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CASE REPORT

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Anaphylactic reaction to tranexamic acid infusion in a six-year-old child: a case report

Nazanin Zibanejad[1,2†], Nikta Nouri[3†] and Sharareh Babaie[1,2*]

Abstract

Background Tranexamic acid (TXA) is commonly considered a safe drug to mitigate bleeding during and after various surgical settings among adults and children. In recent decades, anaphylaxis induced by TXA has been increasingly reported in adults. However, among pediatrics, there are fewer reported cases.

Case presentation We report a case of a 6-year-old female who experienced anaphylaxis after receiving intravenous TXA following unilateral cleft lip and palate repair surgery. She exhibited clinical symptoms involving the cardiovascular system, respiratory system, and skin. Following the administration of epinephrine, corticosteroid, and antihistamine, the patient's symptoms were relieved. A few months after discharge, an intradermal test, yielded a positive result, confirming TXA as the culprit drug.

Conclusion Our report emphasizes the importance of considering anaphylaxis as a potential adverse reaction to TXA in pediatric patients, showing the criticality of rapid diagnosis and appropriate management for a successful outcome.

Keywords Allergy, Anaphylaxis, Case report, Critical care, Pediatrics, Tranexamic acid

Background

Anaphylaxis is a severe systemic response, representing the most critical clinical manifestation of acute allergic reactions that can potentially be life-threatening [1]. Drugs are one of the most prominent triggers of anaphylaxis among adults. Conversely, in children, drugs contribute to less than 5% of anaphylactic shock cases [2].

Tranexamic acid (TXA) is an antifibrinolytic drug, that impedes the formation of plasmin, reducing fibrin clot breakdown and bleeding. In pediatric surgeries, TXA proved to be effective, notably in orthopedic, cardiac, and craniofacial procedures [3]. Until now, various side effects of TXA have been known, including nausea, diarrhea, and less commonly seizure [4]. Nevertheless, anaphylaxis triggered by TXA infusion is rarely reported especially among children.

In this manuscript, we present a case involving a 6-year-old female who developed anaphylactic shock after receiving the second dose of TXA the day after surgical repair of a unilateral cleft lip and palate. In this report, we discuss the importance of rapid diagnosis of anaphylaxis following TXA administration, as well as comparisons with the available pediatric case reports. This case emphasizes the significance of diagnosing and managing TXA's uncommon side effects in pediatric patients and contributes to a better understanding of its potential adverse effects on children.

†Nazanin Zibanejad and Nikta Nouri authors contributed equally to this work.

*Correspondence:
Sharareh Babaie
sharareh.ba@gmail.com
[1] Department of Pediatric Intensive Care Unit, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan 81746-73461, Iran
[2] Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan 81746-73461, Iran
[3] School of Medicine, Isfahan University of Medical Sciences, Isfahan 81746-73461, Iran

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Case presentation

A 6-year-old female patient, resident of Iran, with a known medical history of unilateral cleft lip and palate since birth, was admitted to Imam Hossein Children's Hospital, affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, for elective unilateral cleft lip and palate repair surgery. The patient's medical records indicated a height of 115 cm and a weight of 20 kg at the time of hospitalization. The patient was delivered by cesarean section (CS) due to the prior CS delivery. Previous investigations had revealed the presence of congenital heart disease, specifically a small atrial septal defect (ASD) and a patent ductus arteriosus (PDA) as confirmed by echocardiography. Additionally, the patient suffered from sensory neural hearing loss (SNHL) and used hearing aids. She exhibited normal speech and showed no signs of developmental delay.

The patient had previously undergone several cleft lip and palate repair surgeries, with the first procedure performed at 20 days old. The most recent surgery took place one year before her admission to our hospital. There was no information regarding receiving TXA during/after the previous surgeries. The patient's family did not report any postoperative complications or side effects associated with these surgeries. Moreover, in her medical records, there was no reported information about allergies or asthma. Upon admission to our hospital, the patient underwent a surgical procedure involving the insertion of a unilateral buccinator flap, as well as redoing of unilateral cheiloplasty and primary rhinoplasty.

The day following surgery, the patient had normal vital signs and did not report any postoperative complaints. However, due to continued bloody secretions from the nasopharynx, intravenous TXA at a dose of 10 $mgkg^{-1}$ was administered over one minute. The patient had also received a dose of TXA the previous day during the surgical procedure, exhibiting no complications. Preceding the second administration of TXA, the patient did not receive any other medications or blood/blood-products transfusion. Shortly after the second infusion of TXA ($\approx$ 2-3 minutes), the patient experienced respiratory distress, with oxygen saturation dropping to 83% in room air. Upon respiratory examination, suprasternal retraction and stridor lung auscultation were observed. The patient's vital signs indicated a blood pressure (BP) of 70/33 mmHg, mean arterial pressure (MAP) of 40 mmHg, a pulse rate of 178 beats per minute, and a respiratory rate of 47 per minute. A neurological examination revealed drowsiness and a decreased level of consciousness. The patient responded to painful stimuli by opening her eyes and grimacing. Widespread flushing and erythema were observed in the upper and lower extremities, as well as on the face (Fig. 1). The extremities were warm, with a capillary refill time (CRT) of one second. Patient experienced gastrointestinal symptoms including vomiting. Both the patient's mother and the nurse noted that flushing and other symptoms occurred shortly after TXA administration.

