasation was identified. The extravasation led to superficial skin necrosis and blister formation. To remove the extravasated material thoroughly, liposuction was done and thoroughly removed the extravasated drug from the subcutaneous area.

In our incident, the exact cause of the extravasation is not known as MB was injected through a newly established IV line that was running normally and till the injection of MB, about 800 ml of LR solution had already been infused through an infusion pump. However, our patient had numerous risk factors for extravasation from the vein e.g., old age, vascular fragility, site of cannulation (which was close to joint), multiple attempts at cannulation, cancer, compression of the area by an assistant surgeon standing beside the patient's arm, sedation, and anticoagulation, which may have contributed to the extravasation. Exact proportion of the extravasated drug into the subcutaneous tissue is also not known as it was administered through a running line; however, there are reports of local skin changes caused by as little as 3 ml of MB.<sup>[10,14,17]</sup> In our opinion, we should have avoided slow bolus injection, however, extravasation has been reported even with MB infusion.<sup>[12]</sup> Although the exact cause of the incident is not known, early surgical intervention and thorough removal of the extravasated MB using liposuction avoided tissue damage in this case.

## CONCLUSION

We recommend that bolus injection of MB via a peripheral catheter should be avoided, and the infusion site be closely monitored during and afterward for signs and symptoms of extravasation in an attempt to minimize cutaneous adverse events. In the case of extravasation leading to the cutaneous manifestations, it should be managed promptly to avoid adverse cutaneous, neurological or vascular sequelae. Liposuction should also be considered as an option to thoroughly retrieve extravasated MB.

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