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SYSTEMATIC REVIEW

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A systematic review on the efficacy of tranexamic acid in head and neck surgery

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Abstract

Background: Intraoperative and postoperative blood loss is a major risk in head and neck (H&N) surgery. Recently the use of tranexamic acid (TXA) has been investigated by multiple studies for reducing intraoperative and postoperative bleeding, however reported results are variable.

Objectives: To determine the safety and efficacy of TXA use in H&N surgery.

Methods: Systematic review of MEDLINE, EMBASE, CINAHL, Cochrane Library, PubMed, ClinicalKey, and Clinicaltrials.gov according to the PRISMA guidelines. Studies were included if they reported on intraoperative bleeding, volume or duration of postoperative drain or return to theatre rate for postoperative haemorrhage in adult populations following use of TXA. Risk of bias assessment with Cochrane Risk of Bias (RoB2) tool for randomised controlled trials and Newcastle–Ottawa Scale tool for non-randomised studies.

Results: Sixteen studies were identified (114 407 patients). Eight studies evaluated TXA in major H&N surgery and eight studies in tonsillectomy. Primary outcomes were reduction in intraoperative or postoperative bleeding. Secondary outcomes included the duration of postoperative drain placement and return to theatre rate. No adverse events were reported in any patients. TXA is effective in reducing intraoperative blood loss in tonsillectomy. However, the effect on post-tonsillectomy haemorrhage was unclear. Insufficient evidence exists of benefit of TXA on intraoperative bleeding in major H&N procedures. Postoperative drainage volumes were significantly reduced in most major H&N studies. The duration of drain placement and risk of blood transfusion was unchanged in most cases.

Conclusion: TXA use is safe in H&N patients. Whilst sufficient evidence exists to support the use of TXA in tonsillectomy, insufficient evidence exists to recommend use in major H&N surgery.

KEYWORDS

head and neck surgery, thyroidectomy, tonsillectomy, tranexamic acid

Jameel Muzaffara and Hannah Nieto are joint senior authors.

1 | BACKGROUND

The use of tranexamic acid (TXA) is well established in a trauma settings[1] and postpartum haemorrhage.[2] Postoperative bleeding is a particular concern in head and neck (H&N) procedures as this can cause an airway-threatening haematoma.[3,4] A study by Pollei et al.[5] showed that 67% of all bleeding events in H&N procedures required surgical re-intervention or blood transfusion.

The use of TXA in H&N surgery has been investigated by multiple randomised controlled trials (RCTs).[6–8] TXA is a synthetic analogue of the lysine amino acid that competitively and reversibly binds to plasminogen,[9] rendering it unavailable for lysine residues,[9] thereby preventing the degradation of the fibrin clot. The H&N studies looking at TXA[6–8] have demonstrated variable results. As a result, the efficacy of TXA use in H&N patients is largely unclear.

The objective of this systematic review was to evaluate the role and efficacy of TXA in H&N surgical patients.

Key points

1. The use of tranexamic acid (TXA) significantly reduces intraoperative bleeding rates in adults undergoing tonsillectomy, but not other major head and neck (H&N) operations.
2. The rates of secondary posttonsillectomy haemorrhage do not differ significantly with the use of TXA and continue to present as a major challenge.
3. The rates of postoperative drainage volumes in major H&N operations are significantly reduced with the use of TXA.
4. Topical TXA is illustrated to be more promising with greater clinical reductions in the hospital stay of patients.
5. TXA is safe, with no evidence of increased complications, such as thromboembolism.

2 | METHODS

2.1 | Search strategy

Searches of OVID MEDLINE (PubMed),[10] ClinicalTrials.gov,[11] CINHAL,[12] and PROSPERO prospective database of systematic reviews[13] were made to identify no similar reviews were in progress or in print. The databases were then searched, with the help of clinical librarian, using the terms, 'head and neck procedures' and 'neck surgical procedures'. No limits were placed on language or year of publication in order to case the net as wide as possible and identify all potentially useful studies. The last search was undertaken on 20 June 2022.

Additional key words regarding surgeries and procedures in the neck were identified to form a comprehensive search of all the identified databases. Multiple searches were thus performed using the key words which are listed in the Appendix S1.

2.2 | Selection criteria

Inclusion and exclusion criteria are outlined in Table 1.

2.3 | Data extraction and synthesis

Search studies were independently reviewed by two study team members (WJ and MJ) for first-stage of screening by title and abstract and for second stage of screening by full-text. This was done blindly with voting along with arbitration by a senior collaborator (JM) in the event of discrepancies. The PRISMA reporting guideline were used in this manuscript to report the findings.[14] The PRISMA flowchart (Figure 1) reflects the various stages of inclusion. The data was extracted from all the selected studies by both reviewers using a predesigned Microsoft Excel datasheet. The datasheet included both study and patient characteristics (Appendix S1). PRISMA reporting guidelines have been used to report the findings in this study. Tables 4 and 5 summarise the main characteristics of each included study.

