GYNECOLOGY

Intraoperative tranexamic acid to decrease blood loss during myomectomy: a randomized, double-blind, placebo-controlled trial

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BACKGROUND: Myomectomy is associated with a significant risk of hemorrhage. Tranexamic acid is a synthetic lysine derivative with antifibrinolytic activity used in other surgical disciplines to reduce blood loss during surgery. However, its utility in gynecologic surgery is not well understood.

OBJECTIVE: This study aimed to determine the effect of early administration of intravenous tranexamic acid on perioperative bleeding and blood transfusion requirements in women undergoing myomectomy.

STUDY DESIGN: This study was a double-blinded, randomized, placebo-controlled trial conducted in an academic teaching hospital. Women with symptomatic fibroids thought to be at risk for large intraoperative blood loss who met the following criteria were included in the study: (1) at least 1 fibroid $\geq$10 cm, (2) any intramural or broad ligament fibroid $\geq$6 cm, and/or (3) at least 5 total fibroids based on preoperative imaging. Patients were randomized to receive a single intravenous bolus injection of tranexamic acid 15 mg/kg (intervention group) versus an intravenous bolus injection of saline of equivalent volume (placebo group) 20 minutes before the initial surgical incision. Perioperative bleeding was defined by measuring intraoperative estimated blood loss, change between pre- and postoperative hemoglobin, and frequency of blood transfusions. Estimated blood loss was calculated by combining the blood volume collected within the suction canister and the weight of used sponges. The 2 groups were compared for age; body mass index; perioperative hemoglobin and hematocrit; perioperative blood loss; duration of surgery; blood transfusion requirements; and the number, total weight, and volume of myomas removed.

RESULTS: A total of 60 patients (30 per arm) were enrolled into the study between March 1, 2015, and January 29, 2018. Age, body mass index, baseline hemoglobin and/or hematocrit, number and total weight of myomas removed, and size of myomas did not differ between arms. Of 60 patients, 32 (53%) had laparoscopic myomectomy, 24 (40%) had robotic myomectomy, and 4 (7%) had laparotomy. Median estimated blood loss was 200 mL for the tranexamic acid group and 240 mL for the placebo group (P=.88). There was no difference in median duration of surgery (165 vs 164 minutes; P=.64) or change in perioperative hemoglobin (1.00 vs 1.1 g/dL; P=.64). Patients in the tranexamic acid group did not require blood transfusions; however, 4 patients (13.3%) in the placebo group (P=.11) required blood transfusions.

CONCLUSION: Intravenous administration of tranexamic acid in patients undergoing laparoscopic or robotic myomectomies was not associated with decreased blood loss.

Key words: antifibrinolytics, blood loss, fibroids, hemorrhage, myomas, myomectomy, laparoscopy, robotics, tranexamic acid, transfusion

Introduction

Worldwide, 70% to 80% of women will develop uterine leiomyomas.[1] Most myomas are asymptomatic; however, 25% of women with myomas develop symptoms requiring treatment.[2] For women failing medical management and desiring to preserve fertility and/or their uterus, surgical removal of fibroids (myomectomy) is the most common intervention. Myomectomy, however, is associated with a significant risk of hemorrhage, requiring a blood transfusion in up to 20% of abdominal cases.[3] In particular, higher rates of blood loss are noted in women with fibroids that are larger, more numerous, or in intramural or broad ligament locations.[4,5] As such, various treatments have been suggested to decrease blood loss during myomectomy such as the use of vasopressin, misoprostol, or tourniquets.[6] Despite the many described methods to reduce intraoperative bleeding, massive hemorrhage during myomectomy remains a significant challenge to gynecologic surgeons.

