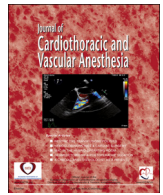




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Case Report

Intraoperative Anaphylaxis to Chlorhexidine During LVAD and Transplant Surgery

Eric Zhou^{*,1}, Purvi S. Parikh, MD^{†,‡}, Marc S. Kanchuger, MD[§],
Leora B. Balsam, MD^{||}^{*}Department of Cardiothoracic Surgery, NYU Langone Medical Center, New York, NY[†]Department of Medicine, Division of Rheumatology, NYU Langone Medical Center, New York, NY[‡]Department of Medicine, Division of Infectious Diseases and Immunology, NYU Langone Medical Center, New York, NY[§]Department of Anesthesiology, Perioperative Care, and Pain Medicine, NYU Langone Medical Center, New York, NY^{||}Division of Cardiac Surgery, UMass Memorial Medical Center, Worcester, MA**Key Words:** perioperative; anaphylaxis; chlorhexidine; left ventricular assist device; LVAD

PERIOPERATIVE ANAPHYLAXIS is a condition that can cause complications during surgical procedures, ranging from minor to severe with cardiovascular and/or pulmonary collapse. Some common etiologic agents include antibiotics, neuromuscular blocking agents, latex, and chlorhexidine,^{1–5} but any medication, blood product, or chemical substance used during the perioperative period has the potential for causing anaphylaxis. Complications from perioperative anaphylaxis can be life-threatening and are associated with a higher mortality rate than anaphylaxis under other circumstances.^{6,7} In this case report, the authors present the clinical course of an end-stage cardiomyopathy patient who experienced two separate episodes of anaphylaxis after exposure to the widely used antiseptic chlorhexidine during two major operations—the first during left ventricular assist device (LVAD) implantation and the second during heart transplantation.

Case Report

Institutional review board approval and waiver of individual consent were obtained prior to publication of this report. A 59-year-old male with diabetes mellitus, sickle cell trait, and

nonischemic dilated cardiomyopathy presented for elective implantation of a HeartMate II LVAD (Abbott Laboratories, Pleasanton, CA). At the time of admission, the patient had a white blood cell count of 8100/μL with an absolute eosinophil count of 1870/μL (normal range 0–600/μL). He also had a two-year history of pruritic papules on his chest, back, and extremities of unclear etiology and chronic eosinophilia. A skin biopsy two years prior to the LVAD operation showed mixed-cell interstitial dermatitis with eosinophils, suggesting the etiology of the pruritic papules to be from chronic drug eruption most likely secondary to his cardiac medications, which included angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. He also had a history of urticarial reaction to the contrast dye iodixanol.

Preoperative transthoracic echocardiography showed left ventricular dilation and severe hypokinesis with a normal right ventricle and mild pulmonary hypertension. The night before the patient's scheduled LVAD implantation, he developed a mild skin rash and pruritus after use of 2% chlorhexidine gluconate cloth wipes on his anterior chest. In the operating room, the patient was induced with midazolam, sufentanil, and vecuronium, and he was intubated endotracheally without difficulty. The patient's neck was prepared with a small amount of chlorhexidine antiseptic, and a central venous

¹Address reprint requests to: Eric Zhou, NYU School of Medicine, 550 First Avenue, Ground Floor, Suite 50, New York, NY 10016.

E-mail address: eric.zhou@nyumc.org (E. Zhou).

catheter was placed. Infusions of vancomycin, cefepime, and fluconazole were initiated at this time as well.

The patient's chest then was prepared with chlorhexidine. Within minutes, the patient developed profound hypotension, with mean arterial pressure rapidly decreasing from 80 mmHg to less than 40 mmHg and heart rate increasing to over 140 beats per minute. The patient also developed considerable wheezing, and ventilation pressure increased from 20 cmH₂O to approximately 35 cmH₂O. Full-body urticaria and later extensive angioedema of the head and neck were noted. The patient immediately was treated with 20 µg of epinephrine, 50 mg of diphenhydramine, and 100 mg of hydrocortisone, which resulted in stabilization of the mean arterial pressure within minutes to approximately 70 mmHg. Anaphylaxis to either antibiotics or chlorhexidine was suspected. After stabilizing the patient, it was determined that the benefits of proceeding with LVAD implantation outweighed the risks of further potential intraoperative complications related to the anaphylactic event. Moreover, it was thought that the advanced stage of the patient's congestive heart failure made postponing the LVAD implantation a greater risk to the patient than resuming the operation after the anaphylaxis. Therefore, LVAD implantation was performed after changing antibiotics to daptomycin and aztreonam and skin antisepsis to povidone-iodine.

