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Review article

Allergy-like reactions to methylene blue following laparoscopic chromopertubation: A systematic review of the literature☆

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ABSTRACT

Methylene blue is commonly used as a tracer in sentinel lymph node mapping for many malignant diseases or chromopertubation during gynecologic laparoscopy. In contrast with other blue dyes such as patent blue V or isosulfan blue, methylene blue rarely causes an allergy-like reaction in patients undergoing sentinel lymph node mapping. However, in chromopertubation, some cases of allergy-like reaction to methylene blue have been reported; these comprise two types: an allergic reaction and methemoglobinemia. In this study, a systematic literature review of allergy-like reactions caused by methylene blue dye following laparoscopic chromopertubation was conducted. A search was conducted in PUBMED, Web of Science, and Scopus from inception until June 2018, using the terms: "methylene blue", "complication", "allergic", "hypersensitive", "lung/pulmonary edema"," methemoglobinemia", "anaphylactic shock", "chromopertubation", "pertubation", "laparoscopic", and "laparoscopy". Ultimately, the eligibility criteria were fulfilled by only 12 case reports. Among 13 cases including our case of severe anaphylactic shock after chromopertubation, allergic reactions were diagnosed in four cases, methemoglobinemia in six, and there was no confirmed diagnosis in three cases; the clinical course consisted of skin changes, blue discoloration of body fluids, respiratory failure, and hemodynamic failure, regardless of the underlying diagnoses. Regarding diagnosis, methemoglobinemia was confirmed with co-oximetry (spectrophotometry). First-line therapy included supportive care for both cases of allergic reactions and methemoglobinemia.

Contents

Introduction

During laparoscopic surgery in gynecology, blue dyes are routinely used in chromopertubation to evaluate tubal patency. Reports have indicated that blue dyes including patent blue V, isosulfan blue, and methylene blue had comparable accuracy in

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sentinel lymph node mapping [1]; however, the associated complications varied.

Adverse reactions to blue dyes are divided two categories: allergic and non-allergic [1]; allergic reactions include skin rashes, erythema, and anaphylaxis and non-allergic reactions include pulse-oximetry changes, blue discoloration of the skin or body fluids, and skin necrosis. Reports have indicated that the incidence of allergic reactions to blue dyes ranged between 0.07% and 2.7% in sentinel lymph node biopsy [2]. Compared with the severe complications of patent blue V and isosulfan blue, those of methylene blue are extremely rare. Due to safety and lower cost, methylene blue is widely used as a tracer [3].

In contrast to the extreme rarity of allergy-like reactions to methylene blue during sentinel lymph node biopsy, cases of adverse reactions have been reported in laparoscopic chromopertubation. The adverse reactions have been reported to be divided into allergic reactions and methemoglobinemia. We report our experience of a case of near-fatal anaphylactic shock and our findings through a systematic review of the literature performed to assess the clinical course of allergy-like reactions.

Case presentation

A 41-year-old woman, G1P0, was referred to our hospital for an ovarian cyst and menorrhagia refractory to medication. Her medical and obstetric/gynecological histories were unremarkable. A right ovarian cyst of 4-cm size and multiple uterine myomas of 2-cm size near the uterine cavity were detected using ultrasonographic examination. Frozen pelvis was suspected during the pelvic examination. The patient was preoperatively diagnosed with ovarian cyst and severe endometriosis and was admitted for undergoing cystectomy and adhesiolysis. The results and findings of preoperative examination, including blood tests, and electrocardiography and chest radiography, were within normal limits.

Based on a strong suspicion of severe adhesions preoperatively, robotic surgery was performed. Cystectomy and adhesiolysis using the da Vinci Si robotic system (Intuitive, Sunnyvale, CA, USA) were performed for the pelvic adhesions. Since she had a desire for future fertility, at the end of surgery, chromopertubation with methylene blue (20 mg in 200-mL total volume of 0.9% sodium chloride solution) was performed, which showed good bilateral tubal patency. After undocking the robotic system and commencing wound closure at the port sites, a drop in her end-tidal carbon dioxide was recorded, and there was occurrence of sudden cardiopulmonary arrest 15 min after injecting methylene blue.