2.4 | Statistical analysis

A decision was made that the minimum number of studies to perform a meta-analysis will be at least three human studies and if heterogeneity between studies is equal to I^2 <40%. If suitable data is available from identified studies, then for each outcome, there would be a statistical analysis with calculated risk ratios and 95% confidence intervals (CIs) using the Review Manager 5.4.1 (updated September 2020).[15]

2.5 | Quality scoring

In order to formally assess the quality of identified studies the Cochrane Risk of Bias (RoB2) tool[16] was utilised to assess risk of bias in the RCTs. Table 2 represents the scoring of each RCT along with colour coding to represent the score visually. For non-RCTs, Newcastle–Ottawa Scale[17] was used to assess the quality of studies (Table 3).

3 | RESULTS

Sixteen studies were identified to be eligible after full-text screening, including a total of 114 407 patients (Figure 1). The studies were split

into two main categories—8 out of the 16 studies were identified to be major H&N surgical studies[6–8,18–22] while the other 8 were tonsillectomy studies.[23–30] The characteristics of the studies for the tonsillectomy studies are defined in Table 4 and for the H&N studies in Table 5, including a breakdown of the type of H&N operations undertaken. There were 941 patients in the H&N studies and there 113 466 patients in the tonsillectomy studies. Much of the discrepancy in numbers was the result of a single large retrospective cohort study with 110 928 patients[27] and another large comparative trial with 1050 patients.[26]

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Population undergoing specified H&N surgeries	No control groups
Male and female patients	Animal population
Head and neck surgical procedures	Oropharyngeal surgeries
Intraoperative blood loss	Nasopharyngeal cancer surgeries
Duration of surgery	
Volume of postoperative blood loss	
Volume of postoperative drain	
Duration of postoperative drain	

3.1 | Risk of bias assessment

The following five domains were used to evaluate the risk of bias in the 10 RCTs as guided by the Cochrane ROB2 tool[15]—randomisation sequence of assessment, allocation concealment, blinding of participants, complete data reporting, selective reporting, and other sources of bias. If a study was 'high' risk in any one of the domains, the overall risk of bias was ascertained to be high.[15] A table representing the

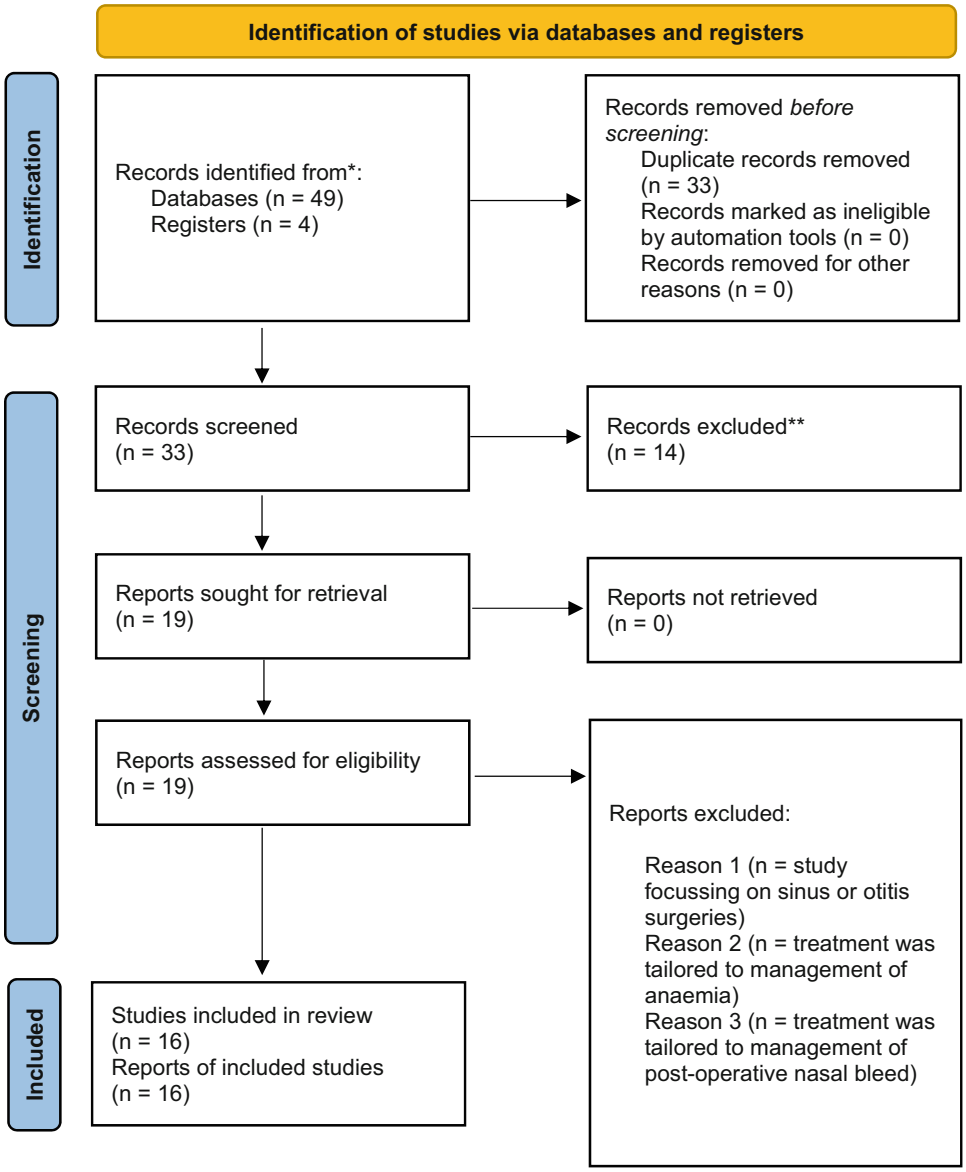

FIGURE 1 PRISMA flow diagram depicting the study selection process. Adapted from (PRISMA).[14] *Source*: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71.

