



Tranexamic Acid and Application in Otorhinolaryngology: Literature Review

Daniela Vicencio S¹, Jai-Sen Leung C², Gary Reyes S³ and Karen García C^{4,5*}

¹Department of Otorhinolaryngology, Hospital Carlos Van Buren, Chile

²Department of Otorhinolaryngology, Hospital Clínico Red-Salud UC-Christus, Chile

³Medical Doctor, Servicio de Salud Bío-Bío, Chile

⁴Department of Otorhinolaryngology, Complejo Asistencial Dr. Sótero del Río, Chile

⁵Department of Otorhinolaryngology, Centro de Referencia de Salud Hospital Provincia Cordillera Chile

Review Article

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***Corresponding author:** Karen García C, Department of Otorhinolaryngology, Centro de Referencia de Salud Hospital Provincia Cordillera, Av. Concha and Toro 3459, 25762300, Chile, Email: karenmgarcia91@gmail.com

Abstract

Tranexamic acid (TA) is an antifibrinolytic drug used for the control of hemorrhages in the different disciplines of medicine. In otorhinolaryngology (ENT) it has multiple applications, both surgical and non-surgical, however, its effectiveness and safety have been controversial over time.

Below is a review of the literature regarding this drug and its use in ENT, for divulgation in our environment.

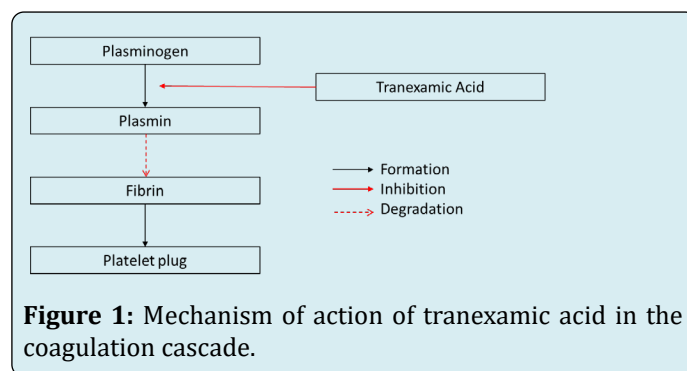
Keywords: Tranexamic Acid; Adenoidectomy; Epistaxis; Postsurgical Hemorrhage; Otorhinolaryngology; Tonsillectomy

Abbreviations: TA: Tranexamic Acid; FDA: Food and Drug Administration; ER: Emergency Room; RCT: Randomized Controlled Trials; HHT: Hereditary Hemorrhagic Telangiectasia; ENS: Nasal Endoscopic Surgery; TAVA: Total Intravenous Anesthesia.

Introduction

TA is an antifibrinolytic drug whose mechanism of action is to interfere in the coagulation cascade by blocking the formation of plasmin and stabilizing the formed platelet plaques. This is achieved as it is a synthetic analog of the amino acid lysine that binds and competitively blocks plasminogen molecules, which finally manages to inhibit the degradation of already formed plaques [1-3]. It is also thought to have an anti-inflammatory effect by inhibiting

the activation of neutrophils, monocytes and complement by plasmin (Figure 1) [4].



Although the United States Food and Drug Administration (FDA) has only approved its use for heavy menstrual

bleeding and as prevention in procedures for patients with hemophilia [5], its indication has been expanded both in the Emergency Room (ER) in the context of patients with polytraumas or upper gastrointestinal bleeding as well as in elective surgeries of different specialties (cardiac, trauma, maxillofacial, and others) [1-4,6-8], which practice has not been exempt from controversies regarding to its safety and efficacy.

TA is actually available in tablet presentation with a maximum dose of 1 to 1.5 grams every eight to twelve hours, having a bioavailability of 30-50% with a half-life of 2-3 hours. It can also be indicated intravenously with 0.5 to 1 gram every eight hours. The renal function of the patients must be taken into consideration and the dosage adjusted if is necessary (Table 1) [9], since 95% is excreted through this route [4,10].

| Route of administration | Condition | Dose |
|-------------------------|---|---|
| Intravenous | Creatinine <1.4mg/dL | No adjustment required: 10 mg/kg or 1 g 3 to 4 times a day |
| | Creatinine ≥ 1.4 a <2.8 mg/dL | Usual dose 2 times a day |
| | Creatinine ≥ 2.8 a <5.7 mg/dL | Usual dose 1 time a day |
| | Creatinine ≥ 5.7 mg/dL Triweekly hemodialysis Peritoneum dialysis | Usual dose every 48 hours or 50% of the usual dose every 24 hours |
| Oral | Creatinine <1.4mg/dL | No adjustment required: 10-15 mg/kg or 1-1.5 g 4 times a day |
| | Creatinine ≥ 1.4 a <2.8 mg/dL | Usual dose 2 times a day |
| | Creatinine ≥ 2.8 a <5.7 mg/dL | Usual dose 1 time a day |
| | Creatinine ≥ 5.7 mg/dL Triweekly hemodialysis Peritoneum dialysis | Usual dose every 48 hours or 50% of the usual dose every 24 hours |

Table 1: Dose adjustment of tranexamic acid in patients with kidney damage.

