

# Cardiac Arrest after Patent Blue V Injection for Sentinel Lymph Node Biopsy in Breast Cancer

Bjorn Telgenkamp · Dennis Japink · Els van Haaren

Department of Surgery, Atrium Medical Centre, Heerlen, The Netherlands

## Key Words

Sentinel node · Patent blue · Anaphylactic shock · Breast cancer

## Summary

**Background:** Sentinel lymph node biopsy (SLNB) is a widely accepted method to determine lymph node status in for instance breast cancer, cervical cancer, or cutaneous melanomas. Although injection of blue dyes facilitates successful detection of sentinel nodes, they have also been shown to cause adverse reactions. **Case Report:** A 62-year-old female patient was referred to the surgical department of the Atrium Medical Centre with a suspicious lesion located in the right breast, detected during population-based screening. Immediately after injection of patent blue V, the patient developed tachycardia on top of preexisting supraventricular tachycardia and showed an instant drop in blood pressure, after which cardiac arrest occurred. These clear symptoms of anaphylactic shock required prompt treatment, and the patient was treated accordingly. **Conclusions:** Anaphylactic shock after injection of patent blue V remains a serious adverse event and warrants awareness. Immediate action with ephedrine, antihistamines, and subsequently corticosteroids can stabilize the patient. Tc-99m, isosulphan blue, and methylene blue can alternatively be used for SLNB, although also not without side effects.

## Schlüsselwörter

Sentinel-Lymphknoten · Patentblau · Anaphylaktischer Shock · Mammakarzinom

## Zusammenfassung

**Hintergrund:** Die Sentinel-Lymphknoten-Biopsie (sentinel lymph node biopsy, SLNB) ist ein akzeptiertes Verfahren zur Bestimmung des Lymphknotenstatus beispielsweise bei Mammakarzinomen, Zervixkarzinomen oder Hautmelanomen. Obgleich die Injektion blauer Farbstoffe die erfolgreiche Bestimmung von Sentinel-Lymphknoten unterstützt, besteht die Gefahr von Nebenwirkungen. **Fallbericht:** Eine 62-jährige Patientin war an die Chirurgische Abteilung des Atrium Medical Centre überwiesen worden, um eine suspekta Veränderung in der linken Brust, welche bei der Krebsvorsorgeuntersuchung entdeckt worden war, näher untersuchen zu lassen. Direkt nach Injektion des Patentblau V-Farbstoffes entwickelte die Patientin Tachykardie zusätzlich zu einer vorbestehenden supraventrikulären Tachykardie, mit sofortigem Abfall des Blutdruckes und Herzstillstand. Diese eindeutigen Symptome eines anaphylaktischen Shocks erforderten ein promptes Eingreifen, und die Patientin wurde entsprechend behandelt. **Schlussfolgerungen:** Anaphylaktischer Shock nach Injektion von Patentblau V ist eine ernstzunehmende Nebenwirkung und muss in Betracht gezogen werden. Durch sofortige Intervention mit Ephedrin, Antihistaminen und anschließend Kortikosteroiden kann der Patient stabilisiert werden. Tc-99m, Isosulphan-Blau und Methylenblau können alternativ zur Durchführung einer SLNB eingesetzt werden; allerdings besteht auch hier die Gefahr von Nebenwirkungen.

## Introduction

Sentinel lymph node biopsy (SLNB) is a widely accepted method to determine lymph node status in for instance breast cancer, cervical cancer, or cutaneous melanomas. Injection of a dye into a lymph vessel adjacent to the tumor site in addition to the use of Tc-99m enables detection of the sentinel node. Several dyes are currently available for this procedure. These include isosulphan blue, patent blue V, and methylene blue. Although injection of blue dyes has facilitated successful detection of sentinel nodes, they have also been shown to cause adverse reactions [1]. Besides local blue staining of the skin, complications vary from minimal tissue responses to mild and severe anaphylactic shock [2]. Especially the latter complication should be taken into account as it may result in death. The incidence of allergic reactions is 1–2.8% [2–8], but consequences can be severe and patent blue V is frequently applied. Therefore it remains imperative to maintain awareness regarding these severe complications. Here we report a severe case of anaphylactic shock after patent blue V injection for SLNB in a breast cancer patient.

