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REPORTS OF ORIGINAL INVESTIGATIONS

Perioperative anaphylactic reactions to central venous and pulmonary artery catheters containing chlorhexidine, sulfadiazine, or latex: a historical cohort study

Réactions anaphylactiques périopératoires aux cathéters veineux centraux et cathéters de l'artère pulmonaire contenant de la chlorhexidine, de la sulfadiazine ou du latex : une étude de cohorte historique

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Abstract

Purpose *Central venous catheters (CVCs) and pulmonary artery catheters (PACs) containing chlorhexidine, silver sulfadiazine, or latex can cause perioperative anaphylaxis. We examined the incidence of and outcomes associated with anaphylaxis caused by CVCs/PACs.*

Methods *In a historical cohort study, we retrospectively identified adult patients fitted with CVCs/PACs at the Mayo Clinics in Minnesota, Arizona, and Florida from 1 January 2008 to 1 March 2018. Potential and confirmed cases of perioperative anaphylactic reactions were individually reviewed and classified.*

Results *During the study period, 39,505 procedures were performed during which CVCs/PACs were inserted. Of these, 2,937 patients with pre-existing chlorhexidine, sulfonamide (sulfa), and/or latex allergies had CVCs/PACs inserted that contained these substances. Perioperative anaphylaxis, in which CVCs/PACs were the confirmed or potential causative agent, occurred during 53 procedures. Seven patients had a preoperatively reported sulfa or latex allergy; no patients had a preoperative chlorhexidine allergy. Six of the seven patients with reported allergies to sulfa or latex had a CVC/PAC inserted that contained these substances. Twenty-four patients with anaphylaxis had postoperative allergic disease consultation; ten of these (42%) underwent skin testing.*

Conclusion *Perioperative anaphylactic reactions related to CVCs/PACs containing chlorhexidine, silver sulfadiazine, or latex were rare in this large historical cohort study. We identified 2,937 patients with pre-existing chlorhexidine, sulfa, and/or latex allergies and had CVCs/PACs inserted that contained these substances. Although few cases of perioperative anaphylaxis attributable to these substances were observed in patients with corresponding allergies, the potential for substantial complication exists. Providers should be aware of the potential for these hidden exposures.*

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Résumé

Objectif *Les cathéters veineux centraux (CVC) et les cathéters artériels pulmonaires (CAP) contenant de la*

chlorhexidine, de la sulfadiazine argentique ou du latex peuvent provoquer une anaphylaxie périopératoire. Nous avons examiné l'incidence et les devenirs associés à l'anaphylaxie causée par les CVC/CAP.

Méthode *Dans une étude de cohorte historique, nous avons identifié rétrospectivement des patients adultes chez lesquels un CVC/CAP avait été installé aux cliniques Mayo du Minnesota, de l'Arizona et de la Floride du 1er janvier 2008 au 1er mars 2018. Les cas potentiels et confirmés de réactions anaphylactiques périopératoires ont été examinés et classés individuellement.*

Résultats *Au cours de la période à l'étude, 39 505 interventions ont été réalisées au cours desquelles des CVC/CAP ont été insérés. Parmi celles-ci, des CVC/CAP contenant de la chlorhexidine, des sulfamides et/ou du latex ont été insérés chez 2937 patients présentant des allergies préexistantes à ces substances. Une anaphylaxie périopératoire, dont l'agent causal confirmé ou potentiel était le CVC/CAP, s'est produite dans 53 interventions. Sept patients présentaient une allergie aux sulfamides ou au latex signalée avant l'opération; aucun patient n'a eu d'allergie préopératoire à la chlorhexidine. Un CVC/CAP contenant des sulfamides ou du latex a été inséré chez six des sept patients ayant signalé des allergies à ces substances. Vingt-quatre patients atteints d'anaphylaxie ont eu une consultation postopératoire pour une maladie allergique; dix d'entre eux (42 %) ont subi des tests cutanés.*

Conclusion *Les réactions anaphylactiques périopératoires liées aux CVC/CAP contenant de la chlorhexidine, de la sulfadiazine argentique ou du latex étaient rares dans cette vaste étude de cohorte historique. Nous avons identifié 2937 patients présentant des allergies préexistantes à la chlorhexidine, aux sulfamides et/ou au latex chez lesquels des CVC/CAP contenant ces substances ont été insérés. Bien que peu de cas d'anaphylaxie périopératoire attribuable à ces substances aient été observés chez des patients présentant des allergies correspondantes, il existe un risque de complication importante. Les fournisseurs doivent être conscients du potentiel de ces expositions cachées.*

Keywords anaphylaxis · central venous catheters · chlorhexidine · latex · sulfadiazine

