Nebulized Tranexamic Acid Use for Pediatric Secondary Post-Tonsillectomy Hemorrhage

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Post-tonsillectomy hemorrhage is a frequent occurrence in the emergency department, and management of potentially life-threatening and ongoing bleeding by the emergency physician is challenging. Limited evidence-based guidelines exist, and practice patterns vary widely. We administered nebulized tranexamic acid to achieve hemostasis in a pediatric patient with associated bleeding cessation prior to definitive operative management. [Ann Emerg Med. 2019;73:269-271.]

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INTRODUCTION

Post-tonsillectomy hemorrhage occurs in 0.1% to 3% of post-tonsillectomy patients, with many presenting to the emergency department (ED) for care. Secondary post-tonsillectomy hemorrhage is defined as bleeding greater than 24 hours postsurgery[1] and typically occurs 4 to 10 days postoperatively as a result of the separation of eschar from the underlying healing tissue, food trauma, infection, or idiopathic reasons.[2] Uncommonly, these bleeding events can be life threatening, with a recent meta-analysis reporting a mortality rate of 1 in 500,000.[3] Given the typical young age of patients undergoing tonsillectomy, management of significant bleeding can be a therapeutic challenge in the ED. Although most patients with ongoing bleeding are taken to the operating room, initial management and stabilization in the ED can be lifesaving.

Limited guidelines in regard to best practice for ED providers exist. The American Academy of Otolaryngology–Head and Neck Surgery guidelines do not report on the best way to control post-tonsillectomy hemorrhage, only noting that surgeons should keep track of their rates of secondary bleeding events.[1] A 2018 survey study of otolaryngologists examined trends in pediatric perioperative management of secondary post-tonsillectomy hemorrhage and reported that ED management strategies for active oropharyngeal bleeding events include fluids (50%), direct pressure (67%), clot suction (33%), silver nitrate (33%), vasoconstrictor-soaked pledgets (0%), epinephrine injections (0%), topical epinephrine (17%), thrombin powder (67%), and labs (50%) (percentages refer to the percentage of respondents who reported this as a management strategy).[4] In young children who undergo tonsillectomy, the oropharynx is typically small and patient cooperation is limited, making many of the above-mentioned management strategies of limited use outside the operating room or without prior definitive airway management. In the ED setting, in which a single provider often needs to manage the patient, controlling a potentially bloody airway is a high-risk procedure that should be avoided whenever possible. To our knowledge, this is the first published report in the peer-reviewed medical literature about the use of nebulized tranexamic acid for an acute secondary post-tonsillectomy hemorrhage; its use was previously discussed in a medical podcast[5] but has otherwise not been widely disseminated.

CASE REPORT

A 3-year-old boy with a ventriculoperitoneal shunt, epilepsy, hypothyroidism, obstructive sleep apnea, and recent tonsillectomy and adenoidectomy 4 days before presentation arrived at the ED with an active post-tonsillectomy hemorrhage. Given the amount of bleeding present on arrival, the child was immediately brought to the resuscitation room. He was afebrile, with a pulse rate of 146 beats/min, respiratory rate of 28 breaths/min, and an oxygen saturation of 100% on room air. Initial blood pressure was unable to be obtained because of limited patient cooperation; the child was thrashing and crying as gurgling sounds and blood emitted from his oropharynx. Despite suctioning, the oropharynx continuously filled with blood, making it impossible to accurately determine which tonsillar fossa was bleeding. Intravenous access was difficult to establish and not immediately achieved. Nebulized racemic epinephrine was initiated within

10 minutes of the patient's arrival; at treatment completion approximately 10 minutes later, hemorrhage control had not abated. Consideration was given to direct pressure, but given the patient's age and limited ability to cooperate, this was not thought to be feasible without intubation. Thus, the decision was made to administer nebulized tranexamic acid. Intravenous tranexamic acid at 250 mg (100 mg/mL) was immediately available and directly nebulized with the Salter Nebutech HDN (Salter Labs, Lake Forest, IL) at a flow rate of approximately 8 L over 2 to 3 minutes without additive normal saline solution within minutes of racemic epinephrine administration completion. Approximately 5 to 7 minutes after completion of the tranexamic acid nebulization, the bleeding stopped. Within the next 15 minutes, intravenous access was achieved and fluid bolus started, samples for laboratory testing were sent, and the patient was taken to the operating room for definitive management by the on-call ear, nose, and throat specialist. Per hospital records, both the CBC count and coagulation profile results were normal; the intubation was easy, with a grade 1 view and successful first-pass attempt; and on direct examination clot filled the entire right tonsillar fossa, with multiple foci of recent hemorrhage visualized after clot removal. No active bleeding was found. The area was subsequently cauterized without complications. No adverse effects of nebulized tranexamic acid were observed.

