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Intrauterine Instillation of Tranexamic Acid in Hysteroscopic Myomectomy: A double blind Placebo Controlled Parallel Groups Randomized Clinical Trial

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Precis: Intrauterine instillation of TXA is recommended during hysteroscopic myomectomy to improve the visual field by reduction in intraoperative bleeding.

Abstract:

Study Objective: To evaluate the hemostatic effect of intrauterine instillation of tranexamic acid with the distention medium during hysteroscopic myomectomy.

Design: Prospective, parallel groups, double-blind, placebo-controlled randomized clinical trial.

Setting: University hospital.

Patients: 80 women with type 0 or 1 submucous myoma undergoing hysteroscopic myomectomy using unipolar resectoscope.

Interventions: The participants were randomly assigned to receive either TXA 1gm for every 1000 ml of the distending medium (intervention group), or 10 ml of placebo (10 ml of 1.5% glycine) in the same form inside every 1000 ml of the distention medium.

Measurements and Main Results: The primary outcome was the change in hemoglobin level 24 hours after the surgery compared to the preoperative values while the secondary outcomes were the surgeon rating of intraoperative bleeding and the quality of operative view, the duration of surgery, the volume of injected media, intraoperative complications and the completion of myomectomy in one procedure. The mean difference in hemoglobin level was 1.11 ± 0.58 gm/dl in TXA group and 1.46 ± 0.61 gm/dl in the placebo group (p value 0.015), Quality of hysteroscopic view was better in TXA group (p value 0.001), with good operative view in 23

(60.5%) of cases in TXA versus 8 (20.5%) in the placebo group, the surgeon rating of bleeding as excessive was reported in one (2.6%) case in TXA group and 9 (23.1%) cases in the placebo group, there was no difference between both groups regarding the duration of surgery, the volume of injected media, completion of myoma resection in one session, and intraoperative complications. 3 cases of uterine perforation with the thermal loop were reported, all were associated with poor operative field in the placebo group.

Conclusion: intrauterine instillation of TXA with the distention medium during hysteroscopic myomectomy resulted in a statistically significant decrease in hemoglobin level reduction 24 hours after the surgery; albeit with minimal clinical significance. TXA resulted in better visualization of the field throughout the procedure.

Keywords: clear hysteroscopic vision**;** distention medium; submucous myoma; tranexamic acid, hemostasis in hysteroscopic myomectomy

Introduction:

Uterine fibroids are the most common benign solid tumours found in the female genital tract; that has been postulated to occur in over 70% of women by the onset of menopause [1].

Fibroids arise from the uterine smooth muscles then migrate to a place of lower resistance becoming subserosal or submucous myomas or remain intramyometrial (intramural myoma) [2].

Submucous myoma usually present with infertility and abnormal uterine bleeding in younger women and hysteroscopic myomectomy is the best minimally invasive therapeutic option. [3]

Successful hysteroscopic myomectomy depends on good visualization throughout the procedure, via the correct distending pressure, continuous irrigation and the use of

electrosurgery to control bleeding [4, 5]. Prolonged procedures that need continuous irrigation under higher pressure are associated with higher risk of excessive fluid absorption and intravasation syndrome due to opened blood vessels within the myometrium. Moreover, the thermal damage of the healthy tissues is increased with the use of the coagulation current. [3, 6]

Tranexamic acid (TXA) inhibits fibrinolysis by blocking the lysine binding site on plasminogen and its topical administration to a bleeding surface as in epistaxis, surgical bleeding sites mainly in orthopaedic surgeries and as a mouthwash in dental surgeries [7-10] have shown to reduce bleeding and transfusion requirement equally to intravenous administration with 90% reduction of plasma concentration. [7, 11, 12]

Decreasing the risk of thromboembolic events with topical administration compared to intravenous route remains controversial. In their meta-analysis; Moskal and Capps found that intravenous TXA increased the risk of deep venous thrombosis, also Emara et al, reported that significant decrease in thromboembolic and cardiovascular complications with topical TXA use. On the other hand others found that it did not differ compared to oral or intravenous route. [13-17] thus, high quality trials are needed to resolve these uncertainties before topical TXA can be recommended for routine use.

The only FDA-approved usage for TXA is for heavy menstrual bleeding and short-term prevention in patients with hemophilia. Topical TXA uses as well as the intrauterine instillation are off label uses of TXA as the manufacturer recommendations limit its administration to slow intravenous injection and oral route; however the only contraindicated routes were intramuscular, Intrathecal and intraventricular injection. [18, 19]

Several authors suggest a 70% reduction in systemic absorption with topical TXA moreover, it is easier to apply, providing a higher therapeutic concentration at the bleeding site, limiting blood

loss with little or no systemic side effects. It is estimated that only a small percentage of the intravenous TXA reaches the target location to inhibit tissue fibrinolysis and stabilise the clot. [20, 21]

Topical TXA concentration varies with different uses; a concentrations of 10–100 mg/mL in total knee arthroplasty was reported, 5% tranexamic acid used as a mouthwash in anticoagulant-treated patients undergoing oral surgery, and patients with traumatic hyphema were treated with tranexamic acid (5%) eye drop.[22- 24]

The aim of the current study was to evaluate the haemostatic effect of intrauterine instillation of TXA in the distention medium during hysteroscopic myomectomy.