Perioperative anaphylaxis is a rare but serious event. Frequently identified causative agents include antibiotics, neuromuscular blocking agents, chlorhexidine, dyes, sugammadex, and latex.[1–6] Some of these agents are found in central venous catheters (CVCs) and pulmonary artery catheters (PACs), which are inserted in the perioperative period for several indications.[7–9] Chlorhexidine is an antimicrobial agent commonly used in the perioperative period and as a coating for CVCs to reduce the risk of infection.[9,10] This prevalent use of chlorhexidine may put patients at risk for allergic sensitization and anaphylactic reactions upon re-exposure to chlorhexidine-containing solutions or devices.[10,11] Silver sulfadiazine is commonly used in combination with chlorhexidine-impregnated CVCs to protect against central-line-associated bloodstream infection (CLABSI).[9] It is unclear whether a reported sulfonamide (sulfa) allergy is a risk factor for allergic reaction to silver sulfadiazine. Latex, present in the balloon of many PACs and valves of CVC sheaths, has long been implicated in severe allergic reactions.[12]

Patients may be at risk for anaphylaxis from CVCs/PACs containing chlorhexidine, sulfa, or latex. We aimed to assess the incidence of and outcomes associated with anaphylaxis caused by chlorhexidine-, silver sulfadiazine-, or latex-containing CVCs/PACs.

Materials and methods

This historical cohort study was approved by the Mayo Clinic Institutional Review Board. Written-informed consent was waived for all patients who had previously granted permission for their health records to be used for observational research (consistent with Minnesota Statute 144.295). We retrospectively searched our electronic health record for all adult patients who underwent surgical procedures between 1 January 2008 and 1 March 2018, and had perioperative CVCs/PACs placed at Mayo Clinic campuses in Minnesota, Arizona, or Florida. Electronic abstraction of CVC/PAC data was unavailable before 2011 at the Florida campus, so data collection from that location began on 1 January 2011. Patients who declined to participate in research, had a CVC/PAC placed at an outside institution, were prisoners, were known to be pregnant, or had an American Society of Anesthesiologists (ASA) Physical Status of V or VI were excluded. The study cohort was identified through the Mayo Clinic's Supply Information Management System and Perioperative DataMart. These institutional databases contain demographic, anesthetic, CVC/PAC, surgical, laboratory, and medication data in multiple perioperative care environments. Data not available in the Perioperative DataMart were extracted using Advanced Cohort Explorer, a resource used to search the electronic health record for structured and unstructured inquiries from the inpatient and outpatient care environments. Both DataMart and Advanced Cohort Explorer have been validated, with continual monitoring of data quality.[13,14]

Demographic and preoperative data were abstracted, including age; sex; body mass index; patient-reported history of allergies (including listed allergy to chlorhexidine, sulfa-containing medications, or latex); history of anaphylactic reaction; and history of atopic disease, mast cell disorder, hereditary angioedema, neurogenic bladder, and spina bifida. All patients were screened for drug/medication, venom, food, pollen, and contact allergies prior to each surgical procedure; all patient-reported and previously documented allergies were reviewed on the date of said procedure, with the reaction type and severity verified. All patients with reported sulfa allergy were included in the sulfa allergy cohort. Catheter-related data included CVC/PAC type, skin preparation solution used for catheter insertion, and manufacturer-confirmed presence of chlorhexidine, silver sulfadiazine, or latex. Intraoperative data included primary procedure type, anesthesia type, ASA Physical Status (I–IV, emergency), surgical skin preparation solution, presence of intraoperative hypotension (systolic blood pressure < 90 mm Hg, mean arterial pressure < 50 mm Hg, or 40% decrease in systolic blood pressure over a five-minute period), anesthesia critical event notes, use of intraoperative cardiopulmonary resuscitation (CPR), cardiac arrest, and intraoperative death. Postoperative data included patient outcomes (hospital length of stay, discharge disposition, and death within 30 days and one year), laboratory data (values of serum tryptase, serum histamine, and chlorhexidine- and latex-specific immunoglobulin [Ig] E) determined within 48 hr after procedure start, and results of allergy consultation. The decision to search for laboratory data within 48 hr of procedure start was to screen for suspected cases of perioperative anaphylaxis for which intraoperative laboratory data may not have been collected or if anaphylaxis may have been identified postoperatively.

Records were screened and reviewed for perioperative anaphylaxis. Chlorhexidine-specific IgE testing was available late in the study period at our institution and was not universally collected for all patients who underwent allergic disease consultation. Cases of potential perioperative anaphylaxis in which the CVCs/PACs may have contained the causative agent were included in a secondary review by study personnel (T. M. P., B. B. S., M. M. S., G. W. V.). Patients included in the final analysis were only those diagnosed with perioperative anaphylaxis in which CVCs/PACs contained the confirmed (after allergy testing) or potential (after clinical review and/or inconclusive allergy testing with no single agent confirmed) causative agent responsible for the acute perioperative event. In patients without formal postoperative allergic disease consultation or allergy testing, a diagnosis of anaphylaxis and potential causative agent(s) were determined through individual health record review. A diagnosis of anaphylaxis was made only if a strong clinical suspicion of perioperative anaphylaxis was identified by study personnel, considering timing of the event and comprehensive review of all perioperative details. A few patients were also included in the final analysis after individual chart review if they had anaphylaxis in which CVCs/PACs did not contain chlorhexidine, sulfa, or latex but they were exposed to one or more of these agents during CVC/PAC insertion.