Cardiopulmonary resuscitation (CPR) was performed, and extracorporeal membrane oxygenation (ECMO) was established through the left-sided femoral vessels. Initially, under suspicion of pulmonary embolus, heparin was injected intravenously. However, absence of embolus and elevated right atrial pressure was determined using intraoperative transesophageal echocardiography, and absence of pulmonary embolism was confirmed through subsequent computed tomography (CT). Passive atelectasis in the bilateral lower lung bases and small amount of pleural effusion were the only findings on the chest CT scan. Cardiac massage was performed for over 18 min.

The patient intubated with ECMO support was transferred to the intensive care unit (ICU). The remainder of the postoperative course was uneventful: while in the ICU, the level of sedation was reduced under intubation and ECMO support, and the patient was able to open her eyes and follow orders of the medical team; stable respiratory and hemodynamic status was achieved, and ECMO support was withdrawn the day following surgery, and she was extubated on the same day; she was discharged on postoperative day 10 without any neurological sequelae.

Recovery of the patient was rapid and without complications, and the postoperative examination was unremarkable. Based on findings through echocardiography and CT, pulmonary embolism as a cause of shock was ruled out, and severe anaphylactic shock was determined. Because the event that occurred toward the end of surgery, it was clear that no therapeutic agent other than methylene blue was newly administered to the patient at the time. Finally, the patient was diagnosed with methylene blue-induced anaphylactic shock. An additional examination was declined by the patient, and the results of skin test could not be obtained.

Methods

A systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. A systematic review of the literature was performed in three computerized databases (PUBMED, Web of Science, and Scopus) with the following search terms: “methylene blue”, “complication”, “allergic”, “hypersensitive”, “lung/pulmonary edema”,” methemoglobinemia”, “anaphylactic shock”, “chromopertubation”, “pertubation”, “laparoscopic”, and “laparoscopy”. Case reports of human patients published in English from inception until June 2018 were eligible for inclusion. Reports lacking clinical data were excluded. Articles identified through manual search of references of the studies identified were also eligible.

A total of 399 articles including

63 articles in PUBMED, 177 in Web of Science, and 99 in Scopus were identified (Fig. 1). Among these, duplications were excluded and review of title and abstract was performed; as a result, 39 full-text studies were accessed. After further excluding studies without sufficient data and including studies by manual review of references, 12 studies were included in the systematic review.

Results

A total of 13 case reports that described complications associated with methylene blue after chromopertubation were identified (Table 1) [4–15]. Among the 13 cases including our case, allergic reactions were diagnosed in four cases, methemoglobinemia in six, and there was no confirmed diagnosis in three cases.

Symptoms

Regardless of underlying diagnoses, clinical course comprised skin changes, blue discoloration of body fluids, respiratory failure, and hemodynamic failure. Timing of the event differed according to the diagnosis. Allergic reactions mostly occurred at $\leq$10 min after injection, whereas methemoglobinemia occurred at $\geq$10 min after injection; however, the timing varied in some cases.

Skin changes were divided into urticaria and blue discoloration (cyanosis-like). Generally, urticaria was considered as allergic reaction, and blue discoloration was associated with methemoglobinemia; however, blue discoloration in concomitant allergic reaction and methemoglobinemia was reported: in one case of allergic reaction, blue-discolored urticaria and papules were observed and blue discoloration was not considered as the sign of methemoglobinemia [5].

Blue discoloration of various body fluids was reported in case of methemoglobinemia. Blue discoloration of urine was noted in both cases, possibly due to dye absorption from the pelvis or bladder. However, in case of methemoglobinemia, blue discoloration of urine as well as stool, or saliva, or vomitus that persisted for several days was reported. One report of methemoglobinemia indicated persistent blue discoloration for 1 week after surgery [7]. The recommendation was that in allergy-like reaction after