By the completion of surgery, the patient had developed extensive facial, neck, and upper-extremity angioedema. An abdominal skin punch biopsy showed mild superficial perivascular lymphocytic infiltrates consistent with resolving urticaria. Serum tryptase levels measured 24 hours after surgery were within normal limits. Angioedema persisted for several days postoperatively despite intravenous administration of hydrocortisone and diphenhydramine, each at a dose of 50 mg every 6 hours. The facial angioedema and laryngeal swelling resulted in delay of extubation until the fourth postoperative day.

The acute onset of severe hypotension, respiratory compromise, facial angioedema, and urticaria after exposure to a potential allergen made it clear that the patient had experienced an episode of anaphylaxis based on established criteria despite normal tryptase levels.⁸ Immediately after the surgery, the etiology of the patient's anaphylaxis was unclear because he had received multiple medications prior to the surgery to manage his congestive heart failure and diabetes, in addition to having been exposed to chlorhexidine and antibiotics during the operation. Although antibiotics are the most common cause of drug-induced anaphylaxis,⁹ hypersensitivity to chlorhexidine was high on the differential diagnosis because the patient demonstrated a cutaneous reaction to this compound the night before the LVAD implantation. Subsequent evaluation in the weeks after the surgery also included Strongyloides antibody, antinuclear antibody, and antineutrophil cytoplasmic antibody testing, which were all negative. Skin prick testing six weeks after LVAD implantation indicated hypersensitivity to chlorhexidine and ceftriaxone.

Thirteen months later, the patient presented for orthotopic heart transplantation at a different medical center. General anesthesia was induced and a central venous line (double-

lumen ARROWg+ard blue, Arrow International, Reading, PA) was placed. Soon thereafter, the patient experienced hemodynamic instability and vasodilatory shock. Chest compressions were performed in addition to administration of epinephrine, norepinephrine, and vasopressin with restoration of hemodynamic stability within one minute. Faint erythema was noted on the anterior chest and posterior thigh. Although hemodynamic instability had been resolved, the procedure was aborted because the overall condition of the patient was considered to be of too high risk for LVAD explantation and heart transplantation. The precipitous drop in blood pressure was later attributed to re-exposure to chlorhexidine in the central venous line, which was impregnated with chlorhexidine. The central line was removed as soon as this was recognized. Five months later, the patient was transplanted successfully.

Discussion

This case report summarizes the clinical course of an end-stage heart disease patient who experienced two separate episodes of anaphylaxis attributed to the antiseptic chlorhexidine. Although the allergy to chlorhexidine was confirmed after chlorhexidine skin preparation sticks were used during LVAD implantation, the patient was exposed a second time with chlorhexidine during attempted heart transplantation at a different medical center, this time in the coating of a central venous line. The patient's clinical course, including both anaphylactic episodes, is summarized in Table 1.

The use of chlorhexidine as an antiseptic agent during surgical procedures is widespread, as multiple studies have shown that it is significantly more effective at preventing surgical site infections than iodine antiseptics.¹⁰ Although the prevalence of perioperative chlorhexidine allergy and anaphylaxis is uncertain, studies in Denmark have shown that approximately 10% of all perioperative allergic reactions are due to chlorhexidine exposure.¹¹ Moreover, a recent literature review demonstrated 36 articles reporting chlorhexidine anaphylaxis in surgical patients from 1984 to 2014, totaling 68 separate anaphylactic episodes.¹² Although anaphylactic reactions to chlorhexidine are rare, it has been noted previously that such episodes often are preceded by milder cases of urticaria or pruritis,^{12,13} as was demonstrated in this patient's clinical presentation. Unanticipated perioperative chlorhexidine anaphylaxis often has resulted in the necessity for chest compressions or abandonment of the surgical operation altogether.¹²

In a patient with a hypersensitivity to chlorhexidine, often-times the most common initial presenting feature is a mild cutaneous reaction to chlorhexidine¹⁴ as seen in this case report. In evaluating a patient with a recent perioperative anaphylactic episode with a suspected hypersensitivity to chlorhexidine, the authors recommend obtaining serial serum tryptase levels within one hour, two to four hours, and 24 hours after exposure.¹⁴ Afterward, it is essential to continue evaluation with an allergist for further investigation, ideally after at least one month has passed from the allergic episode to reduce the rate of false

Table 1
Chronology of the Patient's Clinical Course Culminating in Successful Heart Transplant 18 Months After LVAD Implantation

