

Anaphylactic Reaction to Lymphazurin 1% during Breast Reconstruction Surgery: An Uncommon but Serious Complication

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Summary: Lymphazurin 1% (isosulfan blue dye) is the most frequently used blue dye in the United States, and it is commonly used for sentinel node biopsy in breast cancer patients. Although cases of allergic reaction to lymphazurin have been reported in the general surgery literature, to our knowledge, no cases of an adverse reaction to isosulfan blue have been reported in the plastic surgery literature. We describe a case of an intraoperative biphasic anaphylactic reaction to isosulfan blue in a female patient undergoing bilateral mastectomy and immediate bilateral DIEP breast reconstruction. The severity of her anaphylactic reaction required that we stop flap dissection and abort the reconstruction. Although an allergic reaction is uncommon, recognizing the signs of an acute hypersensitivity reaction is critical to good outcomes in these situations. Given the volume of combined breast oncologic and breast reconstruction surgeries and the increasing number of vascularized lymph node transfer and lymphovenous anastomosis performed annually, it is essential for the plastic surgeon to be cognizant of this rare hypersensitivity reaction. (*Plast Reconstr Surg Glob Open* 2020;8:e3075; doi: [10.1097/GOX.0000000000003075](https://doi.org/10.1097/GOX.0000000000003075); Published online 17 September 2020.)

Lymphazurin 1% (isosulfan blue dye) is the most frequently used blue dye in the United States, and it is commonly used for sentinel node biopsy in breast cancer patients.¹ Allergic reaction to lymphazurin, with severe cases including intraoperative anaphylaxis, has been reported in the general surgery literature.¹⁻⁶ But, to our knowledge, there have been no cases of adverse reaction to lymphazurin reported in the plastic surgery literature. In the following case report, we present a patient undergoing bilateral skin-sparing mastectomy and immediate DIEP breast reconstruction, who developed a severe biphasic hypersensitivity reaction to lymphazurin injection for sentinel node mapping. The severity of her allergic reaction required that we stop flap dissection and proceed with wound closure so that she could undergo

further workup. We also describe a method to leave a “roadmap” to facilitate future delayed flap dissection.

CASE DESCRIPTION

A 49-year-old woman with a pathogenic *BRCA2* gene mutation and left breast invasive ductal carcinoma presented for a bilateral skin-sparing mastectomy, with targeted left axillary lymph node dissection and immediate bilateral DIEP breast reconstruction. Her medical history included hypertension, systemic lupus erythematosus, major depressive disorder, chronic back pain, *BRCA2* gene mutation, and Behcet disease. Penicillin (rash) was her only known allergy. At the start of surgery, she received 5000 units of subcutaneous heparin and 2 g of Ancef for perioperative prophylaxis. Five milliliters of lymphazurin 1% was injected under the left nipple by the Surgical Oncology team for sentinel lymph node biopsy. Twenty minutes after anesthesia induction, the patient became hypotensive and hypoxic, which was managed initially with colloids and intraoperative albuterol (Fig. 1). The patient was otherwise stable, and the surgery continued as planned. After identifying the medial and lateral DIEP perforators and before starting the intramuscular dissection, the anesthesia team noted that the patient was again becoming hypotensive and hypoxic on 100% FiO₂ (Fig. 2).

Cardiac anesthesia was consulted to rule out intraoperative pulmonary embolism (PE). Intraoperative