Material and methods:

A single-centre, parallel-groups, double-blind RCT was performed between April 2017 and December 2018 at the Early Cancer Detection Unit (ECDU) in Ain Shams University Maternity Hospital, Cairo, Egypt. The study methodology was reviewed and approved by the research ethics committee of Ain Shams University and the research review board of the Department of Obstetrics and Gynaecology prior to participants' enrolment. The trial was registered on clinical trials (ClinicalTrials.gov NCT03122782). The study was conducted and reported in accordance with CONSORT guidelines for reporting randomized clinical trials.

The study population was a consecutive series of 80 women with single sub mucous myoma completely within the endometrial cavity or extend less than 50 percent into the myometrium (type 0, I) according to FIGO classification system [25] and smaller than 4 cm in the largest diameter with myometrial free margin more than 1 cm_underwent hysteroscopic myomectomy in ECDU. Pregnant women and women with active pelvic infection, present or history of cervical or uterine cancer, bleeding diathesis or patient on anticoagulant treatment were excluded from the

study. Moreover, we excluded women with cardiopulmonary, thromboembolic, hepatic, or renal diseases, women with uterine septum or structural uterine abnormality or with any contraindication and /or allergy to medication specified in the treatment protocol.

Before study entry, potentially eligible women were informed about the study by the principal investigator and gave informed written consent.

Randomisation and blinding:

The first 80 eligible women were randomly allocated to receive either TXA (Kapron ® 500mg/5ml (Amoun Pharmaceutical co.) 1gm for every 1000 ml of the distending medium (1.5% glycine OTSUKA EGYPT) (intervention group), while in the control group, 10 ml of placebo (10 ml of 1.5% glycine OTSUKA EGYPT) in the same form was injected inside every 1000ml of the distention medium. Allocation to either one of the two groups was in a 1:1 ratio. Randomization numbers were completed using the computer- generated list of random numbers using the Web site Randomization.com ⟨http://www.randomization.com⟩. An independent statistician not involved in the treatment or data collection was responsible for random allocation of participants to the two groups. The final group assignment was sealed in sequentially numbered opaque envelopes. The principal investigator (Hajer Giuma), participants, and the surgeon performing the procedure (Mortada Elsayed) were all blinded in this trial.

Procedures:

All participants were subjected to a detailed clinical assessment including: a detailed history, general and pelvic examination, transvaginal ultrasound to determine the number, size, location of fibroids, and evaluation of the myometrial free margin that is defined as the minimum thickness between the outer edge of the fibroid and inner edge of the uterine serosa; ideally it

should be at least 1 cm thick [2] Office hysteroscopy was performed with the use of a 2.9-mm telescope with continuous-flow sheath (Hopkins II Telescope 30 degrees; Karl Storz GmbH & Co KB) to assess the fibroid location, its intracavitary portion and to exclude associated uterine pathology. The day before surgery all women were re-evaluated by anaesthesiologist and laboratory investigations including complete blood picture, liver and kidney functions, coagulation profile were ordered. Resectoscopic myomectomies were scheduled in the proliferative phase of menstrual cycle by a single experienced operator (33 women with AUB in the form of heavy menstrual bleeding with regular cycles allowing for standardized surgery scheduling in the proliferative phase). The participant was put in the dorsal lithotomy position and leg stirrups were used. Under general anaesthesia, cervical dilatation with Hegar dilators (usually up to 9 mm) then a 9-mm resectoscope ((Karl Storz GmbH & Co KB Tuttlingen, Germany), equipped with a loop electrode was introduced. With the use of 1.5% glycine at room temperature as a medium of distension, infused with a standard intrauterine pressure of 100 mmHg, automatically controlled using a Hamou Hysteromat (Karl Storz GmbH & Co KB Tuttlingen, Germany) with careful measurement of the inflow and the outflow, and calculation of the deficit (the difference between the total amount of solution pumped into the uterus and the amount of fluid recovered from the suction bottle and the fluid lost through the cervix). A maximum fluid deficit allowed was 1,000 mL before the procedure was interrupted and a second surgery was scheduled. Based on the manufacturer recommended maximal dose for intravenous injection is 1 gm that should not be given more frequent than every 6 to 8 hours and the maximal allowed fluid deficit that could be absorbed in the systemic circulation; so TXA 1 gm in 1000 ml of distention medium was used in this study. According to the manufacturer TXA may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions, dextran solutions as well as with heparin.[19] Limitation of the amount of pre-operative, intraoperative and post-operative intravenous fluids as a preventive method for fluid overload was utilized. After the myoma was localized the resectoscopic loop was

