The Effect of Subareolar Isosulfan Blue Injection on Pulse Oximeter Readings

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Abstract Besides several side effects including anaphylaxis, blue dyes are also known to cause false pulse oximeter readings. We aimed to examine the effects of subareolar isosulfan blue injection on pulse oximeter (SpO₂) readings. The study group included 27 patients undergoing SLNB using both radiocolloid and isosulfan blue. Another group of 27 patients constituted the control group. Pulse oximeter readings were compared. SpO₂ decline ≥ 4 % was defined as significant. All but one (96.2 %) of the patients in the study group showed SpO₂ declines, compared to only one patient in the control group. Median $\pm$ Interqartile Range (IR) SpO₂ decrease was 3.0 ± 4.0 % in the study and 0.0 ± 1.0 % in the control group ($p < 0.001$). There were significant (≥ 4 %) SpO₂ decreases in 13 (48.1 %) patients in the study group. Statistically significant differences were noted between the two groups in all recordings between 15 and 180 min ($p < 0.001$). Initial time for SpO₂ fall and the time to the lowest SpO₂ recording were 10.0 ± 10.0 and 40.0 ± 30.0 min respectively. Using subareolar injection, the frequency of false readings is comparable with intraparenchymal injections, and is higher than intradermal injections. Time to peak SpO₂ fall, and the recovery period, are delayed in the subareolar technique.

Keywords Sentinel lymph node · Blue dye · Isosulfan blue · Pulse oximeter

Introduction

The sentinel lymph node is the first node receiving lymphatic drainage from the tumor bed. Sentinel lymph node biopsy (SLNB) was first described by Cabanas in penile cancer, and was also used in malignant melanoma and breast cancer [1–6]. It is accepted as one of the major advances in breast surgery since it avoids unnecessary radical axillary dissections and provides a more dedicated histopathological examination in a limited number of lymph nodes. The technique can be performed using a Tc-99 m labeled radiocolloid, a vital blue dye, or the combination of the two [2]. Isosulfan blue is one of the most commonly used blue dyes for sentinel node identification [7]. It is an aniline dye (2,5-disulfanated isomer of patent blue dye), and was first used for SLNB in breast cancer in 1994 by Giuliano et al. [8]. However, it is not without side effects. Adverse effects such as allergic reactions can occur in 1 % of the cases, which can be accompanied with severe hypotension in 0.5 % of the patients [7–10]. Depending on the local vascularization, blue dye can be quickly reabsorbed into the bloodstream and finally excreted from the body. This results in discoloring of the skin, urine, and body secretions [11]. Although it is not a real hypoxemic state, false SpO₂ readings during pulse oximeter monitoring have also been described [12]. It is related to the incorrect measurement of the saturation value due to blue discoloration of the serum absorbing red light.

This study was conducted after the observation of two significant (11 and 14 %) SpO₂ falls following isosulfan blue injection in the subareolar space during routine SLNB. As a review of the literature revealed limited data about the interference with pulse oximeter readings, we aimed to review the characteristics of SpO₂ declines following isosulfan blue injection into the subareolar space.

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Table 1 Age, tumor histology and surgical method performed in the isosulfan group

Characteristic	Value
Age (years)	
Mean	55
Range	(35–81)
Tumor histology (patient number)	
Benign	7
Malignant	20
Invasive ductal carcinoma (IDC)	15
Invasive lobular carcinoma (ILC)	1
Mixed (IDC + ILC)	1
Others	3
Surgical method (patient number)	
Excisional biopsy	7
Partial mastectomy + SLNB	6
Partial mastectomy + SLNB + AD	4
Total mastectomy + SLNB	5
Total mastectomy + SLNB + AD	5

Material and Methods

The study group (isosulfan group) included 27 consecutive female patients with known breast cancer or BIRADS 5 category breast mass lesion undergoing breast surgery between June 2008 and February 2009. Those patients with additional cardiopulmonary disease or hepatic and renal insufficiency were excluded. The age range was 35–81 (mean 55) years. Details of study group characteristics are given in Table 1. As a control group, 27 patients (15 females and 12 males, age range 20–68 years, mean age 48 years) without evidence of cardiovascular, hepatic, and renal disease scheduled for miscellaneous surgical procedures without blue dye injection were also monitored for oxygen saturation changes. Pulse oximeter (Mindrey PM-9000) readings were recorded from the index finger

Table 2 Number of patients showing SpO₂ declines in isosulfan and control groups for ≥ 2 % and ≥ 4 % cut-off value and their statistical comparisons

	Isosulfan group n (%)	Control group n (%)	Statistics (chi-square)
≥ 2 %	19 (70.4 %)	5 (18.5 %)	$p=0.000$
≥ 4 %	13 (48.1 %)	0 (0.0 %)	$p=0.000$

contralateral to the operation site. Institutional ethical rules were followed and informed consent was obtained from all patients.

