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Review Article

Tranexamic acid in otorhinolaryngology – A contemporary review

Jordan Fuzi [a,*], Gideon R. Budiono [b], Catherine Meller [a], Ian Jacobson [a]

[a] *Department of Otolaryngology, Head and Neck Surgery, Prince of Wales Hospital, New South Wales, Australia*
[b] *Faculty of Medicine, University of New South Wales, Australia*

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Abstract Tranexamic acid (TXA) is an anti-fibrinolytic agent which has been proven beneficial in multiple surgical specialties where significant bleeding can occur. Whilst it has been widely available for over 40 years its use within Otorhinolaryngology is still limited. Operations in Otorhinolaryngology are particularly varied with some such as tonsillectomy having the potential for significant life threatening bleeding. Other operations are performed within small confined surgical fields and even small amounts of bleeding can significantly detriment surgical field and increase technical difficulty and operative time. This review evaluated the current literature on the benefits of tranexamic acid within the field of Otorhinolaryngology and Head and Neck Surgery. Overall TXA was demonstrated to be a safe drug with no major adverse effects including thromboembolic events reported in any study. It has been shown to be of particular benefit in rhinology by improving surgical field, reducing operative time and reducing postoperative swelling and ecchymosis. The benefit in tonsillectomy is less clear and further studies are required to evaluate its potential use in the reduction of post tonsillectomy haemorrhage rates.

* Corresponding author. Department of Otolaryngology, Head and Neck Surgery, Prince of Wales and Sydney Hospitals, Barker St, Randwick, NSW, 2031, Australia.
E-mail address: fuzijordan@gmail.com (J. Fuzi).
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Introduction

Operations in Otorhinolaryngology present varied risks of intraoperative and postoperative bleeding. Some, such as tonsillectomy, bear a risk of substantial postoperative bleeding that is potentially life threatening. The UK National Prospective Tonsillectomy Audit revealed 4.9% of adults (>16 years) will develop a secondary post tonsillectomy haemorrhage (PTH), with 1.4% requiring return to theatre.[1] There is evidence that these rates are even higher with the modern electrocautery and haemostatic techniques.[1]

Tranexamic acid (TXA) is an anti-fibrinolytic agent with proven benefits in multiple surgical specialties where significant bleeding can occur. TXA was shown to reduce maternal death from bleeding in primary post partum haemorrhage without an increase in thromboembolic events.[2] Additionally, TXA administered within three hours of major trauma reduced mortality by 10% in trauma patients with bleeding.[3] Similar results have been demonstrated in orthopaedic trauma surgery, with a large meta-analysis showing a reduction in perioperative blood loss and transfusion requirements without a significant effect on risk of thromboembolic complications.[4] Another meta-analysis of the safety of TXA in major orthopaedic surgery indicated no significant increase in venous thromboembolism associated with TXA.[5] Currently, there is no clear consensus on the benefit of TXA within otorhinolaryngology. This narrative review aims to review the current literature detailing the use of TXA within a number of otorhinolaryngological operations.

Pharmacology of tranexamic acid

Tranexamic acid is a synthetic analogue of the amino acid lysine and promotes anti-fibrinolysis by competitively binding to the lysine-binding sites on both plasminogen and plasmin.[6,7] This prevents attachment to fibrin and precludes activation of plasminogen to plasmin and subsequent fibrin degradation by plasmin. TXA can be administered intravenously or orally, has an oral bioavailability of 30%–50% and has a relatively short half-life of 2–3 h.[6,8,9] It is mostly (95%) excreted via renal clearance and administration must be carefully considered in patients with poor renal function.[8,9] The most common adverse effects of TXA include nausea, vomiting, diarrhoea and abdominal cramping.[10] There is a theoretical possibility of an increased risk of thromboembolic disease, including deep vein thrombosis, pulmonary embolism, cerebral thrombosis and myocardial infarction.[9] This is a major source of concern with regards to TXA prescribing and has led to the avoidance of its use. Acknowledging these concerns, a number of randomised control studies in many different fields have confirmed its safety.[9]

Tonsillectomy

Tonsillectomy, despite advances in technology and modern approaches, remains plagued by the risk of postoperative bleeding. A number of studies have attempted to evaluate the effect of TXA on postoperative bleeding in tonsillectomy (Table 1). Outcomes included total intraoperative blood loss, rates of primary or secondary post tonsillectomy haemorrhage and requirement for further surgery to achieve haemostasis.