TABLE 2 Risk of bias table for RCTs (Cochrane Risk of Bias RoB2 Tool).[15]

	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk of bias	Comments/concerns
Anand et al.	Low	High	High	Low	Low	Low	High	The surgeons were not blinded, however, the drain assessors were blinded.
Thakur et al.	Low	Low	Low	Low	Low	Low	Low	Patients were grouped according to the type of surgical procedure as postoperative drain volume depends on the type and extent of surgery.
Kulkarni et al.	Low	Low	Low	Low	Low	Low	Low	No concerns.
Chen et al.	Low	Low	Low	Low	Some concerns	Low	Some concerns/ medium risk	Not all coagulation profiles available—one of the main outcomes. Seven patients who were randomised but later removed and withdrawn.
Auvinen et al.	Low	Not mentioned	Low	Not mentioned	Low	Low	Some concerns/ medium risk	Patients were not similar amongst both groups—significant higher BMI in TXA group.
George et al.	Low	Low	Low	Low	Low	Low	Low	No concerns.
Santosh et al.	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Low	Low	High	No mention of randomisation and allocation concealment of any participants nor any mention of blinding.
Achakzai et al.	Low	Low	Low	Not mentioned	Low	Low	Low	No concerns.
Babu et al.	Low	Low	Low	Low	Low	Low	Low	No concerns.
Aksoy et al.	Low	Low	Low	Low	Low	Low	Low	No concerns.

scoring of the 10 RCTs in each of the five domains is shown in Table 2.

3.2 | Outcomes assessed

The outcomes reviewed in this study included the mean volume of intraoperative and postoperative blood loss, the mean duration of the surgery, and the postoperative drain duration. Tables 6 and 7 summarise the main findings from the included tonsillectomy and H&N studies, respectively, with the tonsillectomy studies comparing intraoperative blood loss, complication or reintervention rate, and length of surgery. Five of eight studies demonstrated a significant impact on one or all of these measured outcomes. For the H&N studies six of eight independently reported a significant effect, with the impact measured on intraoperative blood loss, duration of surgery, postoperative drain amount, length of postoperative drain duration, and need for transfusion.

3.3 | Intraoperative bleeding

Five tonsillectomy studies reported on mean intraoperative blood loss (mL).[23–25,29,30] Four out of these five studies reported significant reduction in the volume of intraoperative blood loss.[23–25,30] Santosh et al.[23] reported a mean reduction of 40.72 mL in their study group while George et al.[24] reported a reduction of 29.68 mL. Achakzai et al.[30] similarly reported a reduction of 29.59 mL in their study group. Pukhlik et al.[29] reported a much lower reduction at 19 mL. However, all these reductions were found to be statistically significant. The pooled data had significant heterogeneity ($p = 0.001$; $I^2 = 78\%$) with the random-effects model, however, the heterogeneity was not attributable to any one single study (Figure S1 in Appendix S2). All of these studies had intravenous TXA administration intraoperatively or preoperatively. All studies gave doses of at least 10 mg/kg in 100 mL. Intraoperative blood loss was calculated by the use of gravimetric method for measuring the blood accumulated in a suction jar.

TABLE 3 Quality measure of included studies by the Newcastle–Ottawa Quality Assessment Scale.

Study	Selection				Comparability	Exposure			Total score
	Adequate definition of case	Case representativeness	Selection of controls	Definition of controls	By design or analysis	Ascertainment of exposure	Same method of ascertainment	Non-response rate	
Koizumi et al.	*	*	*	*	**	*	*		8
Pukhlik et al.	*	*			*	*	*	*	6
Falbe-Hansen et al.	*	*			*	*	*	*	6
Erwin et al.	*	*			*	*	*	*	6
Dutta et al.	*	*	*		*	*	*	*	7

Meanwhile, of the four major H&N studies reporting on intraoperative blood loss,[6,8,19,21] only Babu et al.[21] reported a significant reduction. The pooled analysis using random effects model (Figure 2) revealed a reduction in the mean intraoperative bleeding in the TXA group in contrast to the control group ($n = 4$ studies (two levels of surgeon experience in the same paper), WMD = −0.21 mL, 95% CI: −0.42 to −0.01; $p = 0.04$). The pooled analysis was homogenous ($p = 0.001$; $I^2 = 15\%$).

