INPLASY

Tranexamic Acid Combined with Advanced Surgical Instruments and Hemostatic Agents for Prevention of Post-Tonsillectomy Hemorrhage in Adults: A Systematic Review, Meta-Analysis, and Single-Center Retrospective Validation

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 March 2026 and was last updated on 20 March 2026.

INTRODUCTION

Review question / Objective The primary objective of this study is to systematically evaluate the prophylactic efficacy of Tranexamic Acid (TXA) in reducing the incidence and severity of post-tonsillectomy hemorrhage (PTH) in adult patients. Furthermore, this review seeks to determine the combined impact of TXA with advanced surgical technologies (e.g., BiZact, Coblator) and topical hemostatic agents (e.g., Floseal, 4DryField) compared to conventional surgical management.

PICOS:
P (Population): Adult patients (>18 years old) undergoing tonsillectomy for benign indications, such as chronic tonsillitis or Obstructive Sleep Apnea (OSA). Patients undergoing Uvulopalatopharyngoplasty (UPPP) will be included but analyzed as a pre-specified separate subgroup, given the distinct anatomical scope and hemorrhagic risk profile of UPPP compared to isolated tonsillectomy.

I (Intervention): Administration of Tranexamic Acid (TXA/Transamin) via any route (intravenous, oral, or topical), either as a standalone prophylactic measure or in combination with advanced surgical instruments (BiZact, Coblator, Plasma blade) or topical hemostatic adjuncts (Floseal, 4DryField, HaemoCer, Tisseel).

C (Comparator): Patients receiving a placebo, no TXA, or those undergoing conventional surgical techniques (Cold steel dissection or standard electrocautery) without the use of advanced hemostatic agents.

O (Outcomes): The primary outcome is the overall incidence of PTH, categorized into Primary (24 hours) hemorrhage. A clinically meaningful reduction in PTH incidence is defined as an absolute risk reduction (ARR) of ≥ 2% or a relative

risk reduction (RRR) of ≥ 25%, consistent with thresholds established in prior tonsillectomy hemorrhage literature. Secondary outcomes include bleeding severity staged by the National Prospective Tonsillectomy Audit (NPTA) 5-grade system, rate of return to the operating room (OR), blood transfusion requirements, and postoperative length of hospital stay (LOS).

S (Study Design): A systematic review and meta-analysis of Randomized Controlled Trials (RCTs), prospective cohort studies, and retrospective cohort studies. Due to the anticipated high clinical heterogeneity arising from the inclusion of both RCTs and observational studies, a stratified analysis by study design will be performed as a pre-specified sensitivity analysis. The global meta-analytic findings will be cross-validated against a single-center retrospective cohort of approximately 3,000 to 5,000 patients from Taichung Veterans General Hospital to ensure real-world clinical applicability..

Rationale Post-tonsillectomy hemorrhage (PTH) remains the most significant and potentially life-threatening complication in adult otolaryngology, occurring in approximately 3–5% of adult patients undergoing tonsillectomy, with secondary hemorrhage rates reported between 2–4%—significantly higher than the 0.5–1% observed in pediatric cohorts. Adult patients face a higher risk of secondary hemorrhage compared to the pediatric population, often compounded by underlying comorbidities such as hypertension or obstructive sleep apnea (OSA).

Tranexamic Acid (TXA), an antifibrinolytic agent, has been increasingly utilized perioperatively to mitigate this risk. However, current systematic reviews and meta-analyses on TXA in adult tonsillectomy have yielded conflicting results, with some suggesting substantial benefit and others showing negligible impact on secondary PTH. Furthermore, the modern surgical landscape has shifted toward a multimodal hemostatic strategy, integrating advanced energy-based instruments (e.g., BiZact, Coblator) and topical hemostatic adjuncts (e.g., Floseal, 4DryField). To date, there is a critical lack of high-level evidence evaluating the combined interaction between pharmacological interventions (TXA) and these technological and mechanical modalities.

