The efficacy and safety of intravenous oxytocin versus Tranexamic acid in reducing blood loss during abdominal myomectomy; A randomized controlled trial

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Abstract

Objectives: The study's objective is to examine the effectiveness and safety of intravenous oxytocin and intravenous tranexamic acid (TXA) in minimising intraoperative bleeding during open myomectomy.

Method:A total of 75 patients who met the inclusion criteria and had uterine fibroid were scheduled for abdominal myomectomy. In a 1:1:1 allocation ratio, patients were randomly assigned to one of three groups. The groups were divided into three categories: Tranexamic acid (group A), oxytocin (group B), and control (group C) (n=25 per group). Estimated blood loss (EBL) during open myomectomy, need for intraoperative and postoperative blood transfusion, operating time, myomectomy time, postoperative hematocrit and hemoglobin, drop in postoperative hematocrit, side effects of TXA and oxytocin, as well as postoperative stay in days, were all achieved in each of the three groups.

Results: patients in TXA group had significantly lower intra operative blood loss than control group (222.16 ±29.55 versus 570.46 ±53.46; p <0.001). Likewise, patients in Oxytocin group had significantly lower intra operative blood loss than control group (234.52 ±28 versus 570.46 ±53.46; p <0.001). There were no statistically significant differences between TXA and Oxytocin groups in intraoperative blood loss (p =1.00). , there were statistically significant differences between the studied groups regarding requirements for postoperative blood transfusion; Patients in TXA group (12%) which were 3 patients and oxytocin (8%) group which were 2 patients had significantly lower need for postoperative blood transfusion than the control group (36%) which were 9 patients ; p =0.031). patients in TXA and Oxytocin groups had significantly higher postoperative hemoglobin

after 6 hrs(TXA 9.92±0.52),(oxytocin 9.81±0.54),(control 8.72±0.62) (p <0.001), postoperative hemoglobin after 24hrs (TXA 9.81 ±0.52),(oxytocin 9.71 ±0.52),(control 8.60±0.64) (p <0.001), postoperative hematocrit after 24 hrs (TXA 29.34±1.53),(Oxytocin 29.20±1.44),(control 26.38±2.28) (p <0.001) , and lower hemoglobin reduction (TXA 0.42±0.18),(OXYTOCIN 0.39±0.12) ,(CONTROL 1.20±0.24) (p <0.001). There were no statistically significant differences between TXA and Oxytocin in the hematological and hemodynamic parameters. There were no statistically significant differences between studied groups in terms of postoperative stay (p =0.8), operative time (p =0.2), and myomectomy time (p =0.05).

Conclusion: Both TXA and IV oxytocin are effective and safe pharmacological approaches for reducing intraoperative blood loss and the need for blood transfusion among women undergoingabdominal myomectomy. However, our results showed that both TXA and IV oxytocin were comparable in efficacy with no superiority of one agent over the other

Key words: Oxytocin –Tranexamic acid – Myomectomy –Hemostasis.

Introduction

The most prevalent pelvic tumor in females is a uterine leiomyoma[1]. They are benign monoclonal tumors that develop from fibroblasts and smooth muscle cells in the myometrium. In women of reproductive age, they often present as abnormal uterine bleeding and/or pelvic discomfort or pressure. Fibroids in the uterus have the potential to have an impact on reproduction (e.g., unfavorable pregnancy outcomes, infertility) [2]. The following is the categorization scheme for fibroid location used by the International Federation of Gynecology and Obstetrics (FIGO): [3]. (FIGO types 3, 4, and 5) Intramural myomas They take place within the uterus's wall. They could enlarge to the point of warping the serosal surface or uterine cavity. The fibroids known as transmural are those that extend from the mucosal surface to the serosal layer. Expectant treatment, pharmacological therapy including hemostatics, hormonal therapy, and analgesics, as well as surgical intervention like myomectomy and hysterectomy, are all used in the management of patients. After consulting with her doctor, the patient chooses her course of treatment from a number of pharmacological and non-pharmacological approaches

that have been tried and evaluated to reduce bleeding after myomectomy. Currently, there is fair-quality data suggesting that oxytocin and tranexamic acid may lessen myomectomy bleeding.

