Efficacy of Tranexamic Acid on Operative Bleeding in Endoscopic Sinus Surgery: A Meta-analysis and Systematic Review

Do Hyun Kim, MD, PhD; Subin Kim, MD; Haram Kang, MD; Ho Jun Jin, MD; Se Hwan Hwang, MD, PhD

Objectives: Tranexamic acid might help control bleeding during surgery because of antifibrinolytic characteristics. We aimed to evaluate the effectiveness of systemic tranexamic acid compared to control in blood loss, operative time, and surgical field and incidence of postoperative emesis and thromboembolism in endoscopic sinus surgery.

Methods: Two authors independently searched six databases (PubMed, SCOPUS, Embase, the Web of Science, Google Scholar, and the Cochrane database) from their inception to July 2018. The included studies compared perioperative tranexamic acid administration (treatment group) with a placebo, and the outcomes of interest were intraoperative morbidities, including surgical time, operative bleeding, and hypotension; postoperative morbidities such as nausea and vomiting; and coagulation profiles.

Results: Seven studies comprising 562 participants were reviewed in this study. Operative time (standardized mean difference (SMD) = −0.60; 95% confidence interval (CI) [−0.93, −0.29]) and intraoperative blood loss (SMD = −0.66; 95% CI [−0.86, −0.46]) were statistically lower in the treatment group than placebo group; and the quality of the surgical field (SMD = −0.80; 95% CI [−1.12; −0.48]) and surgeon satisfaction (SMD = 1.74; 95% CI [1.36; 2.13]) were statistically higher in the treatment group than the placebo group. By contrast, there were no significant differences in the hemodynamic (SMD = 0.08; 95% CI [−0.20; 0.37]) and coagulation profiles (SMD = −0.18; 95% CI [−0.42, 0.07]) of the two groups. Additionally, tranexamic acid had no significant effect on emetic or thrombotic events compared to placebo.

Conclusion: This meta-analysis showed that the systemic administration of tranexamic acid could decrease operative time and blood loss intraoperatively, increasing the satisfaction of surgeons. It did not provoke intraoperative hemodynamic instability, postoperative emetic events, or coagulation profile abnormality. Only a small number of studies were enrolled, so further trials are needed to confirm the results of this study.

Key Words: Tranexamic acid, endoscopic sinus surgery, operative bleeding, operative time, systematic review, meta-analysis.

INTRODUCTION

Because nasal bleeding during endoscopic sinus surgery can cause difficulties in maintaining and managing the airway, general anesthesia is preferred for most patients undergoing nasal surgeries. However, it has been assumed that general anesthesia could cause increased intraoperative bleeding during surgery by lowering capillary resistance. Impairment of intraoperative visibility due to bleeding is also a problem in endoscopic sinus surgery. Bleeding can lead to difficulty in identifying important anatomic landmarks and structures, which can increase the risk of intraoperative complications, prolonging the operating time, and result in incomplete surgery. Multiple methods can be used to reduce intraoperative blood loss and improve visualization of the operative field, including induced hypotension and the use of various anesthetic and vasoconstrictive agents.

Tranexamic acid is an antifibrinolytic drug that can be administered to decrease intraoperative bleeding. In the clotting cascade, tranexamic acid acts as a competitive binder at the lysine site on plasminogen. This prevents fibrinolysis and stabilizes blood clots, potentially reducing further bleeding. The results of several recent studies about the administration of tranexamic acid in endoscopic sinus surgery are encouraging. However, although tranexamic acid is usually well tolerated and is generally considered safe at the usual dosage, nausea and
vomiting are known to be the most common side effects, and hypotension has been observed when it is administered rapidly intravenous. Therefore, it would be necessary to evaluate the favorable effect or adverse effect of tranexamic acid in nasal surgery. Additionally, the incidence of postoperative nausea and vomiting (PONV) after nasal surgery has been reported to be 34% to 65% in various studies, which would be higher than 20% to 30% of incidence of PONV in all surgical patients after general anesthesia. In particular, because the nose and paranasal sinuses are highly vascularized structures, operations involving these regions may cause significant bleeding. Intraoperative hemorrhage could deteriorate the surgical field and increase operative time due to the need for multiple pauses during the surgery for suctioning and packing. Given that sinus surgery continues to be a popular operation and that intraoperative morbidities (bleeding, operative time, and surgeon’s satisfaction) and postoperative nausea and vomiting are the considerable morbidities of nasal surgery, it is important for clinicians to follow effective practices that decrease those morbidities.