Tranexamic acid (TXA) is a synthetic lysine derivative with antifibrinolytic activity that helps prevent clot breakdown. At present, it is widely used clinically to stop heavy menstrual bleeding.[7] A Cochrane review of randomized controlled trials (RCTs) comparing TXA with placebo in almost 5000 patients undergoing nongynecologic surgery showed a reduction in risk of blood transfusion by 39% (relative risk [RR], 0.61; 95% confidence interval [CI], 0.53−0.70) without an increased risk in venous thromboembolism (VTE) or other adverse perioperative outcomes.[8] A randomized, double-blind, placebo-controlled trial was conducted to investigate the antihemorrhage effect of prophylactic TXA (dosage 1 g) in benign laparoscopic and abdominal hysterectomy. The incidence of blood loss >500 mL and reoperation for postoperative hemorrhage was significantly reduced in the TXA group with a calculated number needed to treat of 24.[9]

Four trials have investigated the use of TXA during abdominal myomectomy. In 2008, Caglar et al presented a randomized, double-blind, placebo-controlled

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Why was this study conducted?
Myomectomy is associated with a significant risk of hemorrhage. Therefore, methods to decrease blood loss and allogeneic transfusions are needed.

Key findings
Intraoperative administration of intravenous tranexamic acid 15 mg/kg in patients undergoing a myomectomy was not associated with a decreased rate of perioperative blood loss, allogeneic transfusions, or operative time.

What does this add to what is known?
This is the first study of tranexamic acid administered to patients undergoing a minimally invasive myomectomy and at a dosage of 15 mg/kg. Further studies at higher dosing regimens are needed.

trial of intravenous (IV) TXA 10 mg/kg (maximum 1 g) followed by a continuous infusion of 1 mg/kg/h for 10 hours (maximum 1 g/10 hours) versus placebo in patients. Although there was a 166-mL decrease in perioperative blood loss (P=.12) (a 63-mL decrease in postoperative blood loss [$P<.01$]), no significant difference was found between the 2 groups in terms of change in hemoglobin (Hb) or rate of allogeneic blood transfusion.[10] Another RCT using the same dose in a population with at least 3 intramural fibroids found a 40% reduction in blood loss and a decrease in blood transfusion in women receiving IV TXA.[11] The third RCT investigated the effect of IV TXA as an adjunct to ornipressin. Patients received either ornipressin combined with 1 g TXA or placebo combined with ornipressin. There was no difference in blood loss between the groups.[12] Finally, in 2014, Bennasr et al conducted an RCT in which TXA 20 mg/kg bolus was administered just before the start of an abdominal myomectomy followed by a continuous infusion of 20 mg/kg/h until the completion of the procedure. The authors found a 311-mL decrease in perioperative blood loss ($P<.01$) and a significantly lower number of patients needing a blood transfusion (4 of 11 patients vs 11 of 30 patients; P=.02). However, the change in pre- and postoperative Hb levels between the 2 groups was not significant.[13] No studies address the use of TXA during laparoscopic and/or robotic myomectomy.

Given these conflicting results, further trials with different dosing administration and high-risk patient populations are needed to assess the role of TXA in the reduction of blood loss during myomectomy. In addition, the role of TXA in minimally invasive endoscopic myomectomy is unknown. The purpose of this study is to determine the effect of early administration of a single dose of IV TXA 15 mg/kg on perioperative bleeding (as defined by measured intraoperative estimated blood loss (EBL), change between pre- and postoperative Hb and hematocrit (Hct), and frequency of blood transfusions) in women undergoing a minimally invasive laparoscopic or robotic myomectomy.

Materials and Methods
Subjects were recruited from the clinics of 4 fellowship-trained, high-volume, minimally invasive gynecologic surgeons at George Washington University (GWU) Medical Faculty Associates (MFA). The recruited participants were patients presenting to the hospital for management of symptomatic fibroids (heavy bleeding, pelvic pain or pressure, urinary or bowel symptoms, and/or infertility). Participants choosing uterine-sparing surgery were also considered for this study. Prior data suggest increased utility of TXA in higher-risk patients; therefore, in this study, women between the ages of 18 and 50 years undergoing laparoscopic, robotic, or abdominal myomectomy with a fibroid burden meeting the following