In 2012, Chan et al performed a meta-analysis on 2 trials,[11] demonstrating a statistically significant reduction in intraoperative blood loss when TXA was given as a single dose at induction (32.73 ml, 95 %*CI* -42.66, −22.78, $P < 0.001$).[12,13] However, two more recent studies did not demonstrate benefit from TXA with regards to intraoperative blood loss.[14,15] Brum et al[14] showed no reduction in intraoperative blood loss from a single 10 mg/kg intravenous (IV) TXA dose on anaesthetic induction ($P = 0.18$), and Soliman et al[15] failed to show a statistically significant change in blood loss between their three population groups (A: 15 mg/kg IV TXA administered at anaesthetic induction, B: 15 mg/kg IV TXA administered at anaesthetic induction plus a continued infusion of IV TXA at 5 mg/kg/h, C: no TXA). Most recently in 2016, Santosh et al[16] performed a 50 participant randomised controlled trial, which did demonstrate a statistically significant reduction in mean blood loss (66.12 ml vs 106.84 ml, $P < 0.05$) when TXA was given as a single IV dose at induction. The safety of TXA was confirmed throughout these studies. Only 3 patients developing minor side effects (nausea, vomiting, and headaches) and no significant adverse effects were reported after administration of TXA.

Regarding PTH, there is currently no clear consensus on the effect of TXA administration. Chan et al undertook a meta-analysis of 5 studies ($n = 1670$) investigating the effect of TXA administration on rates of PTH.[17–21] No significant reduction in PTH rates were demonstrated (*RR* = 0.51, 95 %*CI* 0.25, 1.07, $P = 0.08$). Unfortunately, no further subgroup analysis was performed to differentiate primary from secondary haemorrhage. Robb's study suggested a halving of primary PTH rates (0.4% *vs.* 1%) with TXA on induction, when retrospectively compared to a large national audit on tonsillectomy complications.[1,22] Hinder et al[23] have been the first group to evaluate the use of topical TXA postoperatively since Falbe-Hansen et al[19] in 1974 demonstrated a small increase in haemorrhage rates post topical application of TXA (*RR* = 1.30, 95%*CI* 0.60, 2.83).[19] Participants were prescribed a topical TXA solution to be applied from postoperative day 5–10. No significant reduction in secondary PTH rates was demonstrated (19% (study) *vs.* 22% (control), and similarly there was no significant change in requirements for further surgery for haemostasis. Koizumi's large retrospective study demonstrated no benefit from TXA but is limited by its failure to describe and compare dose or duration of TXA administration or account for surgical technique.[24]

Within the current literature, the benefit of TXA for tonsillectomy is still unclear, however the safety of its use has overwhelmingly been demonstrated. PTH is the most significant complication of tonsillectomy. It can result in life threatening blood loss, sometimes requiring further surgery to achieve haemostasis. Given its pharmacodynamics and short half-life, it would be unwise to expect a single dose of TXA on induction to impact secondary PTH. Currently, no study has been undertaken to evaluate the use of routine oral TXA in the post-operative period to

Table 1 Characteristics of studies included — tonsillectomy.

