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Hemostatic Effect of Intrauterine Instillation of Oxytocin in Hysteroscopic Myomectomy: A Randomized Double Blinded Control Trial

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Abstract

Introduction: Uterine myomas are benign, smooth muscle tumors of the uterus that are affected by estrogen and progesterone. Most fibroids are asymptomatic and require no intervention or further investigations. Fibroids arise from the uterine smooth muscles then migrate to a place of lower resistance becoming subserosal or submucous myomas or remains intra-myometrial.

Aim of the Work: The main aim of this study was to investigate whether the intrauterine instillation of oxytocin into the distention medium during hysteroscopic myomectomy will reduce blood loss and improve surgical visibility.

Patients and Methods: This Randomized controlled double blinded clinical trial was conducted at Early Cancer Detection Unit (ECDU) at Ain Shams University hospitals. This study included 60 women who were scheduled to undergo a hysteroscopic myomectomy were divided into two equal groups: Group A (Oxytocin group): 30 women underwent a hysteroscopic myomectomy with the use of 10 IU of oxytocin for every 1000 ml of the distending medium. Group B (Placebo group): 30 women underwent hysteroscopic myomectomy with the use of a sterile bacteriostatic water ampule for every 1000 ml of the distending medium.

Results: Groups were comparable in demographic data (in terms of age) and surgical data sin term of (myoma size and number and duration of surgery) and intraoperative fluids and there was no statistically significant difference between groups. There were significant difference in Hgb and Hct drop in each group but control group showed more mean difference than oxytocin group. Our results showed that groups were comparable in post-operative need of blood transfusion and 2nd surgery and there was statistically significant difference between groups in post-operative Hgb and HCT. Groups were comparable in surgeon evaluation in term of visual fluid clarity and there was statistically significant difference between groups in surgeon rating bleeding. Our results showed that groups were comparable in complications in term of (uterine and medical) and there was no statistically significant difference between groups regarding complications.

Conclusion: Complications during diagnostic hysteroscopy are common. Intrauterine instillation of oxytocin into the distention medium during hysteroscopic myomectomy reduce blood loss and improve surgical visibility. More studies with varied dosages and methods are needed to validate these findings.

Key words: Hemostatic, intrauterine, oxytocin, hysteroscopic myomectomy

Introduction

Uterine myomas are benign, smooth muscle tumors of the uterus that are affected by estrogen and progesterone. Most fibroids are asymptomatic and require no intervention or further investigations.[1] Fibroids arise from the uterine smooth muscles then migrate to a place of lower resistance becoming subserosal or submucous myomas or remains intra-myometrial.[2]

Twenty to fifty percent of fibroids are associated symptoms as abnormal uterine bleeding, congestive dysmenorrhea, pressure symptoms, infertility and recurrent pregnancy losses, especially when these fibroids are submucous.[3]

The standard treatment of symptomatic myomas is hysterectomy for women who have completed childbearing period, and myomectomy for women who wish to preserve fertility hysteroscopic myomectomy currently is the gold standard minimally invasive procedure for the management of symptomatic submucous fibroids.[4]

The classification of submucous leiomyomas is helpful when considering different therapeutic options.[5] The European society for gynecological endoscopy (ESH) classified submucous uterine fibroids according to extent of myometrial involvement into: Type 0 in which the myoma is completely within the endometrial cavity, Type 1 in which the myoma extends less than 50 % into the myometrium and type 2 in which the myoma extends 50 % or more within the myometrium.[6]

Success of hysteroscopic myomectomy depends on good visualization throughout the procedure, via the correct distending pressure, continuous irrigation and the use of electrosurgery to control bleeding. Prolonged procedures that need continuous irrigation under high pressure are associated with higher risk of excessive fluid absorption and intravasation syndrome due to opened blood vessels within the myometrial, moreover, the thermal damage of the healthy tissues is increased with the use of the coagulation current.[7]

Hysteroscopy is best performed when the endothelium is thin, because the uterine cavity is large enough; the hysteroscopic examination is facilitated; removing intrauterine pathologies is easier; the amount of required media is low; the odd of hysteroscopy-related complications is diminished and the patient is more satisfied with the procedure and it's outcome.[8]

