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Intravenous Tranexamic Acid Possible Effects on Ovarian Reserve during Laparoscopic Cystectomy of Endometrioma: Double Blind Randomized Controlled Trial

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ABSTRACT

Background: Numerous gynecologists look for ways to protect ovarian health. To lessen the risk of blood loss, surgeons sometimes prescribe tranexamic acid (TXA).

Objective: The aim of the current work was to examine the potential benefit of tranexamic acid on ovarian reserve and intraoperative blood loss, by comparing the mean differences in anti-müllerian hormone (AMH) levels before and after laparoscopic ovarian cystectomy.

Subjects and Methods: A total of 30 women had ovarian endometriomas were included in the study, the laparoscopic cystectomy was done for ovarian endometriomas in the Endoscopic Unit in Zagazig University Hospitals. They were categorized randomly into two groups; **Group I (control):** consisted of 15 patients who were subjected to intravenous administration of 110 ml of normal saline preceding the incision of the skin. **Group II:** consisted of 15 patients who were subjected to intravenous administration of 1 g tranexamic acid (2 kapron 500 mg 5 ml ampoules) preceding the incision of the skin.

Results: There was a substantial difference between the study group and the control group regarding intraoperative, postoperative, and total blood loss. Postoperative serum AMH at one and six months later after the operation showed significant reported differences, that were higher in Group II. There was a highly statistically significant difference between the studied groups regarding operative time, hospital stay being higher among control group.

Conclusion: The current study's findings lend credence to the hypothesis that reducing the risk of ovarian reserve loss after laparoscopic cystectomy for endometrioma is facilitated by intravenous TXA administration.

Keywords: Tranexamic Acid, Laparoscopic Cystectomy, Endometrioma.

INTRODUCTION

Up to 10% of reproductive women and 20%-50% of infertile women suffer from ovarian endometriosis, also known as endometriomas [(1)]. Pelvic pain, worsening dysmenorrhea, dyspareunia, and infertility are some of the clinical symptoms. Due to their potential to damage healthy ovarian tissues, endometriomas have been associated to decreased ovarian function, ovulation problems, and primary ovarian insufficiency [(1)].

There is some debate on what the best treatment for endometriotic cysts is. Any endometriotic cyst greater than 3 cm in diameter should be treated with a laparoscopic ovarian cystectomy as an initial course of action. Since ovarian cystectomy can alleviate pelvic pain and make the egg retrieval process easier to carry out, it is recommended for women with infertility to have one before undergoing assisted reproductive technologies [(2)].

While laparoscopic ovarian cystectomy has the lowest recurrence rate and the highest rate of spontaneous conception, it also carries the risk of severe ovarian damage. It is theorized that the primary causes of ovarian injury are inflammation brought on by surgical trauma or vascular injury and the loss of viable ovarian follicles after surgery. Surgery for endometriotic cysts, according to a few recent studies, can diminish ovarian reserve [(3)].

Ovarian reserve is diminished when healthy ovarian tissue is lost unintentionally during cystectomy. To evaluate ovarian potential, serum anti-Müllerian hormone (AMH) is the gold standard [(4)].

This hormone indicates how many oocytes are ready to fertilize. In reproductively aged females, granulosa cells release AMH. Endometrioma cystectomy by laparoscopy has been shown in multiple studies to reduce circulating levels of the male hormone AMH [(5)].

Numerous gynecologists look for ways to protect ovarian health. We postulated that if surgical blood loss could be reduced, the surgeon would have better visibility of the operational field and would require less bipolar coagulation to complete the procedure. Damage to blood vessels and normal ovarian tissue would be mitigated. In the current investigation, tranexamic acid (TXA) is used as a pharmaceutical technique to lessen surgical blood loss. When given intraoperatively, TXA has been shown to significantly reduce bleeding and wound complications [(6)].

1 gram every 6 to 8 hours is the typical dose that's suggested [(7)]. There is no recommended daily dosage, however in cases of severe bleeding, the amount may be increased to 4 grams [(8)].

The goal of our study was to examine the potential benefit of tranexamic acid on ovarian reserve and intraoperative blood loss, by comparing the mean differences in anti-müllerian hormone (AMH) levels before and after laparoscopic ovarian cystectomy.