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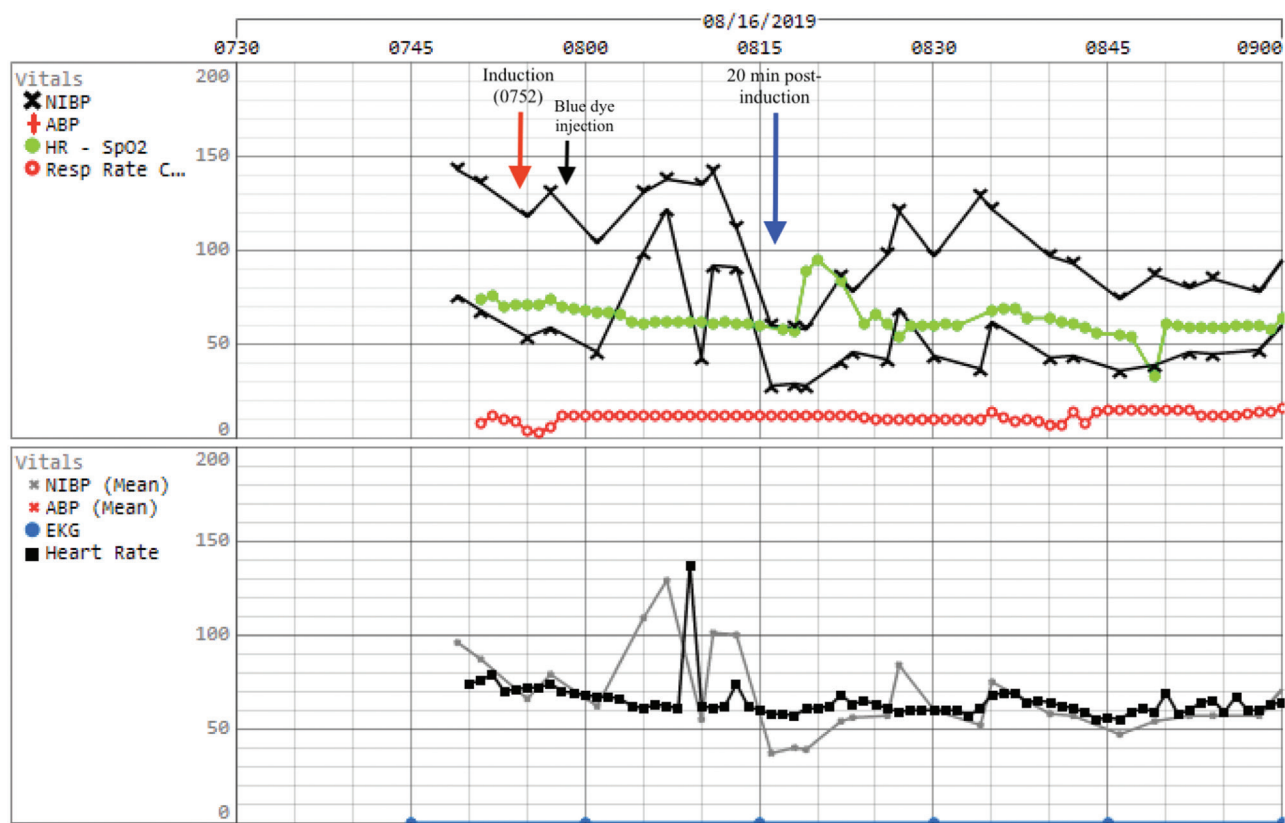


Fig. 1. Anesthesia record showing the first phase of the anaphylactic reaction—hypotension and hypoxia (blue arrow)—shortly after induction and isosulfan blue injection (red and black arrow).

transesophageal echocardiogram showed signs of moderate right ventricular dilation suggestive of PE. Therefore, we decided to abort flap dissection and inotropic medications (phenylephrine and ephedrine), and heparin drip was administered while the surgical wounds were quickly closed. Since the patient's DIEP perforators had already been isolated, we placed Prolene sutures along the medial and lateral perforators as a landmark to facilitate safe identification for future delayed DIEP or muscle-sparing transverse rectus abdominis muscle flap reconstruction.

After closure, the patient was transferred to the post-anesthesia care unit, where repeat bedside transesophageal echocardiogram findings showed that systolic function had normalized. Three hours later, computed tomographic angiography revealed a very small nonocclusive subsegmental right lower lobe PE. Additionally, duplex ultrasound demonstrated no deep venous thrombosis of the lower extremities.

Cardiology and pulmonology services were both consulted, and they agreed that the small subsegmental PE was of insufficient size to explain her hemodynamic collapse in the operating room. Given her acute cardiac and pulmonary deterioration shortly after isosulfan blue injection, rapid improvement with inotropic support, and ruled-out massive PE, she was diagnosed with an anaphylactic reaction to lymphazurin administration.

The patient was extubated later that night after respiratory improvement. Her postoperative course was

complicated by a left chest hematoma, which was washed out in the operating room. On postoperative day 5, the patient was taken back for bilateral breast reconstruction with prepectoral tissue expanders and acellular dermal matrix. She will proceed with postmastectomy radiation therapy followed by delayed bilateral DIEP or muscle-sparing transverse rectus abdominis muscle flap breast reconstruction.

DISCUSSION

Isosulfan blue dye is an aniline dye commonly used in sentinel lymph node biopsy procedures for breast cancer.^{1,2} After subcutaneous/intraparenchymal injection into the breast, isosulfan blue drains into lymphatics carried by interstitial proteins.³ After the dye gets into the venous system, it can interfere with the pulse oxygen saturation absorptive quality, artificially decreasing the perceived hemoglobin saturation in some patients.^{2,3} The reported incidence of isosulfan blue is 1%–3%.^{1,4} Given the prevalence of the dye outside medicine (textiles, manufacturing, household products), patients have an increased chance of exposure and sensitization.¹

Isosulfan blue anaphylaxis is a Type I hypersensitivity response mediated by immunoglobulin E.² Most reactions occur within 15–30 minutes after dye injection.³ Patients can experience a variety of symptoms, including edema, erythema, tachycardia, “blue” hives, bronchospasms, dysrhythmias, vasodilation, and cardiovascular collapse.^{1,2,7}

