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Tranexamic Acid in Rhinoplasty and Septoplasty: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Perioperative bleeding is a challenge in rhinoplasty and septoplasty. Tranexamic acid (TXA) may help reduce this, but its effectiveness is unclear. This systematic review and meta-analysis aimed to evaluate TXA's impact on bleeding in these procedures.

Methods: The protocol was registered a priori to PROSPERO (CRD42023393458). PubMed, Embase, Google Scholar, and Web of Science were searched from inception to October 2023. Eligible studies were randomized controlled trials of adult patients undergoing rhinoplasty or septoplasty. Primary outcomes were intraoperative blood loss, surgery duration, and surgeon satisfaction. A random-effects model was used. Methodological quality was assessed using GRADE. The risk of bias was assessed using Cochrane's RoB 2 tool for randomized studies.

Results: The search yielded 154 results; 11 randomized controlled trials, with 968 patients, were included. The meta-analysis showed a significant reduction in intraoperative blood loss with TXA (MD −39.67; 95% CI: −15.10 to −64.24; $P = 0.002$) and superior surgeon satisfaction in favor of TXA use (SMD −2.73; 95% CI: −5.33 to −0.12; $P = 0.04$). Subgroup analyses for intraoperative blood loss, according to administration routes, were also in favor of intravenous TXA (MD −13.02; 95% CI: −1.65 to −24.38; $P = 0.02$) and oral TXA (MD −44.98; 95% CI: −83.66 to −6.31; $P = 0.02$); no statistical difference was noted in surgery duration (MD −0.99; 95% CI: 0.63 to −2.81; $P = 0.23$). All studies were found to be of high quality, with low bias.

Conclusions: The findings support TXA's efficacy in reducing blood loss during rhinoplasty and septoplasty, with high surgeon satisfaction. *(Plast Reconstr Surg Glob Open 2024; 12:e6275; doi: 10.1097/GOX.0000000000006275; Published online 5 November 2024.)*

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INTRODUCTION

Rhinoplasty and septoplasty represent pivotal procedures in plastic surgery and otolaryngology, both aimed at enhancing facial aesthetics and nasal functionality.[1,2] Notably, the intricate vascular networks predispose these procedures to perioperative bleeding, a critical concern leading to prolonged operative times, compromised surgical visibility, and potential need for blood transfusions.[3] Moreover, bleeding can compromise postoperative aesthetic outcomes by inducing nasal edema and ecchymosis. Given these challenges, using tranexamic acid (TXA), an antifibrinolytic agent, holds promise in optimizing outcomes for patients who undergo rhinoplasty and septoplasty.[4,5]

Disclosure statements are at the end of this article, following the correspondence information.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

TXA inhibits the conversion of plasminogen to plasmin, preventing fibrinolysis, platelet activation, and other inflammatory processes mediated by plasmin.[4,6] Although TXA has demonstrated efficacy in reducing perioperative bleeding across various surgical disciplines,[7] its adoption in rhinoplasty and septoplasty remains limited due to a dearth of compelling evidence supporting its effectiveness. Previous reviews have explored the potential of TXA in mitigating bleeding during nasal surgery,[7–9] generally indicating its capacity to diminish blood loss, shorten operative durations, and enhance surgical field visualization. However, these analyses have been constrained by small sample sizes and methodological limitations and are progressively outdated amid the burgeoning literature. Hence, this review aims to consolidate current clinical evidence and surgeon-reported outcomes pertaining to TXA administration in rhinoplasty and septoplasty versus standard care or placebo. By addressing methodological deficiencies inherent in prior reviews, our endeavor seeks to present a robust synthesis that contributes to the evolving discourse on TXA utilization in facial plastic surgery.

Takeaways

Question: Does tranexamic acid (TXA) use in rhinoplasty/septoplasty reduce perioperative bleeding and duration of surgery and improve surgeon satisfaction, compared with standard care without TXA?