A number of strategies have been put forward to obtain this, including the utilization of vaginal or oral danazol and GnRH analogues preoperatively, these medications lead to reduction of intraoperative bleeding to some extent that the amount of media required for uterine distension is reduced, however, they do not have any control over post-operative bleeding.[9] Also, these medications are expensive with significant complications and needs to be administrated soon enough before the operation to give time to their beneficial effects to take place.[10]

Oxytocin on the other hand, is a uterotonic medication that reduce bleeding through stimulating the uterine smooth muscle contraction and subsequent vascular luminal narrowing. Intravenous oxytocin

has a very short half-life 4-10 minutes.[11] although oxytocin is considered to be a safe drug, it can cause tachycardia, hypotension and antidiuretic effect.[12]

This study is the first double blinded randomized placebo controlled trial to assess the efficacy of intrauterine instillation of oxytocin in women undergoing hysteroscopic myomectomy.

Aim of the work

The aim of this study is to investigate whether the intrauterine instillation of oxytocin into the distention medium during hysteroscopic myomectomy will reduce blood loss and improve surgical visibility.

Patients and methods

This randomized controlled double blinded clinical trial was conducted at Early Cancer Detection Unit (ECDU) at Ain Shams University hospitals. This study included 60 women who were scheduled to undergo a hysteroscopic myomectomy were divided into two equal groups: Group A (Oxytocin group): 30 women underwent a hysteroscopic myomectomy with the use of 10 IU of oxytocin for every 1000 ml of the distending medium. Group B (Placebo group): 30 women underwent hysteroscopic myomectomy with the use of a sterile bacteriostatic water ampule for every 1000 ml of the distending medium about 2 years from May 2021 to May 2023. 60 women who are scheduled to undergo a hysteroscopic myomectomy will be included.

Inclusion Criteria

The subjects must be able to understand and sign the study specific informed consent after explanation of the nature of the study and possible complications, symptomatic submucous myoma (Menorrhagia, recurrent pregnancy loss or infertility), one or two submucous uterine myoma diagnosed by transvaginal ultrasound with a diameter equal to or less than 4 cm and grade 0 or 1 according to classification of the ESH, body mass index less than 35.

Exclusion criteria

Pregnancy, active pelvic infection, history of bleeding disorder or patient on anti-coagulant, patient with cardiopulmonary, hepatic and renal diseases or history of ischemic heart disease, patients with uterine structural abnormality or uterine septum, present or history of cervical or uterine cancer, preoperative administration of GnRH analogues or danazol, allergy or/ and contraindication to medium specified in the treatment protocol, patients with high risk for thromboembolism as hypercoagulopathy.

Group A (Oxytocin group): 30 women will undergo a hysteroscopic myomectomy with the use of 10 IU of oxytocin for every 1000 ml of the distending medium.

Group B (Placebo group): 30 women will undergo hysteroscopic myomectomy with the use of a sterile bacteriostatic water ampule for every 1000 ml of the distending medium.

Study Procedures

Patients were subjected to: History taking: including personal history, menstrual and obstetric history, medical and surgical history, medications, Clinical examination; General and local with special concern about: size and position of the uterus, trans-vaginal 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 the inner edge of uterine serosa. Laboratory evaluation: All participants will have routine blood tests: Complete Blood Count (CBC), serum creatinine, viral markers, coagulation profile and liver function tests.

Surgical procedure:

Office hysteroscopy will be performed the day before the procedure with the use of a 2-9 mm telescope with continuous-flow sheath (Hopkins

II telescope 30 degrees: Karl storz, Tuttlingen, Germany) to assess and confirm the fibroid location, its intracavitary portion and to exclude any associated uterine pathology). Hysteroscopy will be performed in the early proliferative phase (postmenstrual) in dorsal lithotomy position under general anesthesia, cervical dilatation will be done with Hegar dilators then resection of the submucous fibroid using monopolar resectoscope using 1,5% glycine as a distension medium by Lecturer on duty. The intervention group (oxytocin group) will receive 10 IU of oxytocin for every 1000 ml of the distending medium. While in the control group a sterile bacteriostatic water ampule in the same form will be added to every 1000 ml of the distending medium. After completing the procedure, the surgeon will complete a record scale to document estimated blood loss, rating the bleeding (0: no bleeding, I; mild bleeding, II: moderate bleeding, III: severe bleeding, IV: severe bleeding with clots). Also will document the clarity of visual field using 3 point lickert scale as (poor, fair, good).