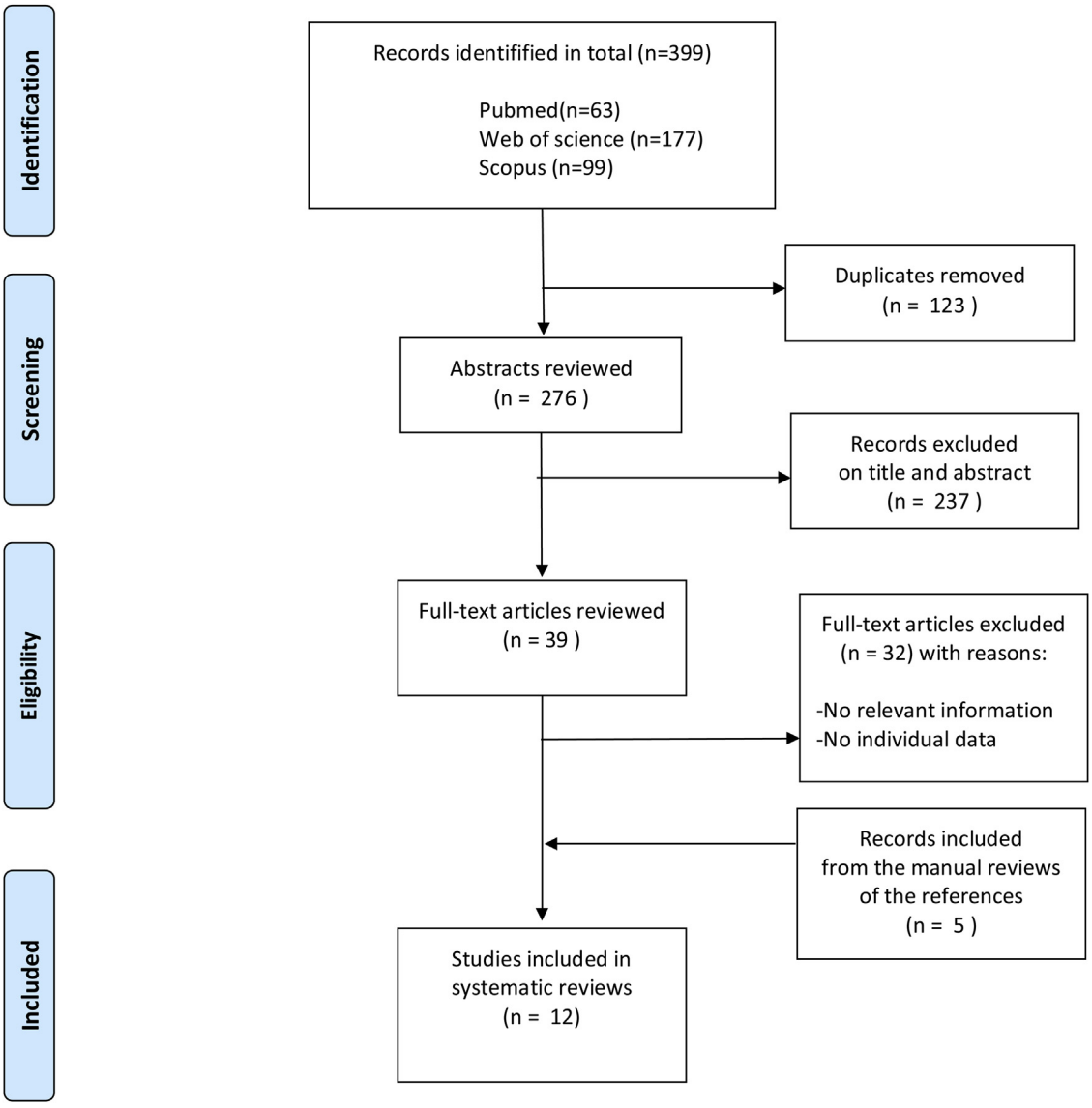

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the search for studies.

chromopertubation, blue-color changes should be assessed by examination of the full body and body fluids.

Systemic involvement that led to respiratory failure was reported in nine cases, hemodynamic instability in four, and shock in two. Hemodynamic change was reported more frequently in case of allergic reaction (3/4, 75%) versus methemoglobinemia (1/6,16%), and there were two cases of shock associated with allergic reaction.

