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Case Report

Severe decrease in SpO_2 and methemoglobinemia following subareolar isosulfan blue administration and clinical relevance

Esra Yüksel[1], Dilek Duman[1], Levent Yeniay[2], Sezgin Ulukaya[1]

ABSTRACT

The level of axillary lymph node involvement in breast cancer is a critical decision factor for adjuvant therapy and the most important indicator of prognosis and survival. Sentinel lymph node biopsy is a minimally invasive technique with low morbidity in axillary staging of breast cancer. Radiocolloid substances (Technetium-99m) and/or blue dyes such as methylene blue or isosulfan blue are used during sentinel lymph node biopsy. Isosulfan blue stain is frequently used in sentinel lymph node biopsy and rarely causes complications. The present case report presents a severe decrease in SpO2 due to methemoglobinemia following isosulfan blue administration as well as skin and urine signs and inconsistency with clinical picture in a 67-year-old, 77 kg, ASA II female case who underwent sentinel lymph node biopsy under general anesthesia.

Keywords: Isosulfan blue, methemoglobinemia, sentinel lymph node biopsy

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[1]Department of Anesthesiology and Reanimation, Ege University School of Medicine, İzmir, Turkey
[2]Department of General Surgery, Ege University School of Medicine, İzmir, Turkey

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Address for Correspondence
Esra Yüksel
e-mail: esrayuksel73@yahoo.com

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INTRODUCTION

Sentinel lymph node biopsy (SLNB) involves staining lymph nodes via regional injection during breast surgery; it is an easily applied implementation with low morbidity and an accuracy rate of over 90%, and has prognostic importance (1). The stains used most frequently for detection of sentinel lymph nodes include isosulfan blue, patent blue, and methylene blue. Isosulfan blue is an aniline dye; it is the 2.5-disulfan isomer of patent blue (2).

Unfortunately, as a disadvantage of regional staining, methemoglobinemia is one of the most frequent complications seen following isosulfan blue injection, in addition to allergic reactions ranging from simple rashes to anaphylactic reactions (3-5). The amount of methemoglobin (MetHb), which is an abnormal form of the hemoglobin molecule, is normally less than 1%. Cyanosis occurs when the blood MetHb concentration exceeds 10% to 15%; weakness following tissue hypoxia, tachycardia, and respiratory distress occur when the MetHb concentration exceeds 35%; and lethargy, stupor, and syncope are observed when the MetHb concentration exceeds 55%. A MetHb concentration of over 70% is fatal unless treated. Methemoglobinemia may occur as a side effect of local anesthetic toxicity or inhaled NO administration. Peripheral oxygen saturation (SpO_2) in methemoglobinemia patients is low and is independent from real partial oxygen pressure (PaO_2) in blood (6). However, the relationship between SpO_2 decrease and the clinical condition of the patient, as well as whether treatment is required, remain unclear.

The present case report introduces a severe decrease in SpO_2 following isosulfan blue administration, as well as skin and urine signs, perioperative process, and inconsistency with clinical condition in a patient who underwent SLNB under general anesthesia.

CASE PRESENTATION

Sentinel lymph node biopsy under general anesthesia was planned for a 67-year-old, 77 kg, 165 cm, ASA II female patient due to left breast cancer. Preoperative characteristics of the patient included warfarin sodium use due to past pulmonary embolus and levothyroxine use for thyroid function disorder. Prior to the surgery, warfarin sodium was replaced with 0.4 ml enoxaparin sodium. Routine laboratory tests revealed mild anemia (Hb 10.4, Htc 33.6). An intravenous route was opened (20 G) in the operating room, and isotonic serum infusion was started. Anesthesia induction of the patient included 1 mg/kg lidocaine, 2 mg/kg propofol, 1 µg/kg fentanyl, and 0.6 mg/kg rocuronium performed under routine ECG, with non-invasive blood pressure, SpO_2, and capnography monitoring; an orotracheal tube (no. 7) was then placed. Initially, the patient's SpO_2 was 99%, her blood pressure was 100/70 mmHg, and her heart rate was 75/minute in room air.