Another critical gap in existing literature is the inconsistent reporting of bleeding severity. Many studies utilize simplified binary outcomes (bleeding vs. no bleeding), which fail to distinguish between minor self-limiting episodes and severe hemorrhages requiring surgical intervention. By adopting the National Prospective Tonsillectomy Audit (NPTA) 5-grade system, this study aims to provide a more granular and clinically relevant assessment of hemostatic efficacy.

Finally, to address the "evidence-practice gap," this study is uniquely designed to perform a single-center retrospective validation using a large-scale institutional cohort of approximately 3,000 to 5,000 patients from Taichung Veterans General Hospital. By cross-validating the pooled global evidence with high-volume real-world data, this research will provide more robust, locally applicable, and statistically powered insights into the optimal multimodal strategy for preventing post-tonsillectomy hemorrhage in adults.

Condition being studied The condition under investigation is post-tonsillectomy hemorrhage (PTH) following tonsillectomy or uvulopalatopharyngoplasty (UPPP) for benign indications, such as chronic recurrent tonsillitis or obstructive sleep apnea (OSA) in adult populations. PTH is traditionally categorized by timing into Primary PTH (occurring within 24 hours postoperatively, often related to surgical hemostasis) and Secondary PTH (occurring after 24 hours, typically between postoperative days 5 to 10, often associated with fibrinolysis and the sloughing of the surgical eschar).
In adult patients, PTH represents a significant clinical challenge due to a higher incidence rate and increased severity compared to pediatric cohorts. To address the limitations of binary reporting (presence vs. absence of bleeding), this study focuses on the clinical severity of PTH as defined by the Steward / National Prospective Tonsillectomy Audit (NPTA) 5-grade staging:
Grade 1: Patient reports a history of bleeding, but no evidence of bleeding is found on clinical examination.
Grade 2: Active bleeding observed, but managed conservatively without surgical intervention.
Grade 3: Severe bleeding requiring a return to the operating room (OR) for surgical hemostasis.
Grade 4: Bleeding necessitating a blood transfusion.
Grade 5: Life-threatening hemorrhage or mortality.

This review specifically examines how pharmacological (Tranexamic acid) and technological (BiZact, hemostatic agents) interventions modify the risk across these different severity grades.

METHODS

Search strategy Electronic Databases: A systematic and comprehensive search will be conducted across the following electronic databases:
• PubMed / MEDLINE
• EMBASE
• The Cochrane Library (CENTRAL)
• CINAHL (EBSCOhost)
• Web of Science (Core Collection)
• ClinicalTrials.gov
• WHO International Clinical Trials Registry Platform (ICTRP)
Search Strategy Overview: The search strategy combines MeSH terms and title/abstract keywords. The logic follows: (Population) AND (Outcome) AND (Intervention OR Comparison OR Synergistic Agents).
Representative Search String (PubMed/MEDLINE): #1 "Tonsillectomy"[MeSH] OR tonsillectomy[tiab] OR adenotonsillectomy[tiab] OR "tonsil surgery"[tiab] OR "tonsil removal"[tiab] OR uvulopalatopharyngoplasty[tiab] OR UPPP[tiab] #2 "Postoperative Hemorrhage"[MeSH] OR "post-tonsillectomy hemorrhage"[tiab] OR "post-tonsillectomy haemorrhage"[tiab] OR PTH[tiab] OR "postoperative bleeding"[tiab] OR "secondary hemorrhage"[tiab] OR "secondary haemorrhage"[tiab] OR "delayed bleeding"[tiab] OR "reactionary hemorrhage"[tiab] OR "return to theatre"[tiab] OR "return to operating room"[tiab] #3 "Tranexamic Acid"[MeSH] OR "tranexamic acid"[tiab] OR TXA[tiab] OR transamin[tiab] OR antifibrinolytic[tiab] OR "Antifibrinolytic Agents"[MeSH] OR "fibrinolysis inhibitor"[tiab] #4 BiZact[tiab] OR coblation[tiab] OR coblator[tiab] OR "plasma blade"[tiab] OR electrocautery[tiab] OR "cold steel"[tiab] OR "cold dissection"[tiab] OR "bipolar diathermy"[tiab] OR "harmonic scalpel"[tiab] OR microdebrider[tiab] OR "radiofrequency ablation"[tiab] #5 "Hemostatic Agents"[MeSH] OR floseal[tiab] OR "4DryField"[tiab] OR HaemoCer[tiab] OR tisseel[tiab] OR "fibrin glue"[tiab] OR "fibrin sealant"[tiab] OR thrombin[tiab] OR "gelatin-thrombin matrix"[tiab] OR "microporous polysaccharide"[tiab] #6 #1 AND #2 AND (#3 OR #4 OR #5)
(The detailed search strings for EMBASE, Cochrane Library, and CINAHL follow the same logic as the PubMed string, adapted for each database's specific syntax/descriptors.)
Selection Filters & Additional Sources:
• Language: Restricted to English language publications.
• Species: Human studies only.
• Manual Search (Snowballing): Reference lists of all included primary studies and relevant systematic reviews will be manually screened.
• Grey Literature: Conference abstracts from major Otolaryngology societies (e.g., AAO-HNS, ASPO, ERS) via EMBASE and ProQuest Dissertations & Theses.
• Trial Registries: ClinicalTrials.gov and WHO ICTRP will be searched for ongoing or unpublished trials.