Date	Medication(s) Administered	Event(s)
Night prior to LVAD implantation	2% chlorhexidine gluconate wipes on chest	Developed mild skin rash and pruritus over chest
During LVAD implantation	Chlorhexidine on chest	Precipitous drop in MAP
		Significant increase in ventilation pressure
	Intravenous vancomycin, cefepime, and fluconazole	Wheezing Angioedema of head and neck Diffuse urticaria
Six weeks after LVAD implantation	N/A	Anaphylaxis workup showed hypersensitivity to chlorhexidine and ceftriaxone via skin prick test
Thirteen months after LVAD implantation, during attempted heart transplant	Chlorhexidine-coated central venous catheter	Precipitous drop in MAP
		Chest compressions with return of hemodynamic stability within 1 minute
		Faint erythema on chest and thigh
		Heart transplant aborted
Eighteen months after LVAD implantation	N/A	Successful heart transplant

Abbreviations: LVAD, left ventricular assist device; MAP, mean arterial pressure; N/A, not applicable.

negatives upon testing. A skin prick test is recommended to identify cutaneous hypersensitivities to suspected allergens. Although there have been no studies looking specifically at the sensitivity and specificity of skin prick testing for chlorhexidine hypersensitivity, previous work has shown that the sensitivity and specificity of skin prick testing for inhalant allergens are 70% to 95% and 80% to 97%, respectively.¹⁵ Due to the possibility of false negatives, in the setting of a negative or equivocal skin prick test result despite high clinical suspicion of hypersensitivity, it is possible to conduct an in vitro allergy test, which has been shown to be an equal alternative to skin prick testing.¹⁶ The most commonly available in vitro allergy tests involve enzyme-linked immunosorbent assays and radioallergosorbent tests. A basophil histamine release assay is also an option for in vitro allergy testing, but it is not readily available in the health care setting in the US. However, basophil activation tests have been used widely in Europe over the past two decades as effective detectors of allergies to neuromuscular blocking agents, antibiotics, and iodinated radiocontrast media.¹⁷

There have been previous reports of patients with known allergic reactions to chlorhexidine being re-exposed to chlorhexidine during subsequent surgical procedures, resulting in repeated bouts of anaphylaxis.^{12,18,19} Oftentimes, these occurred due to the accidental use of chlorhexidine-impregnated surgical devices, such as catheters, or lack of proper broadcasting of knowledge that the patient had a documented allergy to chlorhexidine.^{12,20} In the case the authors present, although the transplant care team was aware of the patient's hypersensitivity to chlorhexidine and ceftriaxone, it is likely that re-exposure occurred due to lack of recognition that the central venous catheter was impregnated with chlorhexidine. Increased awareness that medical devices may contain or be coated with potentially allergenic chemical compounds, as well as conspicuous labeling on the packaging of these devices, may aid in prevention.

Anaphylaxis as a result of exposure to medical devices impregnated with chlorhexidine, although rare, has been

documented throughout the world since the early 1990s after the US Food and Drug Administration approved the incorporation of chlorhexidine into intravenous catheters, topical antimicrobial skin dressings, and implanted antimicrobial surgical mesh. Anaphylactic episodes attributed to these chlorhexidine-impregnated devices caused the Food and Drug Administration in 1998 to issue a public health notice to alert health care providers to the possibility of allergic reaction to these devices.²¹ Moreover, chlorhexidine-impregnated central venous catheters were withdrawn from use in Japan after a large number of reports of anaphylactoid-type events emerged within Japanese patients.²² The occurrence of these anaphylactic events after use of these devices could be diminished if policy changes were enacted that limited or excluded the use of chlorhexidine within medical devices such as central venous catheters. Additionally, routine testing for chlorhexidine hypersensitivities could allow for greater detection of patients at risk for perioperative chlorhexidine allergic reactions and anaphylaxis; however, the cost-effectiveness of this practice is unknown.

Although there has been no systematic identification of populations at risk for chlorhexidine anaphylaxis, it is likely that the patient described in this case report was at greater risk for anaphylaxis given his history of chronic eosinophilia and full body rash. As the use of chlorhexidine for perioperative topical antisepsis increases, surgical teams should be alert to possible allergic reactions to chlorhexidine, especially in patients perceived to be at greater risk for anaphylaxis. As such, sensitivity to chlorhexidine always should be considered whenever a patient experiences a perioperative or periprocedural allergic reaction. Prompt treatment of anaphylaxis, particularly in hemodynamically fragile patients, such as the end-stage cardiomyopathy patient and LVAD patient described, is critical to avoid significant morbidity and mortality.

Summary

In this report, the authors have described the case of a 59-year-old male with nonischemic dilated cardiomyopathy and a history of chronic eosinophilia who presented for LVAD

implantation as a bridge to heart transplantation. Two separate episodes of intraoperative anaphylaxis secondary to exposure to the antiseptic chlorhexidine occurred—the first during LVAD implantation and the second during an aborted heart transplant approximately 13 months later. This report highlights the importance of early recognition of this complication as well as the need for greater awareness of perioperative exposure to potential allergens, including those in chemically coated medical devices. Increased surveillance and diligence will help prevent future life-threatening allergic reactions in the health care setting.

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