All patients underwent lymphatic mapping using the combined method, under gamma probe guidance. Tc-99 m nanocolloid (Nanocoll, Nycomed Amersham Sorin s.r.l., Saluggia, Italy) was injected at the periareolar region intradermally the day before surgery. Five milliliters of isosulfan blue 1 % (Lymphazurin, Wedgewood Pharmacy) injection into the subareolar space was performed following induction of anesthesia. Injections of blue dye were performed with aspiration to avoid intravascular injections. Five minutes of efficient massage was then performed in order to stimulate lymphatic drainage.

SpO₂ values were recorded every 5 min starting with the time of blue dye injection up to 45 min. Subsequently, data collection continued at 15-min interval for a total period of 180 min.

Differences between the two groups for each recording were compared using the Mann–Whitney *U* test. To allow comparison with a previously reported series, two cut-off values, ≥ 2 and ≥ 4 %, were assessed separately and the effects of these two different cut-off values were tested using the chi-square test. A *P* value of ≤ 0.05 was accepted as significant.

Results

The baseline SpO₂ level ranged between 98 and 100 % in blue dye injected patients and 97 and 100 % in the control group.

Fig. 1 The number of patients in study and control groups for each percentage of SpO₂ fall

Table 3 Median $\pm$ Interquartile Range (IR) values for SpO₂ decline starting time and time to peak SpO₂ decline in patients having significant SpO₂ fall in isosulfan group. Results are given both for ≥ 2 % and ≥ 4 % cut-off values

	Median $\pm$ IR (min)
Start of SpO ₂ decline	
Cut-off value ≥ 2 %	10.0 $\pm$ 10
Cut-off value ≥ 4 %	10.0 $\pm$ 10
Time to peak SpO ₂ decline	
Cut-off value ≥ 2 %	40.0 $\pm$ 30
Cut-off value ≥ 4 %	40.0 $\pm$ 30

During 180 min of monitorization, a decrease in SpO₂ was noted in all patients except one in the study population (26/27, 96.2 %). In the control group, oxygen saturations declined in 13 patients and remained almost stable in 14 patients (51.9 %). The frequencies of SpO₂ alterations were significantly different between the study and control groups (chi-square test, $P < 0.001$).

In the control group, maximum SpO₂ decline was observed to be 3 % with a median $\pm$ interquartile range (IR) of 0.0 $\pm$ 1.0 %. Among the 27 isosulfan blue injected patients, maximum SpO₂ decline was found to be 18 % and the median $\pm$ IR SpO₂ decline was 3.0 $\pm$ 4.0 %. Statistical analysis supported the significant difference of SpO₂ changes between the study and control groups (Mann–Whitney U test, $P < 0.001$).

Considering SpO₂ decline of ≥ 4 % as the cut-off value, 13 cases (48.1 %) in the study group showed a decrease in SpO₂. With a cut-off value of ≥ 2 %, there were 19 patients with significant SpO₂ fall (70.3 %). The distribution of patients for various SpO₂ fall levels is shown in Fig. 1. The difference between the two groups using either ≥ 2 or ≥ 4 % cut-off values was also statistically significant (chi-square test, $P < 0.001$) (Table 2).

When the time-related variables of the SpO₂ alterations were reviewed in 13 patients with ≥ 4 % decline, decrease in SpO₂ was found to begin at the 5th minute in 6, at the 10th minute in 5, and at the 15th minute in 2 patients (median $\pm$ IR: 10.0 $\pm$ 10.0 min). SpO₂ reached to the lowest value at the 5th minute in 2, at the 30th minute in 2, at the 45th minute in 3, at

the 60th minute in 5 patients, and at the 120th minute in 1 patient (median $\pm$ IR: 40.0 $\pm$ 30.0 min) (Table 3). The mean SpO₂ values obtained for each SpO₂ recording time are shown in Fig. 2. Statistical analysis revealed a statistically significant difference in all recordings of SpO₂ between 15 and 180 min between the control and isosulfan groups (Mann–Whitney U test, $P < 0.001$).

Review of the overall monitorization recordings during 180 min illustrated that SpO₂ returned to the initial value only in 2 of 13 patients with a significant SpO₂ fall (one patient at 120th and one at 180th minutes). At the 180th minute, 3 patients showed a recovery with a 2 % difference from the baseline value, 3 with a difference of 3 %, and 5 patients with ≥ 4 %.