Findings: This meta-analysis demonstrated that TXA significantly reduces intraoperative blood loss compared with the control groups across various methods of administration. Surgeons also reported greater satisfaction where TXA was utilized. However, the duration of surgery was not significantly affected by TXA.

Meaning: Reduced blood loss and increased surgeon satisfaction suggest that TXA may facilitate more controlled and efficient surgical environments. This could lead to better decision-making and possibly improved aesthetic/functional outcomes in rhinoplasty/septoplasty despite the unchanged operative time.

METHODOLOGY

This systematic review and meta-analysis protocol was registered a priori on the Prospective Register of Systematic Reviews (CRD42023393458).[10] The authors conducted this review strictly adhering to the guidelines set by the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11] The AMSTAR-2 tool[12] was used to evaluate the deficiencies in prior reviews.

Search Strategy

A comprehensive search across 7 databases was undertaken. PubMed, CENTRAL, Embase, Medline, Web of Science, PsycINFO, and Google Scholar were searched, without any restrictions for date, language, or study design, from inception until October 2023. The search strategy employed keywords, medical subject heading (MeSH) terms, and Boolean operators. The following is an example search strategy (PubMed), which was adapted for the other databases: ("rhinoplasty"[mesh] OR "rhinoplasty"[tiab] OR "septoplasty"[tiab] OR "septal surgery"[tiab] OR "nasal septal surgery"[tiab] OR "rhinoseptoplasty"[tiab]) AND ("tranexamic acid"[mesh] OR "tranexamic acid"[tiab] OR "TXA"[tiab]). The search strategies and results from all the database searches are provided in Supplemental Digital Content 1. (**See table, Supplemental Digital Content 1,** which displays the search strategies by database, **http://links.lww.com/PRSGO/D590**.)

Study Selection

The results from the database searches were exported to EndNote 20,[13] and duplicates were removed. Two authors (I.M. and A.A.) independently screened the titles and abstracts of the identified studies from the database searches to choose potentially eligible studies. The reports considered eligible by the authors were sought for full-text retrieval and once again independently screened for eligibility based on the inclusion and exclusion criteria. The lead author (A.K.) was consulted to make a final decision if disagreements arose. Only randomized controlled trials (RCTs) involving adult patients were included. Studies were excluded if they did not report the study's outcomes of interest or did not use TXA before and/or during rhinoplasty or septoplasty in 1 treatment arm and standard care or a placebo in the other. Additionally, studies found to have a high risk of bias (RoB) or be of low quality were excluded from the review. RoB was assessed using Cochrane's RoB 2 tool for RCTs[14] and ROBINS-I for nonrandomized comparative studies[15]; quality was assessed for all studies using the GRADE tool.[16] The screening and selection process was thoroughly documented and updated at every stage, providing reasons for exclusion using a PRISMA flow diagram.

Data Extraction

A data extraction form was predesigned for data collection of variables relevant to this review's primary and secondary outcomes. Following this, data from the included studies' text, tables, and figures were extracted independently by 2 authors (I.M. and A.A.) and added to the predesigned, standardized extraction form. If there were data clarity or completeness concerns, the corresponding authors of the studies of interest were contacted for clarification. If it was not possible to clarify the results or obtain missing data, a full explanation of the nature of the missing data and the impact it could have on the results reported in this review was provided. Data were extracted for various variables; this included study characteristics, notably study ID, title, first author, publication year, study design/setting, outcomes of interest, country/city, study setting, population, sample size, funding, follow-up duration, type of nasal surgery, and inclusion/exclusion criteria. The patient characteristics for collecting data included age, sex, and comorbidities.

