

Increased Post-Operative Complications With Methylene Blue Versus Lymphazurin in Sentinel Lymph Node Biopsies for Skin Cancers

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Background: Sentinel lymph node biopsy (SLNB) is the standard of care in staging of melanoma and other skin cancers. Early studies used lymphazurin (LZ) for SLNB. A national shortage of LZ promoted methylene blue (MB) as an alternate stain.

Objective: This study compares complication rates between LZ and MB in SLNB patients, and the reliability dyes in locating sentinel lymph nodes.

Methods: Charts were reviewed for patients who underwent SLNB for skin cancers between September 2006 and November 2008 at Penn State Hershey Medical Center. The type and quantity of dye, the presence of blue stained sentinel nodes, and any complications were recorded.

Results: Ninety-three patients underwent SLNB (46 LZ, 47 MB). The amount of dye used was similar (avg. 0.93 ml LZ, 1.24 ml MB). The complication rate of LZ was 8.7%, and MB was 25.5%. There was significantly more ($P = 0.003$) skin graft complications in the MB patients (6/12) LZ (0/15).

Conclusions: There is a higher rate of complications with MB, especially with skin grafting. The reported risk of anaphylaxis with LZ has not been reported in volumes <2 ml. The sentinel lymph node identification rate is historically similar between dyes, and in this study was noted to be higher with LZ.

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KEY WORDS: sentinel lymph node biopsy; lymphazurin; skin cancers; blue dye; melanoma

INTRODUCTION

Sentinel lymph node biopsies (SLNB) are standard for the staging of multiple cancer types such as breast, head and neck, colorectal cancer, and skin cancers such as melanoma, and Merkel cell carcinoma [1]. Sentinel lymph nodes are located via preoperative lymphoscintigraphy. This involves peritumoral, or peritumoral defect, injection of a radioisotope such as Technetium-99m. The radioisotope is carried in the lymphatics and filtered by the first lymph nodes encountered. This enables the physician to create a scintigraphic image, and also locate the node intraoperatively with the aid of a gamma probe. Additionally, intraoperative dye is injected intradermally around the cancer or scar and massaged for 5 min. The dye, much like the radioisotope, is taken up by the lymphatics in order to stain the first nodes encountered blue [2]. The combination of these two labeling techniques allows for a sentinel lymph node identification rate of approximately 95%, depending on the anatomic location [3].

SLNB was popularized in the early 1990s for the detection of metastatic melanoma to the regional nodal basin. The first large-scale randomized international trial defining SLNB in melanoma was the MSLT-1 (Multicenter Selective Lymphadenectomy Trial). The researchers in this trial used 2 ml or less of vital blue dye (Lymphazurin or Patent Blue dye) injected intradermally at the site of the malignancy [3]. The vital blue dyes used were Lymphazurin and Patent Blue which are isomers of each other [4]. For simplicity sake in this study we refer to both of these dyes as lymphazurin.

The choice of isomer generally depends on the manufacturing country, as Patent Blue is obtained from Therapex in Canada, while isosulfan blue (Lymphazurin) is a product of U.S. Surgical Corporation in the United States [4]. Hypersensitivity reactions for these dyes are typically cross-reactive, as with most other triphenylmethane dyes [5,6]. Triphenylmethane dyes are commonly found in our everyday environment in dyes for fabrics, cosmetics, paper, and leather. Since the public is in everyday contact with triphenylmethane dyes, there is the possibility of sensitization and subsequent allergic reactions. When vital blue dyes were used for lymphatic mapping in the 1960s–1970s there

was a high rate of allergic reactions (2.5%); however this was believed to be secondary to impurities in manufacturing as the rate has dropped since lymphazurin blue was produced for FDA approved pharmaceutical uses [7].

Multiple studies have shown that lymphazurin effectively stains the sentinel node for identification around 60% of the time when used without a radiolabeled marker such as Technetium-99m [8]. The safety of lymphazurin was confirmed in the MSLT-1 study, with an extremely low systemic complication rate (2/1,173). The only two reactions in the study consisted of blue urticarial reactions without any anaphylactic-type symptoms [3].

Since the introduction of lymphazurin as the standard for SLNB, further studies have been published proposing the use of methylene blue as an alternative stain for SLNBs. These studies have shown methylene blue to be equally efficacious in locating sentinel nodes, and it is notably cheaper than Lymphazurin. Methylene blue is in the phenothiazine family, and chemically dissimilar to lymphazurin. These studies surfaced at an opportune time, secondary to nationwide shortages of lymphazurin as well as some case reports arising describing anaphylactic type reactions with lymphazurin. The incidence of these reactions was reportedly in the range of 1–2% of the studied populations [7,9–11]. Dr. Ian Komenaka at Columbia-Presbyterian Medical Center reviewed the literature of systemic reactions with lymphazurin and compiled their data with three other large institutional studies to determine the rate of allergic reactions with lymphazurin. They found a systemic complication rate of 18/1,663, 13 of which were anaphylactic

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