3.4 | Postoperative drain volume

Six H&N studies measured this in their outcomes, and five reported a significant reduction in the mean postoperative drain volume.[6–8,18,21,22] Again, heterogeneity within included studies was high ($p < 0.00001$; $I^2 = 85\%$) (Figure S3 in Appendix S2).

3.5 | Postoperative drain duration

Three H&N studies reported on postoperative drain duration[6,7,18] and only Anand et al.[18] reported a statistically significant difference in the TXA group ($p < 0.0001$). The pooled data was again found to be to have a high level of heterogeneity ($p = 0.0009$; $I^2 = 82\%$) (Figure S4 in Appendix S2).

3.6 | The clinical impact of TXA

Ten studies reported on the requirement of blood transfusions or the number of re-interventions or the incidences of postoperative haemorrhages.[7,8,18,20,21,25–29] Heterogeneity amongst outcome assessment precluded meta-analysis.[31] Three out of these nine studies reported a clinically significant impact of TXA.[20,21,28]

Babu et al.[21] demonstrated a significant clinical reduction in the number of blood transfusion in the TXA group ($p < 0.011$) and interestingly divided their patients into two groups with different dosages of TXA (10 and 15 mg/kg in volume of 20 mL). They found that it made no difference to the volume of blood loss between the difference concentrations ($p = 0.706$).

Hamid et al.[20] revealed a significant reduction in the return to theatre in the TXA group retrospectively. In the cohort that received intravenous TXA, none of the cases required re-intervention postoperatively whereas the control cohort illustrated that five of those cases required reintervention ($p = 0.041$). Erwin et al.[28] was another randomised trial that proved clinical efficacy of TXA and the only tonsillectomy study that reported a significant reduction in posttonsillectomy secondary haemorrhage incidents ($p = 0.005$) in the TXA group.

Finally, Anand et al.[18] performed a unique study as they investigated the impact of topical TXA in patients undergoing neck dissections, and they were the only study to report a clinically significant reduction in drainage duration and therefore a reduction in length of hospital stay in TXA patients ($p < 0.0001$).

TABLE 4 Main characteristics of the tonsillectomy studies.

Study	Location	Population	Number of patients	Dosage	Route of TXA	Outcomes assessed
Santosh et al.	India	Patients undergoing tonsillectomy	50	10 mg/kg body weight	Intravenous (pre-operative)	Mean intraoperative blood loss.
George et al.	India	Patients undergoing tonsillectomy	100	10 mg/kg body weight	Intravenous (pre-operative)	Mean intraoperative blood loss; time duration of surgery; total blood loss.
Koizumi et al.	Japan	Patients undergoing tonsillectomy	110 928	Not mentioned	Intravenous (postoperative)	Postoperative bleeding events requiring reoperation or blood transfusion.
Pukhlik et al.	Ukraine	Patients undergoing bilateral tonsillectomy	107	10 mg/kg body weight	Intravenous (pre-operative)	Mean intraoperative blood loss; duration of surgery; incidences of intraoperative complications and incidences of postoperative bleeding.
Falbe-Hansen et al.	Denmark	Patients having bilateral tonsillectomy	1050	4% tranexamic acid (gel in a base of 3% sodium carboxymethyl cellulose)	Topical (postoperative)	Postoperative bleeding events requiring surgical re-operation; the mean fall of haemoglobin and haematocrit in both groups.
Erwin et al.	USA 2021	Patients undergoing tonsillectomy that developed posttonsillectomy haemorrhage	1083	Three weight-based doses (250 mg for patients less than 25 kg and 500 mg for over 25 kg)	Nebulised TXA	Postoperative bleeding events requiring surgical re-operation.
Dutta et al.	Nepal 2020	Patients aged more than 15 years who underwent bilateral tonsillectomy	48	Bolus does of 500 mg after induction of anaesthesia	Intravenous (intraoperative)	Mean intraoperative blood loss. Frequency of postoperative bleeding (24 h).
Achakzai et al.	Pakistan 2020	Patients undergoing elective tonsillectomy	100	Injection of 10 mg/kg body weight given 5–10 min prior to surgery	Intravenous (intraoperative)	Total and mean intraoperative blood loss.

4 | DISCUSSION

TXA is employed in many surgical fields, such as for treating haemorrhages in obstetric, spinal, and trauma surgeries.[1,32] The WOMAN trial[2] enrolled more than 20 000 women and illustrated that TXA significantly reduced morbidity due to postpartum haemorrhage by a fifth if administered within the first 3 h of the onset of bleeding (TXA: 1.5% vs. control: 1.9%, $p = 0.045$). The use of TXA is also well documented in the treatment of rapid blood loss in trauma.[33] The noteworthy CRASH-2 study[1] demonstrated significant reductions in the all-cause mortality in trauma settings with the use of TXA (TXA: 14.5% vs. control: 16%; RR 0.91; 95% CI: 0.85–0.97; $p = 0.0035$).

While the use of TXA is well-founded in circumstances involving large amounts of blood loss, H&N surgeries usually involve a much lower blood loss.[34] Previously, within otorhinolaryngology, the use of TXA has been successfully established in the fields of epistaxis[35] and endoscopic sinus surgeries (ESS).[36] Within this review, the use of TXA was assessed on patients undergoing tonsillectomy and major H&N operations.