We hypothesized that preoperative systemic administration of tranexamic acid could improve the intraoperative blood loss and surgical field quality and reduced operative time without significant adverse effects (postoperative nausea and vomiting and thromboembolism events) in adult patients during based on the previous trials. This study aimed to evaluate the effectiveness of preoperative systemic tranexamic acid in comparison to control in improvement of blood loss, operative time, and surgical field, as well as incidence of postoperative nausea and vomiting and thrombotic accidents within postoperative 24 hours among adult patients undergoing endoscopic sinus surgery in randomized controlled studies written in English and published until July of 2018. Surgeon’s satisfaction with the surgical field, hemodynamic instability, and coagulation profiles were also compared as a secondary outcome.

MATERIALS AND METHODS

Search Strategy and Selection of Studies
An electronic database search (PubMed, SCOPUS, Google scholar, Embase, and the Cochrane Register of Controlled Trials) using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was conducted with the goal of identifying all available studies related to an preoperative tranexamic acid from inception of application of tranexamic acid and written in English up to July of 2018. Two authors independently conducted the literature search using the search terms “endoscopic sinus surgery,” “tranexamic acid,” “general anesthesia,” “operative bleeding,” “surgical field,” “operative time,” “satisfaction,” “nausea and vomiting,” “thromboembolism,” and “hypotension.” We complemented the keyword-based searches by the combinations of all possible keywords with hand-screening of references listed in the retrieved articles.

The full texts of studies that were potentially relevant to the topic were obtained if a decision for inclusion could not be made from the abstract alone. Randomized controlled trials that met the following inclusion criteria were eligible for review: the trials studied adult patients receiving endoscopic sinus surgery with the preoperative (before the start of the operation) or perioperative (during the surgery) administration of intravenous tranexamic acid. Studies were excluded if, in addition to sinus surgery, patients underwent procedures, such as turbinate surgery or adenoidectomy, or if multiple reports were based on the same trial data. In cases with missing or incomplete data, attempts were made to obtain further details directly from the authors. Studies were excluded from the analysis if the outcomes of interest were not clearly reported with quantifiable data or if it was not possible to extract and calculate the appropriate data from the published results (Fig. 1).

Data Extraction and Risk of Bias Assessment
Data from eligible studies were extracted using standardized forms and were independently checked by the two reviewers. Outcomes measured were operative time, intraoperative blood loss, surgical field score, surgeon’s satisfaction, intraoperative blood pressure, postoperative coagulation profiles, and the occurrence of postoperative

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**Fig. 1.** Diagram of the study selection process.
nausea and vomiting\textsuperscript{7,8,15,16,18} and thrombotic accidents\textsuperscript{7,8,15,18} (incidence or percentage of patients). These outcomes were compared between the treatment group, which received preoperative (before the start of the operation) or perioperative (during the surgery) intravenous administration of tranexamic acid, and the control group, which received saline administration or the use of another drug.

From the studies marked for inclusion, we abstracted data regarding patient number, grading scale used, intra- and postoperative outcomes, incidence or percentage of adverse effects, and the \( P \) value recorded for the comparison between the treatment group and the control group. The risk of bias for each study was evaluated using the Cochrane risk of bias tool.

