The Effect of Isosulfan Blue Used for Sentinel Lymphnode Biopsy on Methemoglobin Level

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Received Date: July 02, 2018, Accepted Date: August 23, 2018, Published Date: August 31, 2018.
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Abstract

Background: Isosulfan blue and methylene blue have been demonstrated to change pulse oximeter readings. There are also some case reports that isosulfan blue might cause methemoglobinemia (MetHb). Because of increased methemoglobin levels could cause SpO2 changes we aimed in our study to demonstrate whether isosulfan blue used for sentinel lymph node biopsy (SLNB) is increasing methemoglobin level in blood or not and the correspondence of possible methemoglobin changes with SpO2 values.

Methods: Total of 50 patients scheduled for sentinel lymph node biopsy was recruited. After induction of general anaesthesia 5 ml of isosulfan blue was injected into the breast tissue surrounding the tumor site. Arterial blood gas samples were obtained before and 1–15–60 minutes after isosulfan blue injection. SpO2 at sample obtaining time was recorded. SO2 (%), methemoglobin (%) and oxyhemoglobin (%) values was recorded as according to arterial blood gas analysis.

Results: Average methemoglobin values in arterial blood sample analysis prior to isosulfan injection and 1–15–60 minutes after injection were 1.13% (± 0.37), 1.2% (± 0.4), 1.46% (± 0.8) and 1.52% (± 1), respectively. The difference between initial and after 15 minutes (p = 0.024) and after 60 minutes (p = 0.02) was statistically significant.

Conclusion: Isosulfan injections used for sentinel lymph node mapping are increasing methemoglobin level in blood.

Keywords: Isosulfan; Sentinel lymph node biopsy; Methemoglobin

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 of patients with clinically negative lymph nodes. A sentinel lymph node is described as any lymph node which is receiving directly lymphatic drainage from a primary tumor site. SLN hypothesis is based on the theory 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, to the sentinel node [1]. In a randomized trial it was demonstrated that lymph edema, sensory loss, drain usage, length of hospital stay is significantly lower and overall patient quality of life is significantly better in patients mapped with SLNB [2]. This technique is consisting of subcutaneous (SC) injection of 5 ml of isosulfan blue around the primary malignancy. Isosulfan blue is an aniline dye (2.5-disulfonated isomer of patent blue dye). After SC injection, isosulfan is selectively picked up by the lymphatic vessels and thus specifying the lymphatic system draining the injection site and making targeted lymph node excision feasible. Lymphatic nodes and vessels could be distinguished from surrounding tissue by the resultant bright blue color.

Allergic or adverse reactions due to isosulfan blue dye administration have been reported in 0.7–1.9 % of patients [3]. It is also known that isosulfan may cause anaphylactic reactions in some patients [4]. Isosulfan blue and methylene blue have been demonstrated to change pulse oximeter readings. Eventually after its absorption into parenchymal tissue, isosulfan blue’s entry into the bloodstream interferes with spectrophotometric readings. The peak absorption value of isosulfan blue is 635 nm and this is highly close to the standards used by the pulse oximeters. The staining caused via the entering of isosulfan in the bloodstream interfering with photo spectrometric pulse oximetry results may result with monitoring problems during operation [5]. There are also some case reports that isosulfan blue might cause methemoglobinemia (MetHb) [6,7]. Because also increased methemoglobin levels could cause SpO2 changes we aimed in our study to demonstrate whether isosulfan blue used for SLNM is increasing methemoglobin level in blood or not and the correspondence of possible methemoglobin changes with SpO2 values.

Materials and Method

The study was carried on according to the rules in Helsinki Declaration. After obtaining Ethical Committee’s approval and patient’s written consent, fifty female patients, aged 18–80 years, classified as ASA I and II were included in this study. At the time, they were all undergoing SLNB with isosulfan blue staining. The study was carried on between the months June 2011 and April 2012 in Bagcilar Training - Research Hospital and Istanbul University Istanbul Medicine Faculty. The study design was prospective, open and non - randomized.

Exclusion criteria: Patients < 18 and > 80 years of age, ASA status greater than II, male patients, preexisting methemoglobinemia, preexisting hemoglobin anomalies and hemoglobin values lower than 9 mg/dl.

All patients were informed about the study during preoperative
anesthesia visit. On the surgery day patients were taken to the operation theatre and 18 G cannula were inserted in an upper limb vein. Midazolam 0.06 mg/kg was administered intramuscularly (IM) for premedication. Anesthesia was inducted with 2mg/kg propofol, 0.2 µg/kg⁻¹ fentanyl and 0.6 mg/kg⁻¹ rocuronium was used to facilitate tracheal intubation. Anesthesia was maintained with sevoflurane (MAC 1 - 1.5) in N₂O/O₂ (60%/40%). After intubation a 22 gauge arterial cannul was placed in the radial artery of the patient. Patients were ventilated mechanically and rocuronium 0.15 mg-kg⁻¹ added on demand. At the end of surgery anesthetic administration was stopped and the remaining neouromuscular blockade was reversed, if necessary, with neostigmine 0.05 mg/kg⁻¹ and atropine 0.02 mg/kg⁻¹.

