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EDITORIAL

Sentinel lymph node biopsy: anaesthetic implications

Sentinel lymph node biopsy, a procedure widely practiced in the United States, Australia and mainland Europe, is based on the concept of the orderly progression of tumour cells within the lymphatic system [1]. The origins of the technique can be traced back more than 20 years to Cabanas, who demonstrated the existence of a specific draining lymph node in relation to penile cancer, the so-called 'sentinel' lymph node. This sentinel node could be identified after injecting blue dye through the dorsal lymphatics of the penis as the first tumour-draining lymph node to be visualized. The sentinel node was the first site for metastases and often the only affected lymph node [2,3]. Intraoperative lymphatic mapping and localization of the 'sentinel' lymph node has been enthusiastically adopted into clinical practice as a technique for accurate nodal staging in a number of different tumours in particular breast cancer, malignant melanoma and some other solid cancers. Indeed, some consider a negative sentinel lymph node biopsy to be the most important prognostic factor [4] and also that the procedure may be the nodal staging technique of choice in malignant melanoma [5] and in breast cancer [6].

Intradermal injection of a blue dye solution intraoperatively around the primary tumour site is used to visualize the lymphatic vessels. The dye is taken up by the lymphatic system and becomes concentrated in the first draining lymph node that appears stained blue. Biopsy of the sentinel lymph node can reveal whether or not there are lymphatic metastases. The technique can be refined further by the addition of lymphoscintiography; injecting a gamma emitting pharmaceutical (commonly technetium labelled albumin), permits preoperative localization using a gamma camera, confirmed intraoperatively by the use of a hand-held gamma probe. Recently it has been suggested that both radioactive tracer and supravital dye are needed to provide satisfactory (>90% success rate) sentinel node identification [7,8]. This view is supported by the findings of Albertini and his colleagues [9], who reported that in sentinel node biopsy, 69.5% of nodes demonstrated blue staining and 83.5% were 'hot' using isotope scanning, and that by combining the two methods successful localization is achieved in 96% of cases. In contrast, Bostick and Giuliano have suggested that with sufficient experience anyone can use blue dye alone to localize the sentinel node [10].

There are a number of implications of this technique that anaesthetists need to consider. Although a variety of dyes have been used, patent blue V(iolet) (Guerbet Labarotories, Milton Keynes, UK) has become the dye of choice. Patent blue V is a rosaniline dye, which is licensed for subcutaneous and intra-arterial use. In the UK, patent blue V is presented as a 5% w/v solution. Each ampoule contains patent blue V (sodium salt) 0.05 g; sodium chloride 0.012 g; disodium hydrogen phosphate 12 H_2O 0.001 g; water for injection up to volume of 2 mL. Patent blue V is poorly lipid soluble and forms a lyotropic mesophase in high aqueous concentrations. The fraction bound to 4% albumin at 37°C and pH 7.4 ranges from 0.05 to 0.83 attaching to one high affinity and five low affinity binding sites [11]. *In vitro* patent blue V demonstrates peak light absorption in plasma at 640 nm, whilst in whole blood light absorbency is 622–636 nm [12]. Peak light absorption at 640 nm corresponds to the wavelength of the red light used in pulse oximetry [13]. However, an early review [14] stated that intra-arterial patent blue V did not affect the pulse oximeter reading, an assertion that is contradicted by more recent data.

It is an assumption in pulse oximetry that no other light-absorbing molecule other than reduced/oxygenated haemoglobin influences the pulse curve; this is not true in the presence of patent blue V [12]. At 638 nm dye concentration and light absorbency are linearly related [12]. Furthermore, interference of pulse oximetry oxygen saturation reading by intra-arterial patent blue V injection may be prolonged, particularly in anaemic patients [15]. Intra-arterial injection results in the dye being distributed in the peripheral tissues with continuing release over time. It has been suggested that the effect is due to shift of the oxyhaemoglobin dissociation curve [12]. As a result of the

light absorbency at 640 nm of blood containing patent blue V dye, the amount of deoxygenated haemoglobin is overestimated; in other words the saturation indicated by the pulse oximeter is lower than the true value [12]. Larsen and colleagues have proposed that in the presence of patent blue V, evaluation of the oxygen status of blood should be based on arterial blood gas analysis rather than pulse oximetry [12] and this would seem to be sensible advice.

