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Endoscopic Sinus Surgery Perioperative Outcomes after Intravenous Tranexamic Acid: A Double Blind Randomized Controlled Trial

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ABSTRACT

Objective: To determine the effect of a single intravenous dose of tranexamic acid on intraoperative bleeding, duration of surgery and surgical field visualization during endoscopic sinus surgery.

Methods:

Design: Double-Blind, Randomized, Placebo-Controlled Trial

Setting: Tertiary Government Hospital

Participants: 10 patients aged 18-75 years old diagnosed with chronic rhinosinusitis with or without nasal polyposis and unresponsive to medical treatment, who underwent endoscopic sinus surgery from September 2016 to August 2017, were randomly allocated to treatment group and control group, respectively. The "odd" numbers were assigned to the treatment group (intravenous Tranexamic acid) given 1 dose of 100mg/ml (500mg tranexamic acid per 5 ml) tranexamic acid slow intravenous drip 1 hour prior to the procedure, while the "even" numbers assigned to the control group received the same amount of normal saline solution.

Results: The mean duration of surgery of the tranexamic group was 185 minutes (standard deviation, SD 55.23) and the control group was 122.6 minutes (SD 42.03) showing no significant difference (p=.08). The mean blood loss of the tranexamic group was less at 240ml (SD 108.39) compared with the control group at 290ml (SD 74.16), although there was no statistically significant difference (p=.42). Intra-operative surgical field assessed by the surgeon based on the Boezart grading scale showed that 2 (40%) of the tranexamic group had higher bleeding score compared with the placebo group. However, this was not found to be statistically significant (p=.460). Due to the small sample size, a type II error occurred with alpha level of 0.05 and estimated power of 0.0885, with not enough basis to refute that a single dose of intravenous tranexamic acid has no effect in improving surgical field visualization during endoscopic sinus surgery. No drug side effects were noted after administration until after surgery.

Conclusion: Single dose intravenous tranexamic acid in functional endoscopic sinus surgery decreased mean intraoperative blood loss (but this was statistically insignificant) but its effect on surgical field visualization cannot totally be assessed due to small sample size. There was also no change in the observed duration of surgery. No untoward side effects associated were noted from administration of the drug until after the surgery finished.

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Endoscopic sinus surgery (ESS) aims to restore mucociliary function by reestablishing physiologic sinus ventilation and drainage by relieving obstruction in the osteomeatal complex.[1] The most common intraoperative problem encountered in ESS is bleeding in the surgical field making visualization and identification of landmarks difficult.[2] It may also prolong operative time, increase the risk of complications and create difficulty in completing the surgery.[3] It will be beneficial for the surgeon to determine if the use of intravenous tranexamic acid alone would be enough to lessen bleeding and improve surgical field visualization in endoscopic sinus surgery with no known increase in any adverse events thus lessening surgical morbidities. This paper aims to determine the effect of a single intravenous dose of tranexamic acid on intraoperative bleeding and duration of surgery during endoscopic sinus surgery and determine whether the effect of single intravenous dose of tranexamic acid could improve surgical field visualization or would offer no benefit at all during endoscopic sinus surgery.

METHODS

This double-blind, randomized, placebo-controlled trial was performed at a tertiary government hospital from September 2016 to August 2017 with Institutional Review Board and Ethics Committee approval (study protocol code QMMC HEC GCS 2016-022). All patients were voluntarily enrolled and signed a written informed consent.

All patients seen at the Otorhinolaryngology-Head and Neck Surgery Outpatient Department were considered for inclusion in the study if they were between 18-75 years old and had chronic rhinosinusitis with or without nasal polyposis unresponsive to treatment. Excluded were those with cardiovascular disease, renal disease, bleeding diathesis and anemia, history of previous endoscopic sinus surgery and those receiving anticoagulants.

A target population of 12 patients, 6 each in the treatment and control group was computed based on the study of Nuhi S., *et al.*[4] using the result of X_1 107.7 and X_2 189.3 with standard deviation of S_1 45.1 and S_2 51 with 5% margin of error and power of 80%. *(Figure 1)* A total of 14 patients diagnosed with chronic rhinosinusitis with nasal polyposis were enrolled in the study, however 4 from the 14 patients enrolled were discovered to have history of previous ESS hence were excluded. The 10 remaining patients were randomized using simple random sampling. They were asked to pick a folded paper with written number from a bowl. Those who picked the paper with "odd" numbers were assigned to the treatment group (intravenous tranexamic acid) who would receive 1 dose of 100mg/ml (500mg tranexamic acid per 5 ml) tranexamic acid thru slow intravenous (I.V.) drip 1 hour prior to the procedure, while the "even" numbers were assigned to the control group receiving the same amount of normal saline solution, resulting in a total of 5 patients each in the treatment and control group. *(Figure 2)*