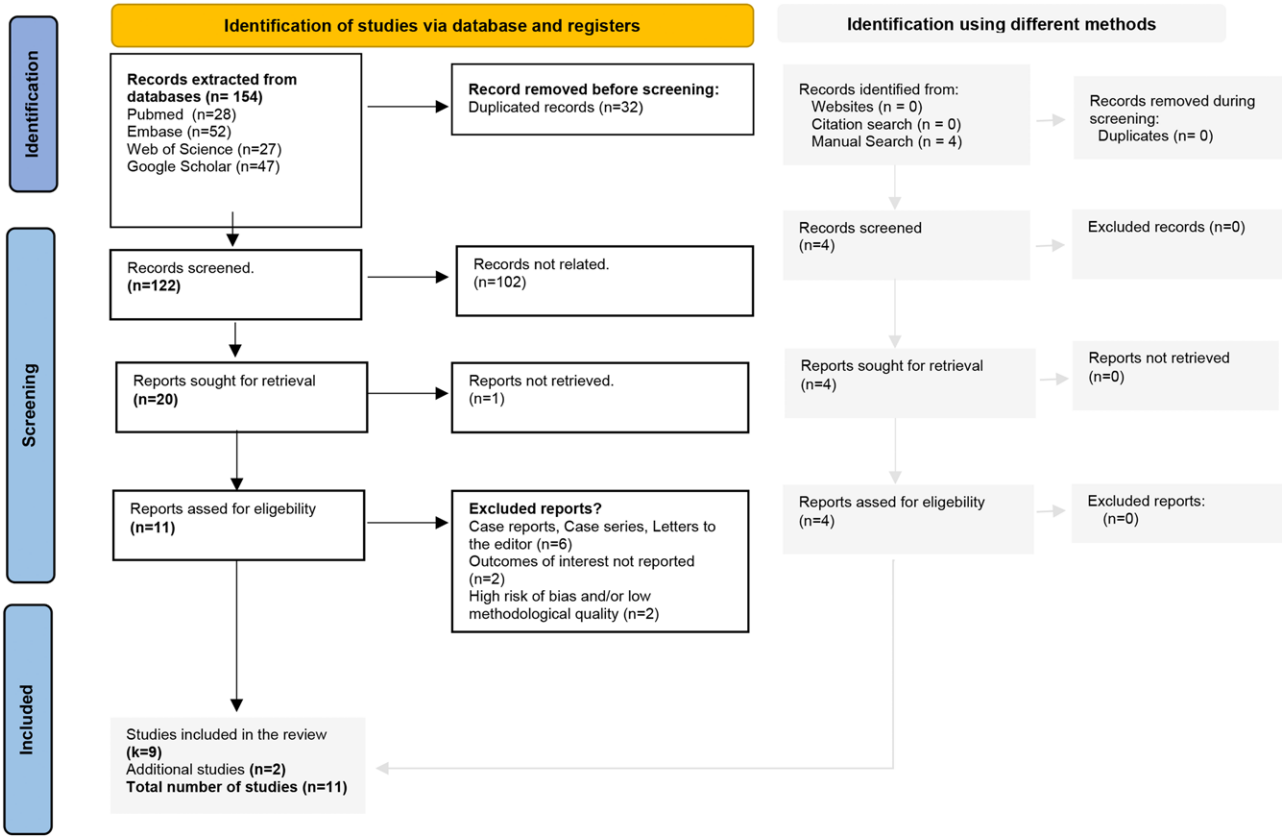

Fig. 1. PRISMA flow diagram: illustrates the stages of article selection for this systematic review, from initial database search to final study inclusion, with numbers at each stage.

The intervention characteristics were the TXA dosage, treatment duration, mode of delivery, and adjunctive therapies. Data were collected for average blood loss, duration of surgery, hematocrit/hemoglobin concentration before and after surgery, efficacy rate, surgical field visibility, surgeon satisfaction, and local and systemic complications. Additionally, data analysis points such as statistical methods used, effect size, confidence intervals, heterogeneity (assessed using the Higgins I^2 statistic), and publication bias (assessed using a funnel plot) were considered in the evidence synthesis. Finally, the study's main findings, limitations, and recommendations for future research were noted, and the findings were also informed.

