



The Effect of Intraoperative Oxytocin Infusion on Irrigation Fluid Absorption During Hysteroscopic Myomectomy: A Randomized Placebo-Controlled Double-Blind Trial

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Abstract

Objectives: One of the most prevalent benign tumors in women is uterine leiomyoma. Large quantities of fluid absorbed during myomectomy may cause serious problems such as volume overload and hyponatremia. The aim was to see how intraoperative oxytocin infusion affected irrigation fluid absorption in individuals having hysteroscopic myomectomy.

Materials and Methods: 50 women between 25-45 years who underwent hysteroscopic myomectomy and had an American Society of Anesthesiologists class I or II were evaluated in this randomized, double-blind clinical trial study. A 250 mL ringer solution containing 15 units of oxytocin was administered at a 125 mL/h in the oxytocin group (group S). In contrast, the placebo group (group P) received 1.5 mL of normal saline in the same amount of Ringer solution. Intraoperative hemodynamic alterations, fluid deficit, decreased hemoglobin, hematocrit, sodium, and albumin levels from baseline, complications, and the incidence of toxicity with the administered solutions were assessed intraoperative and 24 hours later.

Results: Group S had considerably reduced irrigation fluid volume ($P=0.021$) and volume deficit ($P=0.001$). The frequency of hypotension in individuals receiving oxytocin did not differ significantly from the placebo group ($P=0.26$). In group S, serum hematocrit ($P=0.036$) and sodium ($P=0.026$) were decreased significantly.

Conclusions: Intraoperative oxytocin infusion during hysteroscopic myomectomy may be associated with reduced irrigation fluid absorption and the problems that come with it. As a result, this approach might decrease the risks associated with high amounts of irrigation fluid being absorbed during hysteroscopic myomectomy.

Keywords: Hysteroscopy, Myomectomy, Irrigation fluid, Infusion, Oxytocin

Introduction

Uterine leiomyoma is one of the most common benign tumors in the women population (1-5). Their incidence is age-related, ranging from 40-60% at 35 years old to 70-80% at 50 years old (6). Nowadays, operative hysteroscopy is commonly used for endometrial ablation, septal resection, and myoma resection (1).

In selected cases and compared to open surgery, hysteroscopy is a minimally invasive approach with lower morbidity rates, shorter recovery time, lower costs, and fewer undesirable events (7). However, hysteroscopy has been associated with severe consequences such as uterine perforation, bleeding, gas or air embolism, infection, fluid overload, and hyponatremia (8). It is usually required to administer media in the uterine cavity to perform hysteroscopy under direct vision. Glycine 1.5% is one of the low viscosity distending solutions that provide excellent visibility for the surgeon. However, large amounts of fluid absorption during myomectomy might

lead to severe complications such as volume overload and hyponatremia (9,10). In patients under general anesthesia, hypotension and decreased arterial oxygen saturation are among the primary symptoms; pulmonary edema might occur postoperatively (11,12). In increased intrauterine pressure, more and larger vessels in the uterus, and lengthy procedures, higher volumes of fluid could be absorbed (13,14). Several approaches for preventing hysteroscopy-related hypervolemic episodes have been proposed, including careful monitoring of volume deficits, irrigation pressure management, preoperative endometrial thickness reduction, and even anesthetic adjustments (9). Oxytocin is an uterotonic drug broadly used to assist in starting, strengthening delivery, and reducing postpartum hemorrhage. Recent studies have shown the practical effects of oxytocin on lowering bleeding during myomectomy (e.g., hysteroscopic, laparoscopic, and abdominal techniques) thanks to the maintenance of uterine contractile force throughout the surgical procedure

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Key Messages

- Intraoperative oxytocin infusion in hysteroscopic myomectomy might be usefully employed in patients with hysteroscopic myomectomy.

(15). Patients undergoing hysteroscopic myomectomy are prone to higher bleeding rates and more unstable hemodynamics following distention fluid absorption (16).

This study was designed to evaluate the effect of oxytocin infusion on the absorption rate of irrigation fluid in patients undergoing hysteroscopic myomectomy due to a lack of such research and the significant likelihood of hematologic complications related to glycine absorption during hysteroscopic myomectomy.

Materials and Methods

Study design and Participants

This study was conducted on 50 women aged 25-45 years old with I or II physical status based on the American Society of Anesthesiologists (ASA) classification who were scheduled for hysteroscopic myomectomy. The study was conducted at Al-Zahra University Hospital (Tabriz, Iran) from 10 March 2019 to 15 January 2020. Written informed consent was obtained from patients. A two-blocked randomization list assigned patients to study and placebo groups. Inclusion criteria were as follows: The presence of uterine submucosal myomas, hysteroscopic myomectomy, and resection immediately after menstruation. Patients are scheduled for either diagnostic or operative hysteroscopy. Abdominal myomectomy, large uterine myoma (uterus >14 weeks of gestation), sub-serosal myomas, uterine prolapse, pelvic inflammation, or pelvic inflammatory disease were excluded. Before the operation, the intravenous line was placed for all patients, and routine monitoring, including non-invasive blood pressure, electrocardiography, and pulse oximetry, was established for all patients.

Sample Size

To calculate sample size and lack of similar studies, 15 women were included in each group as a pilot study. Afterward, the final sample size was calculated to ensure 80% power and a 5% type 1 error (mean int: 296, mean placebo: 428, common SD: 160). The final sample size was 25 patients for each group using this information.

