Intravenous tranexamic acid and intraoperative visualization during functional endoscopic sinus surgery: a double-blind randomized controlled trial

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Background: **Bleeding during endoscopic sinus surgery (ESS) can hinder surgical progress and may be associated with increased complications. Tranexamic acid is an antifibrinolytic that is known to reduce operative bleeding. The current study was designed to assess the effect of adjunctive intravenous tranexamic acid on intraoperative bleeding and the quality of the surgical field during ESS.**

Methods: **Double-blind, randomized, controlled trial. Patients undergoing ESS for the primary diagnosis of chronic rhinosinusitis with or without polyposis were included. Sample size calculation based on a clinically relevant difference in the Wormald surgical field score yielded a sample of 28. In addition to standard measures to minimize blood loss, study patients received intravenous tranexamic acid with control patients receiving intravenous normal saline. Outcome measures included the Wormald grading scale to assess the intraoperative surgical field and estimated blood loss based on suction container contents with irrigation fluid subtracted.**

Results: **Twenty-eight patients (median age, 45 years; range, 23–80 years) were included in the study. Diagnoses included chronic rhinosinusitis without polyposis (n = 5), chronic rhinosinusitis with polyposis (n = 23). The use of the tranexamic acid was not associated with a statistically significant decrease in estimated blood loss (201 vs 231 mL; $p = 0.60$) or Wormald grading scale (5.84 vs 5.80; $p = 0.93$). There were no adverse events or complications during the study.**

Conclusion: **Adjunctive intravenous tranexamic acid does not appear to result in a clinically meaningful reduction in blood loss or improve visualization of the surgical field during ESS.** © 2012 ARS-AAOA, LLC.

Key Words:
endoscopic surgical procedures; hemorrhage; sinusitis; tranexamic acid; surgical blood loss

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Functional endoscopic sinus surgery (FESS) is frequently used in the treatment of recalcitrant chronic rhinosinusitis (CRS) and chronic rhinosinusitis with polyposis (CRSwP). Excessive bleeding and the consequent reduction in intraoperative visualization can hinder surgical progress. In an effort to reduce bleeding and thus improve visualization many surgeons use techniques such as hypotensive anesthesia or total intravenous anesthesia (TIVA),[1] elevation of the head of the bed during surgery, and administration of local vasoconstrictors.

Tranexamic acid is a medication that can be administered topically or intravenously. In the clotting cascade, it serves to stabilize the fibrin clot[2] and reduces overall bleeding. Tranexamic acid has been used extensively in certain surgical procedures and has been shown to limit bleeding with no increase in adverse events. In coronary artery bypass graft surgery, tranexamic acid was shown to reduce bleeding and the need for blood transfusions.[3] A review of using tranexamic acid in orthopedic surgery has shown it to be safe and decreases perioperative blood loss.[4] For nasal bleeding, tranexamic acid has been suggested to

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reduce the frequency of epistaxis in patients with hereditary hemorrhagic telangiectasia.[5] Furthermore, it improves hemostasis and improves the surgical field when administered topically.[6] However, the topical gel would impair visualization of the underlying structures during ESS. Topical tranexamic acid can only be effectively applied at the conclusion of the operation and would not serve to reduce bleeding during the surgery when visualization is necessary.

The goal of the current study is to determine if the adjunctive measure of intravenous tranexamic acid has any effect on intraoperative visualization and bleeding during ESS.

Patients and methods

Inclusion and exclusion criteria

Patients who had failed medical management for the diagnosis of CRS or CRSwP and were thus undergoing ESS (bilateral complete sphenoethmoidectomies) were eligible for the study. The patients in this study represent a single-surgeon series from a tertiary care center. Patients were excluded from the study if they had a history of hypertension, renal failure, or vascular disease, or if they were American Society of Anesthesiologists (ASA) class III or greater. Patients undergoing any additional surgical procedures such as a septoplasty were also excluded. Health Research Ethics Board (HREB Protocol #00005621) approval and a Health Canada no objection letter was obtained prior to patient enrolment. The study was registered with clinicaltrials.gov on September 15, 2009. Informed written consent was obtained from all participants.

Sample size calculation

Sample size calculation was based on a clinically relevant reduction in surgical field bleeding with the intranasal use of tranexamic acid.[6] This previous work utilized the Wormald grading scale (Table 1) to assess the operative field.[7] For the purpose of the current study, a difference of 1 on the Wormald scale was deemed clinically relevant. The calculation determined that 28 participants total (14 in the tranexamic acid arm and 14 in the placebo arm) would be required for a study with a power of 0.80 and an alpha of 0.05 set for significance.

Statistical analysis

Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Fisher's exact test. A level of significance was considered at $p < 0.05$. Analyses were performed with SPSS Statistics 19.0 (SPSS Inc, Chicago, IL).