Surgery called a myomectomy has the potential to cause serious bleeding. The use of oxytocin to decrease uterine perfusion and consequently bleeding after myomectomy raises questions due to its effectiveness on the postpartum uterus. Oxytocin infusion has been shown to mitigate the hematocrit decline experienced following hysteroscopic myomectomy, according to Shokier et al. [4]. Oxytocin may reduce bleeding and the need for blood transfusions after laparoscopic myomectomy and laparoscopic vaginal hysterectomy, according to Wang et al. [5]. Cetin et al. evaluated the effectiveness of oxytocin infusion in reducing intraoperative bleeding during abdominal myomectomies and discovered that intravenous oxytocin infusion was a safe and practical technique for doing so[6]. Contrary to the serine protease inhibitor antifibrinolytic aprotinin, the usage of tranexamic acid (TXA) has increased.[7,8]**.** Oxytocin is mostly released by the pituitary gland. The contraction of the uterus during labor and delivery is its primary function. The drug of choice for preventing postpartum uterine atony and bleeding is oxytocin, although it should be administered with caution since a 10 IU intravenous bolus of oxytocin may have negative effects on hypovolemic or heart-diseased women.There are 19 oxytocin receptors in the uterus when it is not pregnant, but they are significantly less concentrated than they are during pregnancy. Because of this, oxytocin's therapeutic use outside of pregnancy are restricted[3]. Our study aims to investigate the safety and efficacy of intravenous Oxytocin versus Tranexamic acid in reducing intraoperative blood loss during abdominal myomectomy.

Patient and method

This study was a double-blinded randomized controlled study conducted inKasrAlainy obstetrics and gynecology Hospital, Cairo University, Cairo, Egypt, from May 2019 to April 2021. The research protocol was prospectively filed at clinical trials.gov after being approved by the Cairo University ethics committee (MD-24-2019). All participants received a thorough explanation of the study's purpose and methods from us. Before the trial began, eligible patients who consented to participate gave written informed consents. All patients who visited the Kasr Alainy outpatient gynecology clinic complaining of heavy menstrual bleeding, pain during menstruation, or abdominal enlargement and who underwent abdominal myomectomy met our inclusion criteria and were found to have uterine myomas on ultrasound.

Inclusion and Exclusion criteria:

We include in our paper patient with Age (18-50) years old, Single submucous myoma grade 2, according toFIGO classification**,** Myoma size (5-10 cm) and Symptomatic myomas (heavy menstrual bleeding or pain during menstruation or abdominal enlargement)[4].

We excluded from our paper patient with Subserous or interstitial myomas grades 0,1,3,4,5,6,7,8 according to FIGO classification[4]**,** myomectomy performed by laparoscopy or hysteroscopy, medical conditions (such asuncontrolled hypertension, diabetes mellitus, diseases of the kidneys or liver), blood clotting issues, current anticoagulant medication usage, a priormyomectomy, Tranexamic acid or oxytocin allergies or contraindications, pregnancy, and prior hormonal treatment (GnRH analogues) within the previous six months.

Randomization and Allocation

A computer-generated random numbers table was used to simply randomise the study's participants. Based on a computer-generated random numbers table, participants were randomly assigned to intervention and placebo groups in a ratio of 1:1:1. The allocation sequence was created by a hospital chemist who was not engaged in carrying out the intervention or analysing the results. The research medications and solutions were produced by an independent hospital chemist before being packaged and administered in serially numbered sealed opaque envelopes that were only unzipped one at a time before to the procedures. According to the directions listed on the allocation cards, the anesthesiologists delivered the research drugs. Anesthesiologists, surgeons, outcome assessors, and all other researchers were kept in the dark about the participants' allocation up until the study's conclusion.

Interventions **Preoperative**

Complete history taking, clinical abdominal and pelvic examinations to measure the size and movement of the uterus, reporting of demographic data on included patients, such as age, gravidity, parity, and the number of prior caesarean births, All US exams were conducted by a qualified sonographer with at least five years of expertise in gynecologic sonography, using transabdominal and transvaginal probes (Sonoace R5; Samsung Medison) to precisely detect the location, number, and grade of myoma and other abnormalities. The preoperative CBC, coagulation profile, liver function tests, and kidney function tests are among the preoperative laboratory examinations.