Post operative settings

The duration of surgery & the volume of injected media will be calculated and documented. All patients will be subjected to postoperative hemoglobin & hematocrit 12 hours after the procedure, any intraoperative or postoperative complications (either surgical or medical) will be documented.

Statistical analysis

Data were analyzed using Statistical package for Social Science (SPSS) version 27.0., Quantitative data were expressed as mean± standard deviation (SD) or Median (IQR) when indicated. Qualitative data were expressed as frequency and percentage. The p-value was considered significant as the following: P-value <0.05 was considered significant.

Results

Sixty (60) patients were enrolled in the study. 30 patients in each group. Groups were comparable in demographic data (in terms of age) and surgical data sin term of (myoma size and number and duration of surgery) and intraoperative fluids and there were no statistically significant difference between groups (p-value > 0.05) (table 1).

Groups were comparable in pre and post operative HGB and HCT and there were statistically significant difference between groups in post operative Hgb and HCT (table 2).

Paired t test done for each group and there were significant difference in Hgb and Hct drop in each group but control group showed more mean difference than oxytocin group (table 3).

Groups were comparable in post operative need of blood transfusion and 2nd surgery (table 4).

Groups were comparable in surgeon evaluation in term of visual fluid clarity and there were statistically significant difference between groups in surgeon

Table 1. Comparison between groups as regard demographic data and surgery duration and indication.

DEMOGRAPHIC DATA		GROUP CONTROL (N=30)	GROUP OXYTOCIN (N=30)	P-VALUE T
Age (years)		36.57±4.4	37.60±5.5	0.421
Duration		21.57±11.4	20.30±13.9	0.701
Indication	AUB	20(66.7%)	25(83.3%)	0.136
	infertility	10(33.3%)	5(16.7%)	

Data expressed as mean ± SD, proportion , t = student t test, X2 = chi square test

Table 2. Comparison between groups as regard pre and post operative HGB and HCT.

	GROUP CONTROL (N=30)	GROUP OXYTOCIN (N=30)	P-VALUE T
pre-op HB	11.39±1.7	11.36±1.7	0.945
pre-op Hct	34.57±4.7	34.42±4.8	0.902
post-op HB	10.25±1.4	11.13±1.7	0.035
post -op Hct	30.67±4.1	33.55±4.8	0.015

Data expressed as mean ± SD, t = student t test

Table 3. Comparison between groups as regard pre and post operative HGB and HCT.

		pre-op	post-op	Paired differences	p-value t
Hgb	Control	11.39±1.7	10.25±1.4	- 1.14 ± 0.7	<0.001
	Oxytocin	11.36±1.7	11.13±1.7	- 0.23 ± 0.2	<0.001
HCT	Control	34.57±4.7	30.67±4.1	- 3.9 ± 2.6	<0.001
	Oxytocin	34.42±4.8	33.55±4.8	- 0.86 ± 0.8	<0.001

Data expressed as mean ± SD, proportion , t = student t test, X2 = chi square test

Table 4. Comparison between groups as regard post operative.

	Group Control (n=30)	Group Oxytocin (n=30)	p-value t
Need of blood transfusion	No patients need postoperative blood transfusion		
Need of 2nd surgery	30(100.0%)	27(90.0%)	0.076
	0(0.0%)	3(10.0%)	

Data expressed as mean ± SD, proportion , t = student t test, X2 = chi square test

rating bleeding (table 5).

Groups were comparable in complications in term of (utrine and medical) and there were no statistically significant difference between groups in rating bleeding (table 6).

Discussion

Uterine fibroids are benign, smooth muscle tumours of the uterus that are affected by the levels of estrogen and progesterone. Fibroids are the most common female pelvic tumors, and these can be sonographically identified by ultrasound in up to 70–80% of women before menopause.[13]

Most fibroids are asymptomatic; however, 20-50 percent may be symptomatic causing abnormal uterine bleeding, congestive dysmenorrhea, pressure manifestations, infertility or recurrent pregnancy loss, especially when these are submucous. The standard treatment for symptomatizing myomas is hysterectomy for women with completed families, and myomectomy for those who wish to preserve their fertility. Myomectomy can be performed by laparotomy, laparoscopy or hysteroscopy according to the size, site and number of the myomas.[14]

Hysteroscopic myomectomy is currently considered the “gold standard” minimally invasive approach for the treatment of symptomatic submucous myomas.6 Patients undergoing hysteroscopic myomectomy are liable to significant blood loss, and hemodynamic and hematological disturbances.