Data Analysis

All statistical analyses were performed using RevMan (version 5.4.1; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020).[17] We extracted the mean scores and SDs of blood loss, surgery duration, surgical field visibility, and surgeon satisfaction from the included studies, both groups with and without TXA. A random-effects model was utilized to pool the weighted mean difference and 95% confidence intervals (CIs), and forest plots were generated to assess the results. A significance level of $P < 0.05$ was considered statistically significant. Additionally, heterogeneity among the trials was determined using the Higgins I^2 test by the Cochrane Handbook to assess the suitability of a meta-analysis or, instead, a narrative synthesis.[18]

RESULTS

Systematic Search and Study Selection

The initial database searches yielded 154 articles, of which 122 were screened after removing duplicate reports. Additionally, a thorough examination of reference lists of these articles brought 4 more studies into our consideration set. Eleven studies, all of which were RCTs, were included. This meta-analysis combines results from 968 patients, 492 of whom received TXA; 450 patients were men, and 518 were women. Financial disclosure was provided by 8 of the studies, with 2 of them (Modir et al[19] and Beikaei et al[20]) acknowledging external funding sources. The process from the initial search to the final selection is visually displayed in Figure 1. The characteristics of the studies finally selected for inclusion were tabulated and presented, providing an encompassing view of the research landscape explored. (**See table, Supplemental Digital Content 2,** which displays the details of the included studies, such as study design, location, number of patients, doses of TXA used, and other intervention details, **http://links.lww.com/PRSGO/D591**.)

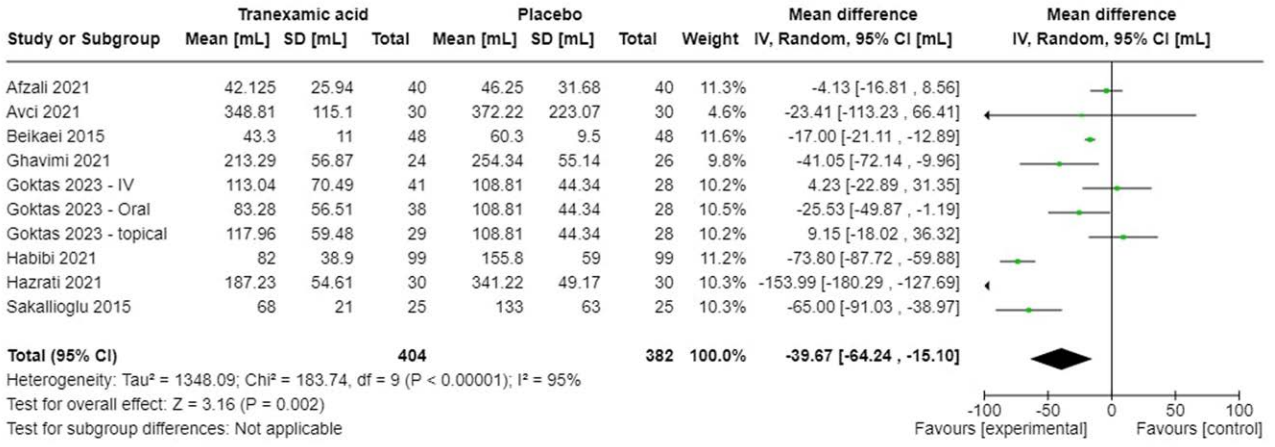

Fig. 2. A forest plot comparing intraoperative blood loss across studies comparing this outcome with a placebo or standard practice.

