

Case Reports

Anaphylaxis and other adverse reactions to blue dyes: a case series

J. D. HOWARD*, V. MOO†, P. SIVALINGAM‡

Department of Anaesthesia, Princess Alexandra Hospital, Brisbane, Queensland, Australia

SUMMARY

We report three cases of anaphylaxis during anaesthesia confirmed on intradermal testing to be related to patent blue V dye (Guerbet – Chemical Abstract Service 3536-49-0). All three cases were associated with moderate to severe hypotension. Two cases had delayed onset, and two were associated with a rash. None of the cases were associated with bronchospasm. In all three patients the interference with pulse oximetry readings contributed to difficulties in management. We recommend the use of a test dose of blue dye prior to surgery, as suggested in the manufacturer's product information. We also recommend high vigilance for possible allergic reactions when patent blue dyes are used for sentinel lymph node mapping, because the presentations may be atypical and the reduced pulse oximetry readings may be a distraction.

Key Words: anaesthesia, anaphylaxis, patent blue V dye

Blue dyes are being used increasingly in oncology surgery, primarily breast and melanoma surgery, to aid in the identification of sentinel lymph nodes^{1,2}. When used in isolation, blue dyes lead to the successful identification of sentinel lymph nodes in up to 96% of cases³. This can be improved up to 99% when they are used in conjunction with preoperatively administered radioisotope-labelled albumin⁴. The blue dye is most suitable in patients with a small tumour and non-palpable lymph nodes, who will have tumour-free sentinel nodes in 66 to 75% cases⁵. These patients are spared from a radical axillary node clearance with its associated pain and disfigurement. However, the use of blue dyes is associated with potential allergic and other adverse reactions. With the patients' consent, we present three cases we encountered over a six-month period who developed serious adverse reactions to blue dye, which were made more difficult to manage due to interference with pulse oximetry readings.

CASE HISTORIES

Case 1

A 52-year-old woman with hypertension controlled with ramipril presented for a wide local excision of a breast lesion and sentinel lymph node biopsy. Anaesthesia was induced with midazolam, fentanyl and propofol and a laryngeal mask airway was inserted. Following induction, the patient received cephazolin 1g intravenously (IV) for routine infection prophylaxis. Anaesthesia was maintained with sevoflurane in oxygen-enriched air. The operating surgeon administered 2 ml of 2.5% patent blue V (PBV) intraparenchymally in the sub-areolar region. Approximately 10 minutes later the patient became bluish grey in colour and her pulse oximetry readings decreased from 97 to 92%. Other vital signs remained stable. Thirty-five minutes into surgery, the surgeon noticed blue wheals on the breast. At the same time she became hypotensive (73/45 mmHg) and her pulse oximetry readings fell to 89%. The urticarial rash was found to extend over her chest, abdomen, upper thighs and arms (Figure 1). There was no evidence of bronchospasm or angioedema.

The patient was treated with a 500 ml bolus of crystalloid, three boluses of metaraminol 0.5 mg and hydrocortisone 100 mg IV for presumed anaphylaxis. Cardiovascular stability returned within 20 minutes and the surgery was completed. Arterial blood gas analysis during this time showed a P_{aO_2} of 64 mmHg

* B.Biomed.Sc., M.B., B.S., Anaesthetic Registrar.

† M.B., B.S., F.A.N.Z.C.A., Visiting Medical Officer.

‡ M.B., B.S., M.D., FFAR.C.S.I., F.A.N.Z.C.A., Senior Consultant Anaesthetist.

Address for correspondence: Dr J. Howard, Princess Alexandra Hospital, Brisbane, Qld 4151. Email: jdhoward_mowat@yahoo.com.au

Accepted for publication on November 3, 2010.



FIGURE 1: Blue urticarial rash. Clockwise from above: contralateral arm, thighs, contralateral chest wall.

and a methaemoglobin level of 4%. Her vital signs remained stable at the completion of the surgery with oxygen saturation readings returning to 99%. After extubation, she was closely monitored in the post-anaesthesia care unit for six hours (as there were no high dependency unit [HDU]/intensive care unit [ICU] beds available). She remained haemodynamically stable and well oxygenated during this period, but complained of itching and was treated with promethazine 25 mg intramuscularly. She had an uneventful recovery and was discharged from hospital the following day. A solitary tryptase level measured one hour after the initial reaction was $8 \mu\text{g/l}$ (normal $<13.5 \mu\text{g/l}$). The patient subsequently underwent intradermal skin testing due to the high index of suspicion of anaphylaxis. The test was strongly positive for PBV within 10 minutes and negative for other substances given during her anaesthetic. Interestingly, the patient also exhibited some cross-reactivity to methylene blue (MB) with skin testing.