SUBJECTS AND METHODS

This prospective interventional trial study included a total of 30 women who had ovarian endometriomas,

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attending at the Laparoscopic and Cytogenetic Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University Hospitals.

Inclusion criteria:
- Intact females of childbearing age (twenty-one to thirty-nine years), having endometriomas >3cm in size with ultrasound, whether single or several sites affected.
- Undergone a laparoscopic cystectomy.

Exclusion criteria:
- Females > 40 years.
- Anatomical or functional ovarian dysfunction; history of pelvic radiation therapy or chemotherapy.
- Menstrual cycle disruptions.
- Ovarian cysts and other ovarian abnormalities were present.
- Pharmaceutical use in the 3 months prior to surgery, including but not limited to GnRH analogues, oral contraceptives, and other drugs that may impact ovarian function.
- Any woman with a high baseline FSH level (greater than 10 mIu/ml) before surgery was considered to have premature ovarian failure.
- Indications or allergies that prevent patient from receiving TXA.
- Preexisting conditions that were at odds with TXA treatment, such as thromboembolic disease.
- AMH concentration below 0.5 ng/ml before surgery.

By using a computer program, the included subjects were categorized randomly into two groups; **Group I (control)** consisted of 15 patients who were subjected to intravenous administration of 110 ml of normal saline preceding the incision of the skin. **Group II** consisted of 15 patients who were subjected to intravenous administration of 1 gram of tranexamic acid (2 kapron 500 mg 5 ml ampoules) preceding the incision of the skin.

All patients were subjected to:
1. **Personal data:** full name, date of birth, place of employment, number of children, their gender, and the youngest child's age, as well as marital status.
2. **Gynecological history:** complete information about menstruation history, any past surgeries, the nature of current ovarian lesion, and any endocrine disorders they had experienced.
3. **Obstetric history:** Birth weight, number of embryos, timing, and outcomes of previous pregnancies and abortions.
4. Body mass index (BMI) determination and full physical looking for indicators of endocrinological issues such hyperprolactinemia, hypothyroidism, or hyperthyroidism.
5. Full gynecological checkup.
6. **Investigations:**
   1. Prior to surgery**,** a **vaginal ultrasound** was done to confirm the diagnosis of chocolate cyst, and a high-resolution transvaginal ultrasound was recommended for all patients on the third day of their third menstrual cycle following surgery. The Proncta ellipsoid formula was used to determine the ovarian volume (Volume = 0.5233 * Height * Length * Width of the ovary in cm). Ovarian volume prior to surgery was calculated by subtracting the volume of the cyst from the total ovarian volume.
   2. **Anti-Mullerian Hormone (AMH) levels** were measured before surgery and again on cycle's day 3 after menstruation had resumed.
   3. **Assessment of the Antral Follicle Count (AFC)**. Once the ovary was found, the transducer was used to navigate the ovary in two dimensions (longitudinally and transversely) so that the antral follicles could be studied. The size of each antral follicle was recorded until the entire ovary was studied. The size of each antral follicle was determined by averaging its two perpendicular diameters (of which one was the greatest dimension). Operated ovarian follicles larger than 2 mm (maximum, 10 mm) in size were calculated.

Operation Technique:

Preoperative preparation:

On the day of their surgeries, patients were hospitalized and required to fast overnight. It was determined that the best time for surgical treatments was between days 4 and 11 of the menstrual cycle, when there was less risk of injuring the corpus luteum.

Laparoscopic ovarian cystectomy:

To eliminate prejudice, it was performed exclusively by the same team of surgeons.

Since endotracheal intubation and general anesthesia made surgical procedures risk-free, no prophylactic antibiotics were required. A 10-mm primary trocar is inserted through an umbilical incision of 1 cm, and two puncture holes are made suprapubic lateral to the rectus muscles for two 5-mm trocars. The abdomen is then inflated with carbon dioxide using a Veress needle to a pressure of 12 mmHg.

The presence of ovarian endometrioma was established after the laparoscope with 5mm ports was inserted to evaluate the peritoneal surfaces, diaphragm, and liver. Sharp dissection was used to free the tissue from all adhesions, and deeply infiltrating endometriosis lesions were excised to the point where anatomical connections were reestablished. Obtuse and precise dissection successfully liberated the ovaries.