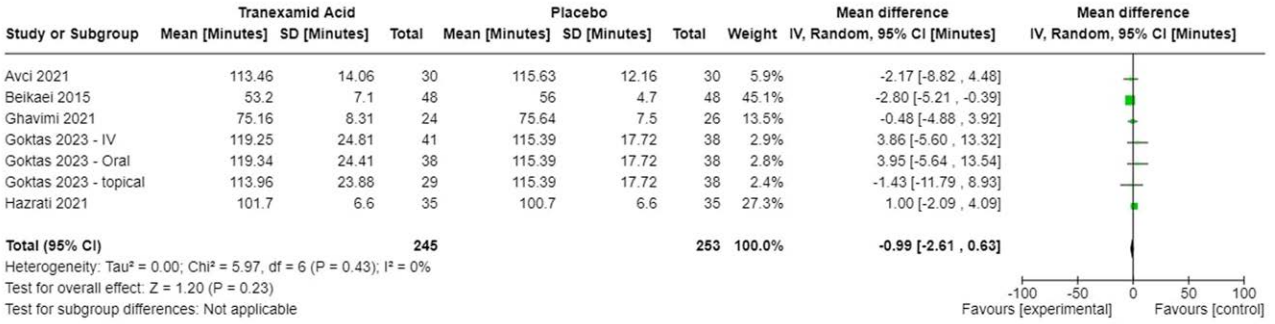

Fig. 3. A forest plot comparing the duration of surgery across studies comparing this outcome with placebo or standard practice.

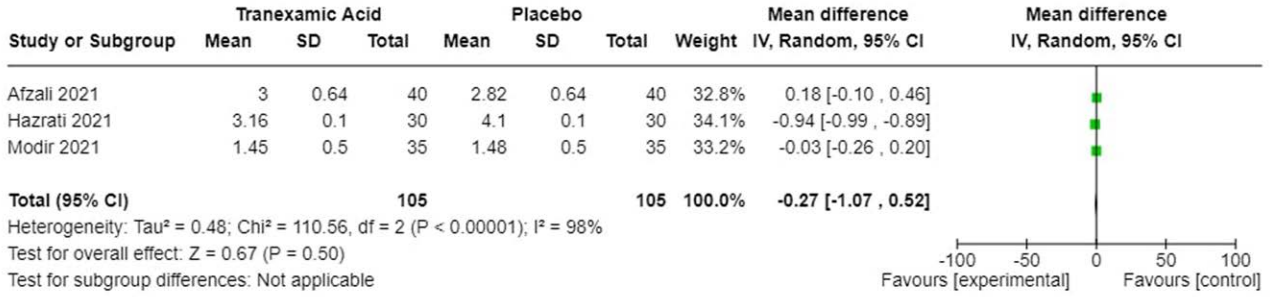

Fig. 4. A forest plot comparing surgeon satisfaction across studies comparing this outcome with a placebo or standard practice.

Intraoperative Blood Loss

Eight studies reported on the primary outcome of intraoperative blood loss. The meta-analysis, illustrated in Figure 2, demonstrates a statistically significant reduction in blood loss in patients administered TXA compared with the control groups [mean difference (MD): −39.67 mL; 95% CI: −15.10 to −64.24; $P = 0.002$].

Duration of Surgery

Data regarding the duration of surgery, pooled and meta-analyzed from 5 studies, are presented in Figure 3. The homogeneous pooled results ($I^2 = 0\%$) did not reveal a significant difference in the duration between TXA and placebo-treated groups (MD: −0.99 min; 95% CI: 0.63 to −2.81; $P = 0.23$).

Surgeon Satisfaction

Three included studies assessed surgeon satisfaction using different Likert scales to measure surgeon satisfaction during the operation. Standardized mean differences were used to meta-analyze scores. Figure 4 shows a statistically significant difference in surgeon satisfaction in favor of TXA versus placebo (MD: −2.73; 95% CI: −5.33 to −0.12; $P = 0.04$).

Subgroup Analyses

Subgroup analyses were conducted to compare the effect sizes of different administration forms of TXA. These