Definitions

The primary outcome, perioperative anaphylaxis, was classified into four groups: *IgE-mediated anaphylactic reaction* (increased serum tryptase value [≥ 11.5 ng·mL^{-1}] and positive skin test findings),[15,16] *non-IgE-mediated anaphylactic reaction* (increased serum tryptase value and negative or equivocal skin test findings), *possible IgE-mediated anaphylactic reaction* (increased serum tryptase value and skin testing not performed), or *possible non-IgE-mediated anaphylactic reaction* based on clinical presentation (tryptase value normal or not measured and/or skin testing negative or not performed). The definitions described above, including the threshold for increased tryptase value (≥ 11.5 ng·mL^{-1}), were used clinically at our institution during the study period. Serum tryptase level can be increased in both IgE-mediated and non-IgE-mediated anaphylaxis. Negative IgE testing after an event could be secondary to false-negative IgE testing, testing not performed to the actual allergen, or a non-IgE-mediated event. Guidelines published after the completion of the current study have abandoned a tryptase value threshold and now recommend an algorithm to define a *clinically relevant increase* in tryptase value using two laboratory samples: (1) serum tryptase at the time of reaction (drawn one to three hours after the event) and (2) baseline serum tryptase (drawn > 24 hr after the event). An increase in serum tryptase at the time of reaction $> 1.2 \times$ baseline $+ 2$ ng·mL^{-1} is considered a clinically relevant increase.[5,6]

Allergy evaluation

Patients with possible perioperative anaphylaxis were expected to be referred from the Department of Anesthesiology and Perioperative Medicine to the Division of Allergic Diseases for postoperative consultation. Evaluation included a thorough clinical history and review of perioperative events and medication administration. Other testing, when clinically indicated, was completed at consultation or four to six

weeks after the intraoperative event, including skin testing (skin prick testing and intradermal testing) and/or repeated measurement of serum tryptase, histamine, and chlorhexidine- and latex-specific IgE. Standardized skin testing protocols were described previously.[2]

Results

During the study period, 37,018 patients underwent 39,505 procedures during which CVC/PACs were inserted (Fig. 1). Patient demographic and procedure characteristics are reported in Table 1. A preoperative sulfa, latex, or chlorhexidine allergy was reported in 5,095 patients (13%). We identified 2,937 patients with pre-existing chlorhexidine, sulfa, and/or latex allergies and had CVCs/PACs inserted that contained these substances. Of the 3,205 patients with a reported sulfa allergy, 2,335 (73%) were fitted with a CVC/PAC that contained silver sulfadiazine; of the 1,798 patients with a reported latex allergy, 551 (31%) had a CVC/PAC that contained latex; and of the 92 patients with a reported chlorhexidine