To avoid damaging the ovarian hilus, the incision for ovarian stripping must be done on the antimesenteric surface. Two atraumatic grasping forceps were used to carefully and gently remove the ovaries in opposite directions when a cleavage plane was discovered between the cyst wall and the ovarian cortex. Mass reduction was achieved by removing the ovarian cyst, opening it with electrocautery, and sucking out the contents.

After the pseudocapsule was removed from the abdomen, the pelvis was irrigated with Heparinized local ringer so that any bleeding sites could be identified and treated with selective minimum (15 watts) bipolar coagulation to prevent further damage to the ovary.

Blood loss estimation:

- The weight difference between the dry and wet surgical drapes in grams (1 g = 1 ml) was added to the volume of liquid in the suction container to determine the total amount of blood lost during the procedure.
- The intra-peritoneal suction drain was checked every 12 hours after surgery, and the patient's blood loss was calculated.
- After that, intraoperative and postoperative blood loss were added together to get the grand amount.
- Blood transfusion needs were evaluated by measuring hemoglobin and hematocrit concentration on days one and three following surgery.
- Blood loss during surgery, as well as postoperative hemoglobin and hematocrit levels, were used to determine the need for transfusions.

Histopathologic Analysis:
Every removed cyst wall was examined for cancerous cells and the diagnosis of endometrioma was confirmed.
Follow up of all cases till 3 months postoperatively then re-assay of AMH at the day 3 of the cycle for the patients had endometriomas confirmed by histopathology.

Ethical approval:
This study was ethically approved by the Zagazig University's. After being fully informed, all participants provided a written consent. The study was conducted out in line with the Helsinki Declaration.

Statistical analysis

To conduct the quantitative study, we used version 20 of the Statistical Package for the Social Services (SPSS). Tables and graphs were used to display the information. The numerical data was presented with their respective means, medians, standard deviations, and confidence intervals. Data visualisations made use of numerical examples, such as frequency and %. The student's t test (T) is frequently used for analysing quantitative data with independent variables. Using Pearson's Chi-Square and Chi-Square for Linear Trend, we analysed data that was qualitatively different from one another (X^2). To be statistically significant, we determined that a P value of 0.05 or lower was necessary.

RESULTS

Table (1) shows the basic characteristics of both groups. No significant differences regarding age , BMI , mean parity and miscarriage rate between both groups.

Table (1): Characteristics of study groups

	Group I (n=15)	Group II (n=15)	P
Age (years)			
Range	25 – 35	24 – 34	0.701[1]
Mean ± SD	30.15 ± 2.81	29.8 ± 2.91	NS
BMI (kg/m²)			
Range	18 – 28	19 – 27	0.139 [1]
Mean ± SD	24.7 ±3.05	23.35± 2.58	NS
Parity			
Range	0 – 2	0 – 3	0.531 [2]
Median (IQR)	1 (1 – 2)	1 (0 – 2)	NS
No. of Previous Miscarriages			
Range	0 – 2	0 – 3	0.271 [2]
Median (IQR)	1 (1 – 2)	1 (0 – 1)	NS

[1]Analysis using independent student's t-test. [2]Analysis using Mann-Whitney's U-test

Table (2) shows the postoperative serum anti-müllerian hormone (AMH) at one month later after the operation . with significant reported differences, that was higher in Group II . no statistically significant difference between both groups as regards AFC parameter with p-value 0.113. Postoperative serum AMH at six month later after the operation . with significant reported differences , that was higher in Group II . as regards AFC was higher in Group II but with no statistically significant difference between both groups with p-value 0.054.

Table (2): Postoperative AMH and AFC at one month and six month later after the operation

Postoperative	Group I (n=15)	Group II (n=15)	*P*
Serum AMH (ng/ml) Mean ± SD	1.9 ± 0.47	2.8 ± 0.46	0.03[1] S
AFC Mean ± SD	3.12±0.76	3.52±0.87	0.113 NS
Serum AMH (ng/ml) Mean ± SD	2.1 ± 0.50	2.8 ± 0.46	0.03[1] S
Serum AFC Mean ± SD	3.72±0.89	4.28±1.05	0.054 NS

[1]Analysis using independent student's t-test.

Table (3) demonstrates a contrast between AMH levels before and after surgery for both groups. The mean pre-operative serum level of AMH were 3.3 ± 0.8 and 3.2 ± 0.68 ng/ml in group1 and group 2 respectively.