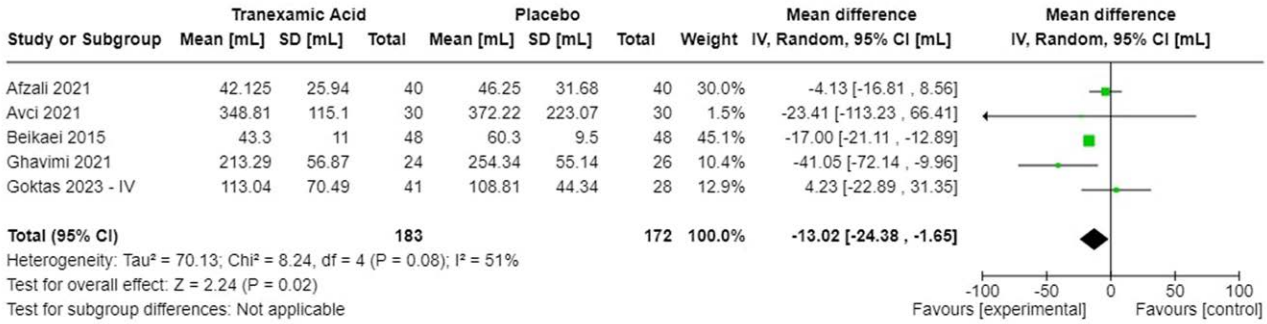

Fig. 5. A forest plot comparing intraoperative blood loss across studies comparing this outcome using IV TXA with a placebo or standard practice.

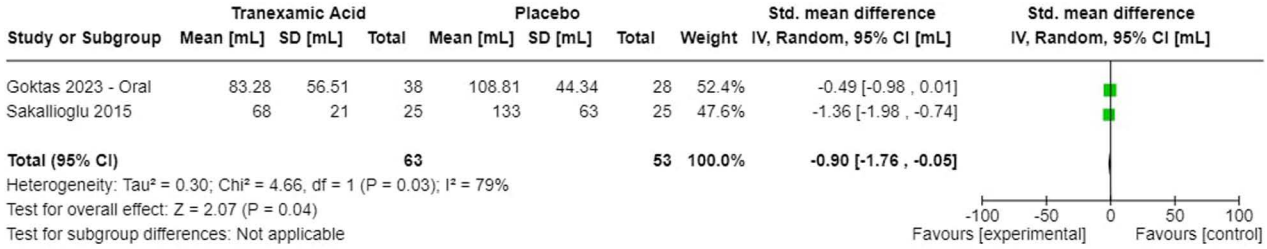

Fig. 6. A forest plot comparing intraoperative blood loss across studies comparing this outcome using oral TXA with a placebo or standard practice.

Fig. 7. A forest plot comparing intraoperative blood loss across studies comparing this outcome using topical TXA with a placebo or standard practice.

included intraoperative blood loss in IV, oral, and topical dosage forms. Figure 5 shows a statistically significant difference in intraoperative blood loss in favor of IV TXA versus placebo in 5 studies (MD: −13.02; 95% CI: −1.65 to −24.38; $P = 0.02$); as does Figure 6 in favor of oral TXA versus placebo, however, with a more significant effect size in 2 studies (MD: −44.98; 95% CI: −6.31 to −83.66; $P = 0.02$). Figure 7 shows no statistically significant difference in intraoperative blood loss with use of topical TXA in 2 studies (MD: −33.18; 95% CI: 48.09 to −114.45; $P = 0.42$).

Methodological Quality Assessment

A quality assessment of included studies using the GRADE tool was systematically tabulated. (**See table, Supplemental Digital Content 3,** which displays the GRADE: quality assessment of included RCTs, **http://links.lww.com/PRSGO/D592**.) All studies were of high quality, and the tool found no concerns in most domains.

RoB Assessment

RoB analyses of the included RCTs are summarized and tabulated in Table 1. All of the included studies have a low RoB according to this analysis, with the majority of domains producing no concerns for RoB.

AMSTAR-2 Assessment

Table 2 evaluates the quality of prior systematic reviews, highlighting critical and noncritical flaws to determine overall confidence in their results. Locketz et al[7] exhibited 4 crucial and 2 noncritical flaws, suggesting a critically low confidence in results. Ping et al[8] and Fuzi et al[9] also both received critically low confidence ratings, attributed to the 3 critical and 3 noncritical flaws of Ping et al and the 6 critical and 3 noncritical flaws of Fuzi et al, indicating significant concerns about the validity of their results. In contrast, with no identified flaws, our review achieved a high confidence rating, underscoring its reliability and the

Table 1. Summary of RoB Analysis for RCTs Deemed Suitable for Inclusion in This Review and Assessed Using the Cochrane RoB 2 Tool