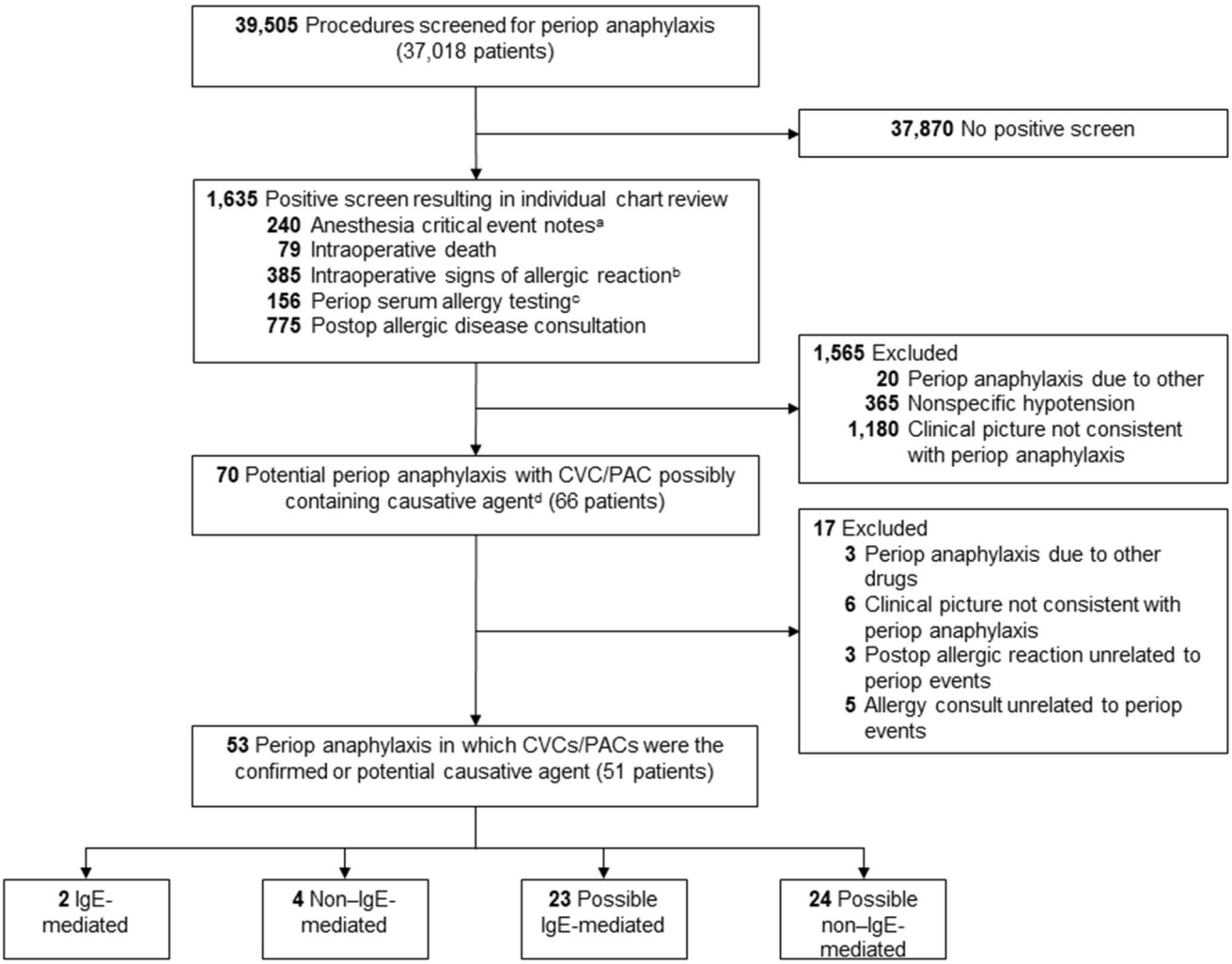

Fig. 1 Flowchart detailing the evaluation of perioperative anaphylaxis in the study cohort. [a]Anesthesia critical event notes detailing cardiopulmonary resuscitation (CPR)/cardiac arrest, cutaneous manifestations, allergic reaction/anaphylactic reaction, death, bronchospasm/wheezing, unplanned reintubation, hypotension, and laryngospasm/respiratory arrest were reviewed. [b]One or more of the following: skin or mucosal signs, hypotension, tachycardia, wheezing and/or bronchospasm, and CPR performed in the operating room. [c]Serum tryptase, histamine, or latex-specific or chlorhexidine-specific IgE testing within 48 hours after procedure start. [d]All patients with clinical features of intraoperative anaphylaxis (hypotension in addition to tachycardia, skin or mucosal signs, or wheezing and/or bronchospasm), intraoperative CPR/cardiac arrest, intraoperative death, anesthesia critical event notes suspecting anaphylaxis, or allergic disease consultation notes detailing perioperative anaphylaxis were individually reviewed. CVC = central venous catheter; IgE = immunoglobulin E; PAC = pulmonary artery catheter; periop = perioperative; postop = postoperative

Table 1 Demographic, clinical, and procedure characteristics

Characteristic	*N* = 39,505
Age (yr), mean (SD)	62.3 (15.2)
Sex, *n*/total *N* (%)	
Men	24,835/39,505 (63%)
Women	14,670/39,505 (37%)
ASA Physical Status, *n*/total *N* (%)	
I	156/36,980 (0.4%)
II	2,185/36,980 (6%)
III	24,491/36,980 (66%)
IV	10,148/36,980 (27%)
Any reported allergy[†], *n*/total *N* (%)	21,287/39,505 (54%)
Preop sulfa allergy, *n*/total *N* (%)	3,205/39,505 (8%)
Preop latex allergy, *n*/total *N* (%)	1,798/39,505 (5%)
Preop chlorhexidine allergy, *n*/total *N* (%)	92/39,505 (0.2%)
History, *n*/total *N* (%)	
Mast cell disorder[‡]	59/39,505 (0.1%)
Atopic disease[§]	7,276/39,505 (18%)
Hereditary angioedema	26/39,505 (0.1%)
Neurogenic bladder	735/39,505 (2%)
Spina bifida	56/39,505 (0.1%)
Primary procedure type, *n*/total *N* (%)	
Cardiac	23,364/39,505 (59%)
General	5,277/39,505 (13%)
Transplant	3,256/39,505 (8%)
Vascular	1,862/39,505 (5%)
Neurologic	679/39,505 (2%)
Orthopedic	654/39,505 (2%)
Urologic	648/39,505 (2%)
Thoracic	230/39,505 (0.6%)
Other	1,359/39,505 (3%)
Missing	2,176/39,505 (6%)
Anesthesia type, *n*/total *N* (%)	
General	37,165/39,505 (94%)
MAC	61/39,505 (0.2%)
Regional	29/39,505 (0.1%)
Other	34/39,505 (0.1%)
Missing	2,216/39,505 (6%)
Procedure duration (min), mean (SD)	258.7 (194.1)