Case 2

A 54-year-old man with rheumatoid arthritis presented for excision of an infrascapular melanoma and sentinel lymph node biopsy. His regular medications included celecoxib, sulfasalazine, methotrexate and pantoprazole. He also had a history of allergy (rash) to pethidine. Anaesthesia was induced with midazolam, fentanyl and propofol, and cisatracurium was used for muscle relaxation. The airway was secured with an endotracheal tube prior to the patient being placed in a lateral position. Anaesthesia was maintained with sevoflurane in oxygen-enriched air. Cephazolin 1g IV was administered for routine infection prophylaxis and morphine 5 mg IV for analgesia. The surgeon

administered 2 ml of 2.5% PBV intradermally around the lesion. Pulse oximetry readings decreased from 99 to 96% in the 20 minutes following administration of the dye. All other vital signs remained stable. However, approximately 35 minutes post-administration of PBV, hypotension (70/35 mmHg) and generalised flushing with urticaria (red) were noted. There was no bronchospasm or angioedema. A clinical diagnosis of anaphylaxis was made. Hypotension was treated with fluids and repeated boluses of adrenaline $100 \mu\text{g}$ IV to maintain an acceptable blood pressure. He also received dexamethasone 8 mg and promethazine 25 mg IV.

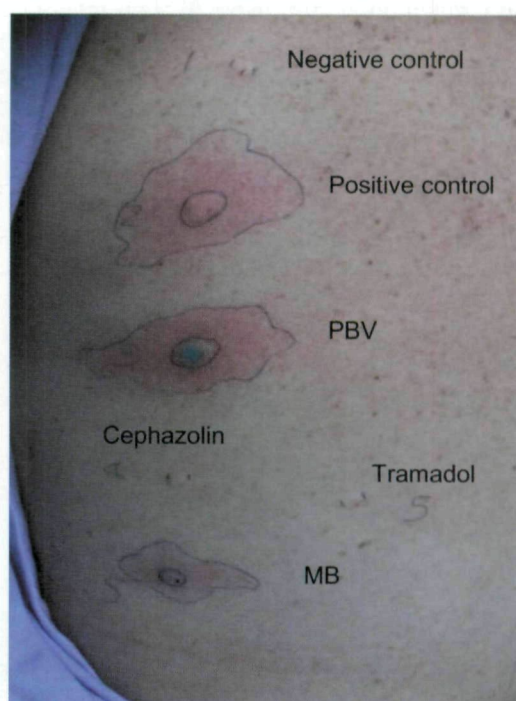


FIGURE 2: Intradermal skin test results for Case 1.

The patient remained haemodynamically stable and the surgery was completed successfully. The patient was extubated and observed for six hours in the post-anaesthesia care unit (as there was no HDU/ICU bed available). He was later discharged to the ward and his remaining postoperative course was uneventful. His serum tryptase level was found to be elevated (18.8 $\mu\text{g/l}$). Subsequent outpatient intradermal skin testing was positive for PBV and negative for other agents administered during his anaesthetic.

Case 3

A 48-year-old woman presented for wide local excision of a right breast lesion and sentinel lymph node biopsy. She had a history of hypertension which was controlled by telmisartan. She had received previous general anaesthetics without complication. She reported an allergic reaction to penicillin since childhood. Anaesthesia was induced with propofol, midazolam and fentanyl, and a laryngeal mask airway was inserted. Anaesthesia was maintained with sevoflurane in oxygen-enriched air. The surgeon administered 2 ml of 2.5% PBV intraparenchymally into the right breast. Ten minutes into the procedure the pulse oximetry readings decreased from 96 to 80%, and the patient became profoundly hypotensive (40/25 mmHg) and bradycardic. The laryngeal mask airway was exchanged for an endotracheal tube. There was no airway swelling or wheeze noted. Her haemodynamics were treated with atropine 0.6 mg IV and repeated metaraminol 0.5 mg IV boluses. An adrenaline infusion was then initiated and titrated to blood pressure response. Subsequently, oxygen saturation improved and her blood pressure stabilised. The surgical procedure was successfully completed. Upon removal of the drapes, a widespread erythematous rash was discovered. The patient required an adrenaline infusion to maintain cardiovascular stability and remained intubated. She was transferred to the ICU for further stabilisation and management. Serum tryptase level measured one hour after the reaction was markedly elevated (52.1 $\mu\text{g/l}$). The patient was extubated and discharged to the ward the following day and had an uneventful recovery. Subsequent outpatient intradermal skin testing was positive for PBV and negative for other agents administered during the anaesthetic.