Study	Type of Study	Participants	Surgical technique	TXA Administration	Timing of TXA dose	Control	Primary Outcome	Main result
Chan, 2017	Meta-Analysis	—	—	Varied	Varied	—	1. Blood loss volume 2.Postoperative haemorrhage rate	1. Mean blood loss by 32.72 ml ($P < 0.001$) 2. T: 400, C: 1270 ($RR = 0.51$, $P = 0.08$)
Brum, 2012	Randomised controlled trial	T: 47 C: 48	Cold Steel Tonsillectomy	10 mg/kg IV	Induction, 8 h, 16 h post	IV saline	Intraoperative blood loss (ml)	T: 135.1 ± 71.4, C: 158 ± 88.1 $P = 0.197$
Soliman, 2015	Randomised controlled trial	T1: 75 T2: 75 C: 75	Extracapsular tonsillectomy — technique not specified	T1: 15 mg/kg IV T2: 15 mg/kg IV bolus + 5 mg/kg/hr infusion	T1: on anaesthetic induction T2: on anaesthetic induction + continuous infusion	No treatment	Intraoperative blood loss (ml)	T1: 46.56 ± 5.92 T2: 47.07 ± 5.96 C: 47.17 ± 5.36 $P = 0.691$
Santosh, 2016	Randomised controlled trial	T: 25 C: 25	Dissection and snare	10 mg/kg IV	3—4 h prior to surgery	No treatment	Intraoperative blood loss (ml)	T: 66.12 ± 40.95 C: 106.84 ± 64.72 $P < 0.05$
Falbe-Hansen, 1974	Randomised Controlled trial	1050 (groups not specified)s	Not specified	4% tranexamic acid topical	Postoperative	5% glucose Topical	Postoperative Haemorrhage (No. of cases)	T: 13 patients C: 10 patients
Robb, 2014	Retrospective analysis	T: 476	Coblation	10—15 mg/kg IV	Perioperative	N/A	Primary Haemorrhage Rate (No. of patients/	2 patients (0.4%) developed bleeding postoperatively
Hinder, 2015	Prospective trial	T: 246 C: 248	Cold steel + bipolar haemostasis or Coblation	0.2% tranexamic acid topical	Postoperative day 5—10	Retrospective cohort — tonsillectomy patients who had not received TXA	Postoperative haemorrhage (T 19%, C 22%) • Postoperative bleeding requiring surgery (T8.9%, C11.3%)	T: 19.1% C: 22.2% $P = 0.44$
Koizumi, 2019	Retrospective analysis	T: 50,501 C: 60,427	Not specified	Intravenous — Dose unspecified	From day of tonsillectomy (otherwise unspecified)	No treatment	Post-tonsillectomy haemorrhage requiring operative haemostasis	T: 1.45% C: 1.33% $P = 0.64$
George, 2011	Randomised controlled trial	T: 50 C: 50	Not specified	10 mg/kg IV	Preoperative	IV saline	Intraoperative blood loss (ml)	T: 36.64 C: 66.32 $P < 0.001$

C: control group, T: trial/intervention group, IV: intravenous, N/A: not applicable, RR: risk ratio.

reduce the risk or severity of post tonsillectomy haemorrhage. Furthermore its role in stabilisation of patients experiencing PTH has yet to be determined. Thus no recommendation can currently be made regarding its use postoperatively in routine tonsillectomy.

Head and neck operations

Head and neck surgery includes a multitude of different operations, some of which can result in significant risk of postoperative bleeding. This is especially problematic when bleeding obscures or compresses a patient's airway. There is little literature on the use of TXA in head and neck cancer surgery (Table 2). In 2015, Das et al performed a randomised control trial evaluating the effect of a single dose of 20 mg/kg IV TXA at anaesthetic induction on perioperative bleeding in unilateral head and neck cancer surgeries.[25] This demonstrated a significant reduction in intraoperative, postoperative and total blood loss in comparison to a control, as well as a significant reduction in requirements for blood, colloid and crystalloid infusions. A similar study subsequently performed by Kulkarni et al, demonstrated a significant difference in post-operative blood loss (Placebo - 200 [120—250] ml *vs.* TXA - 250 [50—1050] ml, $P = 0.009$) but with no significant change in transfusion requirements.[26] This confirms the findings by Chen in 2008, who demonstrated that the use of TXA 10 mg/kg preoperatively with a continuous intraoperative dose resulted in a significant reduction in postoperative blood loss (49.7 ml *vs.* 88.8 ml) without a difference in post-operative drainage duration.[27] Although all studies confirm that TXA administration conveys a statistically significant reduction in blood loss, the authors note the minor clinical significance of the relatively small volumes of blood loss reported.