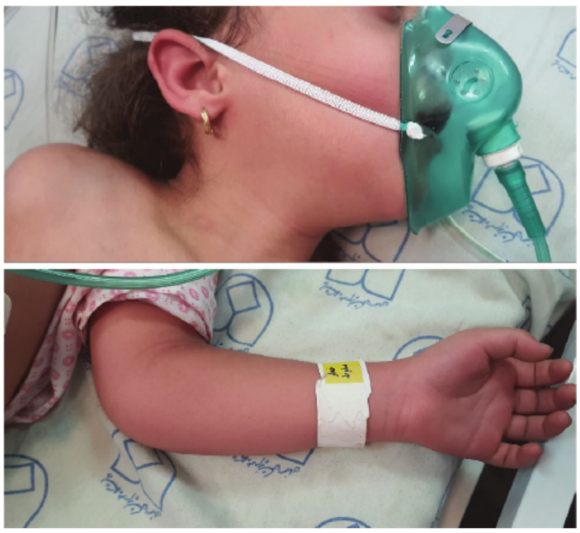

Fig. 1 The patient exhibits generalized flushing

Based on the patient's signs and symptoms, anaphylactic shock due to TXA infusion was suspected. This led us to the immediate administration of intramuscular (IM) epinephrine at a dose of 0.01 $mgkg^{-1}$ according to pediatric advanced life support guidelines (PALS) [5]. Concurrently, the patient received 10 L of oxygen via a simple face mask and 20 $mLkg^{-1}$ of intravenous crystalloid fluid. Following the first dose of epinephrine, the patient showed a slight improvement in alertness, with a BP of 67/34 mmHg and a weak palpable distal pulse. Then, methylprednisolone was administered at a dose of 1 $mgkg^{-1}$, along with an additional 10 $mLkg^{-1}$ of normal saline. Five minutes later, a second dose of IM epinephrine was injected into the opposite lateral thigh. The patient received a total of three doses of epinephrine, administered every 5 minutes. Following the third dose, the patient regained full consciousness, opened her eyes, and began speaking. Vital signs indicated a BP of 93/68 mmHg, with a normal distal pulse. The flushing gradually subsided and resolved, and the stridor improved. Subsequently, the patient was placed on adjunctive treatment with methylprednisolone and chlorpheniramine. As our hospital did not have the required equipment, acute serum tryptase level was not measured in our patient. She was closely monitored for 24 hours in the pediatric intensive care unit (PICU) before being discharged with

a stable general condition. The patient was advised to undergo immunological follow-up.

Three months after discharge, the patient underwent skin tests to confirm immunoglobulin E-mediated (IgE-mediated) hypersensitivity reaction with the following results: 1- a skin prick test (SPT) without dilution yielded a negative result. In this test, histamine (as the positive control) produced a 5 mm wheal, normal saline (as the negative control) produced no wheal, and TXA resulted in a 2 mm wheal, which was considered negative. An intradermal test (IDT) with TXA concentration of 2 $mgmL^{-1}$ exhibited a positive reaction to TXA (a wheal with a diameter of 5 mm was observed). The concentration of TXA for IDT was selected based on the non-irritant concentration values reported in the previous studies [6].

Discussion and conclusion

Despite the publication of numerous diagnostic guidelines, the diagnosis of anaphylaxis remains challenging, as anaphylaxis engages various organs and manifests symptoms similar to those of other medical conditions [7]. In children, the diagnosis becomes even more challenging due to their limited ability to articulate symptoms clearly, the intricacy of assessing vital signs, and the absence of cutaneous symptoms in nearly half of pediatric cases with drug-induced anaphylaxis. Consequently, anaphylaxis in children is more frequently underdiagnosed, implying that the true prevalence of drug-induced anaphylaxis is likely higher than the reported statistics [2].

As of today, the emergency departments lack laboratory tests to diagnose anaphylaxis immediately. Given the time-sensitive nature of diagnosis during the acute phase of anaphylaxis, reliance is primarily placed on the clinical presentation and history of recent exposure to potential allergens. However, laboratory examinations can support the clinical diagnosis of an anaphylactic reaction. One confirming measure that should be performed shortly after the onset of anaphylaxis is the assessment of serum tryptase levels. Even though an elevated tryptase level serves as a strong confirmation for anaphylaxis, with a positive predictive value (PPV) of over 90%, a normal tryptase level does not rule out anaphylaxis, given its negative predictive value (NPV) of around 50% [8].