advanced to the distal end of the myoma, the unipolar electrical cutting current (Valleylab SSE2L; Valleylab, Inc., Boulder, CO) which is the only available device in our hospital; was set at 100 watts and activated with the electrode sinks into the myoma and was drawn toward the operator, shaving off a strip of myomatous tissue that floats in the medium. The procedure was repeated till the base of the myoma was level with the surrounding endometrium. Coagulation current was never used in order to reduce thermal damage of the healthy myometrium. The fragments of tissue were removed by withdrawal of the resectoscope from the outer sheath, allowing the shreds to flow out of the cavity, or they were removed by using a polyp forceps. The surgeon was blinded to the substance injected in the distention medium and After completing the procedure, the surgeon completed a record sheet (Supplemental figure) to document estimated blood loss, rating of bleeding (1=minimal, 2= moderate, 3=excessive) [15], and the clarity of visual field using 3 point visual Likert scale as (poor, fair, good).

Several parameters were used to assess the outcome of surgery; the primary outcome was the change in haemoglobin level 24 hours after the surgery completion compared to the preoperative values as a surrogate measure of haemostatic effect, while the secondary outcomes were the surgeon rating of bleeding amount and the quality of operative view, the duration of surgery, the volume of injected media, intraoperative complications and myomectomy completion in one procedure.

Here insert table 1

Although the surgeon rating of bleeding amount and the quality of operative view are subjective methods for assessment; interobserver variability was avoided by performing all the procedures by a single operator.

Statistical methods:

Sample size calculation for repeated measure was calculated using G power 3.1, assuming moderate effect size, power =0.8, α=0.05, and number of measurements=2 for 2 groups; would result in a total sample size of 66. Moreover, according to two previous studies by Sayyah-melli et al. [5] and Wong et al, [26], the proportion of very clear visual field in the control group was 0.250 according to Sayyah-melli et al. [5] so the proportion of clear visual field with TXA use was assumed to be 0.250 under the null hypothesis and 0.716 under the alternative hypothesis. The test statistic used was Chi- squared test using MedCalc 19.0.7. The significance level of the test was targeted at 0.010. The significance level actually achieved by this design was 0 .011 taking into consideration that 20.0% was added to compensate for attrition problem. According to Wong et al, [26] the proportion of minimal blood loss during hysteroscopic myomectomy in the placebo group was.368 so we assumed that TXA can increase this proportion to.70 and reject the null hypothesis, this would require 40 patients in each arm with a power of 80% and the level of significance of .05 taking into consideration that 15.0% was added to compensate for attrition problem.

Statistical analysis:

On the basis of the normality of the data, continuous variables were compared using Student t tests. Categorical data were compared using $\chi 2$ test. A repeated measures ANOVA was used to assess change in hemoglobin concentration following surgery in both groups. Spearsman's correlation coefficient was used to assess factors affecting mean hemoglobin difference. Multiple regression analysis was used to assess independent predictors of mean hemoglobin difference.Two-sided P value < .05 was considered statistically significant. Data were analysed using SPSS © Statistics version 23 (IBM© Corp., Armonk, NY, USA). Odd's ratio, Relative Risk (RR) and Number Need to Treat (NNT) were calculated.

Results:

Between April 2017 and December 2018, 106 women were assessed for eligibility. 25 were ineligible (10 women with multiple fibroids, 7 with type 2 submucous myoma,2 with fibroid larger than 4 cm,2 cardiac patients ,2 women had associated uterine anomaly, 1woman with previous DVT on anticoagulant ,1woman with active cervicitis) and 1 declined to participate in the study. 80 women were randomized to the intervention (n = 40) and the placebo (n = 40) groups; a woman in TXA group lost to follow up, another case with the procedure was abandoned due to equipment malfunction, and one case with incomplete myoma resection; while in the placebo group no women lost to follow up, however 4 cases (1 with incomplete myoma resection and 3 cases with uterine perforation) were excluded from analysis of the postoperative haemoglobin and the duration of the procedure , as perforation is considered the most common reason for excessive bleeding and the procedure was halted immediately while incomplete resection was due to maximum fluid deficit with anticipated excessive blood loss postoperative.

Here insert figure 1

There was no significant difference between the studied groups regarding the baseline demographic and clinical characteristics (table 2).

Here insert table 2

Regarding the haemoglobin concentration; there was no statistically significant difference between both groups preoperative with mean haemoglobin 11.11 ± 1.02 in TXA group versus 10.73 ± .99 in the placebo group with p value 0.11, while the postoperative mean haemoglobin significantly differ between both groups (10.08 ± 1.16 and 9.26 ± .86 in TXA and placebo groups respectively with p=0.001).