Intervention

A complete history and physical examination were obtained from all participants. Vital signs (blood pressure, respiratory rate and cardiac rate) were recorded after admission and patients > 35-years-old underwent cardiopulmonary clearance. A complete blood count,

where: Z_α, Z_β = corresponds to α and β errors
S_1, S_2 = estimate of the variance or standard deviations from previous study for group 1 and group 2
μ_1, μ_2 = means for groups 1 and 2

$$n = \frac{(Z_\alpha+Z_\beta)^2 (S_1^2+S_2^2)}{(\mu_1-\mu_2)^2}$$

$$n = \frac{(0.05+0.2)^2 (45.1^2+51^2)}{(107.7-189.3)^2}$$

$$n = \frac{0.25\ (4095.01)}{81.6}$$

$$n = 12$$

$$n_1 = 6 \quad n_2 = 6$$

Figure 1. Sample Size Computation (based on two sample comparison of means)

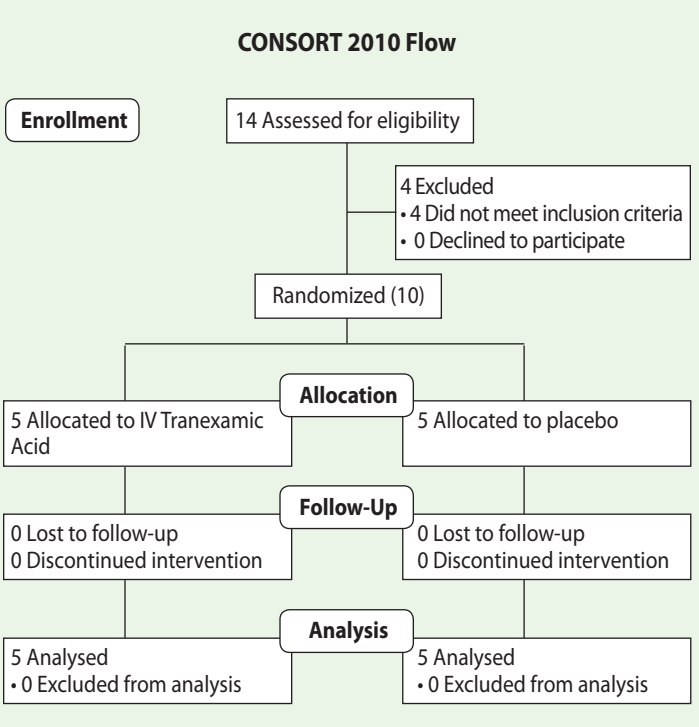

Figure 2. Flow diagram of the progress through the phases of the randomized trial of the two groups.

prothrombin time and partial thromboplastin time were obtained prior to surgery.

The tranexamic group received 1 dose of 100mg/ml (500mg of tranexamic acid per 5 ml) tranexamic acid I.V. through slow drip 1 hour prior to the procedure, while the control group received the same amount of normal saline solution prepared by only 1 person. The surgeons and anesthesiologists were blinded to treatment allocation.

All surgeries were performed under general endotracheal anesthesia using Sevoflurane and venoclysed with lactated Ringer solution. Nasal mucosa was decongested with nasal strips soaked in 1:100,000 epinephrine after induction of anesthesia, prior to surgery. Only 1 surgeon and 1 assist performed all the procedures with different anesthesiologists using the same anesthesia drugs. Vital signs were continually monitored during the surgery and recorded. Duration of the surgery was recorded by the circulating nurse, blood loss was estimated by the anesthesiologist after surgery and the surgeon answered the Boezart grading scale[5] in assessing and grading the surgical field. Complete blood count, prothrombin time and partial thromboplastin time were repeated 6 hours after surgery. Only one person who was not included in the surgery prepared the medications, collated and tabulated all data.

Data Analysis

Demographic variables were assessed using the Pearson chi-square test and 2 sample t-test and described using means and standard deviation. Differences between pre- and post-operative analysis of the treatment and control group were assessed using paired t-test with 95% confidence interval and <0.05 level of significance and Wilcoxon rank sum test and bleeding score was assessed using Fischer exact test. STATA 10.1 (StataCorp., Texas, USA) was used for statistics and data analysis. Testing of null hypothesis was done using the two-tailed test with alpha value of 0.05.