Participant or population The participants included in this review are adult patients (aged > 18 years) who have undergone tonsillectomy or uvulopalatopharyngoplasty (UPPP) for benign indications, including but not limited to:
Chronic or recurrent tonsillitis.
Obstructive Sleep Apnea (OSA) or sleep-disordered breathing.
Tonsillar hypertrophy.
History of peritonsillar abscess.

The review focuses on the adult population due to their distinct physiological response and higher baseline risk of post-tonsillectomy hemorrhage (PTH) compared to pediatric cohorts. Both genders and all ethnicities will be included to enhance the generalizability of the results.

Exclusion Criteria for Participants:
Pediatric patients (under 18 years of age).
Patients undergoing surgery for suspected or confirmed oropharyngeal malignancies (e.g., Squamous Cell Carcinoma).
Patients with known hereditary or acquired coagulopathies (e.g., Hemophilia, von Willebrand disease, or advanced liver cirrhosis).
Patients on long-term anticoagulant or antiplatelet therapy that was not standardized or suspended perioperatively.
The study population is further validated by a single-center retrospective cohort of approximately 3,000 to 5,000 patients from a tertiary medical center, ensuring that the clinical characteristics of the synthesized literature align with real-world surgical demographics.

Intervention The primary intervention under evaluation is the administration of Tranexamic Acid (TXA), commercially known as Transamin, as a prophylactic or perioperative hemostatic measure. The review includes all standardized administration routes:
Systemic administration: Intravenous (IV) bolus or continuous infusion.
Topical application: Local irrigation, soaked gauze packing, or gargle protocols.
Oral administration: Pre-operative or post-operative oral tablets.

A key focus of this review is the synergistic evaluation of TXA when used in conjunction with modern surgical modalities. Therefore, the intervention group also encompasses the concurrent use of:
Advanced Surgical Instruments: Specifically energy-based dissection and hemostatic platforms, including BiZact, Coblator (radiofrequency ablation), and Plasma blade.
Topical Hemostatic Adjuncts: The application of specialized hemostatic agents to the tonsillar fossae, including gelatin-thrombin matrix (e.g., Floseal), microporous polysaccharide hemispheres (e.g., 4DryField, HaemoCer), and fibrin sealants (e.g., Tisseel).
The intervention protocols identified in the literature will be compared and validated against the standardized clinical practices used in our single-center retrospective cohort (n ≒ 3,000–5,000) to determine the optimal combination for reducing post-tonsillectomy hemorrhage in adults.

Comparator The interventions will be compared against the following control groups to establish a baseline for hemostatic efficacy:
Pharmacological Control (Primary Comparator):
Placebo or No TXA: Patients who received either a saline placebo or did not receive any form of Tranexamic Acid (systemic or topical). This group serves as the primary baseline to evaluate the standalone efficacy of TXA.

Conventional Surgical Control (Surgical Baseline):
Cold Steel Dissection: Tonsillectomy performed using traditional metal instruments (e.g., Hurd dissector, snare) with hemostasis achieved via gauze packing or ties/ligations.