**Statistical Analysis**

The meta-analysis of selected studies was performed with R 3.4.3 version statistical software (R Foundation for Statistical Computing, Vienna, Austria). When original data were expressed as continuous variables, the meta-analysis was performed using the standardized mean difference (SMD).\textsuperscript{14} This value suggests that a larger effect size (SMD) indicates that a treatment is more clinically effective. Regarding common cutoff values for SMD, the tranexamic acid effect was considered small when the SMD was smaller than 0.4, moderate mean that effect size is between 0.4 and 0.7, and large when it was larger than 0.7.\textsuperscript{20,21} This method was chosen to calculate effect sizes due to the absence of a standardized scale for use across all studies to assess surgical time, intraoperative blood loss, surgical field score, surgeon’s satisfaction, intraoperative blood pressure, and postoperative coagulation profiles.\textsuperscript{12} In all other cases, the outcomes of the incidence analysis were performed using the odds ratio (OR).\textsuperscript{14} A funnel plot and Egger test were used simultaneously to detect publication bias. Additionally, the Duval and Tweedie trim-and-fill method was used to adjust for missing studies and to correct the overall effect size according to publication bias.\textsuperscript{14} Heterogeneity across enrolled studies was calculated with the \( I^2 \) test: \( I^2 > 50\% \) indicated significant heterogeneity between studies and prevented reliance on a combination of the study results. In these cases, the random-effects model was used to generate pooled effects. Those outcomes that did not present a significant level of heterogeneity (\( I^2 < 50 \)) were analyzed with the fixed-effects model.\textsuperscript{22} Sensitivity analyses were performed to estimate the influence of each study on the overall meta-analysis results.\textsuperscript{14}

**RESULTS**

Seven studies comprising 562 participants were reviewed in this study. The results of the bias assessment and study characteristics were described in Table I. The risk of bias for each study based on the Cochrane risk of bias tool was presented in Table II. Publication bias was not assessed because the number of trials included was insufficient to properly assess a funnel plot or perform more advanced regression-based assessments.

**Administration of Tranexamic Acid Versus Control for Intraoperative Outcomes**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Sample Size</th>
<th>Timing of infusion</th>
<th>Comparison</th>
<th>Outcome Measure Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chhapola (2011)\textsuperscript{6}</td>
<td>100</td>
<td>Before the start of the operation (preoperative)</td>
<td>Single bolus dose of tranexamic acid 10 mg/kg intravenously in 100 mL normal saline over 10 minutes vs. ethamsylate</td>
<td>Operative bleeding Surgical field quality</td>
</tr>
<tr>
<td>Dongare (2018)\textsuperscript{7}</td>
<td>60</td>
<td>Before the start of the operation (preoperative)</td>
<td>Single slow bolus dose of tranexamic acid 15 mg/kg intravenously vs. saline</td>
<td>Operative time Operative bleeding Surgical field quality</td>
</tr>
<tr>
<td>Shale (2015)\textsuperscript{15}</td>
<td>60</td>
<td>Before the start of the operation (preoperative)</td>
<td>Single bolus dose of tranexamic acid 10 mg/kg intravenously in 100 mL normal saline over 10 minutes vs. saline</td>
<td>Operative time Operative bleeding Surgical field quality</td>
</tr>
<tr>
<td>Nuhi (2015)\textsuperscript{18}</td>
<td>170</td>
<td>Before the start of the operation (preoperative)</td>
<td>Single bolus dose of tranexamic acid 15 mg/kg intravenously vs. saline</td>
<td>Operative bleeding Intraoperative blood pressure</td>
</tr>
<tr>
<td>Langille (2013)\textsuperscript{16}</td>
<td>28</td>
<td>Before the start of the operation (preoperative) and during the surgery (perioperative)</td>
<td>Tranexamic acid bolus (15 mg/kg) followed by infusion (1 mg/kg/hr) throughout the operation vs. saline</td>
<td>Operative time Operative bleeding Surgical field quality</td>
</tr>
<tr>
<td>Alimian (2011)\textsuperscript{8}</td>
<td>84</td>
<td>Before the start of the operation (preoperative)</td>
<td>Single bolus dose of tranexamic acid 10 mg/kg intravenously vs. saline</td>
<td>Operative time Operative bleeding Surgical field quality</td>
</tr>
<tr>
<td>Moice (2010)\textsuperscript{19}</td>
<td>60</td>
<td>Before the start of the operation (preoperative)</td>
<td>Single bolus dose of tranexamic acid 10 mg/kg intravenously vs. saline</td>
<td>Operative bleeding Adverse effect (postoperative nausea and vomiting)</td>
</tr>
</tbody>
</table>

PT = prothrombin time; PTT = partial thromboplastin time.
difference between the groups in intraoperative blood pressure (SMD = 0.08; 95% CI [-0.20; 0.37], I² = 0.00%). There was no significant interstudy heterogeneity (I² < 50) in the overall outcomes (Fig. 2).

