

## Olgu Sunumu

# Methemoglobinemia Due to Isosulfan Blue Used for Sentinel Lymph Node Mapping

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### SUMMARY

A 62 year- old woman, weighing 60 kg with ASA I was scheduled for sentinel lymph node biopsy. Her pulse oximetry values rapidly declined to a nadir of 88 % 30 min after subcutaneous injection of isosulfan blue. Arterial blood gas analysis revealed methemoglobinemia ([MetHb] = 5.2 %). Following 3 L/min O<sub>2</sub> administration via nasal CPAP mask and 2x500 mg iv ascorbic acid treatment, methemoglobin levels dropped to 1.7 % after 15 hours. Although abnormal pulse oximetry has already been reported in association with isosulfan blue administration , methemoglobinemia due to isosulfan blue was reported just in a few cases.

**Key words:** Methemoglobinemia, isosulfan

### ÖZET

#### *Sentinel Lenf Nodu İşaretlemesi İçin Kullanılan İsosulfan Mavisine Bağlı Methemoglobinemi*

62 yaşında, 60 kg, ASA I kadın hastaya biyopsi sırasında sentinel lenf nodunu tespit etmek için subkutan isosulfan verildi. İsosulfan mavisine verildikten 30 dk. sonra pulse oksimetre oksijen saturasyonu değerleri hızla % 88'e kadar düştü. Arter kan gazı analizinde % 5.2 methemoglobinemi bulundu. Nasal CPAP maskesiyle 3 L/m O<sub>2</sub> ve 2x500 mg iv askorbik asit tedavisiyle methemoglobinemi 15 saat sonra % 1.7'ye indi. İsosulfan mavisine bağlı anormal pulse oksimetre değerleri daha önce yayınlanmış olmasına rağmen, isosulfan mavisine bağlı methemoglobinemi sadece birkaç olguda bildirilmiştir.

**Anahtar kelimeler:** Methemoglobinemi, isosulfan

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## INTRODUCTION

The status of the axillary lymph nodes is the strongest prognostic indicator for patients with breast carcinoma. Lymphatic mapping and sentinel lymph node biopsy (SLNB) are routinely used for staging clinically lymph node negative patients. A sentinel lymph node is any lymph node which receives its lymphatic drainage directly from a primary tumor site. Sentinel lymph node (SLN) hypothesis is based on the assumption that an existing tumor metastasis will travel directly from the primary tumor site through the efferent lymphatic channels to the first draining lymph node in the regional lymphatic system, ie. the sentinel node.<sup>(1)</sup> In a randomised trial it was demonstrated that the incidence of lymph edema, sensory loss, drain usage, length of hospital stay are significantly lower and overall patient quality of life is significantly better in the SLNB group.<sup>(2)</sup> This technique consists of subcutaneous injection of 5 mL of isosulfan blue on the periphery of the primary focus of malignancy. Isosulfan blue is an aniline dye (2.5-disulfonated isomer of patent blue dye). After injection, isosulfan is selectively picked up by the lymphatic vessels, thus delineating the lymphatic system draining the injection area and making targeted lymph node excision feasible. Lymphatic nodes and vessels are distinguishable from surrounding tissue by the resultant bright blue color.

Allergic or adverse reactions due to isosulfan blue dye usage have been reported in 0.7-1.9 % of the patients.<sup>(3,4)</sup> It is also known that isosulfan may cause anaphylactic reactions in patients.<sup>(5)</sup> Isosulfan blue and methylene blue have been demonstrated to change pulse oximeter readings. Eventually after its absorption

into parenchymal tissue, entry of isosulfan blue into the bloodstream interferes with spectrophotometric readings. The peak absorption of isosulfan occurs at 635 nm which is very close to the standards used by the pulse oximeter. The staining caused by isosulfan in the bloodstream, interfere with pulse oximetry results and accounts for monitoring problems during operation.<sup>(6)</sup>

In this report we would like to present a case of methemoglobinemia diagnosed in a 62-year-old woman operated for breast cancer. This report is also describing pulse oximetric changes after 1 % isosulfan injection for sentinel lymph node identification.