## Case Report

A 62-year-old female patient was referred to the surgical department of the Atrium Medical Centre with a suspicious lesion located in the right breast, detected during population-based screening. The medical history of the patient showed mitral valve prolapse grade II and paroxysmal supraventricular tachycardia. The patient's medication comprised sotalol, digoxin, furosemide, acetylcysteine acid, and losartan. No pre-existing pulmonary disease, more specifically no asthma or chronic obstructive pulmonary disease, was diagnosed. Contact allergies, food allergies and signs of eczema had not occurred before, and she had never undergone surgery. To our knowledge, there was no prior sensitization to patent blue. Breast cancer was diagnosed by mammography and subsequent biopsy. Consequently, the patient was scheduled for a lumpectomy with a sentinel lymph node procedure. Preoperatively, alprazolam was administered. Anesthetic induction and maintenance was achieved with propofol, and sufentanil was used as analgesic. Fifteen minutes following induction of anesthesia, the surgical procedure was started with peri-auricular intracutaneous injection of 1 ml 2.5% patent blue V dye. Immediately after injection of the patent blue V, the patient developed tachycardia on top of her preexisting supraventricular tachycardia and showed an instant drop in blood pressure after which cardiac arrest occurred. These clear symptoms of anaphylactic shock required prompt treatment, and the patient was treated accordingly. Cardiac and fluid resuscitation were started immediately, and anti-anaphylactic therapy was provided with 0.5 mg intravenous (i.v.) bolus of ephedrine, 1 g i.v. hydrocortisone, and 20 mg i.v. tavegil. This resulted in improved cardiac output and successful conversion of the anaphylactic shock. After further stabilizing the patient, the SLNB was continued but the planned lumpectomy was postponed to first stabilize the patient and then plan a second operation depending on the outcome of the SLNB. Postoperatively, the patient was transferred to the intensive care unit for observation for 1 day. The SLNB showed no metastatic disease, and the patient was re-scheduled for a lumpectomy.

The anaphylactic shock was thought to have had two possible causes – the patent blue dye or the latex gloves of the surgeon. To analyze this, a Prick test (skin allergy test) was performed 2 weeks after the anaphylactic shock. The patient was tested for allergy to patent blue V and latex. The

test revealed a positive response to even 100-fold diluted patent blue V as well as to 10-fold diluted patent blue V, and a negative response to latex. The patient developed a 6 mm wheal with erythema within 15 min. This proved a type 4 IgE-mediated allergic response. The control test remained negative.

## Discussion

At present, adequate treatment of breast cancer patients includes tumor mapping with SLNB. This enables detection of the lymph node that is most likely involved in the tumor process. Consequently, based on a histopathological analysis, a decision can be made whether complete dissection of the axillary lymph nodes is required. Sentinel lymph nodes are detected by injection of specific dyes. Currently, patent blue V, isosulphan blue, and methylene blue are available for this procedure. However, there are some reports of patients developing adverse reactions following injection. Symptoms are diverse and can include minor reactions such as urticaria, pruritus, erythema, generalized rash, and blue hives. Severe reactions such as pulmonary edema, bronchospasm, and shock are rare [5, 9]. To the best of our knowledge, no deaths have been reported. Allergic reactions have been graded from I to IV in order of increasing severity: grade I, cutaneous signs; grade II, measurable but not life-threatening signs (including cutaneous effects, > 30% decrease in arterial blood pressure associated with unexplained tachycardia, cough, or difficulty in mechanical ventilation); grade III, life-threatening reactions (cardiovascular collapse, tachycardia or bradycardia, arrhythmias, and severe bronchospasm); and grade IV, circulatory shock and cardiac arrest, respiratory arrest, or both. Based on several retrospective and prospective studies, the estimated incidence of reactions of all grades of severity varies from 1 to 2.8%, with severe (grade III and IV) reactions observed in 0.2–1.1% of cases [5, 10–12]. This case concerned a grade IV anaphylactic reaction by definition.

The incidence of anaphylactic shock after patent blue V is too low to discontinue this approach. Nevertheless, it remains imperative to keep reporting these severe cases in order to uphold vigilance. A sudden drop in blood pressure and increase in heart rate should direct the attention of the operating team towards an anaphylactic shock. Patients can be adequately stabilized with cardiac resuscitation, adrenergic support, mast cell stabilizing medication, and corticosteroids.

Mechanisms underlying allergic reactions to blue dyes have not been fully elucidated. Most likely, an IgE-mediated activation of mast cells causes this allergic response. IgE-based tests such as an enzyme-linked immunosorbent assay (ELISA) and skin Prick test support this view [9, 13]. An IgE-dependent response must of course be preceded by exposure to blue dyes. Since blue dyes are extensively used for commercial purposes such as cosmetics, textile, paper, medical products, sensitization is very well possible. In contrast, the Prick test does not provide an unequivocal true-positive

test [4]. This may be a test-specific characteristic but it also suggests an alternative non-IgE-dependent pathway. Irrespective of underlying mechanisms, treatment remains similar for both causes.