**Administration of Tranexamic Acid Versus Control for Postoperative Adverse Effects**

The incidence of postoperative nausea and vomiting (OR = 0.89; 95% CI [0.44; 1.80], I² = 0.00%) and thrombotic accident (OR = 0.91; 95% CI [0.13; 6.57], I² = 0.00%) showed no significant differences between the groups. There was no significant interstudy heterogeneity (I² < 50) in the overall outcomes (Fig. 3).

Platelet count (SMD = -0.18; 95% CI [-0.42, 0.07], I² = 0.00%), prothrombin time (SMD = 0.16; 95% CI [-0.19, 0.50], I² = 48.36%), and partial thromboplastin time (SMD = -0.17; 95% CI [-0.62, 0.27], I² = 66.92%) showed no significant differences between the groups. There was no significant interstudy heterogeneity (I² < 50) in the overall outcomes except for partial thromboplastin time (Fig. 4).

**Sensitivity Analyses**

Sensitivity analyses evaluated the differences in the pooled estimates by repeating the meta-analyses with a different study omitted each time. All results were consistent with the outcomes given above.

**DISCUSSION**

In this meta-analysis looking at the efficacy of preoperative tranexamic acid in the operative time and surgical field related to the operative bleeding in the adult patients with endoscopic sinus surgery, we found that the operative time, intraoperative blood loss, and surgical field score in the tranexamic acid group were significantly improved compared to control group. In addition, tranexamic acid did not induce the significant adverse effects such as postoperative nausea and vomiting and thrombotic accidents compared to controls. These primary outcomes of this study presented that preoperative tranexamic acid had the beneficial effect on the related operative morbidities as well as operative time without the significant adverse effects. In secondary outcomes, surgeons were more satisfied with the surgical field in tranexamic acid group than control, and there were no significant difference in hemodynamic instability and coagulation profiles between two groups. Therefore, it can be concluded that the preoperative administration of tranexamic acid can have a substantial favorable effect on operative bleeding during endoscopic sinus surgery.

The activation of fibrinolysis during and after surgery is known to be related to surgical trauma, blood loss, consumption of coagulation factors and platelets, administration of crystalloid-like fluid during and after surgery, hypothermia, and more. This phenomenon can induce considerable blood loss and decrease surgical field visibility, which also increases the operative time. Tranexamic acid is a synthetic derivative of the amino acid lysine that blocks the lysine-binding sites of plasminogen, inhibiting plasminogen activation and fibrin binding to plasminogen and therefore impairing fibrinolysis. Several investigations have been conducted to establish the efficacy of tranexamic acid in endoscopic sinus surgery. A previous systematic review that pooled data from those studies documented that tranexamic acid decreased intraoperative blood loss and improved the quality of the operative field for endoscopic sinus surgery.