Standard Electrocautery (Hot Technique): Use of standard monopolar or bipolar electrocautery for both dissection and hemostasis, without the use of specialized energy-based platforms like BiZact or Coblator.

Hemostatic Baseline:
Standard Hemostasis: Patients in whom no specialized topical hemostatic adjuncts (e.g., Floseal, 4DryField, fibrin glue) were applied to the tonsillar fossae, relying solely on conventional surgical hemostatic methods.

Institutional Reference Cohort:
The meta-analytic findings will be cross-referenced with a single-center validation cohort of patients from Taichung Veterans General Hospital who underwent conventional surgery without TXA or advanced hemostatic agents prior to the adoption of the multimodal protocol.

Study designs to be included This review employs a hybrid model: (1) RCTs for high internal validity. (2) Prospective and retrospective cohort studies for real-world evidence. (3) Institutional retrospective validation cohort (n≒ 3,000–5,000; IRB: CE25629B) from Taichung Veterans General Hospital. A stratified sensitivity analysis by study design is pre-specified to evaluate effect size differences between RCTs and observational studies. Exclusions: Case reports, case series (n<30/arm), reviews, animal studies, and abstracts without full-text data.

Eligibility criteria
INCLUSION CRITERIA:
1. Publication Type: Peer-reviewed, full-text articles published in English.
2. Population: Adult patients (aged >18 years) undergoing tonsillectomy or UPPP for benign indications (e.g., chronic tonsillitis, OSA, tonsillar hypertrophy, or peritonsillar abscess).
3. Data Requirements: Studies must provide extractable raw data (sample size and bleeding events) for both intervention and control groups to allow for calculation of Odds Ratios (OR).
4. Technological Specificity: Clear specification of the pharmacological protocol (TXA dosage/route) and/or the surgical modality (e.g., BiZact, Coblator, or conventional techniques).
5. Sample Size Threshold: A minimum sample size of n≧30 per study arm is required to minimize small-study bias.
EXCLUSION CRITERIA:
1.Patient Factors:
Pediatric patients (under 18 years of age).
Oropharyngeal malignancies (e.g., SCC).
Hereditary or Acquired Coagulopathies: Including Hemophilia A/B and all types of von Willebrand disease (vWD), as these conditions require specialized hematological management that confounds TXA efficacy analysis.
Non-standardized long-term anticoagulant or antiplatelet therapy.
2. Duplicate Records: Overlapping datasets or multiple publications from the same cohort.
3. Study Type: Systematic reviews, meta-analyses, editorials, and conference abstracts without accessible full-text data.
4. Incomplete Outcomes: Studies failing to differentiate between primary and secondary hemorrhage.
5. Pre-clinical Research: Animal models, in vitro experiments, and cadaveric studies.
6. Small Study Bias: Studies with fewer than 30 participants per study arm.

Information sources To ensure a comprehensive and saturated literature search, the following information sources will be utilized:
Electronic Databases: We will systematically search PubMed/MEDLINE, EMBASE, the Cochrane Library (Cochrane Central Register of Controlled Trials – CENTRAL), CINAHL (EBSCOhost), and Web of Science (Core Collection). The search period spans from the inception of each database to March 16, 2026.

Trial Registries: To identify ongoing or unpublished studies and minimize publication bias, we will search ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

Grey Literature: We will screen conference abstracts and proceedings from major otolaryngology societies (e.g., AAO-HNS, ASPO, and ERS) via EMBASE and ProQuest Dissertations & Theses.

Hand-searching (Snowballing): The reference lists of all included primary studies, as well as previously published systematic reviews and meta-analyses, will be manually screened to identify additional relevant records.

Institutional Data Source: A unique and significant source for this review is the institutional clinical data warehouse of Taichung Veterans General Hospital. This provides a retrospective validation cohort of approximately 3,000 to 5,000 adult patients, allowing for the cross-validation of global evidence with high-volume real-world data.

Contact with Authors: If necessary, the corresponding authors of primary studies will be contacted via email to request missing or ambiguous data required for the meta-analysis.