Maintenance of anesthesia was provided with 50% O_2/N_2O and 1% to 3% sevoflurane. Ten minutes after subcutaneous administration of 10 ml 1% isosulfan blue by the surgeons into the patient, who was he-

modynamically stable, SpO_2 first decreased to 87% from 99% and then to 75% in minutes despite 100% oxygen support. Meanwhile, blood pressure and $ETCO_2$ monitoring were unremarkable. After verifying that the anesthesia device worked correctly, the airway pressure did not increase, and the endotracheal tube had been placed accurately, a blood sample was taken from the patient for arterial gas analysis. A severe increase was suspected in MetHb concentration because SpO_2 remained at 75% although the concentration of inspired oxygen was 100%; a solution of 2500 mg ascorbic acid in 500 ml 5% dextrose was administered to the patient intravenously until the arterial blood gas results were obtained. However, the arterial blood gas results were as follows: pH: 7.54, $PaCO_2$: 23.3 mmHg, PaO_2: 281 mmHg, SaO_2: 99%, and MetHb: 2.7%. Biochemical analysis revealed a blood MetHb concentration of 2%. Meanwhile, the surgery was rapidly completed. Taking the patient's history of pulmonary embolus into account, her clot quality was evaluated by thromboelastogram to assess hypercoagulability. The thromboelastogram showed a tendency toward hypercoagulability (R period: 6.3 min., K period: 1.1 min, alpha angle: 75.5°, MA: 76 mm, and CI: 2.7). However, because the arterial blood gas parameters were good, the hemodynamics of the patient were stable, and the methemoglobin concentration was not very high, the patient was extubated after surgery; she was relaxed, cooperative, and had adequate respiration. Despite the absence of respiratory or neurological distress, the patient's SpO_2 only increased to 85% within 2 hours with 5 L/min oxygen support via face mask in the operating room as the patient was extubated. At that time, the patient's skin, particularly in the upper part of her body, had turned blue; this was most remarkable in her face. The color of the blood plasma taken from the patient for biochemical analysis was blue. The color of the urine passing through the urinary catheter placed in the intensive care unit was also blue. Twelve hours after 5 L/min oxygen inhalation via mask, the patient's SpO_2 reached 90%. During monitoring in the intensive care unit on the postoperative 1st day, the facial color and urine color of the patient remained blue, her SpO_2 was 92%, and her arterial blood gas levels were as follows: pH: 7.44, PaO_2: 76.1 mmHg, $PaCO_2$: 38.2 mmHg, SpO_2: 99%, and MetHb: 1%. During monitoring in the clinic on the postoperative 2nd day, her SpO_2 was 95% without oxygen support, and her facial and urine color returned to normal. The patient was discharged on the 3rd day without any problem. Written informed consent was obtained from the patient who was presented in this case report.

DISCUSSION

Isosulfan blue is used for SLN marking; it passes into the regional lymph channels after injection and renders the blood visible by dying it blue.

The rapid and sudden decrease in peripheral oxygen saturation in the present case initially suggested to us a new embolus because of the patient's history of pulmonary embolus. However, her stable hemodynamics, lack of decrease in $ETCO_2$ saturation, and normal clot quality by thromboelastogram ruled out this diagnosis.

Allergic and anaphylactic reactions rarely occur due to isosulfan blue; they may also accompany a decrease in oxygen saturation. Recently, it has been demonstrated that isosulfan blue acts as an antigen and causes an IgE-mediated reaction. The incidence of these reactions is between 0.6% and 2.5%. A wide spectrum of symptoms may be seen, ranging from mild (urticaria, erythema) to severe (pulmonary edema, hypotension, vascular collapse) (7). Cinar et al. (8) reported a case of anaphylactic reaction after use of isosulfan blue.

However, the present patient had no symptoms of anaphylactic reaction, such as airway problems or respiratory-circulatory insufficiency. The blue color in her skin, mucosa, and urine were due only to MetHb. Isosulfan blue stain-induced methemoglobinemia was diagnosed based on knowledge of the use of the stain due to the characteristics of the surgical procedure, the high methemoglobin concentration both in arterial blood gas analysis and in further biochemical blood analysis, and the decrease in SpO_2 saturation regardless of normal PaO_2. Upon observing a low SpO_2 saturation regardless of normal PaO_2 and discovering a high methemoglobin concentration in the blood samples, we concluded that this was a case of isosulfan blue-induced methemoglobinemia.

