Pulse Oximetry Desaturation Following The Use Of Isosulfan Blue: Influence Of The Site Of Injection
M Daley, P Norman, J Leak, D Nguyen, T Bui

Citation

Abstract
Purpose: To examine the influence of injection site on pulse oximetry oxyhemoglobin saturation (SpO$_2$), following intraoperative injection of isosulfan blue (IB) into breast or cutaneous melanoma regions.

Purpose: Anesthetic records of 497 patients with breast cancer and 824 with cutaneous melanoma were reviewed. SpO$_2$ was recorded every 15 minutes from 15 minutes before until 120 minutes after IB injection.

Results: The mean SpO$_2$ was lower in the breast than melanoma group at 15-120 minutes after IB injection (p<0.00001). The incidence of desaturation of any severity was higher in the breast (77.9%) than melanoma group (43.1%) (p<0.00001). The incidence of major desaturation (>4% SpO$_2$ decrease) was higher in the breast (20.9%) than melanoma group (1.7%) (p<0.00001). The breast group had a greater maximum SpO$_2$ decrease and lower minimum SpO$_2$ during desaturation (p<0.00001), higher incidence of minimum SpO$_2$<95% (p<0.00001), and earlier desaturation onset (p=0.0088). Risk factors for desaturation of any severity were breast group, higher body mass index, and lower intraoperative FiO$_2$, and for major desaturation were breast group and higher baseline intraoperative SpO$_2$.

Conclusion: Injection of IB into breast tissue was associated with a higher incidence, greater severity, and earlier onset of SpO$_2$ desaturation, compared to intradermal injection into the area surrounding cutaneous melanomas.

INTRODUCTION
Intraoperative lymphatic mapping (IOLM) has become an integral component of the surgical management of many cancer patients. In this procedure, isosulfan blue (IB; Lymphazurin®1%), a vital blue dye, is injected into the tissue immediately surrounding a tumor, where it binds to albumin in the interstitial fluid and travels with the albumin to the regional lymphatic system. In this manner, the lymph node(s) draining the tumor are stained with a deep blue color and can be selectively biopsied.

Although IB initially travels through the lymphatic system, it ultimately enters the systemic circulation, often imparting a bluish hue to the patient’s skin. This colouration frequently mimics cyanosis. Cyanosis-like colour changes are most commonly differentiated from true patient hypoxemia by pulse oximetry, but this method may be unreliable in the presence of IB. Similar to methylene blue, the light absorption peak of IB is 646 nm, which allows the pulse oximeter to interpret IB as deoxyhemoglobin, thus producing spurious decreases in oxyhemoglobin saturation when measured by pulse oximetry (SpO$_2$). Characterization of the usual patterns of SpO$_2$ changes which accompany the administration of IB is important, as it will allow any deviations to be immediately attributed to potentially true patient hypoxemia, and appropriate management to be initiated. As absorption of IB into the systemic circulation may be expected to vary with the site of injection, we postulated that the pattern of SpO$_2$ changes may vary with different injection sites. Previous studies have been limited to 21 to 92 patients, and have included patients with only a single site of IB injection: intraparenchymal injection for breast cancer in three studies and intradermal injection for melanoma in one study. Due to differences between these studies in methodology, definitions of desaturation, outcome variables, patient populations, and institutional practices, it is not
possible to directly compare their results to obtain an accurate assessment of the influence of injection site on the pattern of SpO\textsubscript{2}, changes after IB. The current study was thereby designed to compare the changes in SpO\textsubscript{2} following the intraoperative injection of IB in a large number of patients having either melanoma or breast surgery at a single institution.

**METHODS**

Following approval of our institutional review board, we reviewed the charts of 1714 consecutive patients with cutaneous melanoma or breast cancer who had IOLM with IB from January 1, 1996 to February 15, 2001. To eliminate the potential variability of ventilation associated with spontaneous respirations, only those procedures performed with general anesthesia and controlled ventilation were included. Patients less than 16 years old were excluded due to differences in respiratory physiology between the pediatric and adult age groups.

The anesthetic record of each of the 1624 procedures fulfilling the above criteria was examined. The SpO\textsubscript{2}, inspired oxygen concentration (FiO\textsubscript{2}), and blood pressure data were collected at the following times: 15 minutes before IB injection (preIB); at IB injection (IB); and every 15 minutes after IB injection until 120 minutes after injection. The latter time periods were designated as postIB-15, postIB-30, postIB-45, etc., for 15 minutes, 30 minutes, 45 minutes, etc., after IB injection, respectively. All anesthetic records were non-automated records, in which the information was entered manually by the anesthesia care provider.