The mean haemoglobin difference showed a statistically significant difference between both groups with P value =0.015 albeit with minimal clinical significance. One case showed excessive intraoperative bleeding in TXA group versus 9 cases in the placebo group, none of the cases showed severe bleeding that caused hemodynamic changes or mandated termination of the procedure or blood transfusion (table 2). Using an ANOVA with repeated measures with a Greenhouse-Geisser correction, the mean hemoglobin levels were statistically significantly different ($F(1.00, 77.00) = 210.44$, $p < 0.0001$). Tranexamic acid use elicited a slight elevation of hemoglobin level compared to placebo (10.9 ± 1.01 mg/dL vs 9.7 ±1.11 mg/dL, respectively), (p =0 .000). (Supplemental Table)

Here insert table 2

No statistically significant differences were found between both groups regarding the volume of distention medium utilized, the distention medium deficit and the operative time. Quality of hysteroscopic view was better in TXA group compared to the placebo group with P value <.001. The median operative time did not differ between both groups 20.0 (IQR 15.0 – 25.0) minutes, however the mean operative time significantly decreased with the use of TXA (19.36±6.2 minutes in TXA group versus 28.30 ± 16.23 minutes in the placebo group with P = .002). three cases of uterine perforation occurred in the placebo group for all the procedure was terminated immediately and laparoscopy was done to exclude bowel injury which was found in one case; all perforations were reported to have poor vision of their surgical field (not reaching statistical significance), type 1 myoma, and larger than 3 cm in size.

Here insert table 3

The mean hemoglobin difference significantly correlated with the volume of distention media, the duration of the procedure, the bleeding rating by surgeon, and the quality of operative view

(table 4)

Here insert table 4

A multiple regression was run to predict mean hemoglobin difference from age, myoma size, myoma site, myoma grade, Preoperative hemoglobin and tranexamic acid use. Only the preoperative hemoglobin and tranexamic acid use added statistically significantly to the prediction, p <0 .05. F(6, 47) = 5.41, p =0 .000, R2 = 0.409. (Table 5)

Here insert table 5

In order to evaluate the number needed to be treated with TXA to avoid one excessive bleeding or to obtain good visibility of the operative view the data were collapsed into a 2 X 2 matrix by combining the minimal and moderate bleeding in one category, as well as the fair and poor operative view in one category.

Table 6 showed the measured outcomes registered after the procedures. 60.5% in the treatment group and 20.5% in the control group had had good visual field throughout the procedure, with relative risk 2.95 (95% CI 1.51 to 5.76). The absolute and relative risk reduction was - .40 and -1.95 respectively. The number of women needed to treat was two to obtain one case with good visual field.

Regarding the surgeon rating of bleeding, the surgeon reported that 23.1% in the placebo group and only 2.6% in TXA group had excessive bleeding with relative risk .11(95% CI .015 to .85).The absolute and relative risk reduction was 2.04 and .88 respectively. The number of women needed to treat was five to avoid one case with excessive bleeding.

Here insert table 6

Discussion:

Hysteroscopically directed surgery provides a minimally invasive, simple, well-tolerated method to remove submucous myomas [27], and its success depends mainly on good visualization throughout the procedure, via continuous irrigation under adequate pressure and control of blood loss without increasing the risk of damaging surrounding structures with the use of coagulation current or increasing the intravasation through increasing the distending pressure.

This study is the first double blind randomized placebo-controlled trial to assess the efficacy of intrauterine instillation of TXA in women undergoing hysteroscopic myomectomy. The main finding of our study was that the intrauterine instillation of TXA could decrease the blood loss. Although the postoperative decrease in hemoglobin was statistically significant, its clinical significance is minimal. The subjective finding of surgeon observed blood loss was reported to be less and the visualization throughout the procedure reported to be improved in TXA group, with no reported complications.

The effect of fibroids on the endometrium is global and is transmitted through producing abundant cytokines and growth factors that have a profound impact on adjacent tissues rather than entirely through physical and mechanical disruption. [28] TGF-b secreted by fibroids simultaneously affect endometrial receptivity and menstrual cycle regulation; TGF-b 3 alters the production of plasminogen activator inhibitor-1, antithrombin 3, and thrombomodulin in the endometrium resulting in HMB. [29] So TXA can interfere with the increased plasminogen activators levels found in the endometrium of women with submucous myoma. [30]

Success of hysteroscopic surgical procedures is strongly dependent on constant surgical field visibility so implementing the best strategy to decrease intraoperative blood loss has been a research priority; as injecting a dilute vasopressin solution directly into the submucosal myoma,

[26,31] intracervical administration of vasopressin, [32] GnRH agonist, danazol, [2, 33] Epsilon-aminocaproic acid (EACA) or oxytocin. [30] All have different mechanisms of actions, variable effects, cost, and side effects.

In the current study the decrease in haemoglobin level was less in TXA group P value =0.015 which is of statistical significance, albeit with minimal clinical significance; moreover the quality of hysteroscopic view was significantly better in the tranexamic acid group compared to the placebo group P<.001.

In the same line a previous study reported that intrauterine instillation of EACA during hysteroscopic procedure was associated with diminished intraoperative bleeding and better visualization of the operative field. [4] TXA was reported to have a higher fibrinolytic activity than EACA (8 to 10 times more potent) and it persists longer in the tissues; thus it was used in the current study. [24, 34, 35]

Excessive bleeding occurred in (2.6%) of the study group and (23.1%) of the placebo group. The incidence of excessive bleeding was significantly decreased with TXA administration with a relative risk 11 (95 % CI .015 to .85) with five women needed to be treated to avoid one case excessive bleeding, and in order to obtain one case of good visual field throughout the procedure 2 women needed to be treated with intrauterine TXA with good operative view in 20.5% and 60.5% of cases in the placebo group and TXA group respectively.