Isosulfan blue, which is bound to plasma albumin and is excreted 90%through bile and 10% through urine, causes methemoglobinemia by oxidizing iron in hemoglobin molecules from the ferrous (Fe^{2+}) form to the ferric (Fe^{3+}) form. An increase in MetHb concentration, which is normally less than 1% and has no oxygen-carrying ability, shifts the oxyhemoglobin curve to the left and may cause tissue hypoxia, lactic acidosis, and death in severe cases. A definitive diagnosis of methemoglobinemia can be rapidly made by demonstrating an increase in MetHb via a co-oxymeter. A co-oxymeter is a spectrophotometer that measures light absorption at four different wavelengths and thus differentiates various forms of hemoglobin (oxyhemoglobin, deoxyhemoglobin, methemoglobin, and carboxyhemoglobin) (6).

A mild decrease in SpO_2 saturation after isosulfan blue administration is a routine condition. As such, similar cases have been reported in the literature (5,9,10). Blue urine color has been reported in some cases in addition to the commonly encountered low SpO_2 saturation and methemoglobinemia. There are two cases in the literature in which three of these findings were found (9,10). Unexpectedly, the present patient case had a severe decrease in SpO_2 saturation although the methemoglobin concentration was not very high; more typically, she experienced a remarkable change in the color of her skin-mucosa and, later, her urine, which lasted longer. A severe initial decrement in peripheral oxygen saturation without a color change to blue may suggest other diagnoses. Therefore, it is important to control the airway, respiration, and anesthesia device as soon as possible upon a severe decrease in SpO_2 (75%), as in the present case. Although our diagnosis focused on methemoglobinemia because of the characteristics of the surgical procedure, the diagnosis was made definitive after blood gas analysis showed no abnormality in PaO_2 saturation, an increase in methemoglobin, and a remarkable change in skin color.

Lai et al. (11) detected a decrease from 100% to 89% in a breast cancer case 5 minutes after administration of 4 mL (100 mg) patent blue, which was reflected in arterial blood gas measurements of pH: 7.45, PaO_2: 544.7 mmHg, $PaCO_2$: 35.7 mmHg, SaO_2: 99.9%, and MetHb: 3.5%. It was observed that the pa-

tient's urine and face turned blue; however, SpO_2 saturation returned to normal limits after 2 hours. No additional treatment was given. Methemoglobin was found to be 1.2% in the patient, who was normal a day after surgery, and the patient was discharged after 3 days without any problem (11). In the present case, we attributed the rapid decrease in SpO_2 to 75% and persistent maintenance to the dose of isosulfan blue, which was as high as 10 mL. However, it is interesting that the MetHb concentration was not found to be high in line with the given dose, although it was verified by two different methods. This raises the question of whether skin color may reflect SpO_2 independent of serum methemoglobin concentration. In fact, the patient's SpO_2 may have been sufficient, because the good clinical condition of the patient is more consistent with mild methemoglobinemia than with low SpO_2 saturation.

The first step of methemoglobinemia treatment in severe cases is intravenous administration of methylene blue, which is the antidote. Normally, the low amount of methemoglobin that occurs in blood is rapidly degraded in the erythrocytes by NADH-methemoglobin reductase (cytochrome b5 reductase). There is another methemoglobin reductase system in erythrocytes that uses NADPH as a cofactor. This enzyme is physiologically inactive and becomes active in the presence of certain redox compounds; it reduces the molecule by transferring an electron from NADPH to methemoglobin. The effect of methylene blue in the treatment of methemoglobinemia occurs by this method (11). However, we were unable to obtain methylene blue in our hospital. Therefore, we intravenously administered ascorbic acid, which reduces methemoglobin non-enzymatically *in vitro*. The efficacy of ascorbic acid therapy is not definite; however, the clinical status of the patient remained stable and required no further treatment.

CONCLUSION

Sentinel lymph node biopsy is a less invasive alternative to axillary dissection. However, methemoglobinemia due to dye use is a rare complication of this procedure. In contrast, patients undergoing this operation can be safely monitored with co-oximetry and blood sampling for MetHb.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

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