RESULTS

A total of 10 patients, 2 females and 8 males aged 30-62 years old (median age 52.5 years old and mean age of 51.6 years old) participated in the study, with 5 patients (1 female and 4 males each) randomly allocated to the tranexamic group and to the control group, respectively. *(Figure 2)* The mean (SD) age of the tranexamic group aged 44 - 62 years old and control group aged 30-62 years old was 53.8 (8.01) and 49.4 (13.37) respectively, with no significant age difference between groups (p>.05). *(Table 1)*

There were no significant differences between the tranexamic acid and control groups in preoperative and postoperative vital signs (blood pressure, cardiac rate and respiratory rate) *(Table 2)* as well as in pre- and post-operative hemoglobin, hematocrit, platelet count, prothrombin time and partial thromboplastin time. *(Table 3)*

Table 1. Demographic Data measurements in the two groups

Variable	Tranexamic Acid Group n=5	Placebo Group n=5	*p*-value
Gender:			.78
Male N;(SD)	4(80)	4(80)	
Female N;SD)	1(20)	1(20)	
Age (years)	53.8(8.01)	49.4(13.37)	.55

Data is presented as mean (standard deviation)

There was no significant difference in mean duration of surgery for the tranexamic group at 185 minutes (SD 55.23) compared to 122.6 minutes (SD 42.03) for the control group (p=.08). *(Table 4)* There was less mean blood loss in the tranexamic group at 240ml (SD 108.39) compared with the control group at 290ml (SD 74.16), but there was no statistically significant difference (p=.42). *(Table 4)* Intra-operative surgical field grading noted slight bleeding requiring occasional suctioning in 40% of the tranexamic acid group and control group, slight bleeding requiring frequent suctioning in 20% of the tranexamic group and 60% of the control group, and moderate bleeding requiring frequent suctioning in 40% of the tranexamic group and none of the control group *(Table 5)*. Two or 40% of the tranexamic group had higher bleeding scores compared with the placebo group but this was not statistically significant (Fischer exact test p-value = .46). Based on the Boezaart grading scale grades 1 to 3, only 60% (p_1=.60) of the tranexamic group showed less bleeding in the intraoperative surgical field while 100% (p_2=1) of the control group showed the same effect in improving the surgical field. Due to the small sample size gathered, a type II error was obtained with an alpha level of 0.05 and an estimated power of 0.0885 suggesting that there is not enough basis to reject the null hypothesis that a single dose of intravenous tranexamic acid has no effect in improving surgical field visualization during endoscopic sinus surgery.

No adverse effects such as vomiting, diarrhea, malaise, dizziness, convulsion, hypotension or any signs of thromboembolic events were noted from administration of the drug until after surgery.

DISCUSSION

Our findings suggest that single dose intravenous tranexamic acid in functional endoscopic sinus surgery may decrease mean intraoperative blood loss (though statistically insignificant), but its effect on surgical

Table 2. Difference between preoperative and postoperative hemodynamic measurements in the two groups

Variable	No	Mean	SD	Median	iQr	*df*	*t value*	*p*- value*
Systolic Blood Pressure (mmHg)								
Tranexamic acid group	5	-2	8.37	0	10	4	-0.53	.62
Placebo Group	5	-8	10.95	-10	0	4	-1.63	.18
Diastolic Blood Pressure (mmHg)								
Tranexamic acid group	5	2	8.37	0	10	4	0.53	.62
Placebo Group	5	0	12.25	0	10	4	0	1
Respiratory Rate (cycles/min)								
Tranexamic acid group	5	0.2	3.35	-1	2	4	.13	.90
Placebo Group	5	-6.4	7.83	-3	4	3	-2.78	.07
Cardiac Rate (beats/min)								
Tranexamic acid group	5	-0.6	12.30	-2	11	4	-0.10	.92
Placebo Group	5	6.4	18.56	14	16	4	.77	.48

**Paired t-test used in determining difference between two groups*

Table 3. Difference between preoperative and postoperative coagulation factors in the two groups

Variable	No	Mean	SD	Median n	iQr	*df*	*t value*	*p-value**	*z score*	*p-value#*
Hematocrit (vol%)									1.89	.06
Tranexamic acid group	5	-0.02	0.04	-0.04	0.06	4	-1.04	.36		
Placebo Group	5	-0.07	0.05	-0.07	0.01	4	-3.03	.04		
Hemoglobin (g/L)									1.57	.11
Tranexamic acid group	5	-8	12.19	-14	10	4	-1.47	.22		
Placebo Group	5	-18.6	13.97	-21	5	4	-2.98	.04		
Platelet count(x109/L)									1.36	.17
Tranexamic acid group	5	-11	21.71	-23	31	4	-1.13	.32		
Placebo Group	5	-36	22.52	-37	32	4	-3.58	.02		
Prothrombin time (secs)									-0.84	.40
Tranexamic acid group	5	-0.30	2.35	0.5	1.1	4	-0.29	.79		
Placebo Group	5	0.96	1.20	1.2	0.7	4	1.79	.15		
Partial Thromboplastin Time (secs)									-1.57	.12
Tranexamic acid group	5	-3.94	1.95	-3.8	1.4	4	-4.52	.01		
Placebo Group	5	-1.74	2.14	-2.3	2.3	4	-1.82	.14		