[†] History of at least one reported allergy (drug, food, and/or venom) in the patient's health record at the time of procedure with central venous catheter/pulmonary artery catheter placement

[‡] Including mastocytosis, idiopathic mast cell activation syndrome, and mast cell activation disorder

[§] Including urticaria, asthma, allergic rhinitis, and eczema

ASA = American Society of Anesthesiologists; MAC = monitored anesthesia care; preop = preoperative; SD = standard deviation; sulfa = sulfonamide

allergy, 51 (55%) had a CVC/PAC that contained chlorhexidine. Intraoperative characteristics are reported in Table 2. Surgical skin preparation was performed with chlorhexidine in 98.5% of cases. Postoperative evaluation and outcomes are shown in Table 3. Serum tryptase was measured within 48 hr of procedure start in 92 patients, 56 (61%) of whom had a serum tryptase value less than 11.5 $ng \cdot mL^{-1}$.

Table 2 Intraoperative characteristics

Characteristic	*N* = 39,505
Skin preparation, *n*/total *N* (%)	
Chlorhexidine	29,592/30,042 (99%)
Alcohol	80/30,042 (0.3%)
Betadine	61/30,042 (0.2%)
Other	309/30,042 (1%)
Anesthesia critical event note, *n*/total *N* (%)	225/39,505 (0.6%)
Cardiopulmonary resuscitation/cardiac arrest	71/225 (32%)
Cutaneous manifestations	60/225 (27%)
Death	34/225 (15%)
Allergic reaction/anaphylactic reaction	32/225 (14%)
Bronchospasm/wheezing	15/225 (7%)
Unplanned reintubation	6/225 (3%)
Hypotension	5/225 (2%)
Laryngospasm/respiratory arrest	2/225 (0.9%)
Intraoperative death, *n*/total *N* (%)	79/39,505 (0.2%)

Table 3 Postoperative evaluation and outcomes

Characteristic	*N* = 39,505
Allergic disease consultation, *n*/total *N* (%)	775/39,505 (2%)
Serum tryptase measured[b]	92/39,505 (0.2%)
< 11.5 ng·mL^{-1}	56/39,505 (0.1%)
≥ 11.5 ng·mL^{-1}	36/39,505 (0.1%)
Serum histamine measured[†]	2/39,505 (<0.1%)
Latex-specific IgE assessed	57/39,505 (0.1%)
Chlorhexidine-specific IgE assessed	5/39,505 (<0.1%)
ICU admission	30,061/39,505 (76%)
Complication, *n*/total *N* (%)	
Myocardial infarction	2,227/39,505 (6%)
Stroke	411/39,505 (1%)
Kidney failure	2,980/39,505 (8%)
Liver failure	2/39,505 (<0.1%)
Hospital LOS (days), median [IQR]	6.6 [5–11]
Death, *n*/total *N* (%)	
Within 30 days	1,087/39,505 (3%)
Within one year	3,506/39,505 (9%)
Discharge disposition, *n*/total *N* (%)	38,728/39,505 (98%)
Home	28,839/39,505 (75%)
Skilled nursing facility	4,294/39,505 (11%)
Home health care	3,247/39,505 (8%)
Other	2,348/39,505 (6%)

[†] Measured within 48 hr after procedure start

ICU = intensive care unit; Ig = immunoglobulin; IQR = interquartile range; LOS = length of stay

We identified 51 patients who underwent 53 procedures and had perioperative anaphylaxis in which CVCs/PACs contained the confirmed or potential causative agent (Table 4). Two patients had IgE-mediated anaphylactic

Table 4 Perioperative anaphylaxis

Characteristic	*N* = 53
Type of anaphylactic reaction, *n*/total *N* (%)	
IgE-mediated	2/53 (4%)
Non-IgE-mediated	4/53 (8%)
Possible IgE-mediated	23/53 (43%)
Possible non-IgE-mediated	24/53 (45%)
Age (yr), mean (SD)	57.0 (15.0)
Sex, *n*/total *N* (%)	
Men	43/53 (81%)
Women	10/53 (19%)
Procedure type, *n*/total *N* (%)	
Cardiac	36/53 (68%)
Transplant	5/53 (9%)
Vascular	5/53 (9%)
Other*	7/53 (13%)
Pre-existing allergy, *n*/total *N* (%)	
Sulfa	4/53 (8%)
Latex	3/53 (6%)
Chlorhexidine	0/53 (0%)
Chlorhexidine skin preparation, *n*/total *N* (%)	50/53 (94%)
CVC/PAC additive, *n*/total *N* (%)	
Chlorhexidine/sulfa	28/53 (53%)
Chlorhexidine/sulfa/latex	18/53 (34%)
None[†]	4/53 (8%)
Latex alone	3/53 (6%)
Timing of event, *n*/total *N* (%)	
Intraoperative	50/53 (94%)
Postoperative	3/53 (6%)
Clinical features, *n*/total *N* (%)	
Hypotension + erythema	17/53 (32%)
Hypotension	12/53 (23%)
Hypotension + CPR	6/53 (11%)
Erythema	4/53 (8%)
Combination[‡]	14/53 (26%)
Treatment, *n*/total *N* (%)	
Epinephrine + corticosteroids + antihistamines + vasopressors	38/53 (72%)
Various combinations of epinephrine + corticosteroids + antihistamines + vasopressors	9/53 (17%)
Epi or vasopressor alone	6/53 (11%)
Disposition, *n*/total *N* (%)	
Procedure aborted	5/53 (9%)
ICU admission	53/53 (100%)
Postoperative testing, *n*/total *N* (%)	
Tryptase	45/53 (85%)
Postevent time of measurement	
1–3 hr	43/45 (96%)
> 3–24 hr	2/45 (4%)
Value	
$\geq$ 11.5 ng·mL^{-1}	27/45 (60%)
< 11.5 ng·mL^{-1}	18/45 (40%)