Study design

Our design was that of a double-blind, randomized, placebo-controlled trial with block randomization used to ensure an even distribution of treatment allotment. Only 1 study investigator (A.C.) knew the randomization and was responsible for preparing tranexamic acid solution or normal saline solution. This investigator was not involved in data extraction or analysis. The randomization scheme was not revealed until data had been collected from all patients. The tranexamic acid or normal saline solutions were prepared in 100 mL normal saline intravenous bags so that they appeared indistinguishable to the case anesthesiologist and operating surgeon. The experimental group received tranexamic acid bolus (15 mg/kg) then infusion (1 mg/kg/hour) for the duration of the operation. The control group received the equivalent volume of normal saline.

TABLE 1. The Wormald grading scale[7]

Grade	Assessment
1	No bleeding
2	1–2 points of ooze
3	3–4 points of ooze
4	5–6 points of ooze
5	7–8 points of ooze
6	9–10 points of ooze (sphenoid fills in 60 seconds)
7	Mild bleeding/oozing from entire surgical surface with slow accumulation of blood in postnasal space (sphenoid fills in 40 seconds)
8	Moderate bleeding from entire surgical surface with moderate accumulation of blood in postnasal space (sphenoid fills in 30 seconds)
9	Moderately severe bleeding with rapid accumulation of blood in postnasal space (sphenoid fills in 20 seconds)
10	Severe bleeding with nasal cavity filling rapidly (sphenoid fills in <10 seconds)

All patients received inhalational anesthetic, end-tidal CO_2 was maintained between 30 and 35 mmHg, the head of bed was elevated 15 degrees, and mean arterial pressure was maintained between 60 and 70 mmHg. All patients underwent decongestion of the nasal mucosa, initially with oxymetazoline and subsequently with nasal pledgets soaked in 1:1000 epinephrine. A bilateral intranasal injection was performed in the region of the sphenopalatine artery with 1% lidocaine with 1:100,000 epinephrine. The surgery was then carried out in a standard fashion using intraoperative image guidance, mucosal sparing technique, and a combination of through-cutting instrumentation and microdebrider (Medtronic, Minneapolis, MN).

The primary outcome measure was the Wormald grading scale. This scale requires an endoscopic video of each patient as described.[6] Videos were viewed independently by 2 investigators (E.D.W., L.J.S.) who assigned a Wormald grade for each side of each patient (Fig. 1). Secondary outcome measures included the Peri-Operative Sinus Endoscopy (POSE) score,[8] Lund-Kennedy endoscopic score (assigned on the 1 week postoperative follow-up visit), and total estimated blood loss as calculated by measuring

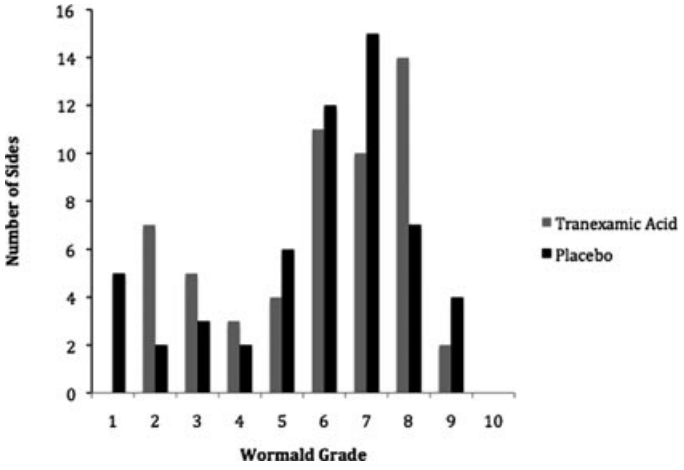

FIGURE 1. Surgical field visualization of the tranexamic acid group vs the placebo group using the Wormald grading scale.

TABLE 2. Intraoperative variables between patients undergoing functional endoscopic sinus surgery for TXA and placebo groups*

Variable	Group 1 (TXA)	Group 2 (Control)	*p*
Sample size (n)	14	14	–
Age (years)	43.5, 13.6 (28–78)	50.0, 16.5 (23–80)	0.55
Males/females	10/4	7/7	0.44
MAP (mmHg)	66.7. 5.4 (55–73)	66.3, 6.2 (58–75)	0.77
$ETCO_2$ (mmHg)	33.0, 1.5 (31–36)	33.2, 2.2 (31–38)	0.98
MAC	1.2, 0.2 (0.97–1.5)	1.26, 0.3 (0.85–2.0)	0.18

[a]Data are reported as: median, standard deviation (range).
$ETCO_2$ = mean end-tidal CO_2 (intraoperatively); MAC = mean minimal alveolar concentration; MAP = mean arterial pressure (intraoperatively); TXA = tranexamic acid.

suction container contents with irrigation fluid subtracted. Data was also collected regarding preoperative acetylsalicylic acid (ASA) and oral steroid use.