Main outcome(s) The primary outcome is the overall incidence of post-tonsillectomy hemorrhage (PTH) in adult patients. To ensure clinical granularity, PTH will be analyzed based on the timing of the hemorrhagic event:
1. Primary PTH: Defined as bleeding occurring within the first 24 hours postoperatively, primarily reflecting intraoperative hemostatic efficacy and surgical technique.
2. Secondary PTH: Defined as bleeding occurring after 24 hours and up to 30 days post-surgery, typically associated with fibrinolysis and the sloughing of the surgical eschar.
Clinical Significance Threshold:
A clinically meaningful reduction in PTH incidence is defined as an absolute risk reduction (ARR) of ≧2% or a relative risk reduction (RRR) of ≧25%, consistent with thresholds established in prior tonsillectomy hemorrhage literature. This threshold ensures that statistically significant findings are also interpreted in the context of clinical relevance.
Effect Measures:
For these binary outcomes (bleeding vs. no bleeding), the primary effect measure will be the pooled Odds Ratio (OR) with its corresponding 95% Confidence Interval (CI). Statistical significance will be set at $p < 0.05$. A random-effects model (DerSimonian-Laird method) will be employed as the primary pooling method to account for expected clinical and methodological heterogeneity across the included studies (e.g., variations in TXA administration route and surgical instruments such as BiZact).

Additional outcome(s) Secondary outcomes will focus on clinical severity, surgical recovery, and patient-reported outcomes to provide a comprehensive evaluation of the multimodal strategy:
1. Bleeding Severity (NPTA Staging): Hemorrhagic events will be meticulously categorized using the National Prospective Tonsillectomy Audit (NPTA) / Steward 5-grade system (Grade 1: History only; Grade 2: Active/Conservative; Grade 3: Return to OR; Grade 4: Transfusion; Grade 5: Mortality).
2. Postoperative Pain Intensity: Pain levels will be assessed using standardized scales, such as the Visual Analog Scale (VAS) or Numerical Rating Scale (NRS). We will specifically analyze pain scores at early (POD 1–3) and late (POD 7) postoperative stages to evaluate the impact of TXA and advanced instruments (e.g., BiZact) on tissue recovery.
3. Surgical Intervention Rate: The proportion of patients requiring a return to the operating room (OR) for secondary hemostasis under general anesthesia.
4. Blood Transfusion Requirements: Incidence of patients necessitating blood product transfusions due to severe PTH.
5. Length of Stay (LOS): The total duration of postoperative hospitalization, measured in days, as an indicator of overall recovery efficiency.
Categorical outcomes will be analyzed using pooled Odds Ratios (OR), while continuous data (Pain scores and LOS) will be synthesized using Weighted Mean Differences (WMD), both with 95% Confidence Intervals (CI).

Data management To ensure data integrity and transparency, the following mechanisms will be utilized for record management and data extraction:

• Literature Selection: Search results from all electronic databases will be exported to EndNote 21 for automated deduplication. The refined list will then be uploaded to Rayyan QCRI for blinded screening. Two reviewers will independently screen titles and abstracts, followed by full-text review. Any discrepancies will be resolved through consensus or by consulting a third senior investigator.
• Data Extraction: A standardized, pilot-tested Microsoft Excel spreadsheet will be used to extract data from included studies. Extracted information includes: (1) Study metadata (author, year, country); (2) Clinical variables (age, surgical indication, comorbidities); (3) Specific interventions (TXA dose/route, surgical modality such as BiZact or Coblator); and (4) Outcomes based on the NPTA 5-grade staging.
• Institutional Data Management: For the single-center validation cohort (n approximately 3,000–5,000), data will be retrieved from the Clinical Data Warehouse (CDW) of Taichung Veterans General Hospital. All institutional records will be de-identified and managed on a secure, encrypted server within the hospital's internal network. Access is restricted to authorized research personnel in strict compliance with the approved IRB protocol (CE25629B).
• Quality Control: To minimize errors, 10% of the extracted data from the literature will be randomly cross-checked by a second investigator. Final datasets will be locked and backed up before being imported into R software (version 4.2.2) for statistical synthesis.

