

Intraoperative anaphylaxis secondary to systemic cooling in a pediatric patient with cold-induced urticaria

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Clinical Implications

- This case highlights the necessity of building a broad differential diagnosis in elucidating the etiology of intraoperative anaphylaxis and suggests that cold-induced anaphylaxis must be considered as the potential culprit in susceptible patients.

TO THE EDITOR:

Intraoperative anaphylaxis is rare, with an incidence of 1:3,500 to 1:20,000 procedures, but is associated with a mortality rate of up to 9%.¹ In his pivotal 1986 study, Fisher described that in 227 patients experiencing intraoperative anaphylaxis, 90% suffered cardiovascular collapse, characterized by a systolic blood pressure of less than 40 mm Hg.² Anaphylaxis is likely underdiagnosed, as anesthesiologists are faced with a myriad of differential diagnoses for intraoperative instability that may share clinical features with anaphylaxis. After anaphylaxis is diagnosed by the anesthesiologist, the allergist has the challenging task of determining the culprit agent. The most common causes are antibiotics and neuromuscular-blocking medications. In addition to considering intravenous (IV) medications administered, the allergist must consider other agents used during the case.²

We present a case of severe intraoperative anaphylaxis in a 15-year-old girl with craniopharyngeal dysostosis, undergoing operative repair of facial anomalies.

Anesthesia was induced with rocuronium, fentanyl, midazolam, and propofol. IV hydration with room-temperature Lactated Ringer's solution was started and continued throughout the case. She received a dose of amoxicillin-

sulbactam for antibacterial prophylaxis. As the operative site was being irrigated with cool fluids containing bacitracin, the patient became hypotensive to 60/30 mm Hg with desaturations to 85% on the ventilator. Breath sounds were distant on the right and absent on the left. The endotracheal tube was repositioned, without effect. Examination revealed diffuse urticaria and angioedema of the lips, at which point anaphylaxis was suspected and managed with boluses of IV epinephrine, followed by an epinephrine infusion, volume resuscitation, albuterol, diphenhydramine, ranitidine, and methylprednisolone. After stabilization in the operating room, she remained intubated, sedated, maintained on continuous epinephrine infusion, and was admitted to the intensive care unit. An intraoperative total tryptase level returned elevated at 20 ng/mL, with a mature tryptase level of 4.5 ng/mL.

The patient was evaluated by allergy 4 weeks later. She had a history of atopy, with food allergy to beans, fish, and shellfish, as well as allergic rhinitis. In addition, since childhood, the patient developed urticaria on exposure to cold temperatures, and would take an antihistamine before known cold exposure. At this visit, skin testing was positive to histamine and selected inhalant allergens (dust mites, tree and weed pollens). Ice cube testing result was negative at 5 and 10 minutes. The total tryptase level had decreased to 2.4 ng/mL. Laboratory assessments of cryoglobulins, complement levels, and anti-IgE receptor antibody were also normal. The IgE level was elevated at 1380 units/mL.

Although all perioperative medications were being considered as triggers, given the temporal correlation between bacitracin's administration and clinical decompensation, it was initially presumed to be the culprit agent. Previously, the patient had used this medication topically without reaction. Approximately 6 months after her procedure, skin prick and intradermal testing were completed to the highest nonirritating concentrations of midazolam, propofol, rocuronium, fentanyl, penicillin G, benzylpenicilloyl-polylysine, ampicillin, and ampicillin-sulbactam based on published literature³⁻⁶ (Table 1). Skin prick testing to bacitracin was negative as was challenge testing to topical bacitracin for both immediate and delayed hypersensitivity reaction. She tolerated challenge to subcutaneous lidocaine

