

Outcomes of large dose Tranexamic acid in endoscopic sinus surgery for chronic sinusitis with sinonasal polyposis

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Background: Bleeding is a major obstacle that faces the nasal endoscopist. The aim of this study was to evaluate the efficacy and safety of large dose tranexamic acid (TA) in endoscopic sinus surgery (ESS) for chronic sinusitis with sinonasal polyposis.

Patients and Methods: In a double-blinded, prospective, controlled study, 60 patients aged 20-50 years were randomly divided into two equal groups. The intervention group received (40 mg/kg) TA at induction of anesthesia followed by continuous infusion at a rate of 1mg/kg/hr. for the whole duration of surgery. The control group received an equivalent amount of saline as a placebo. The amount of blood loss, operative time, surgical field quality and complications were reported.

Results: TA group showed a significant reduction in intraoperative blood loss, improvement of quality of surgical field and less operative time.

Conclusion: Large dose of TA is safe and effective. It has a positive impact on reduction of blood loss, operative time and on surgical field quality without increased risk of complications.

Keywords: Tranexamic acid, Endoscopic sinus surgery, bleeding, chronic rhinosinusitis with sinonasal polyposis.

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Introduction

Endoscopic sinus surgery (ESS) has become the standard surgical modality used for treatment of chronic sinusitis. [1] Bleeding during ESS is a frequently encountered problem that affects the course and outcome of surgery. Bleeding impairs clarity of surgical field and increases the rate of complications. Also, bleeding may increase the duration of surgery which may affect the general condition of patients especially patients with associated co-morbidities. [2,3]

Many methods have been employed to minimize bleeding and to improve visualization during ESS. These techniques include: the use of local vasoconstrictors, elevation of patient head, administration of drugs that decrease systemic blood pressure or heart rate and bipolar cauterization. [4] However, other alternative measures are required; as, none of these methods can alone control bleeding and provide satisfactory surgical field. Of these alternatives is the use of Tranexamic acid (TA). [5]

TA is a synthetic analogue of amino acid lysine. TA exerts its antifibrinolytic action through the reversible block of lysine binding sites on plasminogen molecule. When tissue damage occurs as a result of any surgical procedure, damaged tissues release enzymes such as 'tissue plasminogen activator'. Tissue plasminogen activator converts plasminogen to plasmin and fibrinolysis process is activated. TA prevents fibrinolysis through inhibition of the activity of this enzyme. Many studies have reported the efficacy of TA in achieving hemostasis and improving the surgical field quality in orthopedic and cardiothoracic surgery with minimal or no side effects. [5,6]

In the field of otorhinolaryngology, some studies proved the beneficial effects of topical and systemic TA in controlling blood loss and obtaining satisfactory operative field. Up till now, the extent to which TA can reduce surgical bleeding and

its relationship with the dose of TA remains unclear. [7] The aim of the current study was to evaluate efficacy and safety of large dose of TA on reduction of blood loss, operative time and clarity of surgical field in ESS for CRS with sinonasal polyposis.

Material and Methods

The current study was conducted after being approved by the university ethics committee and an informed written consent was obtained from all patients. The study was conducted as a double-blind, randomized clinical trial at the ENT department, Beni Suef university hospital. The study populations consisted of 60 patients complaining of CRS with sinonasal polyposis not responding to medical treatment and were candidates for endoscopic sinus surgery during the period from February 2016 to June 2017.

Patients were randomly divided into 2 equal groups (30 patients in each group). The intervention group received TA 40 mg as a bolus dose at induction of anesthesia followed by continuous infusion at a rate of 1mg/kg/hr. for the rest of surgical procedure. The control group received an equal amount of normal saline as a placebo.

Patients were enrolled if they had the following criteria: (a) Patients with CRS with sinonasal polyposis (b) Age of 18 to 50 years (c) Hemoglobin >10mg/dl (d) Normal coagulation profile. Patients with the following criteria were excluded: (a) Patients with CRS without sinonasal polyposis (b) patients with any other nasal disease rather than CRS (c) Previous sinus or nasal surgery (d) Having blood diseases or coagulopathy (e) Patients with hepatic or renal disorders (f) Patients with systemic comorbidities (g) Patients using anti-coagulants or NSAID (h) Allergy to Tranexamic Acid (i) Color blindness.

Operative procedures

All patients received oral corticosteroid for 10 days before surgery to reduce inflammation and lessen intraoperative bleeding. All operations were done under general inhalational anesthesia. The anesthesia protocol was the same in both groups. All patients were operated on by the same surgical and anesthesia team. The surgical steps were fixed in all patients. After induction of anesthesia, TA and normal saline solutions were prepared by an anesthesiologist not involved in the study protocol. The anesthesiologist in charge and operating surgeon were not aware of injected drug as the drug is colorless. The intervention group received TA bolus (40 mg/kg) then continuous infusion at a rate of (1 mg/kg/hr.) for the duration of surgery. The control group received an equal amount of normal saline.