At the operation theatre, hemoglobin oxygen saturation (SpO₂), invasive systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP) and baseline electrocardiogram were monitored. After induction of general anaesthesia and sterile preparation of the patient, 5 ml of isosulfan blue was injected into the breast tissue surrounding the tumor site. The injection site was then massaged for 3–4 minutes before the incision. Pulse oximeter (DASH 5000, GE Medical Systems Information Technologies, Wisconsin - USA) measurements were taken from the index finger of the contralateral hand to the operated side. Arterial blood gas samples were obtained before and 1–15–60 minutes after isosulfan blue injection. SpO₂ at sample obtaining time was recorded. SO₂ (%), methemoglobin (%) and oxyhemoglobin (%) values were recorded as according to arterial blood gas analysis results obtained as described. All blood samples were analyzed in Radiometer ABL835 (Diamond Diagnostics, Holliston - USA). At the end of the surgery, patients were transferred to the recovery room and hemodynamic, respiratory and lower extremity motor parameters were monitored and recorded for at least 30 minutes. When the patients were stable they were allowed to transfer to the clinics.

The study’s primary endpoint was methemoglobin changes in arterial blood gas analysis obtained prior and 1–15–60 minutes after isosulfan blue injection. Secondary endpoints were changes at SpO₂, SaO₂ and oxyhemoglobin values. Statistical analysis was performed via SPSS 19 statistical analysis program. All values were given as mean (SD) and Median (Min–Max). Demographic data were analysed with the Sudent’s- t-test. Kruskal Wallis analysis and Mann Whitney U test were used for statistical analysis of measurable data and p < 0.05 value was considered as statistically significant.

Results

The study was conducted in Bagcilar Training - Research Hospital and Istanbul University Istanbul Medicine Faculty during a ten month period. Fifty patients were enrolled. None of the enrolled patients was withdrawn from the study.

The average age (Standard deviation) of the patients involved in the study was 52.6 ± 10.9 years, weight 72.9 ± 9 kg, body mass index 27.7 ± 3.5, hemoglobin 11.8 ± 1.4 g/dl. Patients demographic and intraoperative data were analysed in table 1.

Average methemoglobin values in arterial blood sample analysis prior to isosulfan injection and 1 – 15 – 60 minutes after injection were 1.13% ± 0.37, 1.2% ± 0.4, 1.46% ± 0.8 and 1.52% ± 1, respectively. The difference between initial and after 15 minutes (p = 0.024) and after 60 minutes (p = 0.02) was statistically significant (Table 2).

Average oxyhemoglobin levels in arterial blood sample analysis prior to isosulfan injection and 1–15–60 minutes after injection were 97.2% ± 1.6, 97.2 % ± 0.8, 96.9% ± 1.07 and 96.6 % ± 2.1. The difference between initial value and values after isosulfan injection was statistically not significant (p > 0.005).

Average oxygen saturation determined by noninvasive method of pulse oximetry (SpO₂) prior to isosulfan injection and 1–15–60 minutes after injection were 99.1% ± 0.8, 98.7% ± 1.05, 97.9% ± 1.48 and 97.8 % ± 1.77. The difference between initial value and values after isosulfan injection was statistically not significant (p > 0.005). Average saturation level of oxygen in hemoglobin as measured by samples obtained from arterial blood sample (SaO₂) prior to isosulfan injection and 1–15–60 minutes after injection were 99.3% ± (1.4), 99.5% ± (0.6), 99.4% ± (0.7) and 99.1% ± (1.8). The difference between initial value and values after isosulfan injection was statistically not significant (p > 0.005).

Discussion

Table 1: Patients demographic and intraoperative data.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.64 ± 10.9</td>
<td>53 (26-80)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.96 ± 9.05</td>
<td>74 (48-95)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>27.76 ± 3.53</td>
<td>28.1 (20.3-34.7)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.84 ± 1.38</td>
<td>11.9 (9-14.9)</td>
</tr>
</tbody>
</table>

Table 2: Pulse oximetry and arterial blood gas analysis results. (*) (p < 0.05).

Although average methemoglobin level prior to isosulfan injection was statistically significantly lower than the methemoglobin levels 15 (p = 0.024) and 60 (p = 0.02) minutes after the isosulfan injection, the increased levels were below clinical methemoglobinemia level. The symptoms of methemoglobinemia are generally related to the methemoglobin levels, but cardiovascular and respiratory function and total hemoglobin in blood could also affect the symptoms. Methemoglobin levels above 15% are usually causing black-brown coloured blood and cyanosis. At blood methemoglobin levels above 20%, headache, dizziness, lethargy and tachycardia occur. When methemoglobinemia is more than 45%, tachypnea, heart failure, arrhythmia and seizures are added to the symptoms. Above 70% risk of death is very high [8].