Rhinoplasty

Rhinoplasty can result in moderate intraoperative blood loss, post-operative epistaxis and periorbital swelling and ecchymosis. The potential therapeutic benefit of TXA in elective rhinoplasty has only recently been investigated. There exist 2 similar meta-analyses[28,29] evaluating the findings of five randomised control trials[30—34] (Table 3). The main outcomes assessed included intraoperative blood loss, post-operative swelling and postoperative periorbital ecchymosis. Both McGuire et al and de Vasconcellos et al demonstrated a statistically significant reduction in intraoperative blood loss with TXA in comparison to a control (−41.6 ml, $P = 0.004$)). Amongst these studies, of potential clinical relevance was Eftekharian's demonstration that TXA significantly reduced operative time.[32] Mehdizadeh's randomised controlled trial (RCT) however demonstrated no benefit in this regard from TXA.[34] Amongst the trials, the dosage and route of administration of TXA varies (Table 3), with all regimes demonstrating statistical significance without differences in rates of adverse effects. No significant thromboembolic events were reported within all trials.

Table 2 Characteristics of studies included — head and neck surgery.

Study	Type of Study	Participants	Surgical technique	TXA Administration	Timing of TXA dose	Control	Primary Outcome	Main result
Das, 2015	Randomized controlled trial	T: 40 C: 40	Unilateral H&N cancer surgeries (modified radical supraomohyoid, posterolateral neck dissection)	20 mg/kg IV	15 min before anaesthetic induction	IV saline	1. Intraoperative blood loss (ml) 2. Red cell concentrate transfusion requirements (units)	1. T: 52.34 ± 10.2, C 110.24 ± 13.4 ($p = 0.0001$) 2. T: 8, C: 42 $p < 0.0001$
Kulkarni, 2016	Randomized controlled trial	T: 108 C: 111	Composite resection of mandible + neck dissection + pedicled flaps (single or double)	10 mg/kg IV	20 min after anaesthetic induction	IV saline	Intraoperative blood loss (ml)	T: 750, C: 780 $p = 0.22$
Chen, 2008	Randomized controlled trial	T: 26 C: 29	Modified radical neck dissection, Hemithyroidectomy, Superficial parotidectomy	10 mg/kg IV + 1 mg/kg/h IV	Preoperative + intraoperative	IV saline	1. Drainage tube placement duration (h) 2. Drainage amount (ml)	1. T: 2.69 ± 0.68, C: 3.07 ± 1.13 ($p = 0.146$) 2. T: 49.7 ± 32.6, C: 88.8 ± 89.9 ($p = 0.041$)

C: control group, T: trial/intervention group, IV: intravenous.

Table 3 Characteristics of studies included — rhinoplasty.