Postoperatively, Group II AMH levels increased dramatically.

Table (3): Pre and- postoperative AMH

Preoperative	Group I (n=15)	Group II (n=15)	P
Serum AMH (ng/ml) Mean ± SD	3.3 ± 0.80	3.2 ± 0.68	0.57[1] NS
Postoperative after one month			
Serum AMH (ng/ml) Mean ± SD	3.3 ± 0.80	3.2 ± 0.68	0.57[1] NS
Postoperative after six month			
Serum AMH (ng/ml) Mean ± SD	2.1 ± 0.5	2.8 ± 0.46	0.03[1] S

[1]Analysis using independent student's t-test.

Table (4) shows a comparison of pre- and post-operative AFC in both groups. There was increase in Group II post-operatively but with no significant differences

Table (4): Pre and- postoperative AFC

	Group I (n=15)	Group II (n=15)	*P*
Preoperative Serum AFC Mean ± SD	6.56±1.35	6.52±1.22	0.913 NS
Postoperative after one month			
Serum AFC Mean ± SD	3.12±0.77	3.52±0.87	0.113 NS
Postoperative after six month			
Serum AFC Mean ± SD	3.72±0.89	4.28±1.04	0.054 NS

Table (5) shows that the total, intraoperative, and postoperative blood loss were all greater in the control group than in the study group.

Table (5): Mean and standard deviation of blood loss pre and postoperative in the studied groups

Blood loss	Group I (n=15)	Group II (n=15)	t-test	P
Bleeding during surgery (ml) Mean ± SD	490± 118.8	305± 73.5	5.7	0.005*
Postoperative blood loss Mean ± SD	72± 17.4	66± 14.4	11.4	0.001**
Determine the approximate amount of blood lost (ml) Mean ± SD	652± 161.1	550± 136.4	15.9	0.001**

Table (6) shows that hemoglobin level was significantly higher post-surgery than in control group. The postoperative hemoglobin levels of both groups were significantly lower than the control group. In terms of HCT, postoperative levels were found to be significantly greater in the study group compared to the control group. Statistical analysis showed no significant difference in preoperative HCT between the groups. Further, postoperatively, HCT dropped considerably in both groups, while the decrease was more pronounced in the control than in the study group.

Table (6): Mean and standard deviation of hemoglobin and hematocrit (HCT) pre- and post-operative among the studied groups

Mean hemoglobin	Group I (n=15)	Group II (n=15)	F-test	P
Preoperative hemoglobin Mean ± SD	11.4±0.8	11.2±0.7	2.5	0.08
Postoperative hemoglobin Mean ± SD	10.1±0.8	10.8±0.7	3.6	**0.03***
P-Value^	**0.001****	**0.005***		
Preoperative HCT Mean ± SD	33.86±2.3	33.67±2.8	1.6	0.5
Postoperative HCT Mean ± SD	30.14±3.7	32.38±2.8	3.2	**0.04***
P-Value^	**0.001****	**0.008***		

Table (6) shows that while the study group required less time in surgery than the control group, the control group required longer hospitalization days.

Table (7): Mean and standard deviation of operative time, hospital stay among the studied groups

Variable	Group I (n=15)	Group II (n=15)	P
Operative time (minutes) Mean ± SD	81±19.7	52.5±7.3	**0.001****
Hospital stay (days) Mean ± SD	1.6±0.3	1.3±0.28	0.001**

Table (7) shows that diarrhea and vomiting were more common in the study group, but the difference was statistically significant.

Table (8): Frequency and percentage of side effects among the studied groups

Side effects	Group I (n=15)	Group II (n=15)	test χ^2	P
Nausea	3 (20.0%)	5 (33.0%)	0.9	**0.01****
Vomiting	1 (6.6%)	2 (12.3%)		
Diarrhea	1 (6.6%)	2 (12.3%)		
Absent	10 (66.0%)	9 (40.0%)		

DISCUSSION

Surgery has an important role in management of ovarian endometrioma by laparoscopic approaches or open laparotomy but the first being less invasive. Surgery has double effects on fertility during management of endometriomas [2].

At 1,6 months after surgery, the current study found that women who had laparoscopic cystectomy for endometriotic cysts had less ovarian reserve than women who had not undergone the procedure. Consistent with previous studies' findings [5, 9, 10].