There are adverse reactions to the use of AT, which are mostly mild, highlighting the gastrointestinal ones such as nausea and diarrhea, however, there are reports of cases of thromboembolic events and seizures, the latter in the context of high doses and in patients who were undergoing open heart surgery, however it is recommended not to administer it to neurosurgical patients or patients with a history of epilepsy [4]. It is important to consider the contraindications of this drug, being absolute in the case of isolated traumatic brain injury, increased risk of thrombosis, hypersensitivity to TA, active intravascular coagulation and subarachnoid hemorrhage (due to increased risk of cerebral edema); and relative, advising its use with caution, in those patients with thromboembolic disease, those with bleeding from the upper urinary tract or ureteral obstruction due to clots, or its concomitant use with some procoagulant drugs such as factor IX concentrates [11,12].

Below, we present a summary of the current evidence related to TA and its use in ENT, to facilitate its use in the prevention and treatment of bleeding and its complications.

Uses of TA in ENT

Epistaxis: Epistaxis corresponds to bleeding from the nostrils, it is a common symptom within the general population, with an incidence of at least 60%, of these

10% may require attention in ER. Epistaxis has a bimodal presentation, with a higher incidence in childhood and in older adult patients. 90% of the episodes correspond to anterior epistaxis (compromising Kiesselbach's plexus) and the remaining percentage results from posterior epistaxis (Woodruff's plexus) [13,14]. The last American guideline on epistaxis that was published in 2020 indicates a proposal for the management of epistaxis that begins with compressive measures in the case of being active, associated or not with topical vasoconstrictors, nasal cauterization if the site of bleeding can be identified and if it is not possible observe it, anterior or posterior nasal packing is recommended if the first is frustrating. Regarding the use of tranexamic acid, it mentions that due to the lack of contemporary studies that evaluate the oral and topical use of TA in the management of epistaxis, new studies are required to include this drug in the treatment of nasal bleeding [14].

In 2018, Joseph, et al. [1] publish a meta-analysis that includes six randomized controlled trials (RCT) whose main objective was to determine the effects of TA in any of its presentations compared to placebo or other hemostatic agents in patient's whit epistaxis. Six RCT with a total of 692 participants were included. In the two studies that compared oral TA (administered for one week) versus placebo, a reduction in the risk of re-bleeding in the following 10 days was shown from 69% to 49% with a relative risk (RR) of

0.73. The time to cessation of bleeding in these cases was not reported. Another study compared the topical use of TA versus placebo, a reduction from 66% to 43% was observed, with a RR of 0.66, however the study was considered as low-quality evidence. The remaining analyzes compared TA with other hemostatic agents such as phenylephrine plus lidocaine, it was determined that the time to cessation of epistaxis was significantly shorter in the AT group (70% versus 30% with RR 2.35).

Robb, et al. [15] conducted a review of the literature on the use of TA in ENT, regarding the management of epistaxis, a RCT that compared the effect on the reduction of bleeding time by administering a single intravenous injection of 500 mg of AT with the use of anterior packing (using a tetracycline and vasoconstrictor solution), showing a faster stoppage of nasal bleeding at 10 minutes by the group with AT, in addition to a decrease in rebleeding at 24 hours and improvement in patient satisfaction, which is why the authors recommend TA as the initial treatment of anterior epistaxis.

However, given the fact that there have only been 3 RCTs about uses of TA in patients with epistaxis between 1995 and 2018, new studies incorporating AT in the management of epistaxis, and considering different routes of administration and doses, in different age groups, where the complications resulting from the use of the same drug are considered, could be relevant to evaluate the effectiveness of TA in the control of epistaxis [1,15].

It is important to mention groups of patients with special characteristics such as those who use antiplatelet treatment with aspirin or clopidogrel. There is a prospective, double-blind, randomized study that compares the use of topical TA versus the use of anterior tamponade with phenylephrine in these patients. 100 patients were studied and it was concluded that with the use of TA there was a decrease in bleeding time and less recurrence, so the use of topical AT was recommended in this group of patients [16].

Another particular group of patients are those with epistaxis related to Rendu-Osler-Weber Syndrome or hereditary hemorrhagic telangiectasia (HHT), which is its main symptom, with evidence supporting the use of TA to control epistaxis by reducing the duration of epistaxis itself and the number of monthly episodes of nasal bleeding, with contradictory information regarding the usefulness of its topical administration [17,18].