Table 4 continued

Characteristic	$N = 53$
Baseline tryptase measured[§]	9/45 (20%)
Clinically relevant increase[‖]	9/45 (20%)
Latex-specific IgE	7/53 (13%)
Histamine	2/53 (4%)
Postoperative allergy consultation, *n*/total *N* (%)	24/53 (45%)
Time from event to consult (days), median [IQR]	6.5 [1–36.8]
Skin testing performed, *n*/total *N* (%)	10/24 (42%)
Time from event to testing (days), median [IQR]	44.5 [27.5–119]

*Orthopedic, general, neurologic, or urologic surgery

[†] All four patients were exposed to chlorhexidine and/or latex during CVC/PAC insertion which were potential causative agents of perioperative anaphylaxis

[‡] Combination of hypotension, erythema, bronchospasm, tachycardia, and/or hypoxia

[§] Baseline tryptase measured a minimum of 24 hr after the perioperative event

[‖] Defined as tryptase value at the time of reaction > ([1.2 × baseline] + 2)

CPR = cardiopulmonary resuscitation; CVC = central venous catheter; IQR = interquartile range; PAC = pulmonary artery catheter; SD = standard deviation; sulfa = sulfonamide

reactions shortly after CVC/PAC insertion, the cause of which was determined to be chlorhexidine for one and latex for the other. Neither patient had reported allergies to these substances. Four patients had non-IgE-mediated anaphylactic reactions. Seven patients (13%) had a reported pre-existing sulfa or latex allergy; no patients had a reported chlorhexidine allergy (Table 4). Three patients with a reported sulfa allergy had a CVC that contained silver sulfadiazine; two of three patients with a latex allergy had a CVC/PAC that contained latex; and one patient with both sulfa and latex allergies had a CVC/PAC that contained silver sulfadiazine without latex. All four patients with a sulfa allergy and a CVC that contained silver sulfadiazine had possible non-IgE-mediated anaphylaxis. Of the two patients with a latex allergy and a CVC/PAC that contained latex, one had non-IgE-mediated anaphylaxis, and one had possible IgE-mediated anaphylaxis.

A serum tryptase level was obtained in 45 patients with suspected anaphylaxis (85%), 43 of which were measured one to three hours after the event (Table 4). A baseline tryptase level was obtained in nine patients with anaphylaxis. All nine of these patients had a clinically relevant increase in serum tryptase, three of which occurred despite a tryptase level < 11.5 ng·mL^{-1} at the time of the event. Twenty-four patients with anaphylaxis (45%) had a postoperative allergic disease consultation, and ten of these (42%) underwent skin testing. One patient had a positive skin test finding (latex), and the rest were negative or nondiagnostic.

Discussion

Central venous access with CVCs/PACs is often necessary in the perioperative period. Physicians must balance the risks and benefits of CVC/PAC insertion. Mechanical, thrombotic, and infectious complications are the most frequent risks.[9] Many interventions, such as use of CVCs/PACs containing antimicrobial agents, are recommended to prevent or reduce the rate of infectious complications associated with CVCs/PACs.[9] Practice guidelines set forth by the ASA Task Force on Central Venous Access state, "For selected patients, use catheters coated with antibiotics, a combination of chlorhexidine and silver sulfadiazine, or silver-platinum-carbon-impregnated catheters based on risk of infection and anticipated duration of catheter use."[9]

Central venous catheters used in clinical practice commonly contain the antiseptic agents chlorhexidine and silver sulfadiazine.[17,18] Despite the widespread use of antimicrobial-impregnated CVCs, it is unclear whether these devices decrease the rates of catheter colonization and/or CLABSI compared with nonimpregnated catheters.[9,17,19] Furthermore, exposing patients to CVCs containing these medications is not benign and represents a

substantial risk to patient safety and perioperative outcomes.