Author	Bias Arising from the Randomization Process	Bias Due to Deviations from Intended Interventions	Bias Due to Missing Outcome Data	Bias in the Measurement of the Outcome	Bias in Measurement of the Reported Result	Overall RoB
Afzali et al[21]	No concerns	No concerns	No concerns	No concerns	No concerns	Low
Avci et al[22]	No concerns	No concerns	No concerns	No concerns	No concerns	Low
Beikaei et al[20]	No concerns	No concerns	No concerns	Some concerns	No concerns	Low
Ghavimi et al[23]	No concerns	No concerns	No concerns	No concerns	No concerns	Low
Habibi et al[24]	Some concerns	No concerns	No concerns	No concerns	No concerns	Low
Haddady-abianeh et al[25]	Some concerns	No concerns	No concerns	No concerns	No concerns	Low
Hazrati et al[5]	No concerns	No concerns	No concerns	No concerns	No concerns	Low
Modir et al[19]	No concerns	No concerns	No concerns	No concerns	No concerns	Low
Sakakallioğlu et al[26]	Some concerns	No concerns	No concerns	No concerns	No concerns	Low
Vaghardoost et al[27]	No concerns	No concerns	No concerns	some concerns	No concerns	Low
Goktas et al	No concerns	No concerns	No concerns	No concerns	No concerns	Low

Table 2. Summary of Quality Appraisal of This Study and Older Systematic Reviews Using the AMSTAR-2.0 Tool

Author	Critical Flaws	Noncritical Flaws	Overall Confidence in Results
Locketz et al[7]	4 (item 7; 9; 13; 15)	2 (item 10; 14)	Critically low
Ping et al[8]	3 (item 7; 13; 15)	3 (item 10; 12; 14)	Critically low
Fuzi et al[9]	6 (item 2; 4; 7; 9; 13; 15)	3 (item 5; 6; 10)	Critically low
Khajuria et al—this review	0	0	HIGH

importance of adherence to rigorous research and review standards for credible scientific conclusions.

DISCUSSION

To the best of our knowledge, this systematic review and meta-analysis provides the most methodologically robust and up-to-date assessment of TXA use in rhinoplasty and septoplasty procedures. Our findings confirm that TXA significantly minimizes intraoperative blood loss. These outcomes are consistent with TXA's known antifibrinolytic effects, which have been demonstrated to improve hemostasis and decrease the need for blood transfusions in various procedures, including orthognathic, orthopedic, cardiac, and spinal procedures. This evidence reinforces the value of TXA as an effective adjunct in surgical management, consistent with data from multiple surgical fields.[28–33] Surgeon satisfaction also favored TXA use, echoing the TXA literature from other fields.[34] Our subgroup analyses indicate that although IV and oral TXA administered before or during surgery effectively reduces blood loss, topical application does not show a similar benefit. Notably, based on 2 studies only, the latter finding should be interpreted with caution. First, due to the small sample sizes involved, and also because, although Habibi et al[24] reported significant effects of topical TXA, Goktas et al did not, suggesting that the pooled results might be skewed, raising the probability of a type 2 error (false negative).

Despite the clear benefits of TXA in minimizing blood loss, this review found no significant impact on the duration of procedures. This observation aligns with a prior systematic review,[8] underscoring the need to explore further the complex factors influencing this outcome. As Dolman et al[35] identified, although diminished bleeding can improve visibility within the surgical field, this may not necessarily lead to reduced surgery times if other procedural aspects inherently constrain efficiency improvements. In standardized procedures such as inguinal hernia repair, where surgical steps are well defined, bleeding typically prolongs the operation time, yet in procedures such as rhinoplasty where various techniques are used, bleeding may influence the decision-making process of the surgeon, leading them to opt for less invasive approaches, which, surprisingly, may result in a shortened duration of the procedure. This underlines the complexity of surgical efficiency, highlighting that they are influenced by multiple variables beyond mere reduction in blood loss.