Possible causes of diminished ovarian reserve include heat injury and the accidental removal of healthy follicles during a cystectomy. Parenchymal tissue and a primordial follicle were present in the ovarian samples taken during surgery, indicating normal ovarian function [11]. While electrocauterization techniques like bipolar electrosurgery are commonly used to reduce blood loss during laparoscopic cystectomy, they have the potential to damage ovarian follicles if used excessively [12].

Several methods, including surgical procedures, chemical agents, and pharmaceuticals, have been reported to slow or stop the loss of ovarian reserve following laparoscopic ovarian surgery [13, 14]. Individuals who underwent ovarian cystectomy had a greater postoperative decrease in ovarian reserve compared to those who underwent ovarian ablation (or vaporization) and deroofing; nevertheless, patients who underwent ovarian ablation and deroofing had a higher rate of cyst recurrence [4]. According to a meta-analysis of 1047 individuals, laparoscopic ovarian suture is more effective at preserving ovarian function than bipolar electrosurgery. When compared to bipolar coagulation, a hemostatic sealant agent performed far better. Comparison of ultrasonic electrosurgery and bipolar coagulation found no significant difference [3]. However, there is a lack of literature on how TXA affects ovarian reserve after laparoscopic cystectomy.

TXA is used in a wide variety of conditions where it can assist stop bleeding. TXA (trans-4-(aminomethyl)cyclohexanecarboxylic acid) is a competitive inhibitor of tissue plasminogen activator and is synthesized from the amino acid lysine. It prevents plasminogen activation and fibrin binding to plasminogen by blocking lysine binding sites on plasminogen, therefore inhibiting fibrinolysis. At high concentrations, TXA blocks the formation of the protein plasmin [15]. The evidence that TXA reduces blood loss during major surgery is robust. TXA has been shown to reduce blood transfusion needs by almost a third, according to a major systematic evaluation of many randomised controlled trials (RCTs) involving 10,488 surgical patients[15].

When used for local fibrinolysis, TXA is given intravenously at a dosage of 0.5-1 g (equivalent to 15 mg/kg) every 6-8 hours, but when used for systemic fibrinolysis, a single dose of 1.1 g (10 mg/kg) is given [2].

According to **Heyns *et al.*** [2] meta-analysis, .'s 15 mg/kg is the most common single dose utilised to decrease perioperative predicted blood loss across a variety of surgical procedures. **Abbasi *et al.*** [16] performed research comparing the efficacy of 5 and 15 mg/kg of TXA for sinus endoscopic procedures [2]. TXA 15 mg/kg reduced blood loss more and resulted in a more satisfied surgical field according to the study than TXA 5 mg/kg. For this reason, we selected to study the aftereffects of a single 1 gramme dose of TXA (equivalent to 15–20 milligrams per kilogram of body weight). However, single doses of TXA up to 100 mg/kg were documented during coronary artery bypass grafting [17].

The current study provided evidence of TXA's efficacy in lowering blood loss. TXA resulted in decreased blood loss compared to the control group.

As far as we know, this study is the first to measure the mean difference in AMH levels between before and 1.5 months following laparoscopic ovarian cystectomy to assess the effect of TXA on ovarian reserve. It was discovered that ovarian function can be maintained by intra-operative TXA. Although this study's sample size was limited, a larger future investigation might be done, perhaps even involving many research institutes, in order to corroborate these findings. In line with our findings, TXA has been associated with few adverse events to date [15].

CONCLUSION

The current study's findings lend credence to the hypothesis that reducing the risk of ovarian reserve loss after laparoscopic cystectomy for endometrioma is facilitated by intravenous TXA administration.

Study strength:
- To the best of our knowledge, this study was the first of its kind, randomized controlled trial, and all surgeries were conducted by surgeons with similar levels of experience.
- The results of this study can inform future investigations into the prevention of ovarian reserve reduction during ovarian surgery by providing important information about the optimal dosage and administration methods of tranexamic acid, among other outcome variables like surgeon satisfaction and the relative ease of the operation.

Study limitations:
- Short time follow-up.
- No evaluation of follicle-stimulating hormone [FSH], inhibitor-B, or sonographic indicators of ovarian reserve.

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