Significant reductions in intraoperative blood loss were found with the use of TXA in tonsillectomy patients.[23–25,29,30] Since the overall intraoperative blood loss is minimal during tonsillectomy,[37] the therapeutic importance of these reductions is debatable. Moreover, two of the tonsillectomy studies[24,25] investigated the impact on the duration of the surgery and both reported clinically significant reductions. On the other hand, four tonsillectomy studies reported on the incidences of posttonsillectomy haemorrhage (PTH) events, and only Erwin et al.[28] reported a significant reduction. Koizumi et al.[27] insinuated that the lack of apparent impact of TXA on postoperative haemorrhage rates requiring re-interventions, may be due to the study assessing secondary PTH. Therefore, TXA, given at time of operation, would have been insufficient to provide stability to fibrin clots in

TABLE 5 Main characteristics of the major head and neck (H&N) studies.

Study	Location	Population	Number of patients	Dosage	Route of TXA	Outcomes assessed
Kulkarni et al.	India 2016	Patients undergoing composite resection of the mandible with neck dissection and pedicled free flap	219	10 mg/kg in 100 mL of normal saline	Intravenous (intraoperative)	Intraoperative blood loss, requirement for blood transfusions and postoperative blood loss.
Chen et al.	Taiwan 2008	Patients undergoing modified radical neck dissection, hemithyroidectomy, or superficial parotidectomy	55	10 mg/kg in 100 mL of normal saline	Intravenous (pre-operative)	The volume of postoperative drain, duration of the surgery and the duration of the drain length of hospitalisation.
Hamid and Carswell	UK 2020	Patients undergoing hemithyroidectomy or total thyroidectomy	260	1 g/kg of TXA in 100 mL of normal saline	Intravenous (intraoperative)	Number of patients returning to theatre for postoperative haematoma.
Anand et al.	India 2020	Patients undergoing neck dissection	99	5 mL of TXA (100 mg/mL) to 15 mL of normal saline	Topical (postoperative)	Postoperative drain volume for the first 5 days, duration of the drain and incidences of postoperative complications.
Thakur et al.	India 2019	Patients undergoing hemithyroidectomy, total thyroidectomy (with or without lateral neck dissection), selective/radical neck dissection or parotidectomy	91	10 mg/kg in 100 mL of normal saline	Intravenous (postoperatively)	Blood samples were assessed for prothrombin time, bleeding time, clotting time. and the volume of postoperative fluids and bloods required; postoperative drain volume on postoperative days 1 and 3, duration of the drain.
Auvinen et al.	Finland 1987	Patient undergoing thyroid surgery	76	0.5 g in 1000 mL solution	Intravenous	Intraoperative blood loss and postoperative blood loss.
Babu et al.	India 2021	Patients undergoing elective head and neck cancer surgery (range of procedures not defined)	84	Group 1: 10 mg/kg (20 mL) Group 2: 15 mg/kg (20 mL)	Intravenous	Intraoperative blood loss, duration of surgery (min), postoperative drain volume (mL), number of blood transfusions.
Aksoy et al.	Turkey 2022	Patients undergoing total thyroidectomy	57	Transamine 10% 2.5 mL 250 mg ampoule, Actavis Corp	Topical	The amount of blood drained for 24 h was measured.

these postoperative incidents owing to the short half-life of the TXA. In addition, the exact time and dosage of TXA were not ascertained by Koizumi et al.[27] Erwin et al.[28] produced a unique perspective on the clinical impact of TXA through utilisation of nebulised TXA and reported a clinically significant impact of TXA in posttonsillectomy secondary haemorrhage incidents ($p = 0.005$). However, this study was conducted as a retrospective cohort, hence there is a risk that the true number of incidents might have been under-reported due to differences in surgical techniques and defining features of PTH in each case.

Across the major H&N studies, none of the H&N studies reported a significant decrease in the intraoperative blood loss whether TXA was administered preoperatively or postoperatively. This may potentially have been due to the average perioperative blood loss of the major H&N procedures being much lower[34] than other established areas of TXA, such as cardiac and spinal surgeries where the intraoperative blood loss may be much higher[38] allowing a greater efficacy of TXA.[39] On the other hand, the findings on the impact on the postoperative blood loss were clinically significant with seven H&N surgical studies[6–8,18,19,21,22] reporting a significant decrease in the postoperative drain volume, and the pooled analysis indicated a significant reduction in mean intraoperative volume (with non-significant heterogeneity). The other effects seen in the pooled analysis (Figures S1, S3, and S4 in

TABLE 6 Results of the tonsillectomy studies.