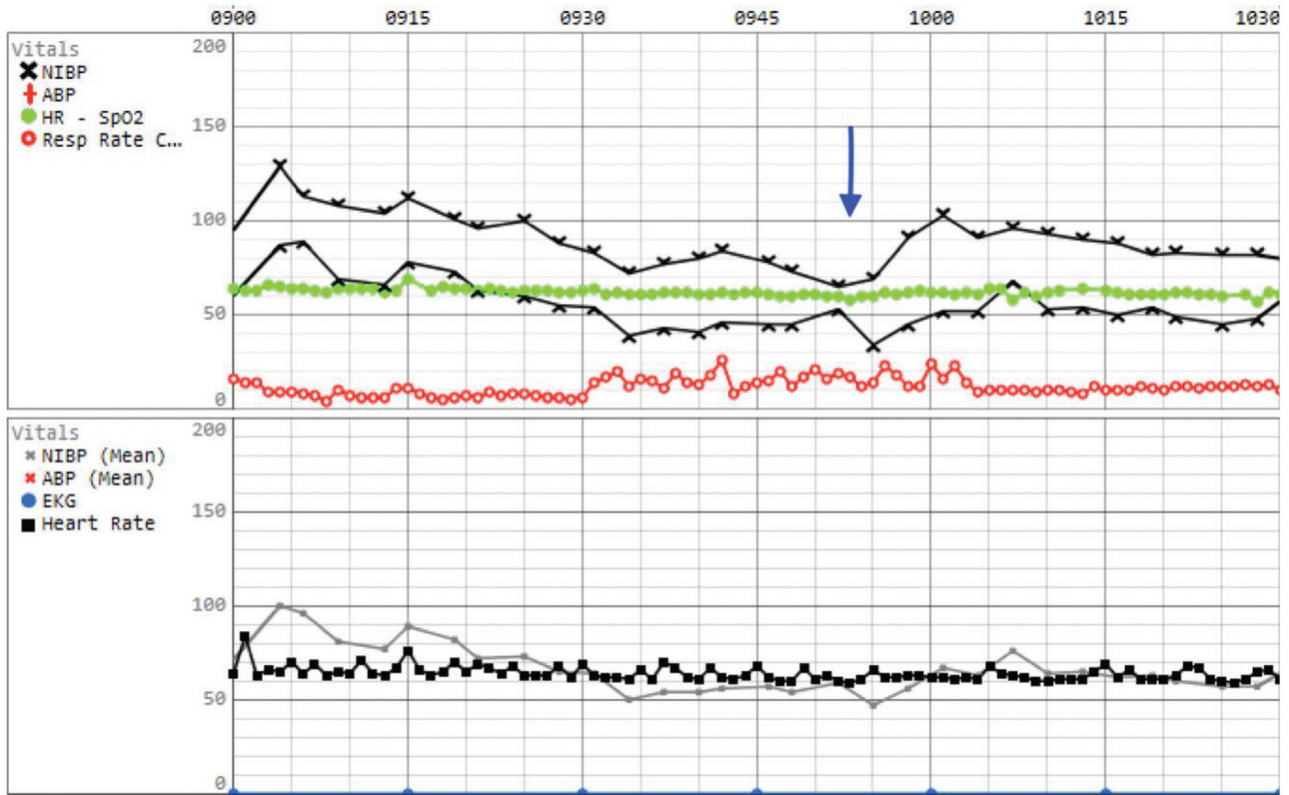


Fig. 2. Anesthesia record showing the second phase of the biphasic anaphylactic response (blue arrow).

An elevated serum tryptase can support an anaphylaxis diagnosis but is not confirmatory.^{2,5} Immediate intervention is necessary, prioritizing blood pressure control and airway management, followed by intravenous epinephrine administration.^{1,2} A delay in epinephrine administration can lead to a biphasic response, with a rebound effect 2–4 hours after the initial event.¹ Antihistamines and corticosteroids can be used as second-line treatment, but corticosteroids may not prevent a biphasic anaphylactic reaction.¹ If an anaphylactic response is suspected, immediate pharmacologic management of anaphylaxis should be initiated.

Given the frequency of anaphylactic reactions, the use of prophylactic medications should be considered. Certain high-volume centers have developed algorithms to differentiate suspected reactions to blue dyes and initiate early interventions in cases of intraoperative anaphylaxis.⁸ Other authors advocate the routine use of diphenhydramine and famotidine, which have been shown to decrease the severity of anaphylaxis, but not the overall incidence rate.⁶ Furthermore, methylene blue dye may be a safer alternative to isosulfan blue, as it is not associated with anaphylactic reactions.⁹

In conclusion, lymphazurin is frequently used by breast cancer oncologist and plastic surgeons for lymph node mapping, and it behooves the plastic surgeon to be aware of this rare but very severe hypersensitivity reaction. Although an allergic reaction is uncommon, knowledge of the signs and symptoms of an acute hypersensitivity reaction is critical to accurate treatment and

optimal patient outcomes. As the number of immediate breast reconstruction surgeries and vascularized lymph node transfer and lymphovenous anastomosis increase over the years, it is almost certain that others will encounter similar situations as described here. Recognition of isosulfan blue anaphylaxis will contribute to improved patient outcomes.

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