DISCUSSION

In 2002, the Therapeutic Goods Administration published an adverse drug reaction warning after six cases of anaphylaxis to PBV in Australia⁶. Adverse drug reactions to PBV and isosulfan blue (ISB) were

also being reported in the international literature around this time⁷⁻¹⁴.

The most commonly used blue dye in Australia and Europe for oncology surgery is PBV 2.5% (Guerbet – Chemical Abstracts Service 3536-49-0), while in the United States it is ISB 1% (Tyco International – CAS 68238-36-8). The names of blue dyes have been used interchangeably in the literature, leading to confusion, so it is recommended that the Chemical Abstracts Service registry number be used when writing scientific papers on blue dyes¹⁵. Another blue dye, MB 1% (Phebra – Chemical Abstracts Service 61-73-4 anhydrous) has been used in medicine for over 70 years, though its use in oncology surgery for lymph node identification has only recently been investigated. PBV and ISB are triarylmethane dyes with similar structures¹⁵. MB is structurally unrelated¹⁶.

Anaphylaxis under anaesthesia is uncommon (0.01 to 0.02%)¹⁷ and in 90% of cases occurs within 10 minutes of exposure to the causative agent. In contrast, life-threatening anaphylactic reactions (systolic blood pressure ≤ 70 mmHg requiring vasopressor support) due to PBV or ISB are more common (0.4 to 1.1%^{9-12,18-20}) and are often delayed in onset. In our cases, the delay was 10 to 35 minutes, by which time the patients were completely draped and surgery had commenced. This is consistent with other publications where the average delay before anaphylaxis was 15 to 30 minutes^{18,21} after dye injection. This likely reflects the slower systemic uptake of an intraparenchymal or intradermal injection.

The earliest signs of anaphylaxis in these cases were hypotension and rash, without any accompanying bronchospasm or airway oedema. Despite the development of widespread rashes, they were not immediately recognised, as the patients were beneath surgical drapes. The blue urticaria experienced in Case 1 is a recognised complication of blue dyes, but has only occasionally been photographed and published^{10,13,14,20}. The considerable time interval between drug administration and adverse reaction, along with the inability to identify the rash, causes a delay in diagnosing anaphylaxis.

The management of a hypotensive episode and the diagnosis of anaphylaxis are further confounded by the interference between blue dyes and pulse oximeters, making them unreliable. This interference is due to the peak light absorption of PBV (638 nm²²) and ISB (646 nm²³) being very close to the 660 nm calibration for deoxyhaemoglobin. Increased light absorption in this region will be interpreted by the pulse oximeter as deoxyhaemoglobin, hence a

reduced percentage of oxygen saturation will be displayed. In practice, the degree and timing of interference with pulse oximetry can be quite variable and is dependent on site of injection. Intravascular injection of blue dyes causes an immediate, profound reduction in pulse oximetry reading which lasts for a few minutes²⁴. When injected intraparenchymally, ISB and PBV can cause a decrease in pulse oximetry by up to 11%²⁵ (average 5%) with the nadir occurring 15 to 30 minutes after injection.

In our cases, the pulse oximetry readings decreased to as low as 92% prior to any signs of an allergic reaction. Various causes of desaturation, such as tube misplacement, hypoxic gas mixture, aspiration, pneumothorax, anaphylaxis or equipment malfunction should be excluded before attributing it to the dye. Doubt over the true oxygen saturation in the setting of presumed anaphylaxis led us to perform blood gas analysis in Case 1, which confirmed impaired gas exchange. Blue dyes do not affect arterial blood gas determination of P_aO_2 ²⁶ as this is not measured using spectrophotometry. However, they can yield falsely elevated methaemoglobin results when measured by co-oximetry using a Siemens analyser as we had used for Case 1^{27,28}. This device-dependent error can be avoided by measuring the methaemoglobin level with a Radiometer ABL® blood gas analyser, which uses a different algorithm. The 4% methaemoglobinaemia for Case 1 was therefore considered a false result, although this was not confirmed.