DISCUSSION

Tranexamic acid is an antifibrinolytic that has been used for many years in the adult setting for trauma, surgery, postpartum hemorrhage,[6,7] menorrhagia, dental procedures,[7] gastrointestinal bleeding events,[6] and hemoptysis.[8] Use in the pediatric population has been less extensive and tailored more specifically to cardiac, spine, and craniofacial surgeries; in these settings, it has been shown to decrease surgical blood loss and transfusions. Tranexamic acid use in pediatric trauma shows promise, but is still under investigation.[9] Tranexamic acid for post-tonsillectomy hemorrhage has been evaluated, but only as a preventive measure, and subsequently found to be ineffective in reducing the number of post-tonsillectomy hemorrhages.[10] Nebulized tranexamic acid has been studied in cases of adult hemoptysis[8] and pediatric diffuse alveolar hemorrhage,[11] and although research here remains limited, current literature shows it to be a potentially feasible therapeutic option, with bleeding cessation time ranging from after a single dose to 2 days of scheduled treatments.[8,11] In accordance with our knowledge of diffuse alveolar hemorrhage literature, our patient received 250 mg of nebulized tranexamic acid. Current pediatric diffuse alveolar hemorrhage studies report nebulized tranexamic acid doses of 250 mg for children weighing less than 25 kg and 500 mg for those weighing greater than 25 kg[11]; for reference, adult intravenous dosing is typically 1 g.[6]

Nebulized tranexamic acid appears to be safe, with no systemic or local adverse effects reported in cases of pediatric diffuse alveolar hemorrhage (including a lack of thromboembolic events, seizures, or worsening of gas exchange)[11]; studies of nebulized tranexamic acid for adult hemoptysis have reported only a single patient who experienced bronchospasm responsive to bronchodilators.[8] This differs from systemic administration, in which adverse effects have ranged from gastrointestinal (eg, nausea, diarrhea, cramping) with oral use, concern for renal toxicity in patients with reduced kidney function, hypotension with rapid administration, and seizures at supratherapeutic doses.[7] Although a multinational prospective trial of intravenous tranexamic acid in adult trauma reported a decreased risk of myocardial infarction and no increase in the risk of thromboembolism, another meta-analysis of tranexamic acid use in surgeries reported uncertainty in regard to the effects on stroke, deep venous thrombosis, pulmonary embolism, and myocardial infarction, leaving some ambiguity about the thromboembolic adverse effects of intravenous tranexamic acid.[6]

Although this single case report of nebulized tranexamic acid for secondary post-tonsillectomy hemorrhage cannot determine causation from correlation, the pharmacokinetics of tranexamic acid support its potential use in this setting. Tranexamic acid acts as a lysine analog that competitively binds to plasminogen, preventing its conversion into plasmin and thereby inhibiting fibrinolysis.[6-8,11,12] In vitro studies have shown that a plasma concentration of 16 μg/mL is the therapeutic threshold for ceasing fibrinolysis. Pediatric studies have shown that an intravenous loading dose of 10 mg/kg over 15 minutes yields a peak plasma tranexamic acid concentration of 137 μg/mL. Our 14-kg patient received 250 mg of nebulized tranexamic acid; if only 1% of the dose reached the tonsillar fossa, drug delivery to the targeted site would still have been significantly greater than that needed to cease fibrinolysis. Moreover, although the above pharmacokinetics apply to intravenous tranexamic acid,[12] it has been hypothesized that topical oropharyngeal administration of tranexamic acid might be exceptionally effective, given that the oral mucosa has a high concentration of plasminogen and low concentration of plasminogen inhibitors.[7] This theory is further supported by the work of Sindet-Pedersen,[13] who reported higher concentrations of tranexamic acid in the saliva and lower

plasma concentrations in patients given topical (mouthwash) compared with oral tranexamic acid.

It could be argued that it was nebulized racemic epinephrine that led to bleeding cessation. Although its onset of action is 1 minute, its clinical effectiveness is typically not appreciated until 10 to 30 minutes postadministration.[14] With our patient having no change in hemorrhage control after racemic epinephrine completion, we believed it prudent to escalate care rather than wait for a medication to work, or potentially fail to work. Given the complementary actions of epinephrine and tranexamic acid on bleeding control, it could also be postulated that it was a combination of the 2 medications rather than a singular drug that controlled the bleed.

Massive secondary post-tonsillectomy hemorrhage can leave the emergency physician with a sense of helplessness when limited ED management strategies fail to stop the bleeding and the operating room is not immediately available. Moreover, in many ED settings, patients may require transfer to institutions with pediatric surgical services, making management even more challenging. Tranexamic acid is a potential new strategy to help with bleeding control. In accordance with limited data and clinical experience, ED providers confronted with an ongoing potentially life-threatening post-tonsillectomy hemorrhage should first consider nebulized epinephrine for its vasoconstrictive properties. If this is unsuccessful, consider administering nebulized tranexamic acid for its antifibrinolytic effects while preparing for airway management and mobilizing surgical teams. Ideally, a randomized controlled trial will more definitively confirm this suggestion. Pending this endeavor, it appears to be a potentially safe, tolerable, and effective management option for children with life-threatening secondary post-tonsillectomy hemorrhage.

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