Study	Design	Delivery of TXA	Effects of TXA	Risk of bias
Santosh et al.	Randomised controlled trial	Intravenous/pre-operative (3–4 h)	Mean intraoperative blood loss—TXA: 66.12 mL; control: 106.84 mL ($p < 0.05$) Significant effect	High
George et al.	Randomised controlled trial	Intravenous/pre-operative	Mean intraoperative blood loss—TXA: 36.64 mL; control: 66.32 mL ($p < 0.005$) There was 4.97% less time taken for surgery in TXA group ($p = 0.7443$) Significant effect	Low
Koizumi et al.	Retrospective observational study	Intravenous/postoperative	Number of reinterventions or blood transfusions—TXA: 1.33%; control: 1.45% ($p = 0.09$), including after PS-matching analysis (TXA: 1.50%; control: 1.47%) ($p = 0.64$) Insignificant effect	High
Pukhlik et al.	Comparative trial	Intravenous/pre-operative (30 min before surgery)	Mean intraoperative blood loss—TXA: 82 mL; control: 101 mL ($p < 0.01$) Reduction in duration of surgery for bilateral tonsillectomy by 6 min in TXA group ($p = 0.01$) However, there was not significant reduction in rates of primary or secondary haemorrhages ($p > 0.05$) Significant effect	Medium
Falbe-Hansen et al.	Prospective comparative double-blind trial	Topical/postoperative (at least 4 min post-surgery)	13 people had haemorrhage in the TXA group and 10 people had haemorrhage in the control group ($p > 0.05$) TXA had no significant impact on the mean fall in haemoglobin or haematocrit levels ($p > 0.05$) Insignificant effect	Medium
Erwin et al.	Retrospective cohort study	Nebulised TXA (three weight-adjusted doses)	14 patients with TXA developed post-op haemorrhage (4.7%), of which four required surgical intervention (29%). 44 patients in the control developed a PTH (5.6%), of which 32 required operative intervention (73%) ($p = 0.005$) Significant effect	Low
Dutta et al.	Retrospective cohort study	Intravenous (intraoperative TXA just before surgery)	The mean intraoperative blood loss in the study group was 92.85 mL whereas in the control group, it was 91.40 mL ($p = 0.785$) There was no incidence of postoperative haemorrhage in either groups. Insignificant effect	Low
Achakzai et al.	Randomised controlled trial	Intravenous (intraoperative TXA just before surgery)	The total and mean blood loss were 1404 and 33.05 mL, respectively, in the study group while they were 3132 and 62.64 mL, respectively, in the control group ($p < 0.05$) Significant effect	Low

Appendix S2) all have significant heterogeneity reported, and therefore cannot be interpreted clinically.

Importantly, only three H&N studies identified clinically significant impact of TXA in their studies. The study by Hamid et al.[20] found a significant reduction of re-interventions in patients undergoing thyroidectomy, however, this was a small retrospective study and the differences observed could potentially be attributable to confounding factors such as surgical experience or patient demographics.[40] Babu et al.[21] was the only study to report a significant reduction in the number of blood transfusions in the TXA group ($p < 0.011$). However, it was also a small-centre study and the authors highlighted that a single dose of TXA could not be rendered sufficient to have a significant therapeutic surgical impact in the 48 h following surgery. In the future, an additional dosage of TXA postoperatively could provide a better view on the requirements of blood transfusions.

Anand et al.[18] reported a significant decrease in length of hospital stay in their TXA group of patients undergoing neck dissections. Neck dissections involve greater operative times[41] than other H&N procedures, and there are greater drainage volumes,[41] potentially explaining the more significant impact of TXA in this setting. The writers also attributed this significance to use the topical application of TXA. As topical administration provides a high-drug concentration at the site of the wound, it avoids the systemic absorption seen in intravenous administration.[39] Hence, surgeons who may be more reluctant to administer intravenous TXA in H&N cancer patients may consider topical TXA as an alternative in patients estimated to be at high-risk for thromboembolic events.[42] However, further information regarding the dosage of topical TXA is needed in order to establish the efficacy of topical TXA in H&N patients. Anand et al.[18] applied topical TXA at a concentration of

TABLE 7 Results of the major head and neck studies.