Anaphylaxis attributed to impregnated CVCs/PACs has been increasingly reported in the medical literature, including in a series of severe and near-fatal anaphylactic reactions to chlorhexidine-containing CVCs in five kidney transplant recipients.[11] Notably, patients undergoing dialysis are susceptible to allergic sensitization and chlorhexidine anaphylaxis given that chlorhexidine is routinely used to disinfect arteriovenous fistulae before initiation of hemodialysis.[11] Another series highlighted three cases of anaphylaxis to chlorhexidine-containing CVCs in cardiac surgical patients.[20] In the current study, heart surgery was the most common procedure type among patients with perioperative anaphylaxis. Anaphylaxis that occurs during cardiotomy is associated with worse outcomes, including fatal anaphylaxis in the perioperative period.[4]

Silver sulfadiazine-containing CVCs should also be considered a potential culprit in perioperative allergic reactions. The exact mechanism of sulfa-related allergic reactions is not completely understood but approximately 3% of the population report a sulfa allergy.[21] Patients with a prior sulfa allergy may be at increased risk for allergic reaction when re-exposed to sulfa-containing medications. Discussion with patients and a thorough history evaluating the details of sulfa or sulfa-related allergic reactions are essential because allergies to nonantibiotic sulfa-containing medications are not believed to increase the risk of allergic reaction to sulfa antibiotics.[22] Yet, confirmed cases of anaphylaxis to sulfadiazine-containing CVCs have been reported.[23]

Latex has been cited as a common cause of perioperative anaphylaxis given frequent patient exposure to latex-containing products. Nevertheless, initiatives to prevent patient exposure to these products have led to substantial decreases in cases of anaphylaxis attributed to latex.[1] Nevertheless, vigilance is still needed because latex is present in valves of CVC sheaths and in balloons of PACs.[12] Catheter manufacturers report a history of allergy to chlorhexidine or sulfa medications as a contraindication to insertion of CVCs/PACs containing these medications. Information on these substances is often more difficult to identify, however, when compared with labeling for latex-containing devices. The education initiatives aimed at decreasing perioperative patient exposure to latex may serve as a framework for introducing similar programs to educate providers about the danger of patient exposure to other medications, especially chlorhexidine.[24]

In the current study, most CVCs/PACs available and used at our institution were impregnated with chlorhexidine and silver sulfadiazine. In addition, 13% of the total study population had allergies to sulfa, chlorhexidine, and latex and had CVCs/PACs inserted that contained one or more of these substances, which exposed these patients to considerable perioperative risk of complication. Similarly, 13% of perioperative anaphylaxis cases were in patients with reported sulfa and latex allergies at the time of CVC/PAC insertion. Nevertheless, the overall incidence of anaphylaxis potentially attributed to CVCs/PACs containing silver sulfadiazine (4/2,335 patients) and latex (2/551 patients) in patients with reported allergies to these substances was low. This should not give providers a false sense of security but rather emphasize the potential for hidden exposure to culprit drugs and highlight the importance of education and awareness regarding a widespread problem.[5]

Despite practice guidelines acknowledging the risk of anaphylaxis from CVCs with chlorhexidine and silver sulfadiazine,[9] clinician education regarding CVCs coated with these agents is lacking.[20] Clinicians should understand that CVCs/PACs contain substances that may increase the risk of allergic reactions in vulnerable patients. Patients with reported allergies should not be exposed to those agents without precautions. We encourage clinicians at our institution to be aware of the contents of lines and devices, but this is challenging given frequent device advances and product improvement. We recommend a system to cross-check the contents of invasive lines/catheters with the patient's electronic health record before insertion to screen for potential patient allergies or intolerance. Figure 2 illustrates the use of a screening system in a clinical algorithm for procedures in which CVC/PAC insertion is required. Ideally, such a system would decrease potential patient exposure and allow for alternative devices to be located and inserted in a timely fashion if a potential allergy is identified. Furthermore, society-based guidelines recommending which patients should receive antimicrobial-coated CVCs/PACs will help inform clinicians and reduce the risk of patient exposure to these medications.

Although anaphylaxis from CVCs/PACs occurs infrequently, anesthesiologists are positioned to promptly diagnose and treat perioperative anaphylaxis. In the current study, anaphylaxis was most often recognized intraoperatively and treated accordingly, which resulted in very few procedures being aborted or canceled. When anaphylaxis does occur, communication with an allergist about potential exposures, including discussion about chlorhexidine-, silver sulfadiazine-, or latex-containing CVCs/PACs is essential for guiding appropriate evaluation and subsequent confirmatory testing.