criteria based on ultrasound or magnetic resonance imaging (MRI) imaging were recruited: (1) any fibroid measuring ≥10 cm, (2) any intramural or broad ligament fibroid measuring ≥6 cm, and/or (3) 5 or more fibroids. Patients with a relative contraindication to TXA were excluded, such as thromboembolic disease, ischemic heart disease, malignancy, hematuria, liver disease, chronic kidney disease, or subarachnoid hemorrhage. In addition, pregnant and nursing women; patients with hypersensitivity to TXA; or patients using any of the following—factor IX complex concentrates, anti-inhibitor coagulant concentrates, and all-trans retinoic acid—within 2 weeks of the planned surgery were excluded from this study. Patients meeting the abovementioned criteria were enrolled after obtaining informed consent. The subjects' baseline serum creatine levels were measured as part of the preoperative laboratory work. Data including age, medical and surgical history, and menopausal status were collected from the medical record during routine preoperative clinic visits 1 to 2 weeks before the surgery. Subjects were asked to discontinue use of combination hormonal contraceptives 2 weeks before the surgery. The study was approved by the GWU Institutional and Ethics Review Board on November 14, 2014 (IRB# 091454). The US Food and Drug Administration approved the use of TXA for the purposes of this study as an investigational new drug. This study is available at clinicaltrials.gov under the identifier NCT02620748. This study was conducted and reported according to the CONSORT guidelines for clinical trials.[14] The Clinical and Translational Science Institute at Children's National provided financial support for this study.

The primary outcome of interest is EBL >250 mL. The sample size was 60 subjects, 30 patients in the placebo group and 30 patients in the intervention TXA group. As this study was started in 2013 before recent studies on abdominal myomectomy, the sample size was calculated based on published data in women undergoing cesarean delivery using a single 15 mg/kg preoperative dose of TXA that showed a statistically

significant reduction in blood loss of 250 mL in women who received TXA compared with those receiving placebo.[15] The sample size was calculated to detect a mean 250-mL difference in EBL between groups with a power of 85% at the 5% significance level. In designing our trial, we anticipated a higher rate of abdominal myomectomies based on our institutional rates of 28.4% for 2011 and 2012. We also anticipated a higher blood loss given that we had a mean (SD) of 341.1 (460.5) for minimally invasive myomectomies and 464.7 (410.8) for abdominal myomectomies from 2011 to 2014. It is possible that as the surgeons at our institution performed more minimally invasive myomectomies, outcomes such as blood loss improved over time, which was reflected in the results of our trial.[16] Secondary outcomes of interest included frequency of blood transfusion and operative time.

Participants were randomly allocated 1:1 to the placebo or intervention group. Randomization was carried out with a computer random number generator using permutated block sizes of 10. A research coordinator, who was not involved in administering the intervention or in assessing outcomes, generated the allocation sequence. The GWU Investigational Drug Services (IDS) pharmacy maintained concealment of the allocation sequence using sequentially numbered opaque sealed envelopes. The IDS pharmacy packaged and dispensed the medication with a label that stated "tranexamic acid 15 mg/kg or 0.9% saline" in a syringe with instructions to administer the drug at a rate of 1 mL/min. The anesthesiologist administered the medication at the time of induction. Apart from the research coordinator and IDS pharmacist, all investigators, surgeons, and anesthesiologists were blinded to the participants' allocation. The patients randomized to receive TXA (n=30) were defined as group 1 and given a single bolus IV injection of TXA 15 mg/kg administered 20 minutes before surgical incision. The remaining participants randomized to receive the placebo (n=30) were defined as group 2 and were given a normal saline IV bolus 20 minutes before surgical incision. The volumes of bolus saline and TXA infusions administered were equal.