ENT Surgery

Minor oral surgery: The topical use of TA has been studied in patients using oral anticoagulants in minor surgical

procedures of the oral cavity. De Vasconcelos, et al. [19] carried out a meta-analysis in which they evaluate the use of TA in dental procedures, including dental and third molar extractions, showing its effectiveness and safety in reducing postoperative bleeding when daily mouthwashes are performed during the first postoperative week. In the same study, as a secondary result, no case of thromboembolic events during the first postoperative week was reported. On the other hand, in minor oral ENT surgery itself, studies are needed to evaluate the use of TA for the control of perioperative bleeding. It is thought that the effect of TA in these surgeries is due to the inhibition of fibrinolytic enzymes present in saliva [4].

Head and Neck Surgeries

In recent years, randomized studies have been carried out to achieve the use of TA in this type of surgery. Chen, et al. [20] evaluated the use of TA during anesthetic induction (in dose of 10mg/kg IV) and intraoperatively (1mg/kg/h IV) in patients undergoing modified radical cervical dissections, suprafacial hemithyroidectomies and parotidectomies, observing a significant decrease in postoperative bleeding in comparison with the control group. Subsequently, other authors have evaluated its use in unilateral oncological surgery of the oral cavity, supraomohyoid neck dissections, modified radical neck dissections, mandibular resection and flap reconstructions, concluding that using TA during anesthetic induction (10-20mg/kg IV) reduced the intraoperative blood loss [21,22]. Recently, the meta-analysis carried out by Alsubai, et al. [23] reports that the use of TA significantly reduces the volume of intraoperative bleeding; however, it does not improve post-surgery hemoglobin levels, neither the days with drainage or the time of surgery.

Tonsillectomy

Tonsillectomy is one of the most common surgical procedures in ENT. Among its most severe complications are post-surgical hemorrhage and death¹¹. Regarding postsurgical hemorrhage, it is divided into primary (within the first 24 hours) and secondary (after the first 24 hours) [2].

A significant number of papers have been published with variable results for post-tonsillectomy bleeding using different antifibrinolytic agents. In a review of the literature and meta-analysis, it was shown that the use of intravenous TA during surgery reduced the volume of bleeding, however it was not possible to demonstrate a reduction in the rate of post-surgical bleeding, this was explained by the short half-life of TA that it would have no effect on secondary bleeding if it was given in a single dose on the day of surgery [15].

Koizumi, et al. [2] report contrary results when studying a cohort of nearly 110,000 patients from 745 hospitals who had undergone tonsillectomy. They compared two groups: those who had received TA from day one of the surgical intervention (n=50,501) with those without the use of the drug (n=60,427), concluding that the administration of TA from the very day of the tonsillectomy would not reduce the risk of surgical reintervention due to secondary bleeding or blood transfusion, despite its safety. In addition, it was shown that TA is not effective in reducing post-surgical hemorrhage, this was explained because secondary bleeding (after the first 24 hours) generally occurs when the tonsillar bed scar falls prematurely due to mechanical trauma (from meals, for example) before the surgical site is completely healthy, therefore, AT-mediated fibrin clot stabilization cannot prevent secondary bleeding.

On the other hand, Chan, et al. [11] carried out a systematic review and meta-analysis on the use of TA in tonsillectomy, reporting safety and a significant reduction in the volume and duration of bleeding using topical TA, but not in the number of patients who develops post-tonsillectomy hemorrhage. In other meta-analysis carried out in 2021 reports that the use of TA reduces intraoperative bleeding by 39 ml on average and reduces the risk of post-tonsillectomy bleeding by 58% [24].

Schwarz, et al. [3] reported a case of a 3-year-old patient, who on his fourth day after tonsillectomy and adenoidectomy presented in the ER with post-surgical hemorrhage, recommending, in the first instance, management with epinephrine nebulization and, if required, proceed with nebulized AT at a dose of 10 mg/kg (ampoules of 100 mg/L), at a flow of 8 L/min for 2 to 3 minutes, although in general terms doses of 250 mg are considered for children weighing less than 25 kg, while for weights greater than 25 kg the dose amounts to 500 mg; all this, while airway management is being prepared and the surgical teams are being activated. For the adult population, the dose of nebulized AT corresponds to 1 gr. Although no adverse effects have been observed in the pediatric population after administration by nebulization of TA due to epistaxis, there is a report of 1 case in the adult population that presented bronchospasm, which in turn was reversed with the use of bronchodilators.