It was demonstrated that isosulfan blue and methylene blue are changing pulse oximeter readings. Eventually after isosulfan blue’s absorption into parenchymal tissue, its entry into the blood could also affect the symptoms. Methemoglobin in blood interferes with spectrophotometric readings. The peak absorption of isosulfan blue is at 635 nm and this is close to the standards used by the pulse oximeter [5]. In our series we also observed SpO₂ decrease, mean initial SpO₂ was 99.1% and it decreased to 98.7%–97.9% and 97.8% after 1–15–60 minutes after isosulfan blue injection but this decrease was statistically insignificant (p > 0.005).
Although isosulfan blue’s interaction with pulse oximeter measurements is well documented, methemoglobinemia incidence related to isosulfan blue is only reported in a few cases [6,7]. Burgoyne described a case in which after isosulfan blue injection pulse oximetry values declined to 85% and 88%, the onset time were 35 min and 30 min after the injection of the dye and arterial blood gas samples revealed methemoglobin levels 6.5% and 5.8%, respectively. In this case they have simulated the phenomenon in vitro by adding isosulfan blue to whole blood and analyzed it in two different gas analyzers and found methemoglobinemia only in one of them, the other analyzer did not second this data and they have concluded that the methemoglobinemia might be spurious [6].

Methemoglobinemia is a rare hemoglobinopathy and is stating to occur when the rate of methemoglobin production is exceeding the rate of methemoglobin reduction and causing high levels of methemoglobin that result from oxidation of hemoglobin’s Fe ions from ferrous (Fe²⁺) to the ferric state (Fe³⁺). In healthy subjects NADH cytochrome-b5 methemoglobin reductase and NADPH methemoglobin reductase are organizing hemoglobin oxidation. Methemoglobin cannot carry oxygen to tissues and therefore can cause hypoxia at high levels [9]. Perioperative methemoglobinemia is often overlooked as a cause of low O₂ saturation, such as due to inadequate ventilation, atelectasis or preexisting respiratory diseases; but it also may occur due to some drugs, such as nitroglycerine, amyl nitrite, sodium nitrite, bisnuth sulfonate, salicylate, quinones, sulfonamide, sulfathiazole, sulfapyridine, sulfathiazole, aniline dye, acetanilide, aminobenzenes, aminophenol, benzocaine, plicocaine and phenacetine. Methemoglobin levels below 15% are usually clinically insignificant in healthy persons but levels about 30 % should be treated [9].

According to El-Tamer isosulfan blue is interfering with pulse oximeter measurements up to 195 minutes. In the same trial the mean time to the maximum change was 35 minutes and median decrease in SpO₂ was 5%, also the mean oximetry SpO₂ desaturation was found as 3-5.6% in methemoglobinemia and the mean time to lowest reading was 25-35 minutes [5]. We cannot demonstrate a profound and statistically significant decrease in SpO₂ values (Table 2) (p > 0.005); probably this is related to our measurement frequency. Vokach-Brodsky stated that in a typical patient a maximum SpO₂ decrease of 3% could be anticipated [10]. In our series initial average SpO₂ level of 99.1% decreased to 98.7, 97.9 and 97.8 % after 1–15–60 minutes after isosulfan blue injection, respectively.

Scheller, et al. investigated the effects of intravenous methylene blue, indocyanine green and indigo carmine injection on pulse oximeter readings and demonstrated that 5 ml intravenous methylene blue can cause large and rapid decrease in SpO₂ values. The mean duration of the SpO₂ fall was 40 seconds and the median SpO₂ was 65% [11]. For ruling out accidentally intravenous or intraarterial administration we also took arterial blood gas samples 1 minute after isosulfan blue injection. But we could not demonstrate any rapid and excessive decrease by oximetry or by blood gas analysis.

Pinero, et al. compared in a controlled trial isosulfan blue’s effects on pulse oximetry readings, oxygen saturation by blood gas analysis and partial oxygen pressure by blood gas analysis recorded before the injection of the dye and 15, 30, and 60 minutes afterward with methylene blue’s in 32 patients going to SLNB but could not demonstrate any significant changes. On the other hand, the investigators did not state whether methemoglobin levels also included in this analysis or not [12].

**Conclusion**

Methemoglobinemia is a rare complication, which is usually caused by chemical substances and drugs. Isosulfan is one of these chemical substances which might cause methemoglobinemia. During isosulfan used SLNB operations anaesthesiologistsshould keep this in mind and perform blood gas analysis in cases of unexpected and unexplained SpO₂ decreases without other perioperative hypoxemia causes.

**References**


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Received Date: July 02, 2018, Accepted Date: August 23, 2018, Published Date: August 31, 2018.

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