Although intrauterine instillation of TXA had a direct effect on bleeding from the myoma bed and improved the clarity of operative field; the median operative time did not differ between both groups while, the mean operative time significantly decreased with the use of TXA this can be due to the operative time in the placebo group ranging between 10.0 – 80.0 minutes with all cases with poor vision had longer surgical time between 50.0 – 80.0 minutes, while in the TXA

group surgical time ranges between 10.0 – 30.0 minutes.

Complete myoma resection may be difficult with the main constrain being the amount of fluid intravasation that can be life-threatening. [26] In this study we had one case of incomplete resection in each group both were terminated when the maximal allowed fluid deficit was reached.

The most frequently reported problem associated with operative hysteroscopy is uterine perforation, which occurs in 1% of patients, however the exact risk of such problems arising during the hysteroscopic myomectomy procedure is difficult to determine as the frequency of complications varies widely by surgeon and operative technique while women with submucous myoma are not at high risk of uterine perforation. [36]

Different rates of perforations were reported in several studies; Corson and Brooks reported 3 cases of uterine peroration in 92 women underwent hyseroscopic myomectomy (3.2%) , and in a study by Darwish there were 2 cases(2.5%) of uterine perforation out of 77 hysteroscopic myomectomies, and Agostini et al, reported 9 cases of perforations during 782 transcervical hysteroscopic myomectomies (1.15%).[38,39,40]

In the current study, the only reported complication was uterine perforation that occurred in three cases all were in the placebo group for all the procedure was terminated immediately and laparoscopy was done to exclude bowel injury which was found in one case. Clinical intravasation syndrome, severe bleeding that caused hemodynamic changes or mandated termination of the procedure or blood transfusion, and other postoperative complications were not reported in either group.

Strengths and limitations:

To our knowledge, this study is the first randomized placebo-controlled trial to assess the efficacy of intrauterine instillation of TXA during hysteroscopic myomectomy; this off label topical application of a cheap, widely available, easily administered drug could be safer than intravenous administration. There is an existing global trend for the topical application of TXA in trauma and surgical patients.

Other strengths of this study was that office hysteroscopy was performed prior to the operative hysteroscopy to ensure that the study participants were appropriate for the study, as well as a single operator performed all the surgeries, to eliminate differences in surgeon technique, experience or the rating of the observed blood loss.

The main limitation of this study was that of the three statistically different findings, only one is objective (haemoglobin change at 24 hours) yet not clinically significant. The visualization and clinical impression of blood loss were subjective; however interobserver variability was eliminated as one surgeon performed the procedures and commented on these subjective variables.

Conclusion: Intrauterine instillation of TXA with the distention medium during hysteroscopic myomectomy resulted lower decrease of postoperative hemoglobin concentration which is likely to be clinically significant. A subjective improvement in visualization of surgical field was noted with topical use of TXA.

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Authors' contribution:

Rasheedy R contributed in literature search, study design, data analysis, data interpretation, and drafted the article, Makled A contributed in study design , data analysis, and supervision; Abou-Gamrah A contributed in study design , statistical analysis And Giuma H was responsible for data collection.

References:

1. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG. 2017;124(10):1501-1512. https://doi.org/ 10.1111/1471-0528.14640.

2. Di Spiezio Sardo A, Mazzon I, Bramante S, Bettocchi S, Bifulco G, Guida M. et al. Hysteroscopic myomectomy: a comprehensive review of surgical techniques. Hum Reprod Update. 2008; 14: 101–119.

3. Mazzon I, Favilli A, Grasso M, Horvath S, Bini V, Carlo Di Renzo G et al.,Risk Factors for the Completion of the Cold Loop Hysteroscopic Myomectomy in a One-Step Procedure: A Post Hoc Analysis. BioMed Research International. 2018; e 8429047. https://doi.org/10.1155/2018/8429047.

4. Sayyah-melli M, Ouladehsahebmadarek E, Taghavi S, Jafary SM, Mostafa GP, Arash K et al. The effect of intrauterine instillation of E-Aminocaproeic Acid during hysteroscopic operations in the management of intractable uterine hemorrhage: A Randomized Clinical Trial. Life Sci.2013; 10(1):1369-1374.

5. AAGL Practice Report: Practice Guidelines for the Management of Hysteroscopic Distending Media. (2013). Journal of Minimally Invasive Gynecology, 20(2), 137–148. https://doi.org/10.1016/j.jmig.2012.12.002.

6. Umranikar S, Clark TJ, Saridogan E, Miligkos D, Arambage K, TorbeE, et al. BSGE/ESGE guideline on management of fluid distension media in operative hysteroscopy. Gynecol Surg. 2016;13(4):289-303. https://doi.org/ 10.1007/s10397-016-0983-z.

7. McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs 2012;72(5):585–617. https://doi.org/10.2165/11209070-000000000-00000.

8. Zahed R, Mousavi Jazayeri MH, Naderi A, Naderpour Z, Saeedi M. Topical Tranexamic Acid Compared With Anterior Nasal Packing for Treatment of Epistaxis in Patients Taking Antiplatelet Drugs: Randomized Controlled Trial. Acad Emerg Med. 2018;25(3):261-266. https://doi.org/10.1111/acem.13345.

9. Kim C, Park SS, Davey JR. Tranexamic acid for the prevention and management of orthopedic surgical hemorrhage: current evidence. J Blood Med. 2015; 6:239–244. https://doi.org/10.2147/JBM.S61915

10. Borea G, Montebugnoli L, Capuzzi P, Magelli C. Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery. An alternative method to discontinuing anticoagulant therapy. Oral Surg Oral Med Oral Pathol. 1993 J;75(1):29-31.

11. Ker K, Beecher D, Roberts I. Cochrane Database Syst Rev. 2013 Jul 23;(7):CD010562. https://doi.org/10.1002/14651858.

12. Hunt BJ. The current place of tranexamic acid in the management of bleeding. Anaesthesia. 2015; Suppl 1:50-3. https://doi.org/ 10.1111/anae.12910.

13. Moskal JT, Capps SG. Meta-analysis of Intravenous Tranexamic Acid in Primary Total Hip Arthroplasty. Orthopedics. 2016; 39(5): 883-892

14.Emara W M, Moez K K, Elkhouly A H. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. Anesthesia: Essays and Researches 2014; 8 (1):48-53.

15. Shin YS, Yoon JR, Lee HN, Park SH, Lee DH. Intravenous versus topical tranexamic acid administration in primary total knee arthroplasty: a meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2017; 25(11):3585-3595. https://doi.org/10.1007/s00167-016-4235-6

16. Yuan X, Li B, Wang Q, Zhang X. Comparison of 3 Routes of Administration of Tranexamic Acid on Primary Unilateral Total Knee Arthroplasty: A Prospective, Randomized, Controlled Study. J Arthroplasty. 2017; 32(9):2738-2743. https://doi.org/10.1016/j.arth.2017.03.059.

17.Luo ZY, Wang HY, Wang D, Zhou K, Pei FX, Zhou ZK. Oral vs Intravenous vs Topical Tranexamic Acid in Primary Hip Arthroplasty: A Prospective, Randomized, Double-Blind, Controlled Study. J Arthroplasty. 2018; 33(3):786-793. https://doi.org/10.1016/j.arth.2017.09.062

18. Chauncey JM, Wieters JS. Tranexamic Acid. [Updated 2018 Dec 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532909/

19. Tranexamic acid 100mg/ml Solution for Injection - Summary of Product Characteristics (SmPC) - (eMC). Medicines.org.uk. https://www.medicines.org.uk/emc/product/8953/smpc. Published 2019. Accessed June 3, 2019.

20.Georgiev GP, Tanchev PP, Zheleva Z, Kinov P. Comparison of topical and intravenous administration of tranexamic acid for blood loss control during total joint replacement: Review of literature. J Orthop Translat. 2018;13:7–12. https://doi.org/ 10.1016/j.jot.2017.12.006

21.Hanna SA, Prasad A, Lee J, Achan P. Topical Versus Intravenous Administration of Tranexamic Acid in Primary Total Hip Arthroplasty: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Orthop Rev (Pavia). 2016;8(3):6792.

https://doi.org/ 10.4081/or.2016.6792.

22.Mao Z, Yue B, Wang Y, Yan M, Dai K. A comparative, retrospective study of peri-articular and intra-articular injection of tranexamic acid for the management of postoperative blood loss after total knee arthroplasty. BMC Musculoskelet Disord. 2016;17(1):438.

https://doi.org/ 10.1186/s12891-016-1293-3

23. Borea G, Montebugnoli L, Capuzzi P, Magelli C. Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery .Oral Surg Oral Med Oral Pathol. 1993; 75(1):29-31.

24. Jahadi Hosseini SH, Khalili MR, Motallebi M. Comparison between Topical and Oral Tranexamic Acid in Management of Traumatic Hyphema. Iran J Med Sci. 2014;39 (2 Suppl):178–183.

25. Munro MG, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3-13. https://doi.org/10.1016/j.ijgo.2010.11.011.

26. Wong ASW, Cheung C W, Yeung S W, Fan H L, Leung T Y, Sahota D S. Transcervical Intralesional Vasopressin Injection Compared With Placebo in Hysteroscopic Myomectomy. Obstetrics & Gynecology,2014; 124(5), 897–903. https://doi.org/10.1097/aog.0000000000000515

27. American Association of Gynecologic Laparoscopists (AAGL): Advancing Minimally Invasive Gynecology Worldwide. AAGL practice report: practice guidelines for the diagnosis and management of submucous leiomyomas. J Minim Invasive Gynecol. 2012;19(2):152-71. https://doi.org/ 10.1016/j.jmig.2011.09.005.