In relation to topical use, Falbe-Hansen, et al. [25] carried out a prospective, double-blind study in which he evaluated the use of TA gel that was applied in the tonsillar fossa in gauzes 4 minutes after tonsillectomy, its results showed that there was no decrease in the risk of subsequent bleeding, nor in a lower decrease in hemoglobin and hematocrit in these patients when using topical TA versus placebo. Hinder, et al. [26] similarly, when using TA solution gargles, concluded that its use does not reduce the risk of postoperative bleeding or

the risk of surgical intervention secondary to it.

Although there are multiple studies regarding the use of TA in tonsillectomy, at the time of performing meta-analyses very few manage to be included, concluding its safety of use and the reduction of intraoperative bleeding, but not its effectiveness in reducing post-tonsillectomy hemorrhage [15]. Most authors mention the lack of evidence in this topic and the need for future studies [11,15].

Adenoidectomy

There is a lack of studies regarding the use of TA in this surgical procedure [15]. The effects of TA in this surgery are extrapolated from patients who have undergone adenotonsillectomy, showing that the use of TA does not significantly reduce bleeding in patients undergoing adenoidectomy or tonsillectomy. However, in those who go to adenotonsillectomy, a significant reduction is observed with its use [27].

Albirmawy, et al. [28] showed a decrease in the volume of intraoperative blood loss and a decrease in primary postoperative bleeding (first 24 hours) with the topical use of 1 g of TA in 10 ml of 0.9% saline solution irrigated through a catheter in the nasopharynx for 5 minutes post adenoidectomy, compared with placebo, in a group of 400 children.

Rhinoplasty

A successful rhinoplasty requires a detailed understanding of the nasal structure necessary to produce a functional and aesthetically pleasing nose. In addition to this, a thorough surgical technique and the management of postoperative edema are essential to achieve the results proposed and requested by each patient. Among the complications, bleeding, ecchymosis, and edema are usually the most frequent, and can cause great concern and discomfort in patients, and can lead to the development of infections with the consequent catastrophic result from the aesthetic point of view and even on rare occasions cause death [29-31]. The use of TA has been postulated as a tool to reduce these complications, during the last years 4 meta-analyses have been published. De Vasconcellos, et al. [32] and McGuire, et al. [33] included in their analysis 5 RCT that showed a decrease in intraoperative bleeding. The schemes used vary among them, however, most include a dose prior to surgery of 10mg/kg IV and some of them indicate 1 g every 8 hours for 1 to 5 days after surgery. Additionally, Ping et al. has reported a significant decrease in eyelid edema and postoperative ecchymosis [34]. The latest meta-analysis published in 2022 by Laikhter, et al. [35] confirms the results obtained previously.

Nasal Endoscopic Surgery (ENS)

ENS requires a visible surgical field for proper recognition of anatomical points in order to avoid complications such as injury to the skull base or orbit, so different techniques have been used to minimize intraoperative bleeding with agents such as epinephrine either topical or injected into the lateral nasal wall, the use of total intravenous anesthesia (TIVA), controlled hypotension and the patient's position with the head at 30° in relation to the horizontal [36].

Langille, et al. [37] describe a RCT in 28 patients undergoing ENS for chronic rhinosinusitis with or without polyps. The patients were divided into two groups: half were prescribed 1 gram of intravenous TA as premedication and the other half was the control group to which this antifibrinolytic was not indicated. It was concluded in this study that TA did not show a decrease in intraoperative bleeding and improvement in visibility in relation to cases that did not have premedication with TA.

Another study compared 200 patients who underwent nasal endoscopic surgery for different reasons (septoplasty, chronic rhinosinusitis, tumor excision, among others), half of whom were prescribed TA as premedication in infusion (500 mg in 100 mL of solution saline for 20 to 30 minutes) and the other half was the control group. It was observed that in the first group there was a decrease in the volume of blood lost by 72.48%, and no adverse effects were reported. In addition, the authors noted that the antifibrinolytic effect lasted up to 8 hours in plasma, reducing the possibility of postoperative bleeding [38].

A meta-analysis carried out by Kang, et al. [39] in 2019 that included 4 primary studies with a total of 226 patients that compared the topical use of TA during surgery with various controls such as its non-use or the use of saline solution, concluded that its use reduced bleeding intraoperatively, as well as improves the visibility of the surgical field.

Conclusion

Hemorrhage, both primary and secondary to surgical interventions and others, is a common reason for consultation in ENT, both in the pediatric and adult population, in which the use of TA within the therapeutic scheme should be considered, since the existing evidence to date refers to decreased bleeding, evolution time, patient satisfaction and decreased costs associated with morbidity. Despite the above, modern studies focused on specific groups are necessary to be able to establish treatment schemes applicable on a large scale within our environment.

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