Relevant examinations

In one report, elevated level of plasma histamine was used to confirm allergic reaction to methylene blue [4]; in that case, skin tests to latex and all other drugs used in surgery were negative, and only that to methylene blue was positive despite no previous contact of the patient with methylene blue, hence the authors' suggestion was that possibility of unknown sensitization due to wide-spread use of the dye in many drugs should be considered. One report described cross-reactivity between patent blue and methylene blue [2].

Methemoglobinemia was confirmed with co-oximetry (spectrophotometry) [16], while the methemoglobin level was used in presumptive diagnosis. Caution was recommended in interpreting oxygen (O_2) saturation in routine pulse oximetry and result of arterial blood gas (ABG) analysis in case of methemoglobinemia, since O_2 saturation is not accurate in methemoglobinemia due to effect of methemoglobin (met-Hb) on light absorbance, and met-Hb could affect the reading of ABGs. Therefore, the O_2 saturation value was different between pulse oximetry and ABGs, and considered for making the diagnosis of methemoglobinemia [15]. The overall finding was that O_2 saturation was decreased under pulse oximetry but normal in ABG in four cases of methemoglobinemia.

Thorough history taking was recommended. Patients with history of glucose-6-phosphate dehydrogenase (G-6PD) deficiency or tuberculosis were among those with methemoglobinemia [12]. In this review, among six cases of methemoglobinemia, five had a history of G-6PD deficiency or tuberculosis. Regardless of diagnosis, hypersensitivity reactions or methemoglobinemia should be suspected in the event of unusual manifestation following use of methylene blue dye.

Table 1
Case reports of allergy-like reaction after laparoscopic chromopertubation.

Case	Authors	Timing (after injection)	Skin change	Discoloartaion of body fluids	Drop of pulse oximetry saturation	ABG PaO2	Lung edema[a]	Hemodynamic instability (use inotropes)	Collpase	Dx	Examination results Medical histories
1	Dewachter et al. [4]	2 min	Urticaria	–	to 80%	–	–	○	–	AS	Elevataion of histamine level prick test(+)
2	Present	10 min	No	No	Collapse	–	–	○	○	AS	–
3	Rzymski et al. [5]	10 min after surgery	Blue-discolored urticaria/ papules	Blue urine	–	–	–	–	–	AS	–
4	Millo et al. [6]	15 min after surgery	Blue dicoloration	–	Collapse	–	○	○	○	AS	Autopsy showed lung edema with blue coloration G6PD (-)
5	Mhaskar and Mhaskar [7]	10 min	Blue dicoloration	Blue urine/ vomitus for 1 weeks	to 54%	Normal	–	–	–	Met	Met-Hb: 9.4%, G6PD (−) history of TB (+)
6	Khandelwal et al. [8]	10 min	No	–	to 92%	Normal	○	–	–	Met	Met-Hb: 3%, G6PD (+)
7	Dhanpal and Joseph [9]	15 min	Blue dicoloration	Blue urine/ stool/saliva for 3 days	to 85%	Normal	–	–	–	Met	Met-Hb:25%, history of TB (+)
8	Biligin et al. [10]	30 min	Blue dicoloration	Blue vomitus	to 86%	Normal	–	–	–	Met	G6PD (+)
9	Rathi et al. [11]	30 min	Blue dicoloration	Blue urine for 1 weeks	to 62%	–	–	–	–	Met	Met-Hb: 8.9%, history of TB (+)
10	Veerendrakumar et al. [12]	5 h (after surgery)	–	Blue urine for 2-3 h	to 85%	–	○	○	–	Met	Met-Hb: 26%, TB-PCR (-)
11	Hariharan et al. [13]	2 min	–	–	to 88%	59 mmHg	○	–	–	unclear	
12	Trikha et al. [14]	2 min	Blue dicoloration	Blue urine	to 60%	50 mmHg	○	–	–	unclear	Met-Hb <1%
13	Yogini et al. [15]	After surgery	–	Blue urine for 1 days	Normal	Normal	–	–	–	unclear	

ABG: Arterial blood gas.
Met-Hb: Methemoglobin.
AS: Anaphylactic shock.
min: minute.
Dx: Diagnoses.
NS: not describedd.
G6PD: glucose-6-phosphate dehydrogenase difficiency.
PCR: polymerase chain reaction.
h: hours.
TB: tuberculosis.
Met: Methemoglobinemia.
[a] lung edema included the cases which was diagnosed by chest X-ray or crepitus sounds by chest auscluation.