Study	Type of Study	Participants	Surgical technique	TXA Administration	Timing of TXA dose	Control	Primary Outcome	Main result
De Vasconcellos, 2018	Meta-analysis	—	—	Varied	Varied	IV saline/ placebo	1. Intraoperative blood loss (ml) 2. Periorbital oedema and ecchymosis	1. Mean difference of 42.28 ($P < 0.01$) 2. Oedema by WMD 0.76 and ecchymosis by WMD 0.94
McGuire, 2019	Meta-analysis	—	—	Varied	Varied	IV saline/ placebo	1. Intraoperative blood loss (ml) 2. Periorbital oedema and ecchymosis	1. Reduction of 41.6 ($P = 0.004$) 2. Reduced significantly
Beikaei, 2015	Randomised controlled trial	T: 48 C: 48	Open rhinoplasty using standard technique	10 mg/kg IV	After anaesthetic induction	IV saline	Intraoperative blood loss (ml)	T: 43.3 ± 11.0 C: 60.3 ± 9.5 $P < 0.001$
Sakallioglu, 2015	Randomised controlled trial	T: 25 C: 25	Open septorhinoplasty with osteotomies and hump reduction	1 g oral + 1 g oral TDS	2 h prior to surgery + 5 days postoperative	Placebo	1. Intraoperative blood loss (ml) 2. Periorbital oedema and ecchymosis	1. T: 68 ± 21 C: 133 ± 63 $P < 0.05$ 2. Less patients in higher grades in Group T ($P < 0.05$)
Eftekharian, 2016	Randomised controlled trial	T: 25 C: 25	Not specified	1 g oral	2 h prior to surgery	Placebo	Intraoperative blood loss (ml)	T: 144.8 ± 60.28 C: 199.6 ± 73.05 $P = 0.005$
Mehdizadeh, 2018	Randomised controlled trial	T1: 15 T2: 15 C: 15	Open rhinoplasty with dorsal hump removal and lateral and medial osteotomies	T1: 10 mg/kg IV T2: 10 mg/kg IV + 8 mg dexamethasone IV	1 h prior to surgery and three doses every 8 h postoperatively	Placebo	Periorbital oedema and ecchymosis	Group T1 and T2 lower than C ($P < 0.01$) but no difference between T1 and T2

C: control group, T: trial/intervention group, IV: intravenous, WMD: weighted mean difference.

Similarly, both postoperative eyelid oedema and periorbital ecchymosis were reduced by TXA within these meta analyses (Table 3).[28,29]

Interestingly, both Mehdizadeh and Sakallioogluu demonstrated a reduction in periorbital oedema and ecchymosis with TXA to a degree similar to the use of systemic steroids.[32,34] The authors suggest the same benefit can be achieved using TXA without exposing the patient to the systemic effects of steroids. Given the efficacy demonstrated, these authors recommend the use of TXA to reduce postoperative periorbital oedema and ecchymosis. Whilst a statistically significant reduction in bleeding was demonstrated, these authors question the clinical significane of an overall small volume of blood loss.

Sinus surgery

Endoscopic sinus surgery is one of the more common procedures performed in otorhinolaryngology. Haemostasis is vital in ensuring optimal visualisation within the narrow confines of the sinonasal cavity. Lack of visibility as a result of bleeding has been identified as a key obstacle in performing sinus surgery.[35] Kim et al[36] have recently performed a meta-analysis on the pre- and perioperative use of systemic TXA in endoscopic sinus surgery (Table 4). Amongst the 7 studies comprising 562 participants, 6 studies utilised a single preoperative 10 mg/kg intravenous bolus of TXA, with one study administering a 15 mg/kg preoperative intravenous bolus followed by a continuous 1 mg/kg/h infusion throughout the operation.[37–43] This analysis found that operative time and intraoperative blood were both statistically lower in the treatment group. As expected, surgeon satisfaction was also statistically higher in the treatment group.[36] Interestingly, there was no difference in the incidence of side effects including thromboembolism, nausea and vomiting, and there was no impact on postoperative coagulation profiles. Unfortunately no subgroup analyses were performed evaluating the two administration methods. A previous meta-analysis performed by Pundir demonstrated similar reductions in intraoperative blood loss and improvements in surgical field (Table 4).[44] This review was limited by significant heterogeneity amongst medication administration and participant recruitment. Similar results were demonstrated by Eldaba, who found that a single 25 mg/kg intravenous dose of TXA on anaesthetic induction reduced intraoperative bleeding resulting in an improved surgical field and shorter operative time.[45] Haemodynamics including heart rate and mean arterial pressure did not differ between the treatment and control groups.