Study participants subsequently underwent laparoscopic, robotic, or abdominal myomectomy performed by 1 of 4 fellowship-trained minimally invasive surgeons. Three of the surgeons were trained under the fourth senior surgeon, and all myomectomies were performed using a similar surgical technique, which has been described elsewhere.[16] All patients were preoperatively evaluated with transvaginal ultrasonography, and MRI was used to identify the location of myoma, size of dominant myoma, and number of myomas present. All patients received general anesthesia, and all were given sequential compression devices for the prevention of deep vein thrombosis. The size, location, and number of myomas removed were noted. Surgeons used standard methods to reduce blood loss during myomectomy (tourniquets, bulldog clamps, vasopressin, and/or cell saver) at their discretion. Intraoperative EBL was calculated by measuring the volume in the suction apparatus and weighing wet sponges. The weight of the sponge found in grams was converted to milliliters by using blood density (1.050 g/mL). A standard amount of 500 mL of irrigation was used in every procedure as a method of standardization. Thus, final intraoperative EBL was calculated by combining the blood volume collected within the suction canister and the weight of used sponges. In addition, patients with a postoperative Hb of <7 g/dL and clinical symptoms of anemia were given a blood transfusion. Postoperative Hb and Hct were drawn 2 hours after surgery given that patients were often discharged on the same day of surgery, and office visit notes were reviewed to compare baseline demographics, preoperative Hb and Hct (collected during preadmission testing, within 3 weeks of surgery), past surgical history, medical history, operative time, fibroid burden, and complications. Complications identified within 90 days of surgery were included for analysis.

The effectiveness of TXA was evaluated by comparing the following parameters between the 2 groups: perioperative, postoperative, and total blood loss; duration of surgery; and blood transfusion requirements. The 2 groups of patients were also compared with respect to the number and size of myomas removed as per the inclusion criteria outlined above. The primary analyses was completed on an "intention-to-treat" basis using Stata version 14 (College Station, TX) for Windows. Groups were compared using *t*-tests when data were normally distributed and Wilcoxon rank-sum tests when data were not normally distributed. Categorical variables were compared using chi-square tests or Fisher exact tests as appropriate. Significance was set at $P<.05$.

Results
In this study, 221 patients were assessed for eligibility. Among 221 patients, 71 did not meet all inclusion criteria and 90 declined to participate. Sixty patients met study inclusion criteria and were enrolled in the study. A total of 59 patients subsequently underwent a myomectomy. One patient randomized to the control group did not undergo myomectomy due to a severe intraabdominal abscess discovered during surgery (Figure 1).