Statistical heterogeneity identified across studies regarding surgery duration and surgeon satisfaction highlights inherent challenges in the facial plastic surgery literature. These variations suggest that a range of factors, such as surgical techniques and patient characteristics, might influence the effectiveness and impact of TXA. For instance, Sakakallioğlu et al administered 1 g of TXA every 8 hours for 5 days, stopping 2 hours before surgery, whereas Beikaei et al administered a single intravenous bolus right after the induction of anesthesia. Despite using a random-effects model to address this variability and provide more conservative effect measures, the diverse approaches in clinical practice highlight the necessity for more uniform research methodologies and TXA administration protocols to determine its true benefits accurately.

This meta-analysis provides valuable insights into the use of TXA in septoplasty and rhinoplasty, showcasing several strengths that enhance its credibility and relevance. The study stands out for its methodological rigor, which includes an extensive literature search, strict inclusion criteria, and detailed statistical evaluations. The AMSTAR-2

tool also identifies our systematic review as the most methodologically robust in the available literature. We have addressed critical flaws found in other studies, such as justifying the exclusion of studies at the screening stage, using a robust tool for RoB assessment, considering the impact of any bias in results interpretation, and evaluating methodological quality. Additionally, we addressed noncritical flaws such as reporting funding sources and discussing heterogeneity of results. A notable feature of this study is that all referenced studies are RCTs, with either double or triple blinding, all of which were rated as level 1 according to the American Society of Plastic Surgeons Rating Levels of Evidence and Grading Recommendations for Therapeutic Studies.[36] Additionally, this review's inclusion of studies spanning diverse ethnic, cultural, and healthcare contexts underscores the universal effectiveness of TXA. This meticulous approach ensures the relevance and reliability of the included studies and significantly contributes to the existing knowledge regarding TXA's utility in nasal surgery.

Although this meta-analysis provides valuable insights, limitations exist due to small sample sizes and variations in TXA dosing and administration methods. These variations potentially lead to overestimations of efficacy and complicate the assessment of publication bias risk. However, these variations reflect real-world clinical practice, enhancing generalizability. Despite a rigorous methodology, divergent study protocols necessitate cautious interpretation of our findings. Heterogeneity across studies underscores the need for future research to adopt standardized protocols, harmonizing dosages, and administration methods to delineate TXA's optimal application in facial plastic surgery. Another limitation of this review is the absence of data to draw conclusions regarding the efficacy of TXA in reducing ecchymoses and edema, which are secondary but important outcomes of its use. Addressing this gap in future studies could provide a more comprehensive understanding of TXA's benefits in surgical settings.

Future research should focus on identifying the optimal regimen for TXA application in rhinoplasty and septoplasty, considering the appropriate dosing, timing, and administration methods tailored to the unique requirements of these procedures. A deeper understanding of the pharmacokinetics and pharmacodynamics of TXA in the context of facial surgery will be essential for enhancing its clinical utility. Moreover, although existing studies predominantly evaluate some short-term outcomes, there is a significant need to explore the impact of TXA on ecchymoses and edema, as well as the long-term effects of TXA on nasal surgery, including its influence on recovery periods. Additionally, broadening the research to encompass patient-centered outcomes such as postoperative recovery experiences, pain levels, and overall patient satisfaction will provide a comprehensive understanding of the actual benefits of TXA in surgical settings. A final consideration for future research is to investigate the rate of occurrence of wound healing complications in rhinoplasty and septoplasty using locally administered TXA, as this is an area that has not been thoroughly explored in the literature previously and has raised concerns, particularly given a recently published case series by Yalamanchili et al.[37]

CONCLUSIONS

In conclusion, this review confirms TXA's effectiveness, particularly in IV and oral formulations, in reducing perioperative bleeding in rhinoplasty and septoplasty, enhancing surgeon satisfaction as a valuable surgical adjunct. These findings strengthen the growing evidence base for TXA's utility. Comprehensive multicenter trials with standardized methodologies are crucial for informing evidence-based clinical practice and shaping policy in facial plastic surgery.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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