Intraoprative

In the 30 minutes before to the start of surgery, all patients received a prophylactic antibiotic in the form of 1 gramme of IV ceftriaxone (Ceftriaxone Sodium 1 G

Kahira 1 vial, Kahira Pharm & Chem. Industry, Cairo, Egypt). Six seasoned gynaecologists with at least 10 years of experience carried out the procedures using a Pfannenstiel incision in accordance with normal practise to guarantee uniformity of research methods. The doctors came to an agreement to standardise the surgical stages and guarantee uniformity in the surgical procedures prior to the trial's commencement. General anaesthesia was given to all patients. Following the skin incision, the abdominal fascia and subcutaneous fat were split lengthwise, and the rectus muscle was split in half. To access the pelvic cavity, the parietal peritoneum was longitudinally dilated. The intestine was then packed after a self-retaining retractor was placed. The number, location, and kind of myomas in the uterus were all carefully examined. The pathology of any more pelvic organs was examined. To minimise postoperative adhesions, uterine incisions were made on the fundus or anterior wall of the uterus wherever feasible. Using either a scalpel or monopolar diathermy, the incision was made. Myomas were gently dissected between the myoma and the pseudocapsule during intracapsular enucleation. The myoma was gently removed by enucleation. Low-voltage feeding vessel coagulation ensured precise hemostasis. One or two layers of interrupted vicryl sutures (Vicryl 1-0 polyglactin 910; Egycryl, Taisier CO, Egypt) were used to seal the myoma bed. Patients scheduled for open abdominal myomectomy were randomly assigned to one of three equal groups. No mechanical tourniquet or local Vaso occlusive medications (such as vasopressin) were administered intraoperatively.

Women in group (A) (the tranexamic acid group) received TXA (kapron ampoule is 500 mg/5 ml, Amoun Co., Qalyubia, Egypt) as a single bolus intravenous injection over a 10-minute period at a dose of 10 mg/kg (up to 1 g). Tranexamic acid will be administered 15 minutes before to skin incision, and then will be continuously infused for 6 hours at a rate of 1 mg/kg/h dissolved in 1 L of saline (up to 1 g/6 h).

Women in group (B) (the oxytocin group) will be administered 10 IU of oxytocin (syntocinon 10 IU, Minafarm, Cairo, Egypt) in 500 ml of saline at a rate of 120 ml/h five minutes prior to the onset of anaesthesia and during the procedure.

Before and during the procedure, women in group (C) (the placebo group) will receive a 500 ml saline infusion at a rate of 120 ml/h.

Haemoglobin and hematocrite postoperative measurements at 6 and 24 hours, respectively Watch your vital signs, see whether you require a blood transfusion, and send myoma tissues for histopathology.

Outcome

Primary result: The blood count in the suction device was added to the total weight of the pads [pad count (wet pad weight dry pad weight)] to determine the intraoperative blood loss in millilitres (ml). Blood density (1.050 g/ml) was used to convert the grammes of swabs' weight to ml .

Additional outcome criteria: operation time, When is myomectomy? Haemoglobin and hematocrit levels pre and postoperatively, as well as levels of haemoglobin drop, postoperative blood transfusion was indicated if the haemoglobin (Hb) level 6 hrs. or 24 hrs. postoperatively was 7g/dL and/or relevant clinical manifestations, as well as the need for massive blood transfusion (more than five blood units).

Statistical analysis

The data were coded and entered using SPSS version 26 (IBM Corp., Armonk, NY, USA), statistical software for the social sciences. For quantitative variables, the results were summarised using the mean, standard deviation (SD), mean difference (MD), and 95% confidence interval (CI). Frequencies (number of occurrences) and relative frequencies (percentages) were used to summarise the data for categorical variables. For comparisons between groups, analysis of variance (ANOVA) with multiple comparisons post hoc test was used for quantitative variables that were normally distributed, whereas non-parametric

Kruskal-Wallis test and Mann-Whitney test were employed for non-normally distributed quantitative data. P-values ≤ 0.05 were considered significant in statistics.

Sample size

The quantity of blood lost during abdominal myomectomy in instances treated with tranexamic acid (G1), oxytocin (G2), and untreated patients (G3) was compared to determine the sample size. According to other studies[2], [5] the mean SD of blood loss in G1 was 346.7 92.1 ml, 189.5 16.7 ml in G2, and 574.3 194.6 ml in G3. In order to detect a difference in blood loss of 100 ml with 90% power using a one-way analysis of variance test, we determined that the minimum appropriate sample size was 25 patients in each arm, for a total of 75 patients. G*Power software (version 3.1.2 for MS Windows, Franz Faul, Kiel University, Germany) was used to calculate the sample size.

Results

We assessed 123 patients to see whether they were eligible for the trial; 48 were rejected; 35 did not match the requirements, and 13 did not want to take part. The final analysis included the remaining 75 eligible individuals who were randomly assigned to the TXA group (25 patients), the oxytocin group (25 patients), or the placebo group (25).

