CASE REPORT

Grade IV anaphylaxis unresponsive to code dose epinephrine in a healthy child presenting for mole removal under general anesthesia

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Hai J, Liu J, Yim MM. Grade IV anaphylaxis unresponsive to code dose epinephrine in a healthy child presenting for mole removal under general anesthesia. Anesthesiol Case Rep. 2021; 4(4):1-3.

Anaphylaxis during anesthesia is rare, especially in pediatric patients. Grade III and IV reactions are life threatening and early epinephrine administration is crucial. We present a case of grade IV anaphylaxis in a healthy child under general anesthesia for an elective surgery that was resistant to code dose epinephrine with infusion. Shortly after anesthesia induction, the patient developed tachycardia and severe hypotension that did not respond to initial escalating doses of epinephrine. To save the child from impending cardiac arrest, we had to administer in rapid succession multiple epinephrine boluses at amounts significantly higher than code dose. Although most anaphylaxis cases respond to 1 mcg/kg-10 mcg/kg epinephrine boluses and infusions, grade IV anaphylaxis can require astonishing amounts of epinephrine. Aggressive management with epinephrine in the face of little or no initial cardiovascular response is necessary in the most severe presentations of anaphylaxis.

Key Words: *Perioperative anaphylaxis; Epinephrine; General anesthesia*

INTRODUCTION

Anaphylaxis is a life-threatening Immunoglobulin E (IgE)-mediated reaction that requires prompt diagnosis and treatment and is characterized by severity classification from I (cutaneous-mucous signs such as erythema/urticaria with or without angioedema) to IV (cardiac arrest) [1]. Though rare, medications most likely to cause anaphylaxis include neuromuscular blocking agents and antibiotics [2]. We describe a case of epinephrine resistant grade IV anaphylaxis in a healthy pediatric patient under general anesthesia.

CASE PRESENTATION

An 11-year-old 40 kg girl with no significant medical history presented for surgical resection of a 1 cm superficial scalp lesion under general anesthesia. The patient received midazolam and fentanyl premedication, followed by propofol and remifentanil for induction and was uneventfully intubated.

Dexamethasone for postoperative nausea and prophylactic cefazolin were administered, and within minutes the patient became tachycardic with heart rate in the 140s and progressively hypotensive to 50 mmHg/20 mmHg. During this sharp decline in cardiac performance, crystalloid and phenylephrine boluses were given without improvement. Differential diagnosis considerations included anaphylaxis, hypovolemia, and anesthetic induced hypotension.

Epinephrine (100 mcg followed by 200 mcg then 300 mcg) was then given without effect, and an operating room code was called to recruit additional resources. Chest compressions were initiated with loss of pulse oximetry and declining end-tidal CO_2 tracings. Anesthetic gases were completely off and 500 mcg of epinephrine was given with return of spontaneous circulation in 1 minute. An epinephrine infusion was started, and arterial and central venous access were obtained by an assisting anesthesiologist and the surgeon respectively. Despite being on vc (Figure 1), episodes of severe hypotension persisted.

Hemodynamics stabilized with additional above code dose (500 mcg) epinephrine boluses administered every 2-3 minutes for 30 minutes. During this time, hydrocortisone, diphenhydramine, and ranitidine were administered for presumed anaphylaxis. Anesthesia was maintained with ketamine and low dose sevoflurane as tolerated. Serum tryptase was sent and post-event analysis revealed it to be elevated at 15.3 at 1 hour (normal <13) and 20.6 at 4 hours from the start of the reaction. There were no mucocutaneous signs or rash appreciated initially as the patient was positioned under the drapes. However, upon return of circulation, piloerection and a whole-body erythema was observed with the drapes removed to obtain additional vascular access. Fortunately, the patient did not exhibit any signs of bronchospasm, and ventilation was adequate throughout the case. After vital signs were stabilized off epinephrine, the pediatric intensivist was consulted to discuss the risks and benefits of expedited extubation. A leak test was positive with the tracheal cuff deflated, and the patient was extubated and transported to the pediatric intensive care unit, where she was observed to have full neurologic recovery in the postoperative period. Upon discharge, the patient was referred to an allergy clinic but did not follow-up.

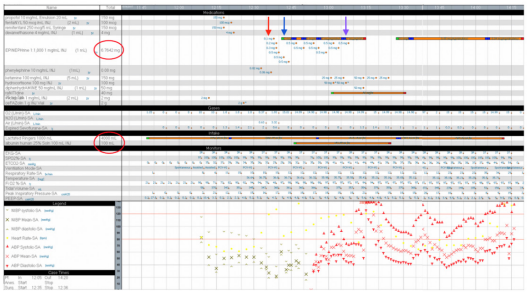

Figure 1) *Perioperative anesthesia course for our patient. Notable was the total epinephrine (6.7 mg) and fluid (4000 mL crystalloid and 100 mL 25% albumin) administration, denoted by the red circles. Red arrow marks time point at which initial epinephrine boluses were administered without effect and chest compressions were initiated. Blue arrow marks time point at which epinephrine infusion was started, and purple arrow marks time point at which the infusion was escalated to 0.7 mcg/kg/min*