However, that review by Pundir et al. had significant methodologic problems. It enrolled five studies to maximize the number of studies, but the authors pooled the data irrespective of the method of application. Among the five enrolled studies, three studies evaluated the efficacy of systemic administration, and two studies measured the effect of topical application. Additionally, Athanasiadis et al. enrolled 10 patients, divided the two nostrils of each single patient into two groups—one study nostril and one control nostril—and then considered themselves to have to enrolled 20 patients. By contrast, the other studies enrolled study group patients and control group patients separately. The heterogeneity of administration and patient enrollment thus complicated the previous meta-analysis and could cause its results to be untrustworthy. Furthermore, tranexamic acid can have adverse hemodynamic effects, including intraoperative hypotension and postoperative emesis and coagulation profile changes. The previous meta-analysis evaluated only the incidence of emesis and thromboembolic events.
Fig. 2. Perioperative tranexamic acid versus control. Standard mean difference of operative time (A), intraoperative blood loss (B), surgical field score (C), surgeon’s satisfaction with the surgical field (D), and intraoperative blood pressure (E). CI = confidence interval.
Fig. 3. Perioperative tranexamic acid versus control. Odds ratio of the incidence of postoperative nausea and vomiting (A) and thrombotic accidents (B). CI = confidence interval.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Odd ratio Fixed, 95% CI</th>
<th>Odd ratio Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dongare (2018)</td>
<td>30</td>
<td>30</td>
<td>3.2% 1.00 (0.02, 52.00)</td>
<td></td>
</tr>
<tr>
<td>Shale (2015)</td>
<td>30</td>
<td>30</td>
<td>19.7% 1.38 (0.28, 6.80)</td>
<td></td>
</tr>
<tr>
<td>Nuhi (2015)</td>
<td>100</td>
<td>70</td>
<td>46.3% 0.51 (0.18, 1.44)</td>
<td></td>
</tr>
<tr>
<td>Alliman (2011)</td>
<td>42</td>
<td>42</td>
<td>27.6% 1.58 (0.41, 6.08)</td>
<td></td>
</tr>
<tr>
<td>Mörse (2010)</td>
<td>30</td>
<td>30</td>
<td>3.2% 1.00 (0.02, 52.00)</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 232 202 100% 0.89 (0.44, 1.80)

Heterogeneity: Q(df = 4) = 2.1094, p = 0.7156, I² = 0.00%

Test for overall effect: Z = -0.3301 (p = 0.7390)

Fig. 4. Perioperative tranexamic acid versus control. Standard mean difference of platelet count (A), prothrombin time (B), and partial thromboplastin time (C). CI = confidence interval.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Std. Mean Difference Fixed, 95% CI</th>
<th>Std. Mean Difference Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dongare (2018)</td>
<td>30</td>
<td>30</td>
<td>24.9% 1.00 (0.02, 52.08)</td>
<td></td>
</tr>
<tr>
<td>Shale (2015)</td>
<td>30</td>
<td>30</td>
<td>24.9% 1.00 (0.02, 52.09)</td>
<td></td>
</tr>
<tr>
<td>Nuhi (2015)</td>
<td>100</td>
<td>70</td>
<td>25.2% 0.70 (0.04, 36.63)</td>
<td></td>
</tr>
<tr>
<td>Alliman (2011)</td>
<td>42</td>
<td>42</td>
<td>25.0% 1.00 (0.02, 51.60)</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 202 172 100% 0.91 (0.13, 6.57)

Heterogeneity: Q(df = 3) = 0.0234, p = 0.9990, I² = 0.00%

Test for overall effect: Z = -0.0886 (p = 0.9285)
Also, since publication of the previous meta-analysis, additional studies have been published.\textsuperscript{7,9,11,12} Therefore, our current meta-analysis is needed.

The effective dose of tranexamic acid is 10 to 15 mg/kg by intravenous infusion, with one or two further doses given at 3-hour intervals, if necessary.\textsuperscript{9} A total dose of 1 g was reported to be enough for most adults, and doses larger than 1 g did not produce hemostatic benefit.\textsuperscript{23} By contrast, a dose lower than 10 mg/kg seemed to be less effective or ineffective for intraoperative bleeding.\textsuperscript{26} Therefore, we included studies with narrow inclusion criteria: preoperative (before the start of the operation) or perioperative (during the surgery) systemic administration methods and 10 mg/kg or 15 mg/kg doses for sinus surgeries under general anesthesia. We considered various effects, such as the surgeon’s satisfaction, intraoperative hypotension, and coagulation profiles, in our comparison between the tranexamic acid and control groups.