Ghorbani et Al[46] performed an RCT comparing the effects of preoperative oral clonidine vs intraoperative TXA on bleeding and surgical field quality. They revealed no significant difference in either domain between the two treatments, but did not compare these treatments to a control.

Kang et al recently performed a review on the use of topical TXA to reduce intraoperative bleeding in sinus surgery.[47] Meta-analysis demonstrated an overall statistically significant reduction in intraoperative bleeding with topical TXA and significantly improved surgical fields. Additionally, no change in haemodynamics was demonstrated. No increased adverse effects (nausea, emesis or thrombosis) were associated with TXA. Of the four studies analysed, three studies compared TXA to saline whereas only Jahanshahi et al[48] demonstrated superiority of TXA with phenylephrine over phenylephrine alone as a control. These authors showed TXA resulted in improved surgical field for the first 30 min and a reduction in operative bleeding (170.49 ml *vs.* 100.10 ml, $P = 0.001$) compared to phenylephrine.

Abbasi's RCT is the only study comparing the efficacy of different dosages of TXA.[49] It demonstrated that a single IV dose of 15 mg/kg IV TXA significantly reduced intraoperative blood loss ($P = 0.003$) and operative time ($P = 0.01$) compared to a 5 mg/kg IV dose, without a significant increase in side effects ($P = 0.55$).

As detailed above, TXA has been shown to significantly reduce intraoperative blood loss and improve surgical field during endoscopic sinus surgery. Throughout the current literature this has resulted in improved surgeon satisfaction and reduced operative time. In addition, TXA has been shown to be safe with no increased reporting of adverse effects. As such, these authors would suggest the use of TXA either as a single intravenous dose or topically in sinus surgery.

Epistaxis

Epistaxis is a common presentation within the emergency department often requiring time consuming and costly treatment.[50,51] A recent Cochrane review analysed 6 studies[52–57] evaluating the use of TXA for patients with epistaxis[58] (Table 5). This found moderate quality evidence that tranexamic acid reduces the risk of re-bleeding within the first 10 days. Of the studies comparing TXA to a control, two trials used TXA as a regular oral dose over several days[55,56] and one study applied a once off topical dose.[52] Subgroup analysis of these two administration modalities favoured a regular oral dosage.[58] No studies reported the requirement of further intervention. Three studies compared topical TXA to other haemostatic agents (epinephrine/lidocaine combination or phenylephrine),[53,54,57] with meta-analysis demonstrating a significantly higher proportion of participants achieving haemostasis within 10 min with TXA. A subsequent meta-analysis by Gottleib,[51] of similar papers,[52–54] evaluating topical TXA reported no significant difference in rates of haemostasis within 30 min but did demonstrate a significant increase in number of patients discharged within 2 h. Additionally, participants were less likely to re-bleed within the first 24 h and at 1 week with TXA.[51] No increase in adverse effects was associated with TXA use in either review.[58]

Hereditary haemorrhagic telangiectasia (HHT) is a hereditary disorder involving structural weakness of the vessel wall, with over 90% of patients with HHT suffering from recurrent spontaneous epistaxis.[59] A recent meta-analysis of three studies[60–62] on the use of TXA for treatment of HHT associated epistaxis revealed no significant benefit on frequency or duration of bleeds, mean haemoglobin levels or quality of life.[63]

Table 4 Characteristics of studies included — sinus surgery.