Study	Design	Delivery of TXA	Effects of TXA	Risk of bias
Kulkarni et al.	Prospective randomised controlled trial	Intravenous/intraoperatively (20 min after induction of anaesthesia)	Intraoperative blood loss TXA: 750 mL; control: 780 mL ($p = 0.22$). Duration of surgery—5.45 in TXA group while it was 5.51 in the control ($p = 0.95$) Postoperative blood loss TXA: 250 mL; control: 320 mL ($p = 0.009$) No difference in requirement for blood transfusion Significant effect	Low
Chen et al.	Prospective randomised controlled trial	Intravenous/preoperatively before incision followed by continuous infusion during the operation.	Intraoperative blood loss of TXA: 86.5 and control: 115.5 mL ($p = 0.392$) Operation duration—TXA: 2.7, control: 2.7 ($p = 0.73$) Postoperative drain volume TXA: 49.7 mL; control: 88.8 mL ($p = 0.041$) Drainage duration TXA: 2.69 days; control: 3.07 days ($p = 0.146$) Significant effect	Medium
Hamid et al.	Retrospective cohort study	Intravenous/intraoperatively at the start of the procedure	Five patients returned to theatre in the control group whereas no patients returned to theatre in the TXA group ($p = 0.041$) Significant effect	Low
Anand et al.	Randomised controlled trial	Topical/at the end of the procedure and before placing the neck drains	Mean operation duration was 206.96 in the TXA group while it was 217.81 in the control group ($p < 0.05$) Mean neck drain output was significantly lower in the TXA group (TXA: 208.29 mL; control: 344.56 mL) ($p < 0.0001$) Drainage duration TXA: 6.11 days; control: 7.56 days ($p < 0.0001$) The incidences of postoperative complications were not significantly different between the two groups ($p > 0.05$) Significant effect	Low
Thakur et al.	Prospective, randomised, double-blind, case–control clinical trial	Intravenous/at the time of surgical wound closure	Mean operation time was 217 in the TXA while 212 in the control group ($p = 0.73$) Postoperative drain volume on postoperative days 1 and 3, 13 mL ($p = 0.31$); 18.6 mL ($p = 0.54$) respectively No significant reduction in the need for postoperative fluids (120 mL; $p = 0.6$) or postoperative blood transfusions ($n = 0.08$; $p = 0.15$) or the duration of the drain in situ (0.04 days; $p = 0.98$) No significant differences in complete blood count and coagulation profile Insignificant effect	Low
Auvinen et al.	Randomised controlled trial	Intravenous/0.5 g dose of tranexamic acid was given at induction of anaesthesia, and during each 8 h of the intraoperative and postoperative 24 h	Mean intraoperative blood loss TXA: 651 mL in TXA; control: 449 mL ($p > 0.05$) Insignificant effect	High
Babu et al.	Randomised, double-blind, controlled study	Intravenous/Group 1 received 10 mg/kg TXA, while Group 2 received 15 mg/kg TXA	The intraoperative blood loss in Groups 1 and 2 were 541.5 mL and 536.0 mL, respectively, compared to 762.5 mL in the control group ($p = 0.025$) Duration of surgery was TXA Group 1: 360, Group 2: 379 whereas in the control it was: 462.50 ($p = 0.125$) There was a significant difference amongst both Groups 1 and 2 compared to the control ($p = 0.0153$; $p = 0.0248$, respectively) in the volume of postoperative bleeding Number of blood transfusions was 17.85% in Groups 1 and 2, whereas it was 50% in the control group ($p < 0.011$) The difference between different dosage of TXA between Groups 1 and 2 were insignificant ($p = 0.706$) Significant effect	Low

(Continues)

TABLE 7 (Continued)

Study	Design	Delivery of TXA	Effects of TXA	Risk of bias
Aksoy et al.	Randomised controlled trial	Topical/intraoperative TXA after thyroidectomy using syringe left for 5 min	The mean value of postoperative drainage output in TXA group was 28.55 mL (21.9–35.1 mL), whereas in the control group it was 51.75 mL (46–57.4 mL) ($p < 0.0001$) Significant effect	Low

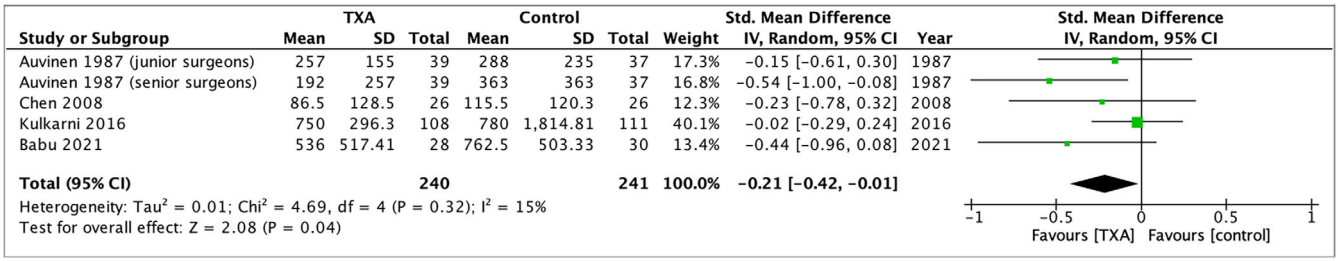

FIGURE 2 Meta-analysis of the mean volume of intraoperative bleeding in the major head and neck (H&N) studies.

25 mg/mL, however, previous studies such as ESS have utilised much higher topical concentrations at 100 mg/mL.[43]

4.1 | Safety profile of TXA

TXA theoretically may potentially increase the likelihood of thromboembolism because it prevents the degradation of fibrin deposits that have already formed,[44] but this effect of TXA has yet to be completely known.[45] None of the H&N studies within this review addressed any thromboembolic complications in their patients. Topical TXA is marketed as a safe technique with less thrombotic effects than intravenous TXA due to reduced systemic reach of topical administration.[46] None of the included studies in this review had long-term (>30 days) follow-up, hence there is concern that some later complications might have been missed. However, there is a low likelihood of developing thromboembolism[47] following a single intraoperative dose of TXA due to its short half-life.[45]