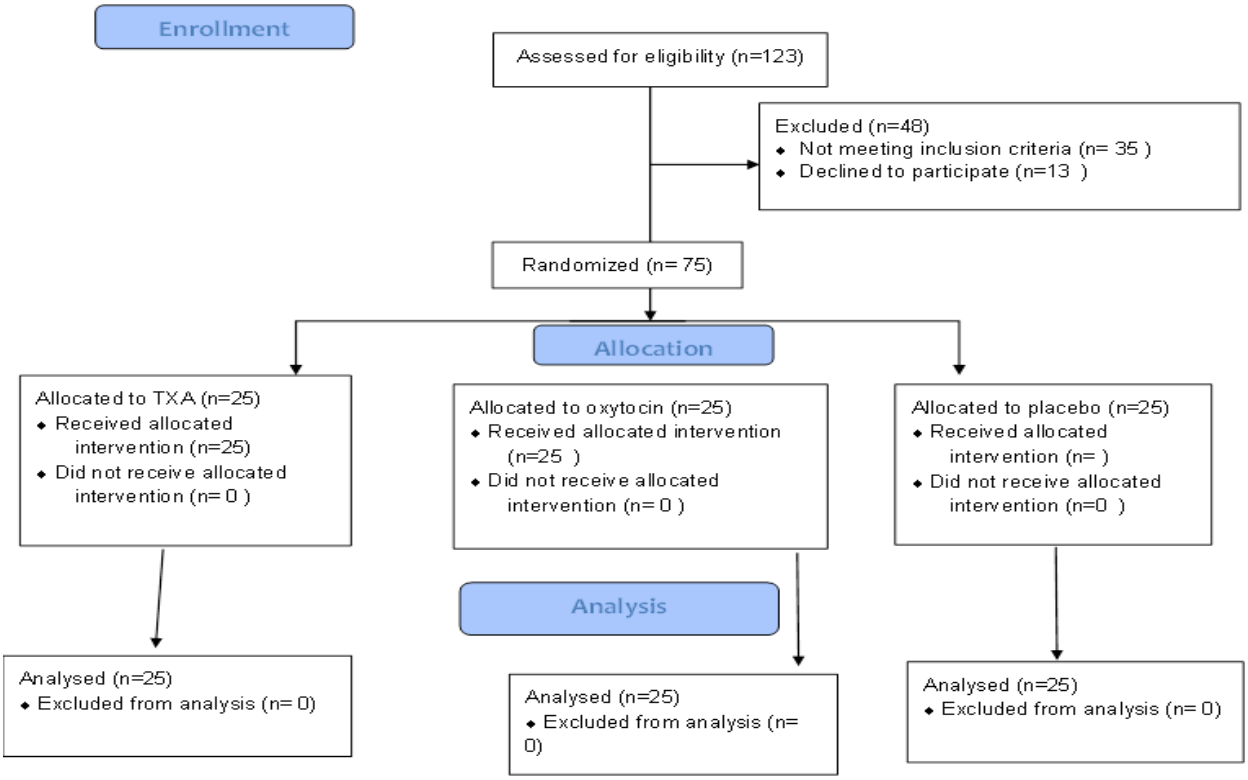

Figure 1: Consort flowchart

Table 1: The Baseline and Clinical Characteristics of the Included Patients

POV	Control group	Oxytocin group	Tranexamic acid group	P value
Age	31.40±2.50	32.68±2.12	31.88±2.33	0.15
Gravidity	1.44±0.82	1.80±1.08	1.92±0.95	0.17
Parity	0.96±0.68	0.92±0.57	0.86±0.68	0.97
Number of previous Cs	0.56±0.58	0.76±0.44	0.66±0.72	0.35
Preoperative Hb	9.82±0.50	10.20±0.53	10.13±0.49	0.059
Preoperative hematocrite	29.40±1.61	30.30±1.49	30.42±1.50	0.059
Size of myoma by U/S in(cm)				0.65
5	6(24.0%)	11(44.0%)	7(28.0%)	
6	11(44.0%)	6(24.0%)	7(28.0%)	
7	6(24.0%)	4(16.0%)	8(32.0%)	
8	1(4.0%)	3(12.0%)	2(8.0%)	