28. Rackow B, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular determinates of endometrial receptivity. Fertil Steril. 2010; 93: 2027–2034. https://doi.org/10.1016/j.fertnstert.2008.03.029.

29. Taylor HS. Fibroids: when should they be removed to improve in vitro fertilization success? .Fertil Steril. 2018; 109(5): 784–785. https://doi.org/10.1016/j.fertnstert.2018.03.003.

30. Sayyahmelli M, Moosazade R, Gharabaghi PM, Nazari F.Comparison of the Intraoperative Outcomes of Intrauterine Instillation of Epsilon-Aminocaproic Acid and Intravenous Oxytocin in Hysteroscopy Surgeries. International Journal of Women's Health and Reproduction Sciences. 2016; 4(2): 68-72.

31. Holloran-Schwartz MB, Harrison K, Gimpelson R. Direct injection of vasopressin during hysteroscopic myomectomy: a case report. J Reprod Med. 2014;59(11-12):614-6.

32.Phillips R D , Nathanson H G, Milim SJ , Haselkorn JS, Khapra A , Ross PL. The effect of dilute vasopressin solution on blood loss during operative hysteroscopy: A randomized controlled trial. Obstetrics and gynecology.1996; 88. 761-6.

https://doi.org/10.1016/0029-7844(96)00282.

33. Sayyah-Melli M, Bidadi S, Taghavi S, Ouladsahebmadarek E, Jafari-Shobeiri M, Ghojazadeh M, et al. Comparative study of vaginal danazol vs diphereline (a synthetic GnRH agonist) in the control of bleeding during hysteroscopic myomectomy in women with abnormal uterine bleeding: a randomized controlled clinical trial. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2016; 196 :48–51. http://dx.doi.org/10.1016/j.ejogrb.2015.10.021.

34. Makhija N, Saruprіa A, Kumar Choudhary S, Das S, Lakshmy R, Kiran U. Comparison of epsilon aminocaproic acid and tranexamic Acid in thoracic aortic surgery: clinical efficacy and safety. J Cardiothorac Vasc Anesth. 2013;27(6):1201-7. https://doi.org/10.1053/j.jvca.2013.04.003.

35. Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol.1980; 14: 41-47

36. Murakami T, Tamura M , Ozawa Y, Suzuki H , Terada Y, Okamura K. Safe techniques in surgery for hysteroscopic myomectomy. Journal of Obstetrics and Gynaecology Research. 2005; 31: 216-223. https://doi.org/10.1111/j.1447-0756.2005.00274.x

38. Corson SL, Brooks PG. Resectoscopic myomectomy. Fertil Steril 1991; 55: 1041–1044.

39. Darwish A. Modified hysteroscopic myomectomy of large submucous myoma. Gynecol Obstet Invest 2003; 56: 192–196.

40.Agostini A, Cravello L, Bewtelle F, Shojai R, Roger V, Blanc B. Risk of uterine perforation during hysteroscopic surgery. J Am Assoc Gynecol Laparosc 2002; 9: 264–267.

Figure legends:

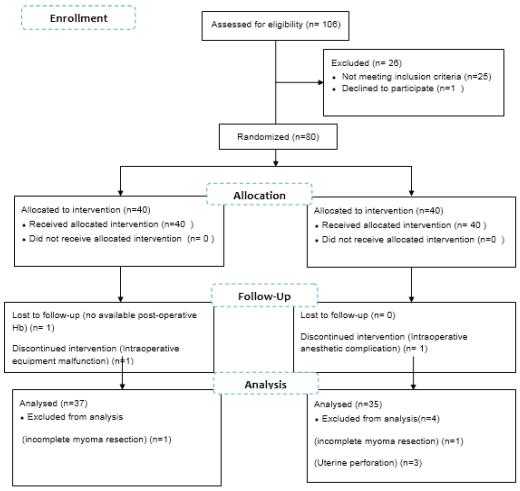

Figure 1: participants flow through the trial

Table 1: the surgeon rating of bleeding amount and the quality of operative view

Variable		Definition
surgeon rating of bleeding amount	Minimal	bleeding was insufficient to interfere with the operation or with the clarity of vision
	moderate	bleeding that obscured the visual field and resolved only with continuous and constant irrigation of the distention media
	excessive	bleeding that would have necessitated intervention other than continuous and constant irrigation of the distention media (it was controlled only by increasing the pressure to tamponade the bleeding from myoma bed)
the quality of operative view	Poor quality	when it was not possible to visualize the entire uterine cavity of and the cornual areas nor adequate visualization of the myoma during more than half of the procedure despite continuous and constant irrigation of the distention media
	fair quality	when it was not possible to visualize the entire uterine cavity of and the cornual areas nor adequate visualization of the myoma during less than half of the procedure despite continuous and constant irrigation of the distention media
	good quality	when it was possible to assess the entire uterine cavity to include the cornual areas from the level of isthmus satisfactorily throughout the entire procedure with adequate visualization of the myoma.