Dye-related allergic reactions can be biphasic, with subsequent hypotension occurring six to eight hours after the initial reaction¹⁰. Ideally patients having suffered an allergic reaction should be kept in a closely monitored environment (ICU/HDU) for at least this length of time. Since no bed was available for Case 1 and Case 2, we decided to observe them for six hours in the post-anaesthesia care unit before discharging them to the ward.

The mechanism of the allergic reaction to blue dyes may be due to cross-linking of pre-formed IgE antibodies, direct mast cell activation or basophil activation. The IgE antibodies to blue dyes have been identified using specific ELISA tests²⁹ though they were not uniformly detected in patients who had allergic reactions to blue dyes. Prior exposure to the dyes is not needed as sensitisation probably occurs by exposure to similar chemicals in foods, cosmetics and textiles⁹.

Elevated serum tryptase levels following suspected anaphylaxis is suggestive of mast cell degranulation. Tryptase levels usually peak within an hour of degranulation and will remain elevated for more

than six hours. Tryptase levels were significantly elevated in Cases 2 and 3, but within the normal limits for Case 1. If there is a strong clinical suspicion of anaphylaxis, the patient should be referred for skin testing irrespective of tryptase result³⁰. When serial tryptase levels are measured during the first six hours post reaction, an increase of 2 µg/l will improve the sensitivity and specificity of the test³¹. In the absence of anaphylaxis, the serum tryptase level does not vary more than 2 µg/l over a short period of time. All three of our cases were referred to an allergy specialist for skin testing.

Skin testing is able to identify the likely causative agent when multiple medications have been given simultaneously prior to an anaphylactic reaction. We recommend intradermal testing over skin-prick testing as there have been several cases²¹ involving negative skin-prick results to blue dyes, when subsequent intradermal tests were positive. All three patients in our series underwent intradermal testing with strongly positive results to PBV. A reaction to both PBV and MB during intradermal testing, as occurred in Case 1, has been reported before^{19,21}. It has been suggested that there may be immunological cross-reactivity between PBV and MB, despite the lack of biochemical resemblance.

Patients taking angiotensin-converting enzyme inhibitors or angiotensin 2 receptor antagonists have been found to have an increased risk of anaphylaxis with blue dyes¹⁸. Interestingly, two of our patients were taking one of these medications. PBV and ISB contain sulphur, but patients with "sulfa allergy" (sulphonamides) are not at increased risk of anaphylaxis to these dyes. Premedication with an antihistamine and a corticosteroid reduces the severity, but not the incidence of allergic reactions³². It is not routine practice to premedicate patients with these agents prior to having blue dye injections.

The product information for PBV states that, "it would seem prudent to test for hypersensitivity by injecting a very small volume of the solution and waiting a few moments to ascertain if there is a reaction". Many surgeons at our institution routinely give patients a test dose in the anaesthetic induction room, but the timing is usually less than 10 minutes before the induction of anaesthesia. It should be noted that the patients in these case series did not receive a test dose prior to surgery for various reasons. Ideally, the test dose should be given to the patient at least 30 minutes before the scheduled surgery, in a monitored environment, with all team members aware of the possibility of allergic reactions.

Our case series sheds additional light on the possibility of allergic reactions during lymph node

mapping surgery and their presentation. It is our practice to inform the patients about the risk of allergy, although the surgeon should also mention this during their consent process. We encourage our surgical colleagues to give a test dose of blue dye prior to surgery. To facilitate this we have the patients brought into the induction room early and attach appropriate monitoring. The test dose is given as soon as the surgeon is available, which means that there can be at least 10 minutes between test dose and induction of anaesthesia. While it would be preferable to observe for a longer period prior to induction, we do not delay induction for this purpose. During the procedure we expect a decrease in pulse oximetry recordings of about 5% from baseline, but we still go through the drill of excluding problems with oxygen delivery or ventilation. If there is doubt regarding oxygen saturation, we have a low threshold for blood gas analysis.