Absence of an allergic response to blue dyes in the past does not imply that the patient has not been pre-exposed, especially when considering their widespread industrial use. Preventive measures such as administration of hydrocortisone, diphenhydramine, and famotidine prior to induction of anesthesia or just before blue dye injection have reduced the severity but not the overall incidence of adverse reactions to dye [14]. Kalimo et al. [4] showed a significant reduction in clinical hypersensitivity reactions after performing a predictive patent blue skin Prick test in patients scheduled for lymphography. Another approach is the use of methylene blue instead of patent blue V. Anaphylactic reactions to methylene blue have rarely been reported but are not uncommon [15,

16]. Methylene blue can be used as an alternative to patent blue V in addition to Tc-99m tin colloid use for patients with breast cancer undergoing SLNB [17].

In conclusion, anaphylactic shock after patent blue V injection remains a serious adverse event and warrants awareness. Immediate action with ephedrine, antihistamines, and subsequently corticosteroids can stabilize the patient. In high-risk patients, preventive anti-allergy medication should be applied before patent blue injection, or alternatively Tc-99m tin colloid, isosulphan blue, or methylene blue could be used for sentinel lymph node imaging.

### Conflict of Interest

The authors declare no conflict of interest.

### References

- 1 Albo D, Wayne JD, et al.: Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. *Am J Surg* 2001;182: 393–8.
- 2 Johansson SG, Hourihane JO, et al.: A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813–24.
- 3 Ingram D, Hewett L, Maddern P: Anaphylaxis to patent blue during sentinel lymph node biopsy. *ANZ J Surg* 2004;74:607–8.
- 4 Kalimo K, Jansen CT, Korman M: Sensitivity to Patent Blue dye during skin-prick testing and lymphography. A retrospective and prospective study. *Radiology* 1981;141:365–7.
- 5 Montgomery LL, Thorne AC, et al.: Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. *Anesth Analg* 2002;95:385–8, table of contents.
- 6 Mostafa A, Carpenter R: Anaphylaxis to patent blue dye during sentinel lymph node biopsy for breast cancer. *Eur J Surg Oncol* 2001;27:610.
- 7 Mullan MH, Deacock SJ, et al.: Anaphylaxis to patent blue dye during sentinel lymph node biopsy for breast cancer. *Eur J Surg Oncol* 2001;27:218–9.
- 8 Tsopelas C, Sutton R: Why certain dyes are useful for localizing the sentinel lymph node. *J Nucl Med* 2002;43:1377–82.
- 9 Wöhrl S, Focke M, et al.: Near-fatal anaphylaxis to patent blue V. *Br J Dermatol* 2004;150:1037–8.
- 10 Cimmino VM, Brown AC, et al.: Allergic reactions to isosulfan blue during sentinel node biopsy – a common event. *Surgery* 2001;130:439–42.
- 11 Cox CE, Salud CJ, Harrinton MA: The role of selective sentinel lymph node dissection in breast cancer. *Surg Clin North Am* 2000;80:1759–77.
- 12 King TA, Fey JV, et al.: A prospective analysis of the effect of blue-dye volume on sentinel lymph node mapping success and incidence of allergic reaction in patients with breast cancer. *Ann Surg Oncol* 2004;11:535–41.
- 13 Woltsche-Kahr I, Komericki P, et al.: Anaphylactic shock following peritumoral injection of patent blue in sentinel lymph node biopsy procedure. *Eur J Surg Oncol* 2000;26:313–4.
- 14 Raut CP, Hunt KK, et al.: Incidence of anaphylactoid reactions to isosulfan blue dye during breast carcinoma lymphatic mapping in patients treated with preoperative prophylaxis: results of a surgical prospective clinical practice protocol. *Cancer* 2005;104:692–9.
- 15 Dewachter P, Mouton-Faivre C, et al.: Severe anaphylactic shock with methylene blue instillation. *Anesth Analg* 2005;101:149–50, table of contents.
- 16 Rzymiski P, Wozniak J, et al.: Anaphylactic reaction to methylene blue dye after laparoscopic chromopertubation. *Int J Gynaecol Obstet* 2003; 81:71–2.
- 17 Simmons R, Thevarajah S, et al.: Methylene blue dye as an alternative to isosulfan blue dye for sentinel lymph node localization. *Ann Surg Oncol* 2003;10:242–7.