Although the results from the CRASH-2 study were remarkable in establishing the utility of TXA in trauma patients. A recent editorial review[32] on the study have pointed out that the lack of developed trauma system in the CRASH-2 study as it took place in undeveloped countries may have led to missed evaluation of incidents. Despite these uncertainties, most studies and meta-analysis in acute trauma prove the general safety and efficacy of TXA[2,33,35] and TXA use remains well-founded in the context of acute trauma.[33]

Further reassurance about the safety of TXA is provided through previous studies. There were no thromboembolic complications in all of the epistaxis trials,[35] however, patients who were considered to be at high risk of thrombosis were excluded.[35] Greater reassurance is provided by the lack of thromboembolic events reported in a retrospective study which included 256 pregnant women.[42] These findings were hopeful as they involved almost two-third cases of caesarean deliveries, which rendered these patients more susceptible to developing thrombosis.[48]

This systematic review did not address microvascular free flap reconstruction in H&N surgery, although this is relevant as many ablative H&N surgeries have microvascular reconstruction during the same procedure. The safety profile of TXA in microvascular reconstructive surgery is explored by Klifto et al.[49] in their article combining three studies covering different anatomical regions.[50–52] Overall, there is a paucity of data, and certainly not enough to combine for a quantitative analysis. Unfortunately, the only H&N study did not report flap-specific outcomes,[52] and there were only four patients (of 99 total) who had TXA. In the studies included in this systematic review Kulkarni et al.[8] included patients who had pedicled free flap reconstruction, rather than microvascular free flap reconstruction, and there were similar flap-specific complications in the TXA and control groups. So, despite the scarcity of evidence, it does appear that there is emerging evidence that TXA is safe in microvascular free-flap surgery, which is reassuring when considering utility of TXA in H&N surgery.[49]

4.2 | Strengths and limitations of this review

The systematic search strategy ensured that all relevant studies were identified and assessed for inclusion, therefore, more clarity was identified in terms of the significance and direction of impact of TXA in H&N patients than individual trials,[53] allowing a more thorough understanding of the gaps in the current literature.[53] However, all systematic reviews are limited by the quality of the primary evidence available.[31] Regarding this, there is automatically a degree of clinical heterogeneity in the H&N studies, as H&N includes a variety of procedures encompassing major maxillofacial resections, thyroidectomy, neck dissections, and parotidectomy—these are anatomically different and vary in invasiveness and length of surgery.

No study was removed based on their quality or risk of bias hence some included studies had low methodological quality with high risk of bias. Whilst 10 out of the 16 included studies were identified to be good or medium quality studies, the size of the patient populations was small in most cases. In addition, six included studies were not RCTs. The timing and drain assessment was not uniform across the studies along with variations in dosage and route of TXA, further adding to the heterogeneity.

Finally, whilst there is a significant difference seen in the meta-analysis between the TXA and control groups in terms of intraoperative bleeding, and a reduction in postoperative drain volume, the significant heterogeneity associated with the drain volume reduction means this is unreliable, and further it does not translate to a reduced length of postoperative drain duration (Figure S4 in Appendix S2). This is particularly important as a reduced duration of postoperative drain would potentially impact the length of patients' impatient stay.

4.3 | Future research

Topical TXA[18,22] and nebulised TXA[28] were illustrated to be more promising with a clinically significant reduction in the hospital stay of patients. However, since there were a limited number of studies exploring these routes and only one of them was an RCT,[18] the current evidence remains inadequate to establish the efficacy of topical and nebulised TXA in H&N patients.

No study has been found to investigate the impact of oral TXA in reducing the risk of postoperative bleeding in H&N patients. As oral TXA has the greater bioavailability than topical TXA,[54] these findings could illustrate greater clinical relevance in H&N patients, potentially reducing the risk of developing secondary PTH in patients, where a single intraoperative intravenous TXA dose was found to be insufficient postoperatively.[26]

Furthermore, several of the major H&N studies[6–8] contained a mix of patients. Hence, mixing those patients may have led to weakening of any significant differences.[47] A subset analysis of thyroidectomy patients would have been particularly interesting, but an adequate number of studies were not available. Therefore, further RCTs with a single type of procedure would be particularly informative.

5 | CONCLUSION

Under the current evidence, TXA administration was proved to be safe and there is significant data to support its utility in major H&N procedures for reducing postoperative blood loss and in tonsillectomy procedures to reduce the volume of intraoperative blood loss. However, there needs to be more stringent evidence in the future to prove the clinical benefits of TXA in H&N surgery.

AUTHOR CONTRIBUTIONS

Hannah Nieto and Jameel Muzaffar envisaged the study. Warda Jamshaid performed the searches with the help of an information specialist librarian, extracted the data, and wrote the first draft of the manuscript. Maryam Jamshaid was the secondary reviewer. All authors reviewed the manuscript, provided critical revisions and take responsibility for the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/coa.14059.

DATA AVAILABILITY STATEMENT

The source data for this systematic review is available from the primary studies cited in the reference list. Datasheets for the systematic review process are available on request from the authors.

ETHICS STATEMENT

This study is a systematic review of primary studies and did not require ethical review. This was confirmed with the HRA Decision Tool at https://hra-decisiontools.org.uk/ethics/EngresultN1.html.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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