In the event of anaphylaxis, management should include resuscitation and supportive measures to restore normal cardiovascular and respiratory variables. The patient should be closely monitored for six to eight hours after the reaction, even if haemodynamic stability has returned to normal. At least two blood samples (one and six hours) for tryptase levels should be taken to confirm the diagnosis of anaphylaxis. Outpatient referral for intradermal skin testing after six weeks is recommended to identify the causative agent, even if tryptase levels have not been elevated.

Several authors^{4,5,33} have recommended the use of MB as an alternative dye for lymph node mapping in breast surgery. It is comparable to PBV and ISB in experienced hands^{34,35}, and in association with radio-labelled albumin, the sentinel lymph node is identified in up to 99% of cases⁴. MB has a far lower rate of allergy and has less interference with pulse oximetry³⁶. However, as ISB and PBV continue to be used, high vigilance should be instituted for possible allergic reactions when these dyes are used for sentinel lymph node mapping.

ACKNOWLEDGEMENTS

The authors would like to thank the patient in Case 1 for allowing us to use the photographs taken during the case and skin testing. We also like to thank Dr Buff Maycock for her assistance with skin testing.

REFERENCES

1. Hill A, Tran K, Akhurst T, Yeung H, Yeh S, Rosen P et al. Lessons learned from 500 cases of lymphatic mapping for breast cancer. *Ann Surg* 1999; 229:528-535.

2. Albertini J, Lyman G, Cox C, Yeatman T, Balducci L, Ku N et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA* 1996; 276:1818-1822.
3. Syme DBY, Collins JP, Mann GB. Comparison of blue dye and isotope with blue dye alone in breast sentinel node biopsy. *ANZ J Surg* 2005; 75:817-821.
4. Blessing WD, Stoller AJ, Teng SC, Bolton JS, Fuhrman GM. A comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping. *Am J Surg* 2002; 184:341-345.
5. Simmons RM, Rosenbaum Smith, SM, Osborne MP. Methylene blue as an alternative to isosulfan blue for sentinel lymph node localization. *The Breast Journal* 2001; 7:181-183.
6. ADRAC. Patent blue V and anaphylaxis. *Aust Adv Drug React Bull* 2002; 21:10.
7. Sprung J, Tully MJ, Ziser A. Anaphylactic reactions to isosulfan blue dye during sentinel node lymphadenectomy for breast cancer. *Anesth Analg* 2003; 96:1051-1053.
8. Efron P, Knudsen E, Hirshorn S, Copeland EM. Anaphylactic reaction to isosulfan blue used for sentinel node biopsy: case report and literature review. *The Breast Journal* 2002; 8:396-399.
9. Montgomery L, Thorne A, Van Zee K, Fey J, Heerdt A, Gemignani M et al. Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. *Anesth Analg* 2002; 95:385-388.
10. Albo D, Wayne JD, Hunt KK, Rahlfs TF, Singletary SE, Ames FC et al. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. *Am J Surg* 2001; 182:393-398.
11. Cimmino VM, Brown AC, Szocik JF, Pass HA, Moline S, De SK et al. Allergic reactions to isosulfan blue during sentinel node biopsy – a common event. *Surgery* 2001; 130:439-442.
12. Leong SPL, Donegan E, Hefernon W, Dean S, Katz JA. Adverse reactions to isosulfan blue during selective sentinel lymph node dissection in melanoma. *Ann Surg Oncol* 2000; 7:361-366.
13. Sadiq TS, Burns WW 3rd, Taber DJ, Damitz L, Ollila DW. Blue urticaria: a previously unreported adverse event associated with isosulfan blue. *Arch Surg* 2001; 136:1433-1435.
14. Kuerer HM, Hunt KK, Singletary SE, Ames FC. Unusual aspects of breast cancer: case 3 – blue hives during lymphatic mapping for breast cancer. *J Clin Oncol* 2001; 19:2573-2574.
15. Scherer K, Bircher A, Figueiredo V. Blue dyes in medicine – a confusing terminology. *Contact Dermatitis* 2006; 54:231-232.
16. Scherer K, Studer W, Figueiredo V, Bircher A. Anaphylaxis to isosulfan blue and cross reactivity to patent blue V: case report and review of the nomenclature of vital blue dyes. *Ann Allergy Asthma Immunol* 2006; 96:497-500.
17. Currie M, Webb RK, Williamson JA, Russell WJ, Mackay P. Australia incidence monitoring study – clinical anaphylaxis: an analysis of 2000 incident reports. *Anaesth Intensive Care* 1993; 21:621-625.
18. Daley MD, Norman PH, Leak JA, Nguyen DT, Bui TP, Kowalski AM et al. Adverse events associated with the intraoperative injection of isosulfan blue. *J Clin Anesth* 2004; 16:332-341.
19. Keller B, Yawalkar N, Pichler C, Braathen LR, Hunger RE. Hypersensitivity reaction against patent blue during sentinel lymph node removal in three melanoma patients. *Am J Surg* 2007; 193:122-124.
20. Hunting AS, Nopp A, Johansson SGO, Andersen F, Wilhelmsen V, Guttormsen AB. Anaphylaxis to patent blue V. I. Clinical aspects. *Allergy* 2010; 65:117-123.