Study	Type of Study	Participants	TXA Administration	Timing of TXA dose	Control	Primary Outcome	Main result
Kim, 2019	Meta-analysis	—	Varied — 5 studies: 10 mg/kg IV, 1 study 15 mg/kg IV, 1 study 15 mg/kg IV + 1 mg/kg/h IV	Varied - 6 studies preoperative, 1 study preoperative + continuous infusion	6 studies IV saline, 1 study ethamsylate	1. Operative time 2. Intraoperative blood loss (ml) 3. Quality of the surgical field 4. Surgeon satisfaction	1. SMD: −0.6, $P = 0.0003$ 2. SMD: −0.66, $P < 0.001$ 3. SMD: −0.80, $P < 0.001$ 4. SMD: 1.74, $P < 0.001$
Pundir, 2013	Meta-analysis	—	Varied — 10 mg/kg IV, 100 mg topical, 500 mg IV, 1000 mg topical, 15 mg/kg IV + 1 mg/kg/h IV	Varied — preoperative, preoperative + continuous infusion, intraoperative	4 studies IV saline, 1 study no control	1.Intraoperative blood loss (ml) 2. Surgical field quality score 3. Operative time	1. MD: −104.10, $P = 0.01$ 2. SMD: −0.74, $P = 0.005$ 3. MD: −7.59, $P = 0.09$
Eldaba, 2013	Randomised controlled trial	T: 50 C: 50	25 mg/kg IV	After anaesthetic induction	IV saline	Intraoperative blood loss (mL)	T: 102 ± 19 C: 153 ± 23 $P < 0.001$
Ghorbani, 2018	Randomised controlled trial	T: 22 C: 30	15 mg/kg IV	After anaesthetic induction	0.2 mg PO clonidine (1—1.5 h preoperatively) + IV saline after induction	Hb reduction (g/L)	T: 1.14 ± 1.04, C: 1.40 ± 0.74 $P = 0.345$
Jahanshahi, 2014	Randomised controlled trial	T: 30 C: 30	Three pledgets soaked with TXA 5% + 0.5% phenylephrine for 10 min in each nasal cavity	Preoperative	Three pledgets soaked in 0.5% phenylephrine for 10 min in each nasal cavity	1.Intraoperative blood loss (mL) 2. Surgical field quality	1. T: 100.10 ± 52.50, C 170.49 ± 45.87 ($P = 0.001$) 2. Group C had more patients in higher grades (0—15 min $P = 0.002$, 16—30 min $P = 0.003$, 31—45 min $P = 0.163$)
Kang, 2019	Meta-analysis	—	Topical — TXA in various concentrations, TXA 5% + 0.5% phenylephrine	Intraoperative	Topical saline, topical 0.5% phenylephrine for 10 min in each nasal cavity	1. Surgical field score 2. Operative time 3. Intra operative blood pressure	1. SMD: −0.71, $P < 0.001$ 2. SMD: −0.89, $P < 0.0001$ 3. SMD -0.25, $P = 0.2954$
Abbasi, 2012	Randomised trial	A: 35 B: 35	A: TXA 5 mg/kg IV B: 15 mg/kg IV	After anaesthetic induction	—	1.Intraoperative blood loss (ml) 2. Surgical field quality 3. Haemodynamics	1. A: 272.74 ± 25.77 B: 242.89 ± 51.77 $P < 0.003$ 2. B > A, $P < 0.005$ 3. No significant difference between groups

C: control group, T: trial/intervention group, IV: intravenous, SMD: standardised mean difference, MD: mean difference, Hb: haemoglobin.

Table 5 Characteristics of studies included – epistaxis.

Study	Type of Study	TXA Administration	Control	Primary Outcome	Main result
Gottlieb, 2019	Meta-analysis	Topical - TXA gel, TXA 500 mg in 5 ml	Varied (placebo/anterior nasal packing)	1. cessation of bleeding within 30 min 2. Discharge within 2 h of treatment 3. Rebleed within 24 h 4. Rebleed within 1 week	1. T: 69.8%, C: 38.8%, $RD = 0.24$ $P = 0.14$ 2. T: 95.9%, C: 8.8%, $RD = 0.87$ $P < 0.001$ 3. T: 4.7%, C 11.7%, $RD = -0.07$ $P = 0.02$ 4. T:4.0, C: 16.3%, $RD = -0.12$ $P < 0.001$
Joseph, 2018	Meta-analysis	100 mg TXA on cotton ball topical, 1 g TXA 8 hourly oral for 10 days, TXA 10% gel once, 500 mg TXA soaked pledget	phenylephrine on cotton ball topical, placebo 8 hourly for 10 days, placebo gel once, epinephrine + lidocaine soaked pledget	1. Percentage of re-bleeding within 10 days	T: 47%, C: 67%, $RR = 0.71$ $P = 0.004$
Hsu, 2019	Meta-analysis	10% TXA nasal spray, 1 g TXA 8 hourly oral	Placebo	1. Frequency of epistaxis (per month)	1. MD: −7.32 $P = 0.26$ 2. MD: −64.80 $P = 0.25$