Table 5. Comparison between groups as regard surgeon rating the bleeding and visual clarity.

		GROUP CONTROL (N=30)	GROUP OXYTOCIN (N=30)	P-VALUE ^{X2}
Surgeon rating the bleeding	No bleeding	11(36.7%)	22(73.3%)	0.006
	Mild	14(46.7%)	8(26.7%)	
	moderate	5(16.7%)	0(0.0%)	
Visual fluid clarity	Bad	2(6.7%)	0(0.0%)	0.09
	Fair	11(36.7%)	6(20.0%)	
	Good	17(56.7%)	24(80.0%)	

Data expressed as, proportion, X2 = chi square test

Table 6. Comparison between groups as regard complications.

		GROUP CONTROL (N=30)	GROUP OXYTOCIN (N=30)	P-VALUE X2
Uterine complications		1(3.3%)	0(0.0%)	0.313
Medical	Nausea	3(10.0%)	5(16.7%)	0.448
	vomiting		No patients detected	
	headache	0(0.0%)	2(6.7%)	0.15
	Abdominal pain	1(3.3%)	2(6.7%)	0.554

Data expressed as, proportion, X2 = chi square test

Many interventions were introduced to reduce the risk of bleeding during myomectomy. These include the use of utero-tonics such as oxytocin, or the use of anti-fibrinolytics such as tranexamic acid.[15]

Oxytocin is a utero-tonic agent that causes myometrial contraction. The potential advantage of oxytocin infusion during hysteroscopic myomectomy is that it can maintains uterine contractility throughout the procedure, and thus, reduce blood loss.[16]

Excessive bleeding during hysteroscopic myomectomy remains a major challenge for the endoscopic gynaecological surgeons. Although many interventions have been described to reduce the intraoperative blood loss, there is a need for a well-designed randomised controlled trials to identify the most efficient interventions, with reasonable safety profiles, to help the perform a safe and curative surgery.[17]

The main aim of this study was to investigate whether the intrauterine instillation of oxytocin into the distention medium during hysteroscopic myomectomy will reduce blood loss and improve surgical visibility.

This Randomized controlled double blinded clinical trial was conducted at Early Cancer Detection Unit (ECDU) at Ain Shams University hospitals. This study included 60 women who were scheduled to undergo a hysteroscopic myomectomy were divided into two equal groups: Group A (Oxytocin group): 30 women underwent a hysteroscopic myomectomy with the use of 10 IU of oxytocin for every 1000 ml of the distending medium, Group B (Placebo group): 30 women underwent hysteroscopic myomectomy with the use of a sterile bacteriostatic water ampule for every 1000 ml of the distending medium.

Groups were comparable in demographic data (in terms of age) and surgical data sin term of (myoma size and number and duration of surgery) and intraoperative fluids and there was no statistically sig-

nificant difference between groups (p-value > 0.05).

Our results were in agreement with study of *Pourfathi et al.*[18], as they reported that the study group (group S, n = 25) received 15 units (1.5 mL) of oxytocin (10 μ/mL/amp) (oxy TIP; Rasht Pharmaceutical Co., Iran) - plus 250 mL ringer solution at the rate of 125 mL/h. In the placebo group (group P, n = 25), 1.5 mL of normal saline was added to the same volume of Ringer's solution and administered simultaneously. There was no statistically significant difference between groups regarding women demographic characteristics.

Similarly, in the study of *Mohamed et al.*[19], included 60 patients scheduled for hysteroscopic myomectomy allocated into 2 groups: group A: received 10 mg/kg of tranexamic acid slowly intravenous after induction of anesthesia, while group B: received infusion of 10 IU of oxytocin at a rate of 400 mIU/min throughout the procedure. There was no statistically significant difference between them regarding the demographic criteria. Additionally, the sizes and grades of the myomas were comparable in both groups, with no statistically significant difference.