9	1(4.0%)	1(4.0%)	1(4.0%)	
Number of myoma removed operatively				1
1	21(84.0%)	23(92.0%)	22(88.0%)	
2	4(16.0%)	2(8.0%)	3(12.0%)	
Gravidity				0.45
nuligravida	3 (12.0%)	3 (12.0%)	2 (8.0%)	
Gravida 1	10 (40.0%)	7 (28.0%)	5 (20.0%)	
Gravida 2	10 (40.0%)	8 (32.0%)	12 48.0%	
Gravida 3 or more	2 (8.0%)	7 (28.0%)	6 (24.0%)	
Parity				0.89
Nullipara	6 (24.0%)	5 (20.0%)	6 (24.0%)	
Para1	14 (56.0%)	17 (68.0%)	14 (56.0%)	
Para2	5 (20.0%)	3 (12.0%)	5(20.0%)	
Number of previous Cs				0.14
Previous. 1 CS	12 (48.0%)	18 (72.0%)	11 (44.0%)	
Previous 2CS	1 (4.0%)	1 (4.0%)	4 (16.0%)	
No previous CS	12 (48.0%)	6 (24.0)%	10 (40.0%)	

Table (1) showed that the age, gravidity, parity, number of previous CS, preoperative HB, HCT,Size of myoma and Number of myoma removed were comparable between three groups with no statistically significant difference between them (p-value > 0.05). there were no statistically significant differences between the three studied groups in terms of gravidity (p =0.45), parity (p =0.89), and the number of previous CS (p =0.14).

Table 2:Intraoperative Blood Loss

	Control group	Oxytocin group	Tranexamic acid group	
Blood loss in ml	570.46± 53.46	234.52±28.00	222.16±29.55	< 0.001

Table 2 showed that there was a statistical difference between the three groups regarding intraoperative blood loss (p <0.001).

Table 3: The Post-hoc Pairwise Comparison of Blood Loss in the study group

post hoc analysis			Mean Difference	P value	95% Confidence Interval	
					Lower Bound	Upper Bound
Intraoperative Blood loss in ml	Control group	Oxytocin group	347.94*	<0.001	321.043	374.837
		Tranexamic acid group	348.3*	<0.001	321.403	375.197
	Oxytocin group	Control group	-347.94-*	<0.001	-374.8370-	-321.0430-
		Tranexamic acid group	0.36	1	-26.5370-	27.257
	Tranexamic acid group	Control group	-348.3-*	<0.001	-375.1970-	-321.4030-
		Oxytocin group	-0.36-	1	-27.2570-	26.537

Table 3. Patients in TXA group had significantly lower blood loss than the control group (222.16 ±29.55 versus 570.46 ±53.46; p <0.001). Likewise, patients in the Oxytocin group had significantly lower blood loss than the control group (234.52 ±28 versus 570.46 ±53.46; p <0.001). There was no statistically significant

difference between TXA and Oxytocin groups regarding intraoperative blood loss (p =1.00).

Discussion

The most frequent benign tumors in females, uterine fibroids afflict roughly one in four women in the United States (US) alone and are the leading cause of hysterectomy. In addition, recent data from throughout the world revealed that, depending on the region, the incidence of uterine fibroids varies from 217 to 3745 instances per 100,000 women-years.[6]. The condition starts with a non-malignant proliferation of the cells of myometrium during the reproductive period (peak incidence at 50 years) that tends to regress after menopause[7].Most fibroids occur in women between the ages of 30 and 40. Most significant risk factors that enhance exposure to greater levels of endogenous oestrogen are present because of the pathology of fibroids. Early menarche, nulliparity, being obese, starting menopause later than usual, and having uterine fibroids in the family are some risk factors.[8].

Although uterine fibroids are asymptomatic in the majority of the affected women, they can lead to many complaints ranging from mild to more severe forms. Previous reports showed that symptomatic females with uterine fibroids present mainly with menstrual abnormalities, pelvic pain and less commonly with infertility or obstetric complications. Therefore, either symptomatic or definitive treatment of uterine fibroids is required in a considerable proportion of the affected females. The treatment options for uterine fibroids include conservative – symptomatic- treatment, myolysis, hysterectomy, and myomectomy[9].

To our knowledge, there are no other comparative trials that compared TXA versus Oxytocin for blood loss reduction during abdominal myomectomy. However, other reports demonstrated that TXA and Oxytocin are effective compared to no treatment in reducing intraoperative blood loss.