## CASE REPORT

A 62-year-old Caucasian woman (156 cm, 60 kg, ASA I) was admitted for SLN biopsy and excision of breast carcinoma. Her medical history revealed HBs antigen positivity and a previous eye operation under general anesthesia without any problem. All preoperative laboratory test results were within normal limits (ALT: 9 U/L, AST 15 U/L, total bilirubin: 0,22 mg/dL, total protein: 7,5 g/dL, albumin 4,43 g/dL). At preanesthetic visit her blood pressure was 155/90 mmHg and electrocardiogram (ECG) showed a normal sinus rhythm of 75 bpm. In the operating room her blood pressure increased to 220/110 mmHg and after premedication with 0.1 µg kg<sup>-1</sup> fentanyl + 0,025 mg kg<sup>-1</sup> midazolam intravenously (iv), it decreased to 150/90 mmHg. After ECG, peripheral blood oxygen saturation (SpO<sub>2</sub>), and noninvasive arterial blood pressure (NIBP) monitoring, anesthesia was induced with iv 2 mg kg propofol<sup>-1</sup>, 0.1 µg kg<sup>-1</sup> fentanyl<sup>-1</sup> and 0.6 mg kg<sup>-1</sup> rocuronium, and trache-

**Table I. Arterial blood gas analysis.**

		OT	IC	IC	IC	IC	IC	IC	IC
time	h:m	17:39	18:57	20:03	21:07	23:05	02:16	07:16	09:21
pH		7,416	7,405	7,42	7,418	7,423	7,428	7,423	7,421
PCO <sub>2</sub>	mmHg	39,1	39,9	37	38,3	35,9	37	36,7	37,1
PO <sub>2</sub>	mmHg	143,8	125,1	123	154	165,2	179,8	105,8	111
Hct	%	36	36,1	38,4	38,1	37,1	35	35,2	35,4
Na	mmol/L	142,2	139,7	141,5	139,6	140,3	138,7	139,4	139,9
K	mmol/L	3,79	3,51	3,73	3,75	3,13	3,4	3,35	3,42
Ca	mg/dL	4,54	4,55	4,63	4,44	4,4	4,34	4,34	4,4
Glu	mg/dL	145	169	187	197	142	169	147	141
tHb	g/dL	11,7	11	11,2	11,1	10,9	10,4	10,2	10,2
SO <sub>2</sub>	%	99	98,7	98,6	99,1	99,2	99,4	98	98,5
COHb	%	0,9	0,8	0,9	0,9	0,9	0,7	1	0,9
O <sub>2</sub> Hb	%	93	93,2	93,3	94,2	95,7	96,4	95,4	96,1
HHb	%	0,9	1,3	1,4	0,9	0,7	0,5	1,9	1,5
MetHb	%	5,2	4,7	4,4	4	2,7	2,3	1,7	1,5

OT: Operation Theatre, IC: Intensive Care

al intubation was performed. Anesthesia was maintained with % 50 N<sub>2</sub>O/O<sub>2</sub> and 1 MAC sevoflurane. Before incision, 5 mL of 1 % isosulfan blue was injected subcutaneously (sc). At that moment SpO<sub>2</sub> was 100 %, blood pressure 125/90 mmHg, and heart rate, 65 bpm. Thirty minutes after injection of isosulfan blue, SpO<sub>2</sub> values started to drop and in less than 5 minutes, SpO<sub>2</sub> was 88 %. Thereafter we started to ventilate the patient with 100 % O<sub>2</sub>. Her blood pressure and heart rate did not change significantly. In each measurement SpO<sub>2</sub> values were between 88-89 %. Auscultation of the lungs were not remarkable. Her hands and feet were also well perfused and warm. We could not find a logical reason for the hypoxia and took arterial blood sample for blood gas analysis. Analytical data of the first blood gas sample taken roughly 1 hour after sc isosulfan injection were as follows: PO<sub>2</sub>: 143.8 mmHg, PCO<sub>2</sub>: 39.1 mmHg, SO<sub>2</sub>: 99 %, carboxyhemoglobin (COHb): 0.9 %, O<sub>2</sub> Hb: 93 %, HHb: 0.9 % and MetHb: 5.2 %. Primary tumor was dissected and we decided to delay axillary lymph node dissec-

tion for one week. The residual effect of muscle relaxants was reversed with 1 mg kg<sup>-1</sup> sugammadex and the patient woke up without any problem except decreased SpO<sub>2</sub> values. We transferred the patient to the intensive care unit (ICU). The patient was administered 3 L/min O<sub>2</sub> with nasal CPAP mask and iv 500 mg ascorbic acid was given.<sup>(7,8)</sup> Totally eight arterial blood gas analyses were performed (Table I). The patient was transferred to the general surgery ward 24 hours later with normal methemoglobin values.