**Paired t-test used in determining difference between two groups*
#Wilcoxon Rank Sum Test used in determining difference between two groups

Table 4. Outcome Measurements in the two groups

Variable	No	Mean	SD	Median n	iQr	*df*	*t value*	*p-value**	*z score*	*p-value#*
Duration of bleeding (mins)						8	2.01	.08	.67	.50
Tranexamic acid group	5	185	55.23	150	90					
Placebo Group	5	122.6	42.03	120	55					
Blood loss (ml)						8	-0.85	.42	-0.96	.34
Tranexamic acid group	5	240	108.39	200	150					
Placebo Group	5	290	74.16	300	50					

**Paired t-test used in determining difference between two groups*
#Wilcoxon Rank Sum Test used in determining difference between two groups

Table 5. Bleeding score between the two groups

Bleeding score (N;%)	Tranexamic Group N;(%)	Placebo Group N;(%)
1	0	0
2	2 (40)	2 (40)
3	1 (20)	3 (60)
4	2 (40)	0
5	0	0

field visualization cannot totally be assessed due to small sample size. There was also no change in the observed duration of surgery.

According to Alimian *et al.*, "several techniques have been suggested to improve the surgical field in sinus surgery however none of them consistently provided a desirable bloodless field for surgeons and unwanted side effects were also noted such as local tissue damage and subsequent bleeding due to the use of bipolar diathermy, hemodynamic instability especially in patients with hypertension or ischemic heart disease due to the use of topical vasoconstrictors and exposing patients to more anesthetic drugs in inducing hypotension leading to more side effects."[4] According to a meta-analysis that reviewed different articles in assessing the effectiveness of intravenous tranexamic acid in endoscopic sinus surgery, intravenous tranexamic acid reduced blood loss and shortened surgical time in endoscopic sinus surgery among patients with chronic rhinosinusitis.[2] However, the additional benefit of tranexamic acid for better field visualization was not clear.[2] This study was undertaken to determine the effect of single IV dose of tranexamic acid in optimizing surgical field visualization without producing any unwanted side effects.

In this study, the use of single dose of IV tranexamic dose in endoscopic sinus surgery decreased mean intraoperative blood loss however insignificantly but its effect on surgical field visualization could not be assessed due to the small sample size. There was also no effect observed on shortening the duration of surgery. The findings were independent from demographic factors or hemodynamic variables. All surgeries were performed by only 1 surgeon and 1 assist and only one person, not included in the surgery, was in charge of the medications and data to be collated to prevent biases.

Tranexamic acid is "a synthetic antifibrinolytic agent that blocks the lysine-binding site of plasminogen, plasmin and tissue plasminogen activator which prevents their association with fibrin hence reducing bleeding."[6] Previous studies[6,7] have already confirmed the favorable effect of tranexamic acid on bleeding tendency in major operations such as patients undergoing cardiac, major orthopaedic transplantation, and prostate surgeries as well as the efficacy of topical and oral forms of tranexamic acid in achieving hemostasis and improving the surgical field in functional endoscopic sinus surgery. Two previous studies to determine the efficacy of intravenous tranexamic acid in functional endoscopic sinus surgery showed favorable effects.[7,8]

Adverse effects of tranexamic acid are rare and include nausea, vomiting, diarrhea, allergic dermatitis, dizziness, hypotension, seizures, impaired vision and achromatopsia (impaired color vision) which are also usually elicited by rapid intravenous infusion.[7] Although the drug might theoretically increase the risk of thromboembolism, a systematic review conducted by Shakur *et al.* regarding the use of tranexamic acid in surgery did not show any statistically significant increase in the risks of any of the thromboembolic events nor kidney failure assessed.[9] During the course of this study, there were no untoward adverse effects associated with the use of the drug noted from administration until the surgery finished.

This study is limited by the small sample size obtained due to the short time span allotted. We recommend that this study be continued

for a longer time frame to be able to produce a larger sample size and validate the preliminary results reported in this study, as well as reflect the overall population of patients undergoing endoscopic sinus surgery. We also recommend that the sizes and grading of nasal polyps be considered as they can also affect bleeding and intraoperative visualization of the surgical field.

In conclusion, without achieving statistical significance, single dose intravenous tranexamic acid in functional endoscopic sinus surgery may decrease mean intraoperative blood loss but not duration of surgery. However, its effect on surgical field visualization cannot totally be assessed due to small sample size.

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