Our results show that intraoperative bleeding was statistically decreased in the treatment (tranexamic acid) group compared with the placebo group. Intraoperative hemorrhage control is one of the most important factors for improving the surgical field to ensure a successful operation. Due to the narrow operative field of the nasal cavity, even slight bleeding can distort the view of the endoscope and increase the occurrence of important structure injuries, cause the surgery to take longer, or even result in inconclusive surgery.\textsuperscript{27} The previous meta-analysis demonstrated that topical or systemic tranexamic acid decreases intraoperative bleeding and enhances surgical field quality,\textsuperscript{24} similar to our results. Reasonably, improvement in the quality of the surgical field correlated with the surgeon’s satisfaction. The operative time was also significantly decreased in the treatment group. Intraoperative bleeding increases the operative time because it creates the need for multiple pauses during surgery for suctioning and packing,\textsuperscript{28,29} which could explain that result. The previous meta-analysis demonstrated that operative time tended to decrease with the use of tranexamic acid compared to controls but without statistical significance, which was different from our result. Pundir et al.\textsuperscript{24} commented that the statistical insignificance was most likely caused by the small sample size that reported that outcome, only two randomized controlled trials (RCTs) with 102 patients. By contrast, we enrolled four RCTs with 232 patients for operative time, which might explain the discrepancy.

The most common adverse effects of tranexamic acid are gastrointestinal, including postoperative nausea and vomiting, but the incidence of those effects was low. With intravenous administration, a rapid bolus injection can cause significant hypotension.\textsuperscript{30} In this study, intraoperative blood pressure and the incidence of postoperative emesis showed no significant difference between the treatment group and the control group. Many studies have suggested that up to 15 mg/kg by intravenous infusion can be recommended in surgical procedures,\textsuperscript{9} and the adverse effects of tranexamic acid are dose-dependent and uncommon at that recommended dose.\textsuperscript{23} The studies enrolled here adopted safe administration protocols, such as a dose of 10 to 15 mg/kg and slow injection.

Despite the safety and tolerance of tranexamic acid, the risk of thromboembolic phenomena has traditionally caused concerns about its use; however, recent studies have suggested that tranexamic acid does not significantly increase the risk of thromboembolism compared to untreated controls.\textsuperscript{31,32} In our meta-analysis, this agent did not induce thromboembolism at all. The coagulation profiles in the treatment group did not differ from those in the control group, which supports the incidence results in our study and is similar with previous results.\textsuperscript{32} The previous studies found a possible association between very high or prolonged doses of tranexamic acid and thromboembolic accidents,\textsuperscript{33} but pre- or perioperative administration with a bolus dose between 10 and 20 mg/kg can be used safely.\textsuperscript{31,32}

In this study, we used I\textsuperscript{2} to measure the degree of heterogeneity among studies. As a result, our study showed that there was no significant interstudy heterogeneity (I\textsuperscript{2} < 50) in the most of outcomes except for partial thromboplastin time. However, despite no statistical heterogeneity between studies, in the practical points there could be some difference between studies of various factors, such as patient characteristics or demographic factors, surgeon skill, intra- and postoperative care, and facility capacity. Because this analysis is performed based on the statistical measurements of the figures, these external factors such as polyps versus no polyps, revision versus primary, and usage of other hemostatic agents could not be considered and reflected in the analysis, which could be the inevitable limitation. Considering these limitations, a large-sample, randomized, controlled clinical study should be performed to provide further evidence on the efficacy of the preoperative administration of tranexamic acid in endoscopic sinus surgery.

Based on our results, the perioperative administration of tranexamic acid could provide positive effects on intraoperative bleeding, the surgical field, and operative time in patients undergoing endoscopic sinus surgery. Compared with controls, it has similar side effects on postoperative emesis, and no incidence of thromboembolism was reported in the enrolled studies. However, considering the number of enrolled studies, further clinical trials are needed to confirm our results.

**CONCLUSION**

This meta-analysis showed that a slow bolus administration of tranexamic acid at a dose of 10 to 15 mg/kg could decrease intraoperative bleeding and operative time and improve surgical field visibility without adverse effects such as nausea and vomiting or thromboembolism. The agent did not induce significant changes in the coagulation profiles. Because of the small number of enrolled studies, however, further clinical trials are needed to confirm those results.

**Acknowledgment**

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