The preIB SpO\textsubscript{2} value was designated as the baseline SpO\textsubscript{2}, and the FiO\textsubscript{2} at that time as the baseline FiO\textsubscript{2}. If a preIB SpO\textsubscript{2} value was not recorded, the procedure was excluded from further data analysis. Individual SpO\textsubscript{2} values were considered invalid, and not used in the data analysis, if the concurrent systolic blood pressure was lower than 90 mmHg or the FiO\textsubscript{2} differed from the baseline FiO\textsubscript{2}. At least two valid SpO\textsubscript{2} values after the injection of IB were necessary for the surgical procedure to be included in the data analysis. A total of 1321 procedures fulfilled the above inclusion criteria and were used for the final data analysis.

For these 1321 procedures, the patients' hospital charts were reviewed to identify the presence of other surgical procedures which were similar to the IB surgery, but did not involve the administration of IB. These were used as controls during data analysis and were designated as “non-IB” procedures. If more than one non-IB procedure was identified for a patient, the procedure whose date was closest to the IB surgery was used for analysis. For the non-IB procedures, the SpO\textsubscript{2}, FiO\textsubscript{2}, and blood pressure data were collected at 15-minute intervals throughout the procedure.

To facilitate comparisons between the SpO\textsubscript{2} data for the IB and non-IB procedures at individual time periods, the approximate time of IB injection after induction of anesthesia was used as a “simulated IB time” for the non-IB procedures. This occurred at 15 minutes after induction for both the melanoma and breast groups. The SpO\textsubscript{2} value 15 minutes prior to the simulated IB time was chosen as the baseline (preIB) SpO\textsubscript{2}, and the FiO\textsubscript{2} at this time was designated as the baseline FiO\textsubscript{2}. The criteria for considering a SpO\textsubscript{2} measurement as valid, and for including the surgical procedure in the data analysis, were identical to the criteria used for the IB surgery.

For each IB and non-IB procedure with valid SpO\textsubscript{2} data, the occurrence of any decrease in SpO\textsubscript{2} below the baseline SpO\textsubscript{2} value was determined. If present, it was referred to as a “desaturation”, and the following data were recorded: time of onset of desaturation; minimal SpO\textsubscript{2} value during the desaturation; time of occurrence of the minimal SpO\textsubscript{2} value; and the maximum decrease in SpO\textsubscript{2} below the baseline SpO\textsubscript{2}. The desaturation was classified as “major” if the SpO\textsubscript{2} decreased > 4% below baseline. If more than one desaturation episode occurred during a surgical procedure, only the first was considered in the data analysis.

Demographic data were collected for each patient. Body mass index (BMI) was calculated using the formula: BMI = weight(kg) / height(m)\textsuperscript{2}. Based on the site of IB injection, patients were assigned to either the melanoma or breast groups. The IB was injected intradermally in the melanoma group and intraparenchymally in the breast group.

Data are presented as mean±1 SD (median;range) unless otherwise indicated. Statistical calculations were performed using Systat® Version 9 (Systat, Inc., Evanston, IL). Unpaired and paired t-tests, one-way ANOVA, repeated-measures ANOVA, chi-square analysis, Fisher's exact tests, and multiple logistic regression analysis were used where appropriate. A p value <0.05 was considered statistically significant.
RESULTS
There were 824 patients with cutaneous melanoma (melanoma group) and 497 patients with breast cancer (breast group). Demographic data for both groups are presented in Table 1.