The participants did not differ in terms of patient characteristics, preoperative blood analysis, or fibroid burden between the TXA and placebo groups. However, patients in the TXA group were twice as likely to have a history of prior abdominal surgery (8 of 30 [26.7%] patients for the TXA group compared with 4 of 30 [13.3%] patients for the placebo group). The number of robotic procedures in the TXA group was higher than that of the placebo group (15 of 30 [50.0%] cases vs 9 of 30 [30.0%] cases). Robotic surgery has been associated with longer operative times; however, in our cohort, operative times were similar for robotic and laparoscopic procedures (177 vs 198 min, respectively). The median age (interquartile range [IQR]) of the patients was 37.4 (5.1) years. The median body masss index (BMI) (IQR) of the patients was 27.2 mg/kg^2 (22.8–37.2 mg/kg^2) in the TXA
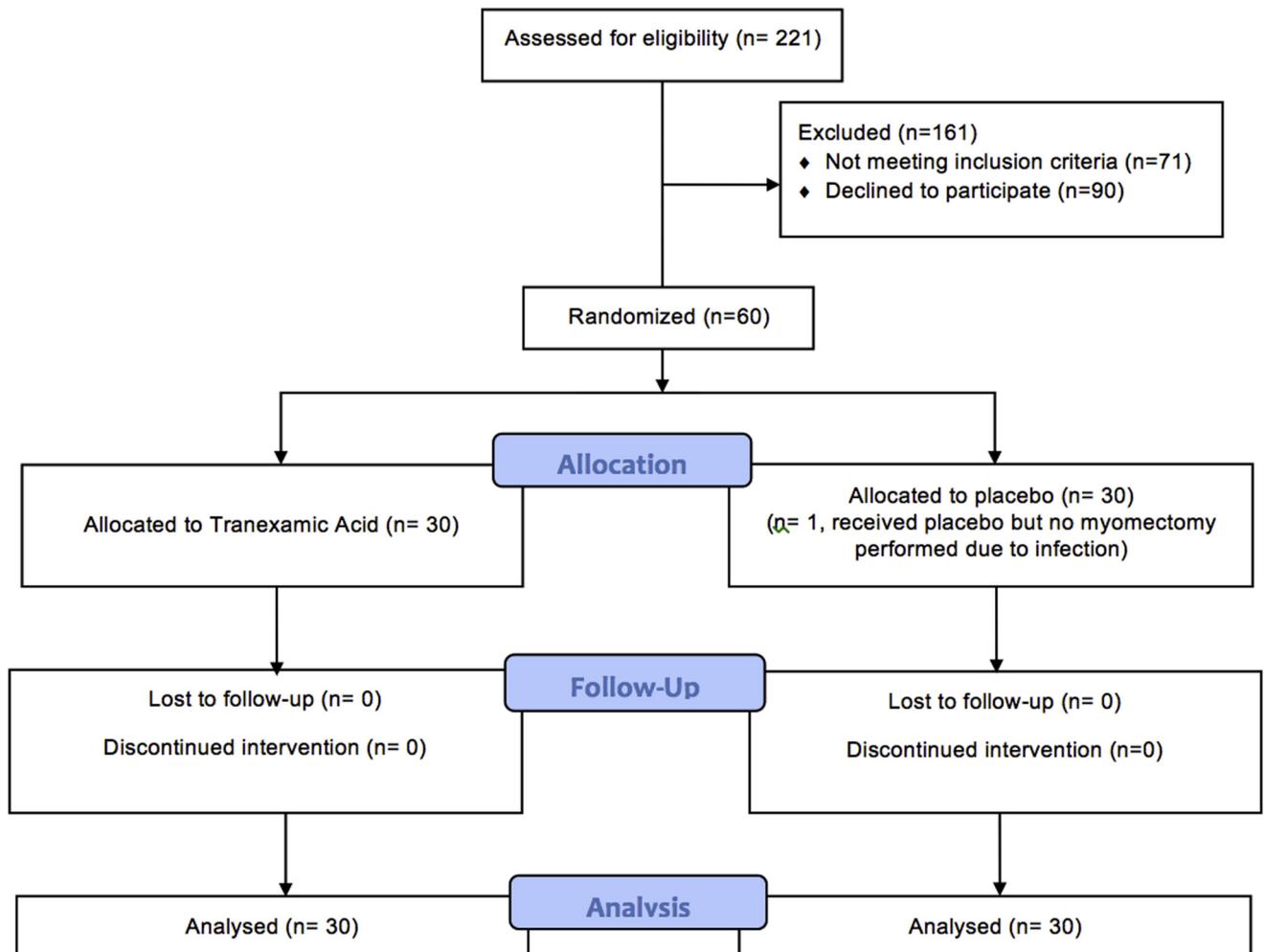
group and 27.7 mg/kg^2 (24.9–32.5 mg/kg^2) in the placebo group. The median number of fibroids removed (IQR) was 5 (3–10) for the TXA group and 6 (3–11) for the placebo group, P=.45. The total weight of fibroids removed (IQR) was 324 g (178–562 g) in the TXA group and 398 g (143–647 g) in the placebo group, P=.87. The largest fibroid (IQR) had a diameter of 8.6 cm (6–10 cm) in the TXA group and 8.5 cm (7–10 cm) in the placebo group, P=.95. Table 1 summarizes the patient demographics, preoperative blood analysis, and fibroid burden in the TXA and placebo groups.

Table 2 summarizes perioperative outcomes for both groups. Median (IQR) blood loss was 200 mL (100–508

mL) in the TXA group and 240 mL (105–605 mL) in the placebo group. Mean change in Hb (IQR) in was 1.00 g/dL (0.10–2.0 g/dL) in the TXA group and 1.1 g/dL (0–1.9 g/dL) in the placebo group. The duration of surgery (IQR) was similar in both arms, 165 minutes (124–230 minutes) and 164 minutes (134–260 minutes), respectively, P=.64. Four women in the placebo group received a blood transfusion, whereas women in the TXA group did not. Other than large intraoperative blood loss (defined as EBL >1000 mL) and blood transfusion, there were no significant complications or adverse events. In particular, there were no thromboembolic events. Of 60 patients, 56 (93%)

underwent laparoscopic (n=32; 53%) or robotic (n=24; 40%) myomectomy, and there were no conversions to laparotomy.