Quality assessment / Risk of bias analysis To ensure the internal validity of the synthesized evidence, two reviewers will independently perform the quality assessment of all included studies. Any discrepancies will be resolved through consensus or by consulting a third senior investigator.
The following standardized tools will be utilized based on study design:
• For Randomized Controlled Trials (RCTs): The Cochrane Risk of Bias 2.0 (RoB 2.0) tool will be applied, assessing domains including the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.
• For Observational and Cohort Studies: The Newcastle-Ottawa Scale (NOS) will be employed to evaluate the selection of study groups, comparability, and ascertainment of outcomes. A score of 7 or higher will be considered high quality.
• Institutional Data Validation: The reporting quality of our institutional retrospective cohort (n approximately 3,000–5,000) will be assessed based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure robust real-world evidence integration.
The results of the risk of bias assessment will be visualized using a "traffic light" plot and a summary bar chart. Studies identified as having a "High Risk" of bias or low NOS scores will be subjected to sensitivity analysis to determine their influence on the overall effect size of TXA and synergistic interventions.

Strategy of data synthesis Analyses will be performed using R software (v4.2.2+) with meta, metafor, and gemtc packages. A random-effects model (DerSimonian-Laird) will be the primary pooling method to account for clinical and methodological heterogeneity.
Effect Measures:
• Binary Outcomes (PTH, Return to OR): Pooled Odds Ratios (OR) and 95% Confidence Intervals (CI).
• Continuous Outcomes (Pain scores, LOS): Weighted Mean Differences (WMD) and 95% CI.
Heterogeneity & Interaction:
Heterogeneity will be assessed via I^2 statistic and Cochran's Q test ($I^2 > 75\%$ indicates high heterogeneity). To investigate the synergistic impact of TXA and advanced instruments (e.g., BiZact), meta-regression will be performed to evaluate whether pharmacological-technological interactions significantly modify effect sizes.
Network Meta-Analysis (NMA):
If sufficient data exist for multiple treatment arms, an NMA will be conducted to simultaneously compare the relative efficacy of TXA, BiZact, Coblator, and hemostatic adjuncts. Consistency between direct and indirect evidence will be evaluated using the node-splitting method.
Hybrid Validation Strategy:
A unique feature is the cross-validation with our institutional retrospective dataset (n ≒ 3,000–5,000; IRB: CE25629B). We will compare pooled ORs from the literature with adjusted ORs from our multivariable logistic regression. Any discrepancies between global evidence and real-world institutional data will be systematically explored.
Publication Bias:
If ≧ 10 studies are available, bias will be assessed via Begg's funnel plots and Egger's test. If asymmetry is detected ($p < 0.05$), the Trim-and-fill method will be used to estimate an adjusted effect size.

Subgroup analysis Subgroup analyses will be prioritized to isolate the core efficacy of Tranexamic Acid (TXA) and explore how additional

surgical factors modify this effect. The following subgroups are pre-specified:
1. TXA Administration Specifics (Primary Focus):
o Route of Delivery: Comparison between intravenous (IV), topical application (e.g., gargle or soaked packing), and oral administration.
o Timing of Intervention: Pre-operative vs. intra-operative vs. post-operative (maintenance) TXA protocols.
o Dosage: Standard dose vs. high-dose TXA regimens, where data permit.
2. Surgical Modality (Advanced Instruments):
o Instrument Impact: Comparison of TXA efficacy when used with advanced energy devices (BiZact, Coblator) versus conventional electrocautery or cold steel.
o Hemostatic Adjuncts: Comparison of outcomes in cases using TXA with vs. without additional topical hemostatic agents (e.g., Floseal, 4DryField).
3. Clinical and Severity Factors:
o Bleeding Severity: Subgrouping based on the NPTA 5-grade system to identify if TXA is more effective in preventing minor (Grade 1–2) vs. severe (Grade 3–5) PTH.
o Patient Comorbidities: High-risk groups (e.g., hypertension or OSA) vs. low-risk groups.
4. Surgical Indication and Scope:
o Indication: Chronic/recurrent tonsillitis vs. OSA / tonsillar hypertrophy. This is essential for isolating the net effect of TXA across distinct clinical populations with varying baseline risks.
o Procedural Scope: Tonsillectomy alone vs. UPPP, given the distinct anatomical scope and hemorrhagic risk profile.
5. Evidence Source Validation:
o Global Literature vs. Institutional Data: Comparison of pooled results from the meta-analysis against our single-center retrospective cohort (n ≒ 3,000–5,000) from Taichung Veterans General Hospital.
A p-value for interaction < 0.05 will be considered statistically significant for identifying meaningful differences between subgroups. All analyses are pre-specified to minimize risk of data-driven bias.