Before start of surgery, a throat pack was inserted to prevent blood transferring to the gastrointestinal tract. Head-up position at level of 30 degrees. All patients underwent decongestion of the nasal mucosa by local infiltration of 1ml of epinephrine (1:200,000) in the middle turbinate, inferior turbinate and agar nasi area. This is followed by application of nasal pledges soaked in epinephrine (1:200,000) in the whole nasal cavity.

The surgery was then carried out in the following sequence. At first, microdebrider was used to clear polyps from both nasal cavities. After that, Anterior and posterior ethmoidectomy, middle meatal antrostomy, sphenoid sinusotomy and frontal sinusotomy were done using cutting forceps and grabbing instruments.

Primary outcome measures were: (a) Intraoperative blood loss which was estimated by calculating the collected blood in a graded suction chamber and reducing the amount of saline used for washing. The throat pack and nasal pledges used during surgery were weighted and converted in to ml and added to blood loss according to Al Kadri. [8] (b) Operative time was recorded from induction to extubation. (c) Quality of surgical field was assessed every 15 minutes from the start of surgery based on Boezart's scale [9] (**Table1**) with a scale from 0 to five. Secondary outcome measures were nausea, vomiting, impaired color vision within 24 hrs. after surgery. All patients were packed with Merozell for 24 h. patients were monitored for surgical complications and drug side effects as nausea, vomiting, thromboembolic complications, fever or convulsions and data were recorded.

Table 1 Surgical Field Quality Based on Boezart's scale. [9]

Grade	Assessment
No bleeding, cadaveric conditions	0
Slight bleeding, no suction required	1
Slight bleeding, occasional suctioning required	2
Slight bleeding, frequent suctioning required	3
Bleeding threatens surgical field few seconds after suction is removed.	
Moderate bleeding, frequent suctioning required	4
Bleeding that threatens surgical field directly after suction is removed	
Severe bleeding, constant suctioning required	5
Bleeding appears faster than can be removed by the suction; surgical field severely threatened and surgery usually not possible	

Table 2 Demographic data, duration of surgery and blood loss for both groups

	(TA group) (n= 30)	(control group) (n= 30)	P value
Age (years)	35.97±13.53	37.40±12.38	0.670
Sex (male/female)	16/14	22/8	0.090
Net blood loss(ml)	155.50 + 64.93	276.50+ 63.44	<0.001
Operative time(min)	41.77+9.03	54.93+11.46	<0.001

Data are presented as means and standard deviation.

Table 3 Quality of surgical field according to Boezart scale

Quality of Surgical Field	Group A	Group B	Total	P value
Grade 1	2 (6.7%)	0 (0.0%)	2	<0.001
Grade 2	13 (43.3%)	0 (0.0%)	13	
Grade 3	11 (36.7%)	9 (30.0%)	20	
Grade 4	4 (13.3%)	16 (53.3%)	20	
Grade 5	0 (0.0%)	5 (16.7%)	5	

Data were expressed as number of patients and percentages.

Statistical analysis

Calculation of sample size was done using the operative field bleeding score as the main variable. The calculation determined 30 patients in each group. Statistical analysis of the collected data was performed using SPSS version 20 (SPSS, Inc., Chicago, IL, USA). Quantitative data were presented as mean and SD and were analyzed by using one-way analysis of variance test. Qualitative data was presented as numbers and percentages and were analyzed using χ^2 -test and Fisher's exact test. P-value less than 0.05 was considered significant.

Results

A total of 60 patients scheduled for ESS complaining of CRS with sinonasal polyposis were included in the study between February 2016 and June 2017. Demographic data, Operative time and net blood loss are shown in **(Table 2)**. There was no significant difference between groups as regards to demographic data ($P > 0.05$).

Table 2 showed significant differences between groups A and B as regard intraoperative blood loss. The mean amount of blood loss during surgery was 155.50 ± 64.93 ml for group A and 276.50 ± 63.44 ml for group B with a p value < 0.001 . The duration of surgery was significantly less in TA group (41.77 ± 9.03 min.) compared to the control group (54.93 ± 11.46 min).

Based on Boezaart's scale, the quality of the surgical field showed significant difference between TA and control groups **(Table 3)**. The majority of patients in the intervention group (80%) were in grade 2 and 3 while; the majority of the patients in the control group (83.3%) were in grade 3 and 4. Furthermore, no patients in the control group were in grade 1 and 2 while, 14 patients in the intervention group were in grade 1 and 2 (46.7%). No patient in the intervention group was in grade 5, while 5 patients in the control group were in grade 5.