Figure 1
Table 1: Demographic Data For Patients With Procedures Involving The Injection Of Isosulfan Blue

<table>
<thead>
<tr>
<th></th>
<th>Melanoma (n=824)</th>
<th>Breast (n=497)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>61.5±15.3 (51, 16-90)</td>
<td>55.3±11.7 (65, 26-84)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Gender</td>
<td>343 females, 481 males</td>
<td>492 females, 56 males</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>ASA Class</td>
<td>2.2±0.6 (2; 1-4)</td>
<td>2.2±0.6 (2; 1-4)</td>
<td>NS *</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>27.9±6.7 (27, 16-59.1)</td>
<td>27.2±6.8 (26, 16-62.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Volume of IB (mins)</td>
<td>2.4±0.8 (2.4, 0.2-6)</td>
<td>5.0±0.7 (5, 1-10)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Preoperative SpO₂</td>
<td>99.2±1.5% (98, 91-100)</td>
<td>98.8±1.3% (99, 92-100)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Intraoperative FIO₂</td>
<td>56±12% (55, 30-100)</td>
<td>57±11% (60, 26-100)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative Baseline SpO₂</td>
<td>99.4±0.8% (100, 96-100)</td>
<td>99.6±0.9% (100, 96-100)</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory Disease</td>
<td>30% (24.9%)</td>
<td>99 (19.9%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Current Cigarette Smoker</td>
<td>14% (17%)</td>
<td>63 (12.7%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>20% (25.0%)</td>
<td>121 (24.3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

As shown in Figure 1, the mean SpO₂ during IB surgery was significantly lower than baseline at each 15-minute time period from postIB-15 to postIB-105 for the melanoma group, and from the time of IB injection to postIB-120 for the breast group. The mean SpO₂ was significantly lower for the breast than the melanoma group at all times from postIB-15 to postIB-120. The lowest mean SpO₂ occurred at 45 minutes after IB injection for the breast group, and 60 minutes after injection for the melanoma group.

Figure 2
Figure 1 Legend: Mean SpO₂ at 15-minute time intervals for the melanoma and breast groups during surgery involving the injection of IB. The time periods correspond to the following times: PreIB = 15 mins before IB injection (= baseline); IB = at time of IB injection; PostIB-15 = 15 mins after IB injection, PostIB-30 = 30 mins after IB injection, PostIB-45 = 45 mins after IB injection, etc. * p < 0.005 vs. baseline SpO₂ for melanoma group † p < 0.00001 vs. baseline SpO₂ for melanoma group Å‡ p < 0.00001 vs. melanoma group

As shown in Table 2, the minimum SpO₂ during surgery (including all patients in each group, whether or not they desaturated) was significantly lower in the breast than the melanoma group. The incidence of desaturation of any severity was significantly higher in the breast than the melanoma group. The incidence of major desaturation was also significantly higher in the breast group. The breast group had a significantly greater maximum decrease in SpO₂ during desaturation, lower minimum SpO₂ during desaturation, and higher percentage of procedures with a minimum SpO₂ <95%. The time of onset of desaturation was significantly earlier for the breast than the melanoma group. The time of minimum SpO₂ during desaturation did not differ significantly between groups.
Table 3 presents data regarding potential risk factors for desaturation of any severity and major desaturation. The results of univariate and multivariate analyses are included. The breast group was an independent risk factor for both desaturation of any severity and major desaturation, by multivariate analysis.

SpO₂ data were obtained from non-IB procedures for 181 patients: 121 from the melanoma group and 60 from the breast group. The types of non-IB procedures are listed in Table 4. For both the melanoma and breast groups, the non-IB and IB procedures had similar preoperative SpO₂, intraoperative FiO₂, and baseline intraoperative SpO₂ values (p>0.05).
Table 4: Types Of Non-Ib Procedures Used As Control Data For Each Group

<table>
<thead>
<tr>
<th>Melanoma Group (n=121)</th>
<th>Breast Group (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure: number of patients</td>
<td>Procedure: number of patients</td>
</tr>
<tr>
<td>completion lymph node dissection: 96</td>
<td>minor plastic surgery reconstructive procedure of the breast: 26</td>
</tr>
<tr>
<td>wide local excision of the cutaneous melanoma: 10</td>
<td>partial or total mastectomy: 14</td>
</tr>
<tr>
<td>hyperthermic limb perfusion with chemotherapeutic agent: 6</td>
<td>completion axillary node dissection: 10</td>
</tr>
<tr>
<td>plastic surgery reconstructive procedure at the cutaneous melanoma site: 3</td>
<td>breast biopsy: 3</td>
</tr>
<tr>
<td>evacuation of seroma or hematoma after IB procedure: 3</td>
<td>incision and drainage/debridement of the breast after IB procedure: 3</td>
</tr>
<tr>
<td>above elbow amputation: 1</td>
<td>evacuation of hematoma after IB procedure: 2</td>
</tr>
<tr>
<td>teeth extraction: 1</td>
<td>mastectomy plus completion axillary node dissection: 1</td>
</tr>
</tbody>
</table>