Oxytocin receptors are found in myometrium and fibroid tissues. Oxytocin elicits prostaglandin release, decreasing uterine perfusion. Increased uterine contractility directly impacts the vascular architecture of the uterus, decreasing blood flow to the arteries and fibroids.[20]

Uterine myomectomy and polypectomy are among popular conventional and minimally invasive gynecological procedures in hysteroscopy. Despite numerous advantages of the hysteroscopic, absorption of irrigation fluid is one of the complications leading to hypervolemia in 3-6% of women. Hypotonic solutions, including a mixture of mannitol and sorbitol or glycine, are broadly used as hysteroscopic irrigation fluid. These solutions might be associated with complications such as hypervolemia, dilutional hyponatremia, and glycine, and its derived metabolites toxicity. The most dangerous complication is the intravasation of the fluid electrolyte imbalances caused by Glycine (hyponatremia, hypoproteinemia, and low hematocrit). Women complain of nausea, vomiting, headache, and confusion. Pulmonary and brain edema can occur. Intravasation of the fluid is the most serious complication. Glycine overload resulted in electrolyte abnormalities (hyponatremia, hypoproteinemia, and low hematocrit).[21]

The present study showed that Groups were comparable in pre and post-operative HGB and HCT and there was statistically significant difference between groups in post-operative Hgb and HCT. Paired t test done for each group and there was significant difference in Hgb and Hct drop in each group but control group showed more mean difference than oxytocin group.

Our results showed that groups were comparable in post-operative need of blood transfusion and 2nd surgery and there was no statistically significant difference between groups in post-operative Hgb and HCT. Groups were comparable in surgeon evaluation in term of (rating of bleeding and visual fluid clarity) and there was statistically significant difference between groups in rating bleeding.

Our results were supported by study of *Wang et al.*[22], as they reported that an oxytocin infusion of 15 IU in 125 mL was administered to abdominal and vaginal myomectomy cases. Blood loss and blood transfusion rates were significantly higher in the group without oxytocin infusion than in the group with oxytocin infusion. Oxytocin receptors in the uterus and fibroid tissue lead to contractile prostaglandins synthesis and release. Oxytocin infusion was associated with a significantly decreased intraoperative blood loss and glycine deficit.

In the study of *Pourfathi et al.*[18], the amount of injected and collected media fluid and its deficit were significantly lower in the oxytocin group. Also, the rate of decreased serum hematocrit after surgery

was significantly lower than the placebo group. However, their values remained within the normal range in the two groups. Intravascular absorption of irrigation solution, which might occur during hysteroscopic surgeries through the vasculature or fallopian tubes opening into the peritoneum, could result in hypertension or other hemodynamic imbalances, hematological disorders, pulmonary edema, increased intracranial pressure, and even organ failure. The decline of serum hematocrit was significantly lower in the study group. ($\chi 2$ value was 4.36, P=0.036, ≥ 3 decreased HCT parameter between two groups was assessed). Preoperative Hb and hematocrit values were similar between groups.

Furthermore, *Atashkhoei et al.*[23], stated that women were randomly assigned to two groups. In the study group (n = 40) oxytocin 30 IU in 500 ml normal saline; and in the placebo group (n = 40) pure normal saline was administered during myomectomy. The groups were similar with respect to preoperative clinical data. Intra-operative approximate blood loss in the study group (189.5 ± 16.72 ml) was significantly lower than the placebo group (692.25 ± 89.93 ml) (95% CI 672.54–711.96; P < 0.0001). The need for blood transfusion was significantly lower in the study group. Blood transfusions were required for three (7.5%) patients in the study group and 10 (25%) patients in the placebo group (95% CI 15.5–34.5%; P < 0.001). Preoperative hemoglobin and hematocrit values were similar between groups. Reduction in these variables at 24 hours after surgery was more in the placebo group than the study group (P < 0.0001 for both parameters).

In the study of *Mousa et al.*[24], fifty women scheduled for hysteroscopic myomectomy (HM) were randomly assigned into two groups. Ttranexamic acid (TXA) or oxytocin (OXY). TXA showed significant decrease of heart rate 30 and 45 min and 1 and 2 h when compared with OXY. Post-operative Hb and Hct showed significant decrease ($p < 0.001$) in TXA compared with OXY. CVP in TXA displayed significant increase ($p < 0.001$) 15 min after spinal blockade and 30 min, 45 min, 1 h and 2 h. Serum sodium showed significant decrease in TXA ($p < 0.001$) compared with OXY nearly throughout study period.