Discussion

The monitorization of oxygen saturation using pulse oximetry has become a standard method in patients undergoing surgical procedures with general anesthesia. The mechanism of measuring SpO₂ using a pulse oximeter is based on emitting a light at a wavelength of 660 nm that is measured with a photodetector after passing through the tissue. False pulse oximeter reading due to blue dyes is a well-described phenomenon, and therefore no additional invasive monitoring is recommended in patients without cardiopulmonary diseases [13]. Although there are no comparative studies evaluating the effect of blue dye dosages and injection routes on side effect occurrence rates in the literature, in the light of previous reports, injection technique and the type of blue dye are thought to be two major factors that may influence the absorption of the dye into the vascular compartment, and thus the severity and duration of SpO₂ falls on pulse oximeter readings. Oxygen saturation falls are documented to be around 2 % when blue dye is injected intradermally, and may exceed 5 %, especially when the dye is injected in tissues with high blood supply, such as the uterine cervix [14, 15].

In the literature there are a few series evaluating interaction of blue dyes with pulse oximeter readings. The two most widely used blue dyes, methylene blue and isosulfan blue,

Fig. 2 Mean SpO₂ values obtained for each SpO₂ recording time is shown. Values obtained between 15 and 180 min reveal statistically significant difference

are compared in the study of Pinero et al., and methylene blue has been found to interfere less with pulse oximeter readings. With the exception of Pinero's study, in which injection was performed around the areola, dyes are usually injected peritumorally in breast tissue and intradermally in melanoma patients [13, 14, 16, 17]. However, in SLNB practice, periareolar or subareolar injection routes for radiocolloid and/or blue dyes are becoming more common, with the advantages of injection facility and higher success rates [18, 19]. Subareolar injection of blue dye combined with periareolar radiocolloid injection is the currently used method in our institution, and the effect of subareolar injection of the blue dye on SpO₂ changes is evaluated in this study.

In the study group receiving blue dye injection, the median $\pm$ IR SpO₂ decrease was found to be 3.0 ± 4.0 %. The ratio of SpO₂ decline was in concordance with the previous reports [13, 17, 20]. It is noted that in similar studies using isosulfan blue, any SpO₂ decrease or SpO₂ decrease as low as 2 % is accepted as clinically significant [14, 20]. Since there might be slight alterations in pulse oximeter readings even in the absence of an interfering factor, we designed a control group that may also aid in defining a cut-off value for significant SpO₂ change. Considering that the maximum SpO₂ decline observed in the control group was 3 %, we defined ≥ 4 % as a cut-off for significant SpO₂ change. At this cut-off value, almost half of the patients (48.1 %) exhibited significant SpO₂ change. The percentage of patients having SpO₂ decline reaches 70.3 % when the cut-off value is accepted as ≥ 2 %. While the frequency of SpO₂ decrease appears to be higher in the study of Momeni et al., in which frequency of SpO₂ declines is given as 20 % for ≥ 2 % and 5 % for ≥ 4 % cut-off values, this might be related to the difference in injection routes and injected tissues. These authors have used intradermal injection of isosulfan blue in patients with melanoma [14]. However, comparable results were reported in the study of El-Tamer et al., evaluating the effect of isosulfan blue injection into breast parenchyma [15].

Starting time (Median $\pm$ IR) for SpO₂ decrease and time to peak SpO₂ decrease were 10.0 ± 10.0 min and 40.0 ± 30.0 min, respectively, in our study. Time to the lowest SpO₂ value was found to be delayed for approximately 10 min when compared with several studies using intradermal injections in melanoma and intraparenchymal injections in breast carcinoma [13, 14]. In another work published by Pinero et al., isosulfan blue injected around the areola yielded a peak SpO₂ fall 30 min earlier than our study group at 15 min [16].

During 180 min of monitorization, only 2 patients with significant SpO₂ fall returned to their baseline values; one at 120 min and the other at 180 min. While the current number of patients is quite limited, this finding is discordant with the results of a study evaluating the effect of intraparenchymal isosulfan injection. In this study, return to baseline value was noted at 95 and 110 min, respectively, if 1 and 2 % difference

from baseline values was considered acceptable [13]. In our 13 patients with significant SpO₂ fall, when 2 % difference from the initial SpO₂ value was considered acceptable, a total of 4 cases could approach to the initial reading.

In conclusion, we have noted that false SpO₂ readings may frequently be recorded in patients receiving subareolar isosulfan blue injection for SLNB. The decline of SpO₂ may extend beyond 4 % in almost half of the patients. The time to the lowest SpO₂ and recovery period was found to be longer in cases using the subareolar injection route when compared with the reported values using intraparenchymal and intradermal routes. Therefore, it is important for anesthetists and physicians performing blue dye injection in their practice, besides serious side effects secondary to allergic reactions, potential differences related to injection route or blue-dyes should be considered when evaluating the pulse oximeter readings.

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