View Point

Diagnostic application of patent blue V in sentinel lymph node biopsy for breast cancer – Is it time for a change?

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Abstract

Sentinel lymph node biopsy (SLNB) was introduced in the 1990s, as a minimally invasive procedure for staging the axilla with less morbidity to the traditional axillary lymph node dissection and is now standard management of the axilla in the early breast cancer. SLNB using the combined technique of blue dye and radioisotope is currently the recommended method for lymphatic mapping, and studies have shown high identification rates (IR) (>95%) and low false-negative rates (FNR) 5–10%. However, there are several reports raising awareness regarding patent blue V dye-induced peri-operative anaphylaxis. The main aim of this article is to highlight the emergence of patent blue dye as a new allergen and present evidence regarding the utility of alternative safer methods of evaluation of early breast cancer without compromising IR.

Key Words: Allergy, blue dye, breast cancer, sentinel node

The evaluation of axillary status in patients with invasive breast cancer is paramount for assessing prognosis and stratifying adjuvant therapy. Sentinel lymph node biopsy (SLNB) was introduced in the 1990s to stage the axilla when preoperatively negative (clinically and imaging). This is a minimally invasive procedure for staging the axilla, with lesser morbidity, and is now considered the best practice in the management of early breast cancer.

SLNB using a combination of patent blue V (PBV) (patent blue dye; also called triphenylmethane dye or E131) and radioisotope is the currently recommended method for lymphatic mapping, and studies have shown high identification rates >95% and low false-negative rates of 5–10%.[1] However, there are several reports raising awareness regarding PBV-induced peri-operative anaphylaxis.

The main aim of this article is to highlight the emergence of patent blue dye as a new allergen and present evidence regarding the utility of alternative safer methods of evaluation of early breast cancer without compromising identification rates.

Anaphylaxis during general anesthesia (GA) is a serious event leading to severe cardio and/or respiratory arrest. It often leads to abandonment of the procedure and admission to intensive care, thus delaying a lifesaving surgical treatment. A large study in France reported neuromuscular blocking agents, antibiotics, and latex as leading allergens responsible for anaphylaxis during GA with PBV listed as a rare culprit (0.6% of immunoglobulin E [IgE]-mediated anaphylaxis).[2] In the first multicenter UK study[3] and a subsequent report,[4] we highlighted the emergence of PBV as a culprit allergen in 5–8% cases of near-fatal IgE-mediated anaphylaxis during GA. Allergic reactions to PBV pose serious challenges to the anesthetists. It can induce refractory anaphylaxis requiring prolonged inotropic support and interfere with oxygen saturation measurement, thus potentially delaying the identification of early signs of anaphylaxis and delivery of prompt treatment, which is crucial for a favorable outcome. Another important feature of PBV-induced anaphylaxis is the time lag (~15–30 minutes; 60 minutes in some cases) between administration of the dye and manifestation of early allergic signs.[5]

A recent study has highlighted that anaphylaxis during GA is more common than previously estimated in the United Kingdom.[6] In a large survey undertaken in Yorkshire, United Kingdom, Savic *et al.* reported 1 in 2297 cases, although this figure could be much higher (1 in 353) since a significant number of cases with relatively less severe clinical manifestations are not referred for specialist evaluation.

Are there safer alternatives to patent blue dye and what are the identification rates with other techniques?

First, methylene blue dye is worth considering. It is rarely implicated in allergic reactions and has comparable identification rates to blue dye when either used singly or in combination with a radioisotope.[7] Methylene blue is a small molecule and considered less allergenic.

Second, the use of radioisotope alone to avoid the blue-dye complications and problems with blue dye obscuring the surgical field has been studied. A randomized control trial demonstrated no advantage for dual agents in SLNB detection.[8] Although a recent systematic review showed a high identification rate for the combined approach (radioisotope and blue dye), there was no statistical significance post-neoadjuvant chemotherapy and it did not reduce false-negative rate in comparison to radioisotope alone. The use of radioisotope presents logistic challenges with respect to health and safety issues related to radiation.

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Third, SLNB can also be performed by employing superparamagnetic iron oxide (SPIO) magnetic tracer injected into the breast and the use of a handheld magnetometer for detection during the procedure. The first trial to assess this method showed noninferiority in comparison to standard dual tracer. Several clinical trials have since evaluated this technique and a meta-analysis by Zada *et al.* showed identification rate of 97.1%, concluding that the magnetic technique was noninferior to the standard technique and a low false-negative rate at 8.4%.[9] These studies did report adverse reactions.

Fourth, there is increasing evidence to support the use of indocyanine green (ICG) fluorescence for SLN detection in early breast cancer. The near-infrared fluorescence imaging system utilizes the characteristic spectrum of ICG and imaging visualizes lymphatic flow and allows direct detection of axillary SLN. ICG appears to be safe with fewer allergic reactions (0.01% vs. 0.07–2.7% for blue dye). A systematic review of 12 studies assessed the diagnostic utility of ICG for SLN detection compared to radioisotope alone and showed no significance differences highlighting the former as an useful alternative.[10]

In conclusion, patent blue dye carries a real risk of triggering near-fatal refractory anaphylaxis during GA albeit in a small proportion of patients and is best avoided. Recent evidence favors alternative approaches for SLNB in breast cancer including SPIO, methylene blue, or ICG ± radioisotope without compromising identification rates. In conclusion, there are exciting novel alternatives to replace patent blue dye for sentinel node biopsy localization.

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Conflicts of interest

There are no conflicts of interest.

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