Comment
Principal findings
To our knowledge, this is the first study describing the use of TXA to prevent hemorrhage in patients undergoing minimally invasive (laparoscopic and/or robotic) myomectomy. The results of this study suggest that a single dose of TXA 15 mg/kg administered 20 minutes before incision is not associated with a reduction in intraoperative blood loss, operative time, or rates of blood transfusion during minimally invasive

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TABLE 1
Patient characteristics, preoperative blood analysis, and fibroid burden

Characteristic	Total (N=60)	Tranexamic acid (n=30)	Placebo (n=30)
Age, mean (SD)	37.4 (5.1)	37.1 (4.9)	37.6 (5.3)
Body mass index, median (IQR)	27.5 (24.1, 33.7)	27.2 (22.8, 37.2)	27.7 (24.9, 32.5)
Prior abdominal/pelvic surgery, n (%)	12 (20.0)	8 (26.7)	4 (13.3)
Baseline Hb (g/dL), median (IQR)	12.3 (10.7, 13.3)	12.5 (11.1, 13.6)	12.1 (10.3, 12.9)
Baseline Htc (%), median (IQR)	37.6 (34.2, 40.2)	37.8 (35.1, 40.5)	37.6 (33.1, 39.8)
Myomas removed, median (IQR)	5 (3, 10)	5 (3, 10)	6 (3, 11)
Total weight of fibroids (g), median (IQR)	362 (174, 600)	324 (178, 562)	398 (143, 647)
Largest myoma (cm), median (IQR)	8.6 (7, 10)	8.6 (6, 10)	8.5 (7, 10)
Laparoscopic myomectomy, n (%)	32 (53.3)	13 (43.3)	19 (63.3)
Robotic myomectomy, n (%)	24 (40.0)	15 (50.0)	9 (30.0)
Abdominal myomectomy, n (%)	4 (6.7)	2 (6.7)	2 (6.7)

Hb, hemoglobin; *Hct*, hematocrit; *IQR*, interquartile range; *SD*, standard deviation.

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myomectomy in women with a high fibroid burden.

Results

This study also contributes to the available literature in that it assesses TXA at a higher single dose administration (a single dose of 15 mg/kg administered 20 minutes before incision). Single-dose administration may be ideal in resource-limited settings where fibroid burden and associated perioperative morbidity and mortality are very high. A TXA dose of 15 mg/kg was selected because it was shown to decrease mean total blood loss of 262 mL and decrease the need for a blood transfusion compared with placebo among women undergoing cesarean delivery (*P*=.02).[15]

One might assume that a lower-risk population could explain the absence of benefit of TXA in our study as the majority of these procedures were completed laparoscopically or robotically rather than abdominally. However, fibroid burden (average number and size of fibroids removed) was similar to previous TXA studies for abdominal myomectomy, and our study criteria

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TABLE 2
Perioperative outcomes

Perioperative outcome	Tranexamic acid (n=30)	Placebo (n=30)	P-value[a]	OR
Total blood loss (mL), median (IQR)	200 (100, 508)	240 (105, 605)	.88	
Duration of surgery (min), median (IQR)	165 (124, 230)	164 (134, 260)	.64	
Change in Hb, pre-op to post-op (g/dL), median (IQR)	1.00 (0.10, 2.0)	1.1 (0, 1.9)	.53	
Change in Hct, pre-op to post-op (%), median (IQR)	2.8 (0.6, 6.0)	4.0 (−0.3, 6.2)	.89	
EBL >500, n (%)	8 (26.7)	8 (26.7)	1.00[b]	1.0
EBL >1000, n (%)	4 (13.3)	0	.11[c]	N/A
Blood transfusion on ward, n (%)			.11[c]	N/A
None	30 (100.0)	26 (86.7)		
1 unit	0	2 (6.7)		
2 units	0	1 (3.3)		
4 units	0	1 (3.3)		

EBL, estimated blood loss; *Hb*, hemoglobin; *Hct*, hematocrit; *IQR*, interquartile range; *N/A*, not available; *OR*, odds ratio.

[a] P-values calculated using Wilcoxon rank-sum test unless otherwise indicated; [b] P-value calculated using chi-square test; [c] P-value calculated using Fisher's exact test.