C: control group, T: trial/intervention group, RD: risk difference, RR: risk ratio, MD: mean difference.

In summary, the available literature suggests that topical administration of TXA in epistaxis may shorten time to haemostasis and facilitate earlier discharge, whilst systemic administration of TXA may reduce rates of representation within the first week. The safety of this drug was demonstrated throughout the literature.

Discussion

Tranexamic acid has recently been demonstrated to be of particular benefit in the reduction of bleeding in a number of surgical specialties. These authors endeavoured to review its use within otorhinolaryngology, a surgical specialty that contains a wide variety of operations. Some can result in devastating bleeding whereas others become extremely technically difficult when bleeding occurs due to the narrow confines of the surgical field. Tonsillectomy is a common ENT procedure that bears a high risk of significant postoperative bleeding which can be life threatening and require further surgery. The majority of trials to date have assessed the effect of TXA on intraoperative blood loss and have demonstrated a statistically significant reduction. However, total intraoperative blood loss in tonsillectomy is low and as such the clinical significance of these reductions is questionable. The authors consider secondary PTH as the single most important outcome in tonsillectomy, and further studies evaluating the effect of regular post-operative TXA on secondary PTH rates are required.

The benefit of TXA within rhinology is clearer. It has been shown to reduce postoperative swelling and ecchymosis in rhinoplasty when compared to a control. Its therapeutic benefits are similar to pulse steroids, however given the many adverse effects of systemic steroids, TXA may be the more favourable treatment. Total intraoperative blood loss within sinus surgery is clinically low and post-operative transfusions are rarely required. However, given the narrow confines in which this operation is performed, bleeding can often impair visualisation and significantly increase the difficulty and duration of the operation.[35] Both intravenous and topical TXA have been shown to reduce operative time, intraoperative blood loss and surgeon satisfaction in sinus surgery. Interestingly, no study has directly compared topical tranexamic acid to topical vasoconstrictors within sinus surgery. Jahanshahi et al did demonstrate that TXA + phenylephrine resulted in reduced intraoperative bleeding and improved surgical field in comparison to phenylephrine alone, however did not compare TXA alone to phenylephrine. These authors routinely use topical intranasal lignocaine and adrenaline prior to commencement of endoscopic sinus surgery and a study evaluating the efficacy of both therapies and their potential adverse effects would be highly beneficial.

The evidence for TXA use in epistaxis is more heterogeneous with some studies showing shorter time to haemostasis whilst others failed to demonstrate benefit. However, a recent Cochrane review demonstrated moderate quality evidence that oral TXA reduced rates of rebleeding within 10 days in comparison to a control. As such, regular oral TXA should be considered for high-risk

patients to reduce rates of rebleeding after initial treatment of epistaxis.

A major hesitancy towards the use of TXA is the potential increased risk of thromboembolic events. Throughout this review there is overwhelming evidence that systemic and topical TXA incur minimal to no significant increase in major adverse events, particularly thromboembolism. In some studies there were a few reports of minor side effects including nausea and vomiting however these were short lived.

Conclusion

Within this review TXA has been shown to be a safe drug used for the reduction of bleeding. In otorhinolaryngology specifically, the clinical benefit of its use in rhinology and epistaxis has been demonstrated, however definitive confirmation of clinical benefit remains to be determined in other areas of otorhinolaryngological surgery.

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Declaration of Competing Interest

None.

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