Mohamed et al.'s (2019) comparison of the safety and effectiveness of oxytocin against TXA in lowering perioperative blood loss following hysteroscopic myomectomy is consistent with our results. In this research, 60 patients who were scheduled for hysteroscopic myomectomy were divided into two groups and given either 10 mg/kg of TXA or 10 IU of oxytocin as an intravenous infusion. The volume of intraoperative blood loss and the need for postoperative blood transfusion were similar across the two research groups[15].

In a 2012 study, Mousa et al. randomly allocated 50 women undergoing hysteroscopic myomectomy to receive either TXA (15 mg/kg) or oxytocin (400 mU/min). They observed no significant difference between the two groups in terms of the need for blood transfusions, which is similar to our study[16].

Fusca et al.'s (2019) study, for instance, looked at how well TXA reduced postoperative blood loss in female myomectomy patients. Up to June 3, 2017, electronic bibliographic databases were searched. In three trials, women who had abdominal myomectomy were included. In comparison to control arms, TXA substantially decreased both intraoperative blood loss and postoperative blood loss by a mean difference of 213.1 mL (95% CI -242.4 to -183.7) and 56.3 mL (95% CI -67.8 to -44.8), respectively[17].

In order to evaluate the effectiveness and safety of TXA for minimising blood loss and the need for transfusions in patients having open myomectomy, et al. (2017) conducted a meta-analysis. Four RCTs with 328 patients each satisfied the requirements for inclusion. The meta-analysis revealed that there were substantial variations in total blood loss across groups[5].

In their 2008 study, Caglar et al. sought to characterise the impact of TXA usage on perioperative and postoperative bleeding as well as the need for blood

transfusions in myomectomy patients. A total of 100 instances from the patients who had myomectomy were examined. Group I consisted of the patients (n=50) randomly assigned to receive tranexamic acid, while Group II consisted of the patients randomly assigned to receive saline. When postoperative and overall blood loss were evaluated between the two groups, statistically significant differences were discovered[18].

The efficiency and safety of using oxytocin to lessen blood loss after abdominal myomectomy were evaluated by Atashkhoei et al. in 2017. Two groups of women were randomly allocated. During myomectomy, oxytocin 30 IU in 500 ml of normal saline was given to the study group (n = 40), while pure normal saline was given to the placebo group (n = 40). In comparison to the placebo group, the estimated intraoperative blood loss in the study group (189.5 16.72 ml) was considerably lower (95% CI 672.54-711.96; P 0.0001)[9]. The study group saw much less need for blood transfusions. Blood transfusions were necessary for three (7.5%) study group participants and ten (25%) placebo group participants (95% CI 15.5-34.5; P 0.001).

In a study by Shokeir et al. (2011), they examined the impact of oxytocin drip on intraoperative bleeding and irrigation fluid (glycine) deficit during hysteroscopic endometrial resection. They found that the oxytocin drip significantly reduced the need for blood transfusions and intraoperative bleeding when compared to the placebo group[4].

Samy et al.'s study in 2019 included a network meta-analysis and systematic review of perioperative non-hormonal pharmacological therapies for bleeding control during open and minimally invasive myomectomy. 26 randomised control trials (RCTs; N = 1627) were a part of this investigation. Although the evidence was of poor quality, network meta-analysis showed that oxytocin, ornipressin,

misoprostol, bupivacaine with epinephrine, and vasopressin were beneficial in lowering myomectomy blood loss for minimally invasive procedures (9 RCTs; 474 patients). According to a subgroup analysis of minimally invasive myomectomy treatments, oxytocin and ornipressin had the best rankings for reducing blood loss. Although the data is of low quality, network meta-analysis showed that vasopressin plus misoprostol (MD 652.97 mL, 95% CI 1113.69, 174.26), oxytocin, TXA, and misoprostol were effective for open myomectomy (17 RCTs; 1,153 patients). Vasopressin combined with misoprostol performed the open myomectomy with the least amount of blood loss.[19].

Strengths and Limitations

Based on a comprehensive literature search, our study is the first RCT to compare IV oxytocin and IV TXA in reducing intraoperative blood loss in open abdominal m**yo**mectomy and the randomized study design and proper blinding of allocation,and strict adherence to consort guidelines for reporting RCTs were points of strength in our study.

Limitations

small sample size in each study group, absence of combination groups and Not using different doses of drugs.

Conclusion

The study concluded That most successful treatment for minimally invasive myomectomy is oxytocin. To successfully limit blood loss during open myomectomy, a combination of uterotonics and peripheral vasoconstrictors is required..

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