21. Mertes PM, Malinovsky JM, Mouton-Faivre C, Bonnet-Boyer MC, Benhaijoub A, Lavaud F et al. Anaphylaxis to dyes during the perioperative period: reports of 14 clinical cases. *J Allergy Clin Immunol* 2008; 122:348-352.
22. Newton DW, Breen PJ, Brown DE, Mackie JF Jr, Kluza RB. Physicochemical characteristics of patent blue violet dye. *J Pharm Sci* 1981; 70:122-127.
23. Coleman RL, Whitten CW, O'Boyle J, Sidhu B. Unexplained decrease in measured oxygen saturation by pulse oximetry following injection of Lymphazurin 1% (Isosulfan Blue) during a lymphatic mapping procedure. *J Surg Oncol* 1999; 70:126-129.
24. Scheller MS, Unger RJ, Kelner MJ. Effects of intravenously administered dyes on pulse oximetry readings. *Anesthesiology* 1986; 65:550-552.
25. El-Tamer M, Komenaka I, Curry S, Troxel A, Ditkoff B, Schnabel FR. Pulse oximeter changes with sentinel lymph node biopsy in breast cancer. *Arch Surg* 2003; 138:1257-1260.
26. Koivusalo AM, Von Smitten K, Lindgren L. Sentinel node mapping affects intraoperative pulse oximetric recordings during breast cancer surgery. *Acta Anaesthesiol Scand* 2002; 46:411-414.
27. Kieckbusch H, Coldeway S, Hollenhorst J, Haeseler G, Hillemanns P, Hertel H. Patent blue sentinel node mapping in cervical cancer patients may lead to decreased pulse oximeter readings and positive methaemoglobin results. *Eur J Anaesthesiol* 2008; 25:365-368.
28. Burgoyne LL, Jay DW, Bikhazi GB, De Armendi AJ. Isosulfan blue causes factitious methemoglobinaemia in an infant. *Paediatr Anaesth* 2005; 15:1116-1119.
29. Wöhrle S, Focke M, Hinterhuber G, Stingl G, Binder M. Near fatal anaphylaxis to patent blue V. *Br J Dermatol* 2004; 150:1037-1038.
30. Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *BJA* 1998; 80:26-29.
31. Brown SA, Blackman KE, Heddle RJ. Can serum mast cell tryptase help diagnose anaphylaxis? *Emergency Medicine Australasia* 2004; 16:120-124.
32. Raut CP, Hunt KK, Akins JA, Ross MI, Singletary SE, Marshall GD et al. Incidence of anaphylactoid reactions to isosulfan blue dye during breast carcinoma lymphatic mapping in patients treated with preoperative prophylaxis. *Cancer* 2005; 104:692-699.
33. Thevarajah S, Huston TL, Simmons RM. A comparison of the adverse reactions associated with isosulfan blue versus methylene blue dye in sentinel lymph node biopsy for breast cancer. *Am J Surg* 2005; 189:236-239.
34. Nour A. Efficacy of methylene blue dye in localisation of sentinel lymph node in breast cancer patients. *The Breast Journal* 2004; 10:388-391.
35. Golshan M, Nakhli F. Can methylene blue only be used in sentinel lymph node biopsy for breast cancer? *The Breast Journal* 2006; 12:428-430.
36. Pinero A, Illana J, Garcia-Palenciano C, Canizares F, Canteras M, Canadillas V. Effect on oximetry of dyes used for sentinel lymph node biopsy. Are there differences? *Arch Surg* 2004; 139:1204-1207.

Copyright of Anaesthesia & Intensive Care is the property of Australian Society of Anaesthetists and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.