## DISCUSSION

Pulse oximetry is a standard noninvasive monitorization technique of anesthesia. The principle of pulse oximetry depends on a combination of spectrophotometric analysis and plethysmography. Pulse oximetry determines concentrations of oxyhemoglobin and reduced hemoglobin perfusing the tissue by measuring the absorbance of light at two wavelengths, ie. 660 and 940 nm. Various factors, such as lighting conditions, patients movement,

electrocautery usage, hypothermia, vasopressors, poor perfusion and anemia may interfere with SpO<sub>2</sub> values.<sup>(9)</sup> Isosulfan blue and methylene blue have been demonstrated to change pulse oximeter readings. Eventually after its absorption into parenchymal tissue, entry of isosulfan blue into the bloodstream interferes with spectrophotometric readings. The peak absorption of isosulfan blue is at 635 nm and this is very close to the standards used by the pulse oximeter.<sup>(6)</sup>

Methemoglobinemia is a hemoglobinopathy and it occurs when the rate of methemoglobin production exceeds In these circumstances, ferrous (Fe<sup>2+</sup>) ions in hemoglobin transforms into the ferric state (Fe<sup>3+</sup>) during oxidation of hemoglobin resulting in higher levels of methemoglobinemia. In healthy subjects NADH cytochrome-b5 methemoglobin reductase and NADPH methemoglobin reductase regulate this oxidation process. Methemoglobin cannot carry oxygen and therefore can cause tissue hypoxia.<sup>(8)</sup> Perioperative methemoglobinemia is often overlooked as a cause of low O<sub>2</sub> saturation, such as due to inadequate ventilation, atelectasis or preexisting lung diseases; but it also may occur due to toxic effects of some drugs, such as nitroglycerine, amyl nitrite, ethyl nitrite, sodium nitrite, bismuth subnitrate, silver nitrate, quinones, sulfonamide, sulfathiazole, sulfapyridine, sulfathiazole, aniline dyes, acetanilide, aminobenzenes, aminophenol, benzocaine, prilocaine and phenacetine.<sup>(8)</sup>

The symptoms of methemoglobinemia are usually related to the methemoglobin levels, but cardiovascular and respiratory function and total hemoglobin in blood could also affect the symptoms. Methemoglobin levels above 15 % cause black-

brown colored blood and cyanosis. At levels above 20 %, headache, dizziness, lethargy and tachycardia occur. When its value is more than 45 %, tachypnea, acidemia, heart failure, arrhythmia and seizures develop. At levels above 70 % risk of death is high.<sup>(10)</sup>

The mean oximetry SpO<sub>2</sub> desaturation was found as 3 % - 5.6 % in methemoglobinemia and the mean time to lowest reading was 25-35 minutes. El-Tamer et al.<sup>(6)</sup> demonstrated that isosulfan blue interfered with pulse oximeter measurements for 195 minutes.

Scheller et al.<sup>(11)</sup> investigated the effects of iv methylene blue, indocyanine green and indigo carmine on pulse oximeter readings and demonstrated that 5 mL iv methylene blue injection could cause large and rapid decrease in SpO<sub>2</sub>. The mean duration of the SpO<sub>2</sub> fall was 40 seconds, the median SpO<sub>2</sub> was 65 % and the mean time for returning baseline value was 3 minutes. In our case SpO<sub>2</sub> started to decrease 30 minutes after isosulfan injection so we refrained from intravenous or intraarterial injection.

Although interaction of isosulfan blue with pulse oximeter measurements is well documented, incidence of methemoglobinemia after its usage is reported in a few cases.<sup>(12,13)</sup> There is also a controlled trial about the effects of methylene blue versus isosulfan blue usage in SNLB.<sup>(14)</sup> Pinero et al.<sup>(14)</sup> compared isosulfan blue with methylene blue in 32 patients who were undergoing SLNB and obtained arterial blood samples for blood gas analysis but could not demonstrate any significant changes in blood gas analysis. On the other hand, the investigators did not state whether methemoglobin levels also

included in this analysis or not.

Burgoyne's<sup>(12)</sup> case is similar to ours in many aspects. In Burgoyne's case and in our case, pulse oximetry values declined to 85 % and 88 %, the onset time was 35 min and 30 min after dye injection, and arterial blood gas analyses revealed methemoglobin levels as 6.5 % and 5.8 %, respectively. In that case they have simulated the phenomenon in vitro by adding isosulfan blue to whole blood and analyzed it in two different gas analyzers and only one analyzer detected the presence of methemoglobinemia. They concluded that the methemoglobinemia could be spurious.<sup>(12)</sup> We performed 8 consecutive analysis in the same gas analyzer and obtained consecutive decreasing of methemoglobinemia in all of them and therefore we thought that it was not spurious.

Methemoglobin levels below 15 % may seem clinically insignificant but levels about 30 % should be treated.<sup>(8)</sup> First choice of the treatment is methylene blue 1-2 mg/kg, which acts as an accelerator of methemoglobin breakdown and a co-factor of methemoglobin reductase which converts methemoglobin to leukomethylene blue in the presence of nicotinamide adenine dinucleotide phosphate and provides nonenzymatic reduction of MetHb.<sup>(10)</sup> Some cases could also respond to ascorbic acid, however ascorbic acid acts slowly than methylene blue. We used ascorbic acid (vitamin C) because methylene blue was unavailable in our hospital. After 15 hours, methemoglobin level returned to normal limits. In prilocaine induced methemoglobinemia methemoglobin levels decreased more rapidly (from 29 % to 10.9 % in 2 hours) after administration of ascorbic acid.<sup>(15)</sup> Therefore we are assuming that intrinsic mechanism via methemoglobin

reductase could have been more effective than ascorbic acid in our case.