In practice, a relatively small volume of the blue dye is injected intradermally by the operator. It is unlikely, therefore, that this will result in direct intravascular injection. However, uptake of sufficient dye can result in interference with transcutaneous oxygen saturation readings. Typically, there is a decrease in pulse oximeter oxygen saturation reading. The onset occurs between 30 s and 23 min following injection and lasts from 20 min to several hours [13]. In an early case report, McEwan and Lamb reported a reduction in pulse oximeter saturation (S_PO_2) reading from 99% to 94% in an 8-year-old child, which occurred within seconds of patent blue injection and resolved over 30 min [16]. Arterial blood gas analysis revealed a normal partial pressure of oxygen of 32 kPa with the child breathing 50% oxygen [16]. In another case report, Morrell and colleagues [13] injected a relatively large volume (2.5 mL in total) of 10% patent blue V (rather than the more usual 5%). The pulse oximeter saturation reading decreased to 92%, despite the patient breathing 50% oxygen, yet the arterial partial pressure of oxygen (30 kPa) and co-oximeter saturation values (97.6%) were both normal. Saito and colleagues [15] injected 0.5 mL 5% patent blue dye, which resulted in a pulse oximeter saturation (S_PO_2) of 88%, yet arterial blood gas sampling revealed an oxygen saturation (SaO_2) reading of 99.8%. In a small case series of 25 consecutive patients breathing spontaneously under stable general inhalational anaesthesia (inspired oxygen concentration 35%; end-tidal carbon dioxide concentration 4.5–6.0 kPa) the author recorded mean (95% confidence interval) oxygen saturation readings of 97.5% (97–98%). After injection of patent blue V dye (no more than 0.5 mL) during sentinel lymph node biopsy for malignant melanoma, the median (range) decrease in oxygen saturation was 2% (0–5%) (unpublished data). This is in keeping with all of the previously published reports cited above.

It has been noted that with routine preoperative lymphoscintigraphy, the incidence of 'false negative' sentinel nodes and the rate of recurrence in the regional node basin are low. Several radiopharmaceuticals have been developed for lymphoscintigraphy. The most frequently used are technetium^{99m} nanocolloidal albumen, technetium^{99m} sulphur colloid and technetium^{99m} antimony trisulphide colloid [17]. The first and second of these are both available in Europe. The second is the only registered tracer for lymphoscintigraphy in the United States. Technetium^{99m} DTPA-mannosyl-dextran is a recent addition, which is still undergoing evaluation. The dose of radiation administered is of the order of 0.5–1.0 mCi, with technetium having a half-life of 6 h. It has been suggested that further studies are needed to establish more clearly the intralymphatic kinetics of the various radiopharmaceutical agents [10]. Standard precautions should be taken for the handling of radioactive isotopes, including samples for pathological examination. In addition, the safety of using radioactive tracers in pregnant patients has not been resolved and many workers avoid the procedure in such patients until after delivery of the baby.

There are reports of adverse reactions to patent blue V administered orally [18] and parenterally [19–22]. A recent communication reported anaphylaxis to blue patent V dye successfully treated with hydrocortisone and chlopheniramine in a patient in whom sentinel lymph node biopsy was being conducted for carcinoma of the breast [19]. Similarly, Quiliquini and his colleagues [20] and Barber [21] have reported anaphylaxis to patent blue. Injection of patent blue was followed by generalized urticaria, swelling in the throat with constriction and difficulty in breathing. In another communication, Woltsche-Kahr and colleagues [22] reported a case of anaphylactic shock following peritumoural injection of patent blue during a sentinel node biopsy procedure for staging of malignant melanoma. A positive intradermal test confirmed that the patent blue V was the trigger.

Excretion of the dye results in discolouration of the urine, which may be dramatic and worrying for patients who need to be warned of this innocuous side-effect. Less innocuous is the tattooing of the skin around the dye injection site that may persist for some months.

Each year, 794 000 women world-wide are diagnosed with breast cancer. Sentinel lymph node biopsy has been proposed as an indispensable tool for the staging and treatment of breast cancer [1,6]. Sentinel lymph node biopsy may be appropriate for patients with T1 and T2 stage disease [23], although a new 'pN0' category has been added to the TNM classification of breast cancer based on the sentinel node biopsy [24]. The incidence of malignant melanoma in the United States, reported as 10–12 per 100 000 of population, roughly equates with the approximately 4000 new cases per year in the UK. The ability to stratify patients prognostically and to identify which patients should proceed to completion dissection of the regional lymph nodes basin are considered to be important arguments for the widespread use of the procedure and there is at least one ongoing multicentre trial of sentinel lymphadenectomy.

Sentinel lymph node biopsy is much more challenging for breast cancer than for malignant melanoma and there is still controversy concerning the worth of sentinel lymph node biopsy in relation to breast cancer. At the present time, a clear consensus on sentinel lymph node biopsy does not exist [23,25]. In contrast, the World Health Organisation has recommended that for malignant melanoma, sentinel lymph node biopsy should become the standard procedure for patients with an estimated risk of nodal metastases >10% (i.e. melanoma tumour thickness >1 mm or graded as Clark level IV) [26]. Thus, on balance, sentinel lymph node biopsy, an accurate technique with minimal morbidity, would seem to have become accepted as standard practice in the treatment of malignant melanoma [23]. Despite the continuing debate regarding the worth of sentinel lymph node biopsy, it is likely that many more anaesthetists will in the future become involved in this procedure, particularly if it becomes standard practice in the management of breast cancer. Anaesthetists should all be aware of the anaesthetic implications of the procedure particularly with regard to interference with pulse oximeter oxygen saturation readings.

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