Treatment and prognosis

First-line therapy was considered as supportive care in case of allergic reactions as well as methemoglobinemia according to severity of hemodynamic change, and included administration of steroids for an allergic reaction and diuretics for pulmonary edema. One report indicated that a patient with methemoglobinemia but without anemia or cardiovascular disease could tolerate a high level of met-Hb and supportive care was considered as adequate [17]. Additional treatment included blood transfusion, exchange transfusion, and ascorbic acid; ascorbic acid was administered for methemoglobinemia in two cases.

Prognosis was good in most cases, since severe allergy-like reactions were uncommon. Only three cases had complication of hemodynamic instability, of which, two cases required cardiopulmonary resuscitation. Two cases had anaphylactic shock including our case, and one case of mortality due to severe allergic reaction in a previous study [6]. In that study, a 30-year-old woman collapsed in the recovery room 15 min after laparoscopic surgery with chromopertubation and died despite sustained resuscitative efforts; the autopsy finding was pulmonary edema. In our case, because the event occurred when the patient was under general anesthesia and our hospital is a tertiary center well-equipped to handle emergencies, the systemic changes requiring emergency management were immediately identified and CPR/ECMO was promptly administered.

Discussion

Blue dyes are commonly used as tracers in a variety of surgeries and provide many clinical advantages. Compared with radiotracers, the blue dyes are safe for use in many situations. However, blue dyes are considered as medications that can cause adverse events and allergic reactions.

Adverse reactions to blue dyes in lymph node mapping were analyzed in prior reports. A systematic review of anaphylactic responses to blue dyes during sentinel lymph node mapping by Bezu et al [2] indicated the rate of allergic reactions to patent blue V and isosulfan blue of 0.07–2.7%; whereas, an absence allergic reactions to methylene blue in sentinel lymph node mapping. The author concluded that methylene blue seemed to be safer, although skin necrosis as a non-allergic reaction to

methylene blue was reported. Another review by Ramin et al indicated that methylene blue had the highest safety-level among the blue dyes, considering its frequent use in medical practice [1].

Both reviews indicated that there was occurrence of allergy-like reaction to methylene blue in chromopertubation regardless of rarity of such reaction in sentinel lymph node mapping and high rate of methemoglobinemia as a non-allergic reaction following chromopertubation.

Met-Hb is a ferric hemoglobin (Hb) that cannot bind to oxygen. Met-Hb also shifts the oxygen dissociation curve and reduces oxygen release in tissue. Therefore, excess met-Hb leads to functional anemia and metabolic acidosis. Methylene blue at low-concentration reduces the reversal of met-Hb to Hb; whereas, at high concentration of methylene blue, met-Hb oxidizes the ferrous iron of Hb, changing Hb to met-Hb. Thus, methylene blue dye is considered as a treatment for methemoglobinemia. However, the use of methylene blue is ineffective and should be avoided in patients with G-6PD deficiency because of the chemical mechanism [17]. Met-Hb has a normal level of <3% (mean, 1%) of the total Hb; however, at level of >10%, there is cyanosis and skin discoloration, subsequently at > 20%, tachycardia and dyspnea, >50%, seizures and shock, and >70%, death [17].

Our study has a limitation due to rarity of allergy-like reactions to methylene blue. Nevertheless, our study outlined the clinical course of allergic reactions and methemoglobinemia, and highlighted the overlapping symptoms and distinctive features that enable diagnosis. The review raised several clinical questions as follows: reasons for more frequent reports of allergy-like reactions to methylene blue in laparoscopic chromopertubation versus sentinel lymph node mapping; incidence of allergic reactions and methemoglobinemia; and impact of the chromopertubation procedure on methemoglobinemia status. Further analysis focused on these issues is needed.

Conclusion

Methylene blue dye was commonly used in clinical practice and rarely associated with complications. The case of hypersensitivity reaction(s), particularly occurrence of an unusual event following use of methylene blue dye should be regarded with a high index of suspicion.

Disclosure statement

All authors declare no conflicts of interest and nothing to disclose.

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