Methemoglobinemia is a rare complication, which is usually caused by chemical substances and drugs. Isosulfan is one of these chemical substances which may cause methemoglobinemia. During isosulfan usage in SLNB operations anesthesiologists should keep this in mind and perform blood gas analysis in cases of unexpected and unexplained SpO<sub>2</sub> decreases after eliminating other causes of perioperative hypoxemia.

## REFERENCES

1. Cody HS 3rd, Fey J, Akhurst T, et al. Complementarity of blue dye and isotope in sentinel node localization for breast cancer: univariate and multivariate analysis of 966 procedures. *Ann Surg Oncol* 2001;8:13-9. <http://dx.doi.org/10.1007/s10434-001-0013-9> PMID:11206218
2. Mansel RE, Fallowfield L, Kisin M, et al. Randomized multicenter trial of sentinel node biopsy versus Standard axillary treatment in operable breast cancer: The ALMANAC trial. *Journal of the National Cancer Institute* 2006;98:599-609. <http://dx.doi.org/10.1093/jnci/djj158> PMID:16670385
3. Montgomery LL, Thorne AC, Van Zee KJ, et al. Isosulfan Blue dye reactions during sentinel lymph node mapping for breast cancer. *Anesth Analg* 2002;95:385-8. PMID:12145056
4. Cimmino VM, Brown AC, Szocik JF, et al. Allergic reactions to isosulfan blue during sentinel node biopsy; a common event. *Surgery* 2001;130:439-42. <http://dx.doi.org/10.1067/msy.2001.116407> PMID:11562667
5. Sprung J, Tully MJ, Ziser A. Anaphylactic reactions to isosulfan blue dye during sentinel node lymphadenectomy for breast cancer. *Anesth Analg* 2003;96:1051-3. <http://dx.doi.org/10.1213/01.ANE.0000048709.61118.52>
6. El-Tamer M, Komenaka IK, Curry S, et al. Pulse oximeter changes with sentinel lymph node biopsy in breast cancer. *Arch Surg* 2003;138:1257-60. <http://dx.doi.org/10.1001/archsurg.138.11.1257> PMID:14609878
7. Choi A, Sarang A. Drug-induced methaemoglobinemia following elective coronary artery bypass grafting. *Anaesthesia* 2007;62:737-40. <http://dx.doi.org/10.1111/j.1365-2044.2007.05000.x> PMID:17567353

8. Cho SS, Park YD, Noh JH, et al. Anaesthetic experience of methemoglobinemia detected during general anaesthesia for gastrectomy of advanced gastric cancer: A case report. *Korean J Anesthesiol* 2010;59:340-3. <http://dx.doi.org/10.4097/kjae.2010.59.5.340> PMID:21179297 PMCID:2998655
9. Mihm FG, Halperin BD. Noninvasive detection of profound arterial desaturation using a pulse oximetry device. *Anesthesiology* 1985;62:85-7. <http://dx.doi.org/10.1097/00000542-198501000-00020> PMID:3966675
10. El-Husseini A, Azarov N. Is threshold for treatment of methemoglobinemia the same for all? A case report and literature review. *Am J Emerg Med* 2010;28:748.e5-748.e10.
11. Scheller MS, Unger RJ, Michael JK. Effects of Intravenously Administered Dyes on Pulse Oximetry Readings. *Anesthesiology* 1986;65:550-2. <http://dx.doi.org/10.1097/00000542-198611000-00023> PMID:3777490
12. Burgoyne LL, Jay DW, Bikhazi GB, et al. Isosulfan blue causes factitious methemoglobinemia in an infant. *Paediatr Anaesth* 2005;15:1116-9. <http://dx.doi.org/10.1111/j.1460-9592.2005.01578.x> PMID:16324035
13. Gur I, Afshari S, Kilkenny JW. Sudden false oxygen desaturation and factitious methemoglobinemia after subcutaneous injection of isosulfan blue (lymphazurin). *Am Surg* 2011;77:383-5. PMID:21375867
14. Pinero A, Illana J, Garcia-Palenciano C, et al. Effect on Oximetry of Dyes used for Sentinel Lymph Node Biopsy. *Arch Surg* 2004;139:1204-7. <http://dx.doi.org/10.1001/archsurg.139.11.1204> PMID:15546820
15. Kizilyildiz SB, Sonmez B, Karaman K, Çaksen H. Toxic methemoglobinemia due to prilocaine use. *J Emerg Med* 2010;38:663-5. <http://dx.doi.org/10.1016/j.jemermed.2008.02.033> PMID:18554857