TABLE 1. Results of medication and ice cube testing

Medication testing (all performed 6 mo postop)	Concentration for skin prick test	Concentration for intradermal testing	Result of testing	Result of challenge and location completed
Penicillin components (PRE-PEN, Penicillin G, ampicillin) ³	(6.0×10^{-5} M, 10,000 units/mL, 25 mg/mL)	(6.0×10^{-5} mol, 10,000 units/mL, 25 mg/mL)	Negative	Successful to amoxicillin (outpatient)
Ampicillin-Sulbactam ³	25 mg/mL	25 mg/mL	Negative	Successful (outpatient)
Bacitracin ointment ⁴	500 unit/g	Not completed	Negative	Successful (outpatient)
Bacitracin solution ⁴	150 units/mL	Not completed	Negative	Successful (outpatient)
Fentanyl ⁵	0.05 mg/mL	0.0005 mg/mL, 0.005 mg/mL	Negative	Successful (OR)
Lidocaine ⁵	10 mg/mL	0.1 mg/mL, 1 mg/mL	Negative	Successful (OR)
Midazolam ⁶	1 mg/mL	0.025 mg/mL, 0.25 mg/mL	Negative	Successful (OR)
Propofol ⁵	1 mg/mL	0.01 mg/mL, 0.1 mg/mL	Negative	Successful (OR)
Rocuronium ⁵	10 mg/mL	0.01 mg/mL, 0.1 mg/mL	Negative	Successful (OR)
Ice cube testing	5 min	10 min	Negative at 4 wk and 10 wk, Positive at 6 mo	

OR, Operating room.

without any reactions. She also completed successful oral challenge to amoxicillin and underwent successful IV challenge to ampicillin-sulbactam.

The result for ice cube testing performed 10 weeks postoperatively was again negative. Given her negative skin testing results and successful completion of drug challenges to all the other potential agents involved, there remained a high suspicion for cold-induced anaphylaxis. Therefore, the ice cube test was repeated again 6 months after the reaction, and this time the patient developed an 11-mm wheal and 30-mm flare.

The elevated intraoperative tryptase level, negative skin and intradermal testing results, successful completion of medication challenges, and positive ice cube testing results supported the diagnosis of intraoperative anaphylaxis induced by irrigation at cool temperature. Avoidance of cold exposure, including during surgical procedures, was recommended. It was advised that the other medications used in this case could be cautiously administered in the future in a carefully monitored setting. With these precautions in place, she underwent a surgical procedure, oronasal fistula repair, 8 months later. She received midazolam, propofol, rocuronium, fentanyl, lidocaine, and ampicillin-sulbactam perioperatively without any reactions.

There are published cases regarding the successful management of adult patients with known cold-induced urticaria undergoing procedures such as coronary artery bypass grafting that are often completed using hypothermic protocols. This literature offers valuable insight regarding intraoperative management. Careful attention should be paid to the ambient temperature, and warming blankets should be used.⁷ In another successful coronary artery bypass grafting, corticosteroids as well as antihistamines were administered preoperatively in a patient with known cold-induced urticaria.⁸ The prompt use of epinephrine, antihistamines, beta-agonists, and steroids is life-saving in patients suffering cold-induced anaphylaxis and integral in preventing possible cardiovascular collapse.

Cold exposure as an etiology for perioperative anaphylaxis must be considered in those predisposed to cold urticaria, especially in atopic patients who are at higher risk for intraoperative anaphylaxis.

To our knowledge, this is the first case of intraoperative cold-induced anaphylaxis in a pediatric patient. This report also emphasizes the need to delay and/or repeat *in vivo* tests for immediate allergy such as skin testing or ice cube testing to avoid false-negative results if these tests are performed in the initial few

weeks following an anaphylactic reaction. When anaphylaxis to insect venom is suspected on the basis of history, but initial testing result is negative, it is recommended to repeat testing 3 to 6 months after the initial event given the potential for false-negative results.⁹ Similar to anaphylaxis to venom, if suspicion is high for cold as the culprit in a predisposed patient, repeat testing 3 to 6 months after the event should be considered given the possibility of anergy as similar mechanisms may be involved.

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