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To cite this article: Sadeghi Ramin, Fani Pakdel Azar & Hasanzadeh Malihe (2011) Methylene blue as the safest blue dye for sentinel node mapping: Emphasis on anaphylaxis reaction, Acta Oncologica, 50:5, 729-731, DOI: [10.3109/0284186X.2011.562918](https://doi.org/10.3109/0284186X.2011.562918)

To link to this article: <https://doi.org/10.3109/0284186X.2011.562918>



Published online: 17 Mar 2011.



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LETTERS TO THE EDITOR

Methylene blue as the safest blue dye for sentinel node mapping: Emphasis on anaphylaxis reaction

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To the Editor,

Anaphylaxis reaction to blue dyes being used in medical practice is a major concern for health care providers. Traditionally methylene blue is considered as the safest and its use is actually encouraged by many authors [1]. This is most likely due to rarity of the literature reporting anaphylaxis to methylene blue. Recently a case of anaphylactic reaction to this blue dye has been published in your journal [2] and motivated us to systematically report the available literature in this regard, having in mind the ever-growing use of these dyes in oncology and sentinel node biopsy.

Sentinel node biopsy is an important procedure in surgical oncology for lymphatic staging of certain solid tumors especially breast cancer [3], melanoma [4], as well as gynecological malignancies [5]. This technique can decrease the morbidity of regional lymph node dissection without compromising the accuracy of metastatic lymph node detection [6].

Modern sentinel node mapping technique involves blue dye [7], radiotracers, or both in combination [2,8]. Although each method have been used with satisfactory results (e.g. blue dye only in environments without access to nuclear medicine facilities [7]), it is usually accepted that combining both can decrease the possibility of getting false negative (pathologically negative sentinel lymph node despite positive regional lymph node basin) results [9].

Several blue dyes are now in use for sentinel node mapping including isosulfane blue, Patent Blue V, and methylene blue [10]. The accuracy of these dyes for sentinel lymph node mapping was comparable in several studies [11–13].

An important aspect of various blue dyes being used in sentinel node mapping is the cost, and methylene blue is the cheapest and the most available [14]. This is an important concern in areas with limited resources.

Adverse reactions to blue dyes while being used for sentinel node mapping are another issue of utmost importance. These adverse reactions can be divided into two categories: allergic and non-allergic. Allergic reactions include urticaria, skin rash, erythema, and anaphylaxis. Non-allergic reactions are interference with pulse-oximetry, blue discoloration of the skin or body fluids, and skin necrosis [1,10].

In a recent systematic review by Bézu et al. [1] the adverse reactions to various blue dyes have been addressed fully. Adverse skin reactions are more common with methylene blue and can be in the form of skin necrosis which is very problematic [10]. However, interference with pulse oximetry is less common with methylene blue compared to isosulfane blue and Patent Blue V dyes [15]. Allergic reactions (including life-threatening anaphylaxis) were consistently reported more frequently for Patent Blue V and isosulfan blue dyes (0.9% for ALMANAC [1] and 0.7% for NSABP B32 trials [16]) compared to methylene blue [12,17]. This is more impressive

when having in mind the frequent use of methylene blue in everyday medical practice (treatment of methemoglobinemia, detection of fistulae, etc) [10]. Actually Bézu et al. did not find any report regarding anaphylaxis reaction due to methylene blue for sentinel node mapping [1] and considering this fact, lower cost, and comparable accuracy, it is usually accepted that methylene blue is the safest among the blue dyes.

However the actual situation is not that simple. Life-threatening anaphylactic or anaphylactoid reactions to methylene blue (not related to sentinel node mapping) have been reported in the literature. This was first reported by Trikha et al. following intra-uterine injection of methylene blue in 1996 [18]. Millo et al. reported another case of fatal pulmonary edema after administration of methylene blue during diagnostic laparoscopy [19]. The other two cases were during intra-uterine injection of 1% methylene blue for determination of tubal permeability [20], and during laparoscopic chromopertubation with methylene blue [21]. However, only Dewatcher et al. proved methylene blue as the cause of reaction by a cutaneous test [20].

Besides the above-mentioned case reports, only three groups reported life-threatening anaphylaxis reaction to methylene blue during sentinel lymph node mapping. In 2008, Teknos et al. reported anaphylactic reaction to methylene blue in the form of pulmonary edema during sentinel node mapping for breast cancer. However, they did not confirm the hypersensitivity to methylene blue by skin testing [22]. In 2010, Jangjoo et al. reported another case of anaphylactic reaction to methylene blue during sentinel lymph node procedure which was confirmed by the prick test [2]. In the most recent case, Oomah et al. reported anaphylaxis reaction to methylene blue in a 62-year-old female which was also confirmed by the prick test [23].

It is also worth mentioning that methylene blue and Patent Blue V can have DNA damaging effects which can be of clinical relevance [24]. This should be evaluated more in patients receiving blue dyes. Cross-reactivity between patent blue and methylene blue has been reported by Keller et al. in three patients [25] which shows that allergic reactions to blue dyes are not that simple and needs more extensive and dedicated evaluation.

In conclusion, considering the rare occurrence of anaphylactic reactions to methylene blue, it seems that this dye is the safest among the blue dyes being used in sentinel node mapping. However, the mentioned case reports show that life-threatening anaphylactic reactions do occur with methylene blue. Surgical teams should be aware of this fact and

having the equipment to manage this grave complication is of utmost importance.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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