Sensitivity analysis To ensure the robustness and stability of the pooled effect sizes regarding Tranexamic Acid (TXA) efficacy and its synergistic interactions, the following sensitivity analyses will be performed: 1. Leave-one-out Method: Each study will be iteratively removed one at a time to determine if any single study disproportionately influences the overall Odds Ratio (OR) for post-tonsillectomy hemorrhage (PTH) or significantly alters the level of statistical heterogeneity (I2). 2. Impact of Study Quality: The analysis will be re-run by excluding studies identified as having a "High Risk" of bias (RoB 2.0) or those scoring < 7 on the Newcastle-Ottawa Scale (NOS). This ensures that the primary conclusions on TXA are not driven by low-quality evidence. 3. Sample Size Threshold: A sensitivity check will be conducted by restricting the analysis to studies with a larger sample size (n ≥ 100 per study arm) to evaluate whether the effect size of TXA remains consistent compared to the full analysis including all studies meeting the minimum threshold of n ≥ 30 per arm.

Language restriction The search is restricted to English-language publications to ensure accurate data extraction and consistency with the institutional validation cohort.

Country(ies) involved Taiwan. All authors are affiliated with the Department of Otolaryngology-Head and Neck Surgery, Taichung Veterans General Hospital.

Other relevant information The distinguishing feature of this systematic review and meta-analysis is its Hybrid Validation Approach. While the primary analysis synthesizes global evidence from randomized controlled trials and cohort studies, the findings will be cross-validated against a large-scale, single-center retrospective dataset from Taichung Veterans General Hospital (n ≒ 3,000–5,000 patients).
This dual-layered methodology is designed to address the "evidence-practice gap" in adult tonsillectomy, particularly regarding the synergistic use of Tranexamic Acid (TXA) with advanced surgical platforms like BiZact and topical hemostatic adjuncts (e.g., Floseal). By integrating real-world surgical outcomes with pooled literature data, this study aims to provide a more robust and clinically applicable protocol for reducing both bleeding severity (NPTA grading) and postoperative pain in adult patients.
The institutional component of this research has been formally approved by the Institutional Review Board (IRB) of Taichung Veterans General Hospital (Protocol Number: CE25629B). The screening and selection process for the systematic review will be managed using the Rayyan QCRI platform to ensure a blinded and transparent review workflow.

Keywords Tranexamic Acid; Transamin; Post-tonsillectomy hemorrhage; Tonsillectomy; BiZact; Hemostatic agents; Postoperative pain; Meta-analysis; Adult.

Dissemination plans The results of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed otolaryngology or evidence-based medicine journal. Target journals include Laryngoscope,

Otolaryngology–Head and Neck Surgery, JAMA Otolaryngology–Head & Neck Surgery, and Clinical Otolaryngology, selected based on their scope and impact factor relevance to adult tonsillectomy and hemostatic management. The findings will also be presented at major international otolaryngology conferences, including the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Annual Meeting and the European Rhinologic Society (ERS) Congress, to facilitate timely dissemination to the clinical community. The institutional validation component of this research, conducted under IRB protocol CE25629B at Taichung Veterans General Hospital, will be reported in full compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure transparent and reproducible real-world evidence integration. The complete search strategies, data extraction templates, and statistical analysis code (R scripts) will be made available as supplementary materials upon publication to support reproducibility and open science principles.

Contributions of each author

Author 1 - Yi-Ting Yao - drafted the protocol manuscript, developed the comprehensive search strategy, and performed the preliminary literature screening and data extraction process.
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Author 2 - Shih-An Liu - conceptualized the research question, provided clinical guidance on the study design, and supervised the protocol development and final revision.
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