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were chosen to identify a high-risk population. Our median specimen weight was 362 g, number of myomas removed was 5, and the largest fibroid had a diameter of 8.6 cm. Our operative time of approximately 165 minutes in both arms was comparable with other reports studying patients undergoing myomectomy with a greater surgical complexity (Vargas, 188 minutes in the minimally invasive surgery group, 169 minutes in the abdominal group; Garguilo, 118 minutes in the laparoscopic surgery group, 195 minutes in the robotic surgery group).[16,17]

Clinical and research implications

The effect of TXA during minimally invasive myomectomy may be dose dependent similar to recent studies in abdominal myomectomy. Other authors have reported that there is no significant reduction in EBL and transfusion rates at 10 mg/kg followed by continuous infusion in a low-fibroid-burden population or in addition to ornipressin; however, there are studies that have reported significant reduction in EBL and transfusion rates at higher dosing of 20 mg/kg followed by continuous infusion.[10,12,13] All the providers in this study used known adjuvant methods of hemostasis such as vasopressin, which helps to explain the low overall transfusion rates.

In addition, in this study, the rate of blood transfusion was 6.7%, which is low compared with other reports of cohorts with a large myoma burden (Vargas, 5.8% minimally invasive myomectomy group, 13.8% abdominal myomectomy group; Shaaban, 27.3%; Sinha, 18.1%; and Zhao, 5.7%).[11,16,18,19] Interestingly, all 4 transfusions occurred in the placebo group. We may have been underpowered to see a difference in the 2 main outcomes (intraoperative blood loss and transfusion rates) given the low rates of complications in the overall cohort. However, it is possible that the utilization of TXA is best prescribed for open abdominal myomectomies with higher EBL rather than minimally invasive procedures. Thus, larger RCTs at higher dosing regimens are needed.

Strengths and limitations

This study has several strengths. The study design used was a randomized, double-blind, placebo-controlled trial according to the CONSORT statement, and the data in Table 1 suggests appropriate randomization. All surgeons were fellowship-trained minimally invasive gynecologists, with 3 of the surgeons trained by the fourth senior surgeon. Because of this similarity in training, all procedures were performed with similar technique, limiting significant bias imposed by surgeon experience.

However, this study also has several limitations. We were possibly underpowered to see a difference in blood loss <250 mL in the overall context of low blood loss (median 200 mL; IQR, 103−529 mL). At the time of designing this study, we based our power calculation on data from our institution showing an average blood loss of 313 mL for laparoscopic and/or robotic procedures and 427 mL for abdominal myomectomies in 2013.[16] However, as the number of minimally invasive myomectomies increased, blood loss decreased significantly over the years among all surgeons as they adapted other previously described methods to reduce blood loss during myomectomy.[16] We were also likely underpowered to detect differences in rare complications. The interpretation of change in Hb and Hct as an outcome is limited for 2 reasons. First, preoperative Hb and Hct were collected within 3 weeks of surgery and may have varied significantly from the values on the day of surgery. Second, postoperative Hb and Hct were collected 2 hours after surgery, possibly before equilibration, owing to standard same-day discharge for all minimally invasive myomectomies.

Our study included 3 surgical approaches to myomectomy (conventional laparoscopy, robotic-assisted laparoscopy, and laparotomy), which had varying outcomes such as operative time and blood loss. In a subanalysis of only minimally invasive laparoscopic or robotic myomectomy, no difference in our primary outcome was seen. In addition, the same number of abdominal myomectomies was present in each treatment arm. Moreover, surgeons used other methods aside from TXA (tourniquets, bulldog clamps, vasopressin, and/or cell saver) at their discretion, which may have influenced blood loss and transfusion rates. The setting was a medium-sized academic teaching hospital where all surgeons have high case loads. Although results may be translatable to a similar specialized environment, they are less likely to be generalizable to the general gynecologic practice.

Conclusion

In patients undergoing laparoscopic or robotic myomectomies, there was no difference in blood loss for those receiving a single IV administration of TXA 15 mg/kg compared with those receiving placebo. ∎

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