As shown in Figure 2, the mean SpO₂ at every 15-minute time period during the non-IB surgery was similar to the baseline SpO₂, for both the melanoma and breast groups. For the melanoma group, the mean SpO₂ during the IB surgery was significantly lower than during the non-IB procedures from the time of IB injection to postIB-105. For the breast group, the mean SpO₂ during the IB surgery was significantly lower than during the non-IB surgery from the time of IB injection to postIB-120. For the melanoma group, the lowest mean SpO₂ occurred at 45 minutes after IB injection during the IB surgery and at 105 minutes after the simulated injection time during the non-IB procedures. For the breast group, the lowest mean SpO₂ occurred at 30 minutes after injection during the IB surgery and at 75 minutes after the simulated injection time during the non-IB procedures.

As shown in Table 5, the minimum SpO₂ during surgery (including all patients, whether or not they desaturated) was significantly lower during the IB procedures than the non-IB surgery, for both the melanoma and breast groups. The incidence of desaturation of any severity was greater during the IB surgery than the non-IB surgery for both the melanoma and breast groups. The incidence of major desaturation was significantly greater during the IB than the non-IB surgery for the breast group but not the melanoma group. The maximum decrease in SpO₂ during desaturation was significantly greater and the minimum SpO₂ during desaturation was significantly lower during the IB surgery compared to the non-IB procedures for the melanoma group. The breast group exhibited trends toward the maximum decrease in SpO₂ during desaturation being greater (p=0.062) and the minimum SpO₂ during desaturation being lower during the IB surgery (p=0.061), but these did not achieve statistical significance. A minimum SpO₂ <95% occurred in only two procedures, both of which were breast IB surgery.
For both the melanoma and breast groups, there were trends toward the onset of desaturation occurring earlier during the IB surgery than the non-IB procedures, but these did not achieve statistical significance (p=0.054 and 0.056, respectively). Likewise, there were trends toward an earlier occurrence of minimum SpO$_2$ during desaturation with the IB surgery for both the melanoma and breast groups, but these were also not statistically significant (p=0.068 and 0.11, respectively).

**DISCUSSION**

Despite the pulse oximeter's undisputed role in revolutionizing the assessment of patient oxygenation, its measurements must be interpreted with caution. A wide variety of factors can influence its reliability as a monitor of true patient hypoxemia, including the administration of a number of dyes. The SpO$_2$ is determined spectrophotometrically based on the pulse-added differential absorption of light at two different wavelengths: 660 and 940 nm. As such, any substance in the arterial blood which absorbs light at either of these wavelengths may influence the SpO$_2$ value. Substances which predominantly absorb light at 660 nm will be interpreted as deoxyhemoglobin, and produce a spuriously low SpO$_2$. IB, with its absorption peak of 646 nm, appears to function in this manner. The current study demonstrates that the site of injection has a major influence on the SpO$_2$ changes which occur after the intraoperative administration of IB. Injection in the breast region resulted in almost twice the incidence of desaturation compared to injection in the area surrounding cutaneous melanoma lesions (77.9% vs. 43.1%, respectively). As well, the severity of desaturation was greater for the breast than the melanoma group, as demonstrated by lower mean SpO$_2$ values at every 15-minute time interval from 15 to 120 minutes after IB injection, a lower minimum SpO$_2$ during surgery (including all patients in the group, whether or not they desaturated), a higher incidence of desaturation classified as major, a greater maximum decrease in SpO$_2$ during desaturation, a lower minimum SpO$_2$ during desaturation, and a higher percentage of procedures with a minimum SpO$_2$ <95%.

These results confirm the suggestion from previous studies that IB injection into the breast region may be associated with a higher incidence of desaturation than injection at melanoma sites. In the two prior studies of breast surgery which provided incidence values, desaturation was identified in 95% and 100% of the patients, whereas the only previous study of melanoma patients reported an incidence rate of 82%. However, as explained in the INTRODUCTION section, these studies differed from each other in many aspects, and it was not appropriate to directly compare their results. Including both breast and melanoma patients in our current study allowed a more valid comparison of the two sites of IB injection.