TXA is widely used in surgical settings in children and adults due to its efficacy in reducing blood loss and the need for transfusion of blood without increasing the risk of thromboembolism [9]. Current studies recommend administering a loading dose of 10-30 $mgkg^{-1}$ followed by an infusion rate of 5-10 $mgkg^{-1}h^{-1}$ when using TXA for pediatric trauma or surgery [10]. Although TXA has been considered a safe drug [9, 11], rare instances of hypersensitivity reactions have been documented, emphasizing the importance of monitoring for adverse reactions following TXA administration. The first case was a 72-year-old man who developed an anaphylactic reaction to TXA during coronary artery bypass graft surgery [12]. Subsequently, other case reports among adults also highlighted the possibility of TXA-induced anaphylaxis [13–16].

TXA-induced anaphylaxis has been predominantly reported among adults, while a few occurrences are documented among adolescents (Table 1). For the first time, Chiem et al. reported a delayed anaphylactic reaction following the administration of TXA during posterior spinal fusion surgery in an adolescent patient [17]. In line with our case, the patient had prior uneventful anesthetic experiences.

In our patient, unlike the aforementioned cases, the administration of TXA was the only medication given

Table 1 Comparison of the reported cases of anaphylactic shock induced by TXA among pediatrics with our case

Study	Ref. [17]	Ref. [19]	Ref. [6]	Our case
Age[a]	15	13	15	6
Age group	adolescence	adolescence	adolescence	childhood
Sex	male	male	female	female
Allergy history	-	asthma	asthma, hay fever	negative
TXA dosage	5 $mgkg^{-1}$ bolus and 5 $mgkg^{-1}h^{-1}$	15 $mgkg^{-1}$ bolus	1 g bolus	10 $mgkg^{-1}$ bolus
SPT[b]	-	negative	negative	negative
IDT[c]	positive	positive	positive	positive
TXA concentration used for IDT	10 $mgmL^{-1}$	-	10 $mgmL^{-1}$	2 $mgmL^{-1}$
Initial tryptase level	elevated	not elevated	-	-

[a] years

[b] Skin prick test

[c] Intradermal test

before the onset of clinical symptoms, which helped us to narrow down to the diagnosis of anaphylaxis. Moreover, the prompt and positive response to IM epinephrine supports our diagnosis of anaphylaxis. This aligns with the European Academy of Allergy and Clinical Immunology (EAACI) guidelines [18], which emphasize the importance of recognizing cutaneous, respiratory, cardiovascular, and gastrointestinal symptoms in diagnosing anaphylaxis.

Our report highlights the possibility of drug-induced anaphylaxis and the significance of close monitoring of the patient's side effects following the drug administration, even in instances where the drug is known to have minimal risk of anaphylaxis (such as TXA). Due to the extensive use of TXA in surgical procedures for children and adults and the life-threatening nature of anaphylactic reactions, practitioners should always consider the possibility of allergic and anaphylactic reactions following TXA administration, especially among pediatrics. In general, the clinical team should remain vigilant for both early and late severe allergic reactions, even to drugs that are used routinely in the clinics. Practicing in this manner will allow physicians to make a diagnosis within a reasonable time frame and initiate appropriate management, which increases the likelihood of a successful outcome.

Abbreviations

ASD	Atrial septal defect
BP	Blood pressure
CRT	Capillary refill time
CS	Cesarean section
EAACI	European academy of allergy and clinical immunology
IDT	Intradermal test
IG	Immunoglobulin
IM	Intramuscular
MPA	Mean arterial pressure
NPV	Negative predictive value
PALS	Pediatric advanced life support
PDA	Patent ductus arteriosus
PICU	Pediatric intensive care unit
PPV	Positive predictive value
SNHL	Sensory neural hearing loss
TXA	Tranexamic acid

Authors' contributions

N.Z.: Conceptualization, Investigation, Project administration, Supervision, Validation, Writing - review & editing. N.N.: Data curation, Investigation, Writing - original draft, Writing - review & editing. S.B.: Conceptualization, Investigation, Project administration, Supervision, Validation, Writing - review & editing.

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Availability of data and materials

Data from this case report is available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

This case report has been approved by the ethics committee of Isfahan University of Medical Sciences (approval ID: IR.ARI.MUI.REC.1402.087) based on the ethical standards in the declaration of Helsinki. A written informed consent was obtained from the patient's legal guardian.

Consent for publication

The legal guardian of the patient provided written informed consent for the publication of this report, in compliance with the journal's patient consent policy.

Competing interests

The authors declare no competing interests.

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