While, in the study of *Agostini et al.*[25], administration of oxytocin during myomectomy did not reduce preoperative blood loss.

In the study of *Shokeir et al.*[26], forty-eight women were included in the study and divided into two groups. For group A: one ampoule of oxytocin (10 U/mL/amp) was added to 500 mL Ringer's lactate solution running at a rate of 400 mU/min during surgery. In group B, one ampoule of saline solution was added to the Ringer's solution and run at a similar rate. Although operating time, volume of distension fluid used, decrease in albumin level and hematocrit were less in the oxytocin than in the saline group, the differences were not statistically significant. The ethanol levels in blood, decrease in serum Na+, and glycine deficit were significantly lower in the oxytocin than in the saline group (17.4 ± 3.8 vs 25.3 ± 4.2 mg/ml, 6.7 ± 1.2 vs 9.1 ± 0.9 mEq/L, and 0.49 ± 0.08 vs 0.66 ± 0.05 L, respectively; p <.05).

Furthermore, *Mohamed et al.*[19], stated that the mean difference between the preoperative and postoperative hemoglobin (Hb) levels for patients in the oxytocin group was -1.27 (±0.84), while in the tranexamic acid group, it was -1.14 (±0.83) with no significant difference (p= 0.558). By percentage, the hemoglobin level was reduced by 11.06 % with SD ±6.46 in the oxytocin group, and by 10.21 % (SD±7.29) in tranexamic acid group with no significant difference (p= 0.636). In oxytocin group, the mean difference between preoperative and postoperative hematocrit (Hct) levels was -4.29 (±2.86), while in the tranexamic acid group, it was -4.54 (±2.80) with no significant difference (p= 0.730). Hematocrit levels were reduced by 11.83 % (SD ±7.34) in the oxytocin group, and by 12.91 % (SD±7.58) in

tranexamic acid group with no significant difference (p= 0.577). No patients needed blood component transfusion in either group.

Moreover, *Nasr Al-Deen et al.*[27], revealed that the study participants were randomized to one of two groups; Group 1 included 30 women received 30 IU of (Oxytocin) in 500 ml normal saline administered during abdominal myomectomy and Group 2 included 30 women received only saline infusion administered during the surgery. The estimated blood loss was significantly lower among oxytocin group in comparison to the control group as well as significantly higher Postoperative hemoglobin and hematocrit with significantly lower Hematocrit reduction.

Although oxytocin is considered to be a safe drug, it can cause tachycardia and hypotension, and it has negative inotropic, antiplatelet, and antidiuretic effects. Major side-effects of oxytocin include hypotension, tachy-arrhythmias or hyponatremia.[26]

Our results showed that groups were comparable in complications in term of (uterine and medical) and there was no statistically significant difference between groups regarding complications.

While, in the study of *Pourfathi et al.*[18], the frequency of hypotension inwomen receiving oxytocin did not show any significant differences between the placebo group. Whereas studies showed t that oxytocin's most common side effects were hypotension, tachyarrhythmias, and hyponatremia.[28] It seems that few side effects in the present study might be due to the low dose of oxytocin used and the low sample size.

Atashkhoei et al.[23], demonstrated that no major side-effects were observed in either group.

Also, *Mohamed et al.*[19], demonstrated that uterine perforation was the only operative complication that occurred during the study. This occurred in one case in each group. Both cases were due to false passage of the Heggar's dilators used to dilate the cervix in order to pass the resectoscope. Both cases were managed conservatively, with no further complications, and the procedures postponed. Nausea was the only reported medications adverse effect recorded during the study. It occurred in 3 cases of oxytocin group and in 2 cases of tranexamic acid group with no statistical difference between 2 groups (p=0.643). The patients reported none of the other investigated adverse effects (headaches, syncope, or nasal congestion), and there were no arrhythmias observed by the anaesthestists. No cases were reported to show thrombotic events within one week postoperatively.

The present study had some limitations. The small sample size is the main limitation. Also, it is a single center study, is another limitation.

Conclusion

Complications during diagnostic hysteroscopy are common. Intrauterine instillation of oxytocin into the distention medium during hysteroscopic myomectomy reduce blood loss and improve surgical visibility. More studies with varied dosages and methods are needed to validate these findings.

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