Results

Twenty-eight patients were enrolled between March 2010 and November 2011. Fourteen patients were enrolled in the tranexamic acid group and 14 were enrolled in the normal saline group. Diagnoses included CRS without polyposis (n = 5) and CRSwNP (n = 23). Table 2 shows the intraoperative variables between groups. The median age of all participants was 45 (range, 23–80), with 17 males and 11 females. There were no statistically significant differences in age between the study and control groups ($p = 0.55$). No patients in either group used ASA preoperatively. There was no difference in preoperative oral steroid use between groups ($p = 0.32$). There was no difference between groups with respect to the mean arterial pressure ($p = 0.77$) and end-tidal CO_2 ($p = 0.98$). Table 3 shows the outcome comparison between groups. The Lund-Mackay

TABLE 3. Outcome comparison between patients undergoing functional endoscopic sinus surgery for TXA and placebo groups*

Outcome	Group 1 (TXA)	Group 2 (Control)	*p*
Wormald Scale score[a]	5.8, 1.9 (2.5–8.5)	5.8, 2.0 (1–8)	0.89
Lund and Mackay score[a]	11, 1.9 (7.5–12)	10, 2.7 (2.5–12)	0.85
Preoperative POSE score[a]	13, 3.4 (3–15)	13.5, 4 (6–17)	0.24
Postoperative POSE score[a]	5.5, 1.5 (4–7.5)	6.5, 1.3 (6–8.5)	0.13
EBL (mL)	115, 173 (30–600)	200, 112 (100–400)	0.40
OR time (minutes)	121.5, 24.2 (63–152)	131.5, 26.3 (83–177)	0.14

*Data are reported as: median, standard deviation (range).
[a]Scores are reported as an average between left and right sides.
EBL = estimated blood loss; OR = operating room; POSE = Perioperative Sinus Endoscopy; TXA = tranexamic acid.

radiologic grading scores were equivalent for both groups ($p = 0.85$). The POSE scores are shown in Table 3. The preoperative and postoperative POSE score showed no difference between groups. There was no difference in surgical time between groups ($p = 0.14$).

There was no statistically significant difference ($p = 0.89$) between groups in terms of surgical field visualization as measured by the Wormald grading scale with mean values of 5.84 vs 5.80 for the tranexamic acid and normal saline groups, respectively. There was no difference between groups in terms of estimated blood loss (201 vs 231 mL mean blood loss in tranexamic acid and normal saline groups, respectively; $p = 0.40$).

All surgical procedures were completed and there was no limitation of surgical progress by bleeding in any of the cases. There were no operative complications and all patients were discharged home the same day of surgery.

Discussion

Blood loss during ESS can present a challenge to surgeons, particularly in cases of massive polyposis or in patients with hypertension. Surgeons and anesthetists have developed several methods to minimize blood loss during surgery such as preparing the nose with local vasoconstrictors, use of hypotensive anesthesia, and elevating the head of the bed during surgery. Despite these measures, surgeons may still encounter cases in which bleeding may hinder surgical progress. Poor visualization during sinus surgery could theoretically lead to misidentification of structures and result in complications or incomplete surgery. Surgeons have an interest in decreasing bleeding during surgery and tranexamic acid has a proven benefit in other surgical procedures. The current study was developed to determine if tranexamic acid had any impact on intraoperative bleeding or visualization.

The current study employed strict inclusion and exclusion criteria to ensure a homogeneous population. Patients

with hypertension were excluded to ensure that a standardized anesthetic protocol could be maintained to eliminate intraoperative blood pressure as a confounding variable. The strict inclusion criteria led to a relatively long enrolment period, which is a potential weakness of this study. A recent work[9] found an improvement of the surgical field using the Boezaart grading scale[10] and a nonvalidated surgeon satisfaction scale. For this referenced study a smaller dose of tranexamic acid (10 mg/kg bolus with no ongoing infusion) was used. The populations of the present study and the referenced study are similar in that both patient groups were treated for CRS. In the referenced study, however, they did not use any topical vasoconstrictors nor did they use a microdebrider—thus their study cannot be applied to standard practice in North America. The current study was designed to assess if tranexamic acid is useful as an adjunct with standard ESS and this work has shown that it is not useful for the purpose of reducing bleeding or improving surgical visualization.

Previous studies that have shown a difference in bleeding with tranexamic acid have looked at cardiac and orthopedic surgical procedures with large volumes of blood loss.[3,4] The blood loss itself during ESS is generally not a major consideration, averaging less than 400 mL in the vast majority of cases; rather it is the surgical field visualization that is of greater importance for sinus surgeons. There is a good rationale regarding the use of tranexamic acid during ESS. Any medication or protocol that decreases bleeding may help to increase intraoperative visualization and help with surgical progression and allow for a more complete surgical procedure. Tranexamic acid is generally a safe medication[11] and there were no adverse events associated with its use in our study. However, the current work has employed a rigorous study design and has shown that intravenous tranexamic acid offers no benefit as an adjunctive measure during ESS. As such, we would not recommend its routine use in ESS. However, based on other studies it may have a role in select cases wherein intraoperative visualization presents significant challenges.

Conclusion

Used as an adjunct to standard perioperative techniques, tranexamic acid does not improve intraoperative visualization or result in a clinically meaningful difference in blood loss during ESS for the treatment of CRS or CRSwP.

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