The desaturation incidence values in our study were lower than the previous reports. This may be at least partly attributable to the retrospective nature of our study and the use of SpO$_2$ data from manually recorded anesthetic records. Some decreases in SpO$_2$ may not have been recorded by the anesthesia care provider if they were considered by the individual to be “minor” or “unimportant”. As well, the recording of the SpO$_2$ data at 15-minute intervals may have allowed transient or intermittent changes to remain undetected. The discrepancy may also reflect the failure of the previous studies to control for hypotension. Poor peripheral perfusion is a well established cause of decreases in pulse oximetry measurements, and we attempted to diminish its influence by excluding SpO$_2$ data during which the systolic blood pressure was <90 mmHg.

The mechanism through which the site of injection influences the effects of IB on pulse oximetry measurements.

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**Figure 7**

Table 5: SpO$_2$ And Desaturation Data For Patients With Both Ib And Non-Ib Procedures
Pulse Oximetry Desaturation Following The Use Of Isosulfan Blue: Influence Of The Site Of Injection

may be related to differential absorption of the dye into the systemic circulation. Although the volume of IB injected was higher in the breast than the melanoma group, volume per se was not an independent variable influencing the incidence of desaturation during multivariate analysis. The breast group received injections in the relatively vascular breast parenchyma, whereas IB in the melanoma group was injected into less vascular intradermal regions. More rapid absorption into the systemic circulation would be anticipated in the breast group, thereby producing higher peak arterial blood levels and greater effects on SpO₂ values. The earlier onset of desaturation in the breast group further supports the suggestion that IB injected into this region was absorbed more quickly. Measurement of IB blood levels after injection into different body regions will be necessary to more conclusively address this issue.

In addition to the site of injection, multivariate analysis identified three other variables as independent risk factors for the occurrence of desaturation. An increased incidence of desaturation of any severity was associated with a lower FiO₂ and higher BMI. These observations are consistent with our current understanding of the influence of FiO₂ and obesity-related ventilation/perfusion mismatch on hypoxemia. The only factor in addition to the injection site which was associated with an increased incidence of major desaturation was a higher baseline intraoperative SpO₂. This may be a function of our definition of major desaturation, which required a specific (> 4%) decrease in SpO₂ from baseline. If the minimum SpO₂ attained depends primarily on the quantity of IB within the arterial blood and is unrelated to the initial SpO₂, those patients with a higher baseline SpO₂ would be expected to experience a larger decrease in SpO₂.

The breast and melanoma groups differed from each other with respect to a number of demographic factors. This was not unexpected due to the non-randomized nature of our study. None of the differing factors were identified as independent variables influencing the incidence of desaturation during multivariate analysis, except the BMI. The breast group had a lower BMI than the melanoma group, whereas a higher BMI was associated with an increased incidence of desaturation of any severity. Thus, the difference in the incidence of desaturation of any severity between the melanoma and breast groups may have been more pronounced if the groups had similar BMI values.

As many factors may effect pulse oximetry measurements in addition to IB injection, it was important to provide control data from patients who had surgery which did not involve IB. In the only previous study which has included a control group, 84 consecutive patients having IOLM surgery for cutaneous melanoma were examined: IB was administered to the first 60 patients and no dye was administered to the next 24. Demographic data for the IB and control groups were not compared. In our study, we used the patients as their own controls, thereby eliminating much of the variability attributable to differences in a variety of patient factors. Procedures performed at our institution which were similar to the IB surgery were used for the control, non-IB surgery data, and direct comparisons between the IB and non-IB procedures only included the 181 patients with non-IB data.

The non-IB surgery data support the premise that IB was the major cause of desaturation observed during the IB procedures. For example, the mean SpO₂ for both the melanoma and breast groups did not decrease below baseline at any of the time periods examined during their non-IB surgery. Desaturation was observed during the non-IB surgery but the incidence was less than during the IB procedures for both the melanoma and breast groups. As well, most parameters reflecting the severity of desaturation revealed less pronounced decreases in SpO₂ during the non-IB surgery, compared to the IB procedures.

CONCLUSIONS
In summary, the site of injection has a major influence on the pattern of pulse oximetry changes following the intraoperative injection of IB. Injection of IB into breast parenchymal tissue was associated with a higher incidence, greater severity, and earlier onset of pulse oximetry desaturation, compared to intradermal injection into the area surrounding cutaneous melanomas. These observations may be attributable to faster absorption of IB from the more vascular breast tissue, compared to the less vascular intradermal sites.

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References
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