Early postoperative nausea was reported in 10% of intervention group and 5 % of control group, showing no significant differences between both groups. There were no other side effects of TA reported as vomiting, confusion, or thromboembolic events and there were no surgical complications in both groups. All surgical procedures were completed and there was no need to stop surgical progress in all cases.

Discussion

Bleeding during ESS is the main surgical challenge for all nasal endoscopyists. It may slow progress of surgery, increase rate of complications or it may result in stop of the procedure. Meanwhile, better visualization of the operative field is mandatory to achieve the goals of surgery and to avoid complications. [2,13]

Although the amount of blood loss in ESS is not that extensive as in cardiac, gynecologic and orthopedic surgery, any minimal bleeding impairs visualization and hence, increases the incidence of complications and prolongs operative time. [1,2,4]

Many tools were advocated to minimize intraoperative bleeding and to improve visibility of the surgical field. The commonly used methods are hypotensive anesthesia, local vasoconstrictors, bipolar cauterization, elevation of the head of the bed and the use of anti fibrinolytics. [8]

TA is a synthetic lysine analogue. It binds to lysine binding sites on plasminogen and inhibits binding to fibrin, thus blocks the process of fibrinolysis. TA proved efficacy in

orthopedic and cardiothoracic surgery. The current study was designed to examine the safety and efficacy of using large dose TA in ESS for CRS with sinonasal polyposis, as regard intraoperative blood loss, operative time and quality of surgical field. [9]

In our study, there was a significant decrease in intraoperative bleed loss, significant improvement in surgical field quality, and reduction in operative time in TA group compared to placebo group.

In the field of otorhinolaryngology, the role of intravenous TA in controlling blood loss during ESS is controversial. Some authors proved the beneficial effect of TA, while others see that it has no benefits.

Our results are in agreement with the results of Moise et al., [10] who conducted a study in 2009 on 60 patients candidates for ESS. The study group received 10 mg/kg TA and the control group received normal saline. Intraoperative and postoperative blood loss was decreased up to 50% in the group received TA.

In 2011, the results of Moise et al. were verified by Alimian and Mohseni. [11] They conducted a study on 84 patients undergoing ESS and evaluated the effects of TA (10 mg/kg) on hemorrhage and surgical field quality. They found that intravenous TA effectively improved blood loss (184 ± 64 mL in TA group compared to 312 ± 75 mL in control group) and the surgeon was more satisfied with the surgical field than the placebo group.

Other studies were not in agreement with our study. In 2010 Mottaghi et al. [12] conducted a study on 50 patients undergoing ESS. 25 patients in the study group received 500mg of intravenous TA and the control group received normal saline. There was no significant difference between both groups as regards intraoperative bleeding and surgeon satisfaction scores.

In 2013 Langille et al. [13] published similar poor results. 28 patients with the diagnosis of CRS were enrolled in his study. 14 patients were in the TA group and 14 were in the saline group. The intervention group received TA bolus (15 mg/kg) then infusion (1 mg/kg/hr.) for the duration of the operation. The control group received the equivalent volume of normal saline. The use of TA was not associated with statistically significant decrease in overall blood loss (201 vs 231 mL; $p = 0.60$) or significant improvement in surgical field quality according to Wormald grading scale (5.84 vs 5.80; $p = 0.93$).

The possible explanations for poor results obtained by some authors may be the relatively small sample size in the intervention groups (25 patients in the study of Mottaghi et al. and 14 patients in the study of Langille et al.).

Another possible explanation may be attributed to the dose regimen of TA. In the field of otorhinolaryngology, most publications that used TA in ESS used relatively small doses ranging between 5 and 25mg/kg. In our study we used a large dose of TA (40mg/kg followed by continuous infusion at a rate of 1mg/kg/hr.) as it is usually used in cardiac and orthopedic surgery. [2,3]

Most literatures that investigated TA in ESS addressed patients with a variable diagnoses. In our study, we targeted patient complaining of allergic sinonasal polyposis. Patient with CRS without polyps, antochoanal polyps, sinonasal tumors or any other nasal lesions were excluded. We wanted to avoid the effect of variations in pathology on outcomes and duration of surgery.

Postoperative nausea was greater in the intervention group than in the control group, but the difference was not significant ($P>0.05$). No significant difference was found between the TA groups and the saline group as regard the occurrence of thromboembolic events.

The main limitation of the present study is the limited number of patients. Other studies with a larger scale of patients are needed to confirm our results. In conclusion, using large doses of TA in ESS for sinonasal polyposis is safe and effective. Its use resulted in reduction of intraoperative bleed loss, operative time and improvement of surgeon satisfaction with the surgical field. Also, the use of large dose of TA was well tolerated by patients and was not associated with increased risk of side effects of TA. We recommend that TA should be added to the routinely used drugs to control bleeding during ESS.

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