DISCUSSION

Perioperative immediate allergic reactions are rare but may be life-threatening. Approximately 50%-60% of reactions are attributed to specific immune activation by IgE antibodies, while the remainder are due to nonspecific activation mediated by mast cells or mast cell-independent mechanisms [3]. They most often occur around the time of anesthesia induction, as seen in

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Received: *May 17, 2021,* **Accepted:** *June 1, 2021,* **Published:** *June 7, 2021*

our patient, and are graded I-IV on the Ring and Messmer scale of clinical severity (Table 1). Grades I and II are non-life-threatening and more likely caused by nonspecific direct mast cell degranulation, while grades III and IV satisfy the clinical criteria for anaphylaxis and are more likely IgE-mediated [3]. Our patient, who had severe hypotension and impending cardiovascular collapse without initial mucocutaneous symptoms, was classified as grade IV.

TABLE 1

Clinical severity scale of immediate hypersensitivity reactions, adapted from ring and messmer7

Grade	Clinical findings
I	Mild cutaneous-mucous signs: Erythema, urticaria +/- angioedema
II	Non-life-threatening cardiovascular reaction: cutaneous-mucous signs with associated hypotension, tachycardia, dyspnea, or gastrointestinal disturbances
III	Life-threatening cardiovascular reaction: cardiovascular collapse, tachycardia, or bradycardia +/- cardiac dysrhythmia, +/-bronchospasm, cutaneous-mucous signs, +/-gastrointestinal disturbances
IV	Cardiac arrest

The incidence of perioperative anaphylaxis in patients undergoing anesthesia is variable, ranging from one in 3,500 to 20,000 anesthetic procedures, with overall mortality rate ranging from 0.001% to 9% [2]. For pediatric patients, the incidence is about 2.7 out of 100,000 cases with no known mortalities [4]. Not only is our case of pediatric grade IV anaphylaxis under general anesthesia rare, it is the first reported case initially resistant to multiple code-doses of epinephrine.

Cornerstones of anaphylaxis management are early epinephrine administration (1 mcg/kg for grade III/IV cases, up to the pediatric code dose of 10 mcg/kg) and massive volume resuscitation with crystalloid fluid (30 mL/kg-100 mL/kg) [3]. Prompt removal of the offending agent and cessation of anesthetic is also warranted. In case of epinephrine resistance, vasopressin and methylene blue may also be considered [4]. Our patient initially showed minimal improvement despite escalation of epinephrine dosing, and repeated code-doses were necessary before she was stabilized.

As this case illustrates, early diagnosis and aggressive treatment with repeated administrations of epinephrine in suspected anaphylaxis can be lifesaving. Notably, workgroups across different countries have increasingly recommended escalating doses of epinephrine [3]. A 2015 World Health Organization survey however indicates that of the community 0.47% mortality rate of anaphylaxis, approximately 80% did not receive epinephrine until cardiac arrest occurred. Another study reported delay in starting anaphylaxis-specific treatment in 25% of cases [5], illustrating the potential difficulties inherent in recognition of perioperative anaphylaxis.

Additionally, a lack of preparedness for administering unprecedented code-doses of epinephrine may also contribute to this delay. While attempting to stabilize our patient, we had exhausted our supply of epinephrine in the operating room and code cart and had to utilize supply lines from other areas of the hospital. Thus, this case demonstrates the importance of ensuring additional reserve stores of epinephrine are readily available at all times should its use be necessary in rare but life-threatening events.

Antibiotics have been implicated as the most common cause of perioperative anaphylaxis in the US with neuromuscular blockers as the second most common [2]. In the UK, the reverse is true and antibiotics are the second most common cause of anaphylaxis with rates of 4 per 100,000 administrations, making up 44% of 260 total anaphylaxis cases in the Royal College of Anaesthetists' 6th National Audit Project (NAP6). The majority of cases presented almost uniformly rapidly within 5-10 minutes, and the most common initial clinical feature was hypotension, noted in 42% of the antibiotic anaphylaxis cases [5]. Similarly, our patient exhibited progressively worsening hypotension within minutes of antibiotic administration.

Clinical practice guidelines developed by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) classify elective head and neck procedures as predominantly clean or clean-contaminated. For clean procedures, no antibiotics are recommended, while clean-contaminated procedures may warrant a single dose of cefazolin, although there is equivocal evidence of its benefit [6,7]. Our patient did not follow up with allergy clinic, preventing us from confirming the identity of the allergen. Given the timing of medications and incidence of anaphylaxis in the United States, we considered cefazolin to be the likely inciting agent and revisited its indication in this procedure class.

CONCLUSION

Pediatric perioperative anaphylaxis is a rare life-threatening event that can result in a devastating conclusion to an otherwise innocuous procedure and anesthetic. Vigilance and early consideration of anaphylaxis leading to prompt, frequent, and high dose or beyond code dose epinephrine boluses may be needed to achieve a positive outcome; even in the setting of severe epinephrine resistant anaphylaxis where epinephrine may appear to have no initial effect. Additionally, this life-threatening event may have been avoided with strict antibiotic stewardship.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FINANCIAL DISCLOSURE

This article has no funding source

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