Table 2: the baseline demographic and clinical characteristics among the study groups

		Tranexamic Acid Group	Placebo Group	P	95% CI
Age (Yrs.) Range Mean ±SD		 24.0 – 49.0 37.63 ± 5.33	 26.0 – 46.0 37.17 ± 5.41	.71	-2.04 to 2.96
BMI (Kg/m2) Mean ± SD		30.8 ± 2.21	31.1 ± 2.20	.75	-0.72 to 1.32
Parity Range Median (IQR)		0 – 5 0 (0 – 2)	0 – 6 0 (0 – 2)	.58	----
Previous spontaneous miscarriages Range Median (IQR)		0 – 8 0 (0 – 0)	0 – 6 0 (0 – 0)	.65	----
Indication for myomectomy: N(%) AUB Infertility		 12 (31.57%) 26 (68.42%)	 11 (28.20%) 28 (71.79%)	.94	----
Myoma size (largest dimension, cm) Range Mean ± SD		 1.0 – 4.0 2.60 ± .72	 1.0 – 4.0 2.29 ± .67	.06	-.62 to .005
Myoma site Anterior wall Fundal Posterior wall		 8 (21.05%) 24 (63.16%) 6 (15.79%)	 14 (35.90%) 21 (53.85%) 4 (10.26%)	.32	-----
FIGO classification SM myoma type 0 type 1		 9 (23.68%) 29 (76.32%)	 12 (30.77%) 27 (69.23%)	.61	-----
Hemoglobin concentration (gm/dL)	Preoperative	11.11 ± 1.02	10.73 ± .99	.09	-.849 to .089
	Postoperative	10.08 ± 1.16	9.26 ± .86	**.001**	-1.29 to -0.34
	Mean difference	1.11 ± .58	1.46 ± .61	**.015**	.072 to .627
Surgeon rating of bleeding	Minimal	23 (60.5%)	8 (20.5%)	**.001**	-----
	moderate	14 (36.8%)	22 (56.4%)		
	Excessive	1 (2.6%)	9 (23.1%)		

Table 3:the hysteroscopic operative outcomes in both groups

	Tranexamic Acid Group	Placebo Group	P
Volume of distention medium (L) Range Median (IQR)	 1.2 – 6.0 3.0 (3.0 – 5.0)	 1.3 – 7.0 4.0 (3.0 – 6.0)	.21
Distention medium deficit (mL) Range Median (IQR)	 200.0 – 1000.0 500.0 (500.0 – 1000.0)	 100.0 – 1000.0 600.0 (500.0 – 1000.0)	.80
Operative time (min) Range Median (IQR)	 10.0 – 30.0 20.0 (15.0 – 25.0)	 10.0 – 80.0 20.0 (15.0 – 25.0)	.55
Quality of hysteroscopic view Poor Fair Good	 1 (2.6%) 14 (36.8%) 23 (60.5%)	 9 (23.1%) 22 (56.4%) 8 (20.5%)	**<.001**
complete resection of myoma	37 (97.37%)	35 (89.74%)	.20
Incomplete resection of myoma	1 (2.63%)	1 (2.56%)	
Uterine perforation	0 (0%)	3 (7.69%)	

Table 4:the correlation between mean HB difference and other variables

	Mean hemoglobin difference	
	rho	P value
Volume of distension media	0.395	0.000
Duration of the procedure	0.395	0.000
Myoma size	-0.130	0.311
Bleeding rating by surgeon	0.360	0.001
the quality of operative view	0.360	0.001

Spearsman's correlation

Table 5: Multiple regression analysis for predictors of mean hemoglobin difference:

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-4.022	1.320		-3.046	0.004	-6.678	-1.366
age	-0.017	0.015	-.0141	-1.161	0.252	-0.047	0.013
Preoperative hemoglobin	0.400	0.087	0.580	4.608	0.000	0.225	0.574
Myoma site	0.231	0.123	0.230	1.874	0.067	-0.017	0.480
Myoma grade	0.082	0.216	0.046	0.380	0.706	-0.353	0.517
Tranexamic acid use	0.612	0.166	0.461	3.676	0.001	0.277	0.947
Myoma size	0.134	0.125	0.137	1.074	0.288	-.0117	0.385

Table 6: Event rates for excessive bleeding and improvement in clarity of vision:

Event rates	**proportion of good visual field**	
Control event rate	20.5%	
Experimental event rate	60.5%	
Improvement criterion	Point Estimate	95% CI
Absolute risk reduction	- .40	- .56 to -.18
Relative risk reduction	-1.95	-4.76 to -.151
Number needed to treat	2	2 to 5
Odds ratio	5.94	2.15 to 16.3
Relative risk	2.95	1.51 to 5.76
Event rates	proportion of excessive bleeding	
Control event rate	23.1%	
Experimental event rate	2.6%	
Improvement criterion	Point Estimate	95% CI
Absolute risk reduction	2.04	.053 to .358
Relative risk reduction	.88	.14 to .98
Number needed to treat	5	5 to 19
Odds ratio	.090	.010 to .751
Relative risk	.11	.015 to .85