On the basis of patient exposures and suspected agents, skin prick, intradermal, and serologic testing may be indicated. A serum tryptase level was measured within one to three hours of intraoperative anaphylaxis in 81% of

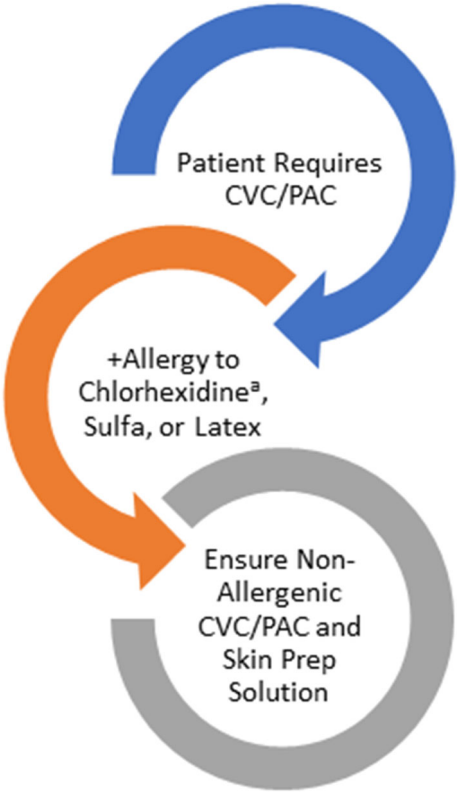

Fig. 2 Recommended steps before central venous catheter or pulmonary artery catheter insertion. [a]Consider high-risk exposure to chlorhexidine in patients with repeated exposure (e.g., disinfection of hemodialysis fistula, urethral catheterization with chlorhexidine gel). CVC = central venous catheter; PAC = pulmonary artery catheter; Prep = preparation

study patients, but the essential steps of postoperative allergic disease consultation and confirmatory skin testing[2] were only performed for ten of the 24 patients (42%) referred for allergy consultation. We recommend reflexively ordering serum tryptase laboratory testing consistent with international guidelines (postevent tryptase within one to three hours and baseline tryptase $>$ 24 hr after the event)[5,6] and allergic disease consultation when perioperative anaphylaxis is reported in the patient's electronic health record. Appropriate and timely evaluation after anaphylaxis is essential for identifying causative agents, avoiding future exposure, and ensuring safe and comprehensive perioperative patient care.

Of note, concomitant medications used to treat acute perioperative reactions may interfere with subsequent skin testing in the days immediately after the event. Skin testing should ideally be performed four to six weeks after the event to ensure reliable skin test reactivity and limit false-negative results.[6] Skin testing used by the Mayo Clinic Division of Allergic Diseases has been described previously.[2] Patients exposed to chlorhexidine and/or latex should have skin prick testing and intradermal testing in addition to serologic testing for chlorhexidine-specific IgE and/or latex-specific IgE.[10] Patients exposed to sulfa-containing medications including silver sulfadiazine should have a thorough review of exposure to sulfa-containing medications, but no blood tests are commercially available and skin testing has not been validated. Challenge testing may be indicated at specialized centers and under appropriate supervision.[25]

Limitations

This historical cohort study relied on accurate and complete documentation of pre-existing patient allergies and intraoperative events, such as clinical features of anaphylaxis. Patient-reported allergies are generally unreliable; thus, a thorough review of reported and documented allergies is essential before perioperative care. Furthermore, the incidence of reported sulfa allergy in the current study is higher than that reported in the literature,[21] potentially due to an elderly patient population with higher likelihood of prior exposure to sulfa-containing antibiotics. In addition, the inability to determine if a patient-reported sulfa allergy was true hypersensitivity to sulfa antibiotics, may limit the generalizability of the results herein. Because of the acute nature of anaphylaxis, data may not have been recorded by anesthesia personnel in some instances. Many patients in this cohort who had suspected perioperative anaphylaxis were not referred for postoperative allergy consultation; thus, it is possible that allergy referrals were overlooked for these patients. Also, patients may have elected to undergo allergy testing outside our institution or did not complete recommended testing, so definitive conclusions regarding the incidence of anaphylaxis secondary to allergen-containing CVCs/PACs cannot be made. Furthermore, changes to the diagnostic criteria of perioperative anaphylaxis have occurred since the onset of the current study. Therefore, the incidence and causes of suspected events herein should be interpreted in the context of clinical practice at the time of the event.

Determining a single causative agent responsible for perioperative anaphylaxis is extremely difficult. No allergy testing is available for sulfa-containing medications, so a diagnosis of sulfa allergy depends on personal history. Similarly, serum chlorhexidine-specific IgE analysis was not available for the entirety of the study period. The lack of follow-up and/or definitive allergy testing limit definitive conclusions about causality in these patients and may have resulted in an overestimation of the incidence of anaphylaxis in this study. Furthermore, the study cohort consisted largely of an older, male population that underwent cardiac, transplant, and vascular surgery, which may influence the incidence of anaphylaxis due to

prior sensitizing events and limit the study's generalizability to more heterogeneous cohorts.

Conclusion

In this large historical cohort study, we identified 2,937 patients with pre-existing chlorhexidine, sulfa, and/or latex allergies and had CVCs/PACs inserted that contained these substances. Fortunately, perioperative anaphylactic reactions attributable to chlorhexidine-, silver sulfadiazine-, or latex-containing CVCs/PACs were rare. Future studies are needed to accurately determine the incidence of anaphylactic events in patients with reported pre-existing allergies. Standard procedures should also be established to identify perioperative anaphylaxis, ensure subsequent testing, and record the results appropriately.

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