Randomization

Later, these 50 patients were randomly allocated into two study groups using a simple randomization method. Patients were allocated into study and placebo groups, according to a two blocked randomization list that was prepared using online software (<https://www.sealedenvelope.com/>) at a 1:1 ratio.

Interventions

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.

Infusion of the solutions was immediately started after the induction of general anesthesia and discontinued at the end of the procedure. Infusion of solutions immediately started after general anesthesia induction and was discontinued at the end of the procedure. Another IV cannula and a Foley catheter were placed to obtain blood samples and monitor urine output, respectively. General anesthesia after standardized preoxygenation was induced using midazolam 0.03 mg/kg remifentanyl 1 µg/kg, propofol 1.2-1.5 mg/kg, and later appropriate size laryngeal mask airway (LMA) was replaced, based on the recommendations of the manufacturer. Anesthesia was maintained using total intravenous anesthesia (propofol infusion 50-100 µg/kg/min and remifentanyl 0.1-1/min, respectively). Later, women were placed in the lithotomy position. The hysteroscopist started the procedure with a cervical dilatation with Hegar no. 9. 1.5% glycine solution was used for uterine cavity clearance and distention at different speeds with intrauterine pressure less than 120 mm Hg using hysterometer flow monitoring. The amount of irrigated fluid and total volume of the collected fluid, including fluid in the canister and sources of the spill, was recorded. The fluid deficit was defined as the difference between the amount of the injected and irrigated fluids. Hemodynamic variables, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR), were recorded before the anesthesia induction (baseline) and later at 5, 10, 20, 30, and 60 min intervals until the patient was discharged from post-anesthesia care unit (PACU). Bradycardia (HR < 50 bpm/min), hypotension (BP < 100 mm Hg) and fluid deficit > 1500 mL were treated by atropine (0.01-0.02 mg/kg), ephedrine 5-10 mg with 200-300 mL IV solution, and intraoperative 20-40 mg furosemide, respectively. Blood samples were achieved before and after the procedure to monitor hemoglobin (Hb), hematocrit (Hct), and serum sodium and albumin levels. Hb, Hct, and serum sodium and albumin levels. Complications of administered solutions (hypotension, tachycardia, bradycardia, and ST depression), glycine toxicity, and hypothermia (hypotension, arterial oxygen saturation, pulmonary edema) were evaluated intraoperatively and until 24 hours postoperatively. All participants (i.e., women, anesthesiologists, surgeons) were unaware of the studied solution. The assistant anesthesiologist was responsible for preparing solutions. Two fixed anesthetists and one gynecological surgeon, who were all blinded to the treatment solution, were responsible for the anesthetic

and surgical management of the women during the study.

Data Analysis

For both the intervention and non-intervention groups, an independent samples *t* test was done to evaluate the means of normally distributed numeric independent variables. When the normality assumption was violated, the Mann-Whitney U test was performed as a nonparametric counterpart to the independent samples *t* test, and the median was given. The chi-square test was used to determine the relationship between two categorical variables. Statistical significance was defined as a *P* value of less than 0.05. SPSS version 21 (SPSS, Chicago, IL, USA) was used to examine the data.

Results

Figure 1 shows the flowchart diagram of the study. There was no statistically significant difference between groups regarding women demographic characteristics (Table 1). Intra- and postoperative data were presented in Table 2. The comparison of the women's hemodynamic status during the procedure showed that systolic blood pressure, DBP, MAP, and HR values were significantly lower in group P than in group S. Table 2 represents the volume of injected and collected irrigation fluid. The lack of volume during the procedure and declining serum hematocrit and sodium levels at the end of the surgery were lower, which were lower in group S ($P < 0.05$).

Intra-operative approximate used irrigation solution (mL) in the study group (2300 mL) was significantly lower than the placebo group (3200 mL) ($P < 0.05$). The fluid deficit (mL) in the study group (200 mL) was significantly lower than the placebo group (400 mL) ($P < 0.05$). The

Table 1. Demographic and Surgical Variables of Two Groups

Variable	Group S (n = 25)	Group P (n = 25)	P
Age (y)	38.72 ± 7.22	37.12 ± 6.37	0.410 ^a
Weight (kg)	75 (10.5)	72 (12.5)	0.057 ^b
Height (cm)	162 (7)	161 (5)	0.358 ^b
Gravid			0.723 ^c
0	4 (16)	5 (20)	
1	9 (36)	6 (24)	
2	8 (32)	11 (44)	
3	4 (16)	3 (12)	
Fundal height (wk)	12 (2)	12 (1)	
Size of the myoma in ultrasound (mm)			
Length	38 (3)	38 (2.5)	0.805 ^b
Width	33 (2)	34 (2)	0.340 ^b

Normally and non-normally distributed quantitative variables were presented as mean ± SD and median (IQR: Interquartile range), respectively. Qualitative variables were presented as number (%).

^aIndependent sample *t* test; ^bMann-Whitney; ^cChi-square test.

decline of serum hematocrit was significantly lower in the study group. (χ^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.

Table 3 presents the peri-operative complications and their management in 14 cases. Hypotension during the procedure was (18%) (3 and 6 cases in groups O and P, respectively) ($P = 0.26$). The most content undesirable effect of treatment was related to crystalloids (16%) ($P = 0.018$). There was no statistically significant difference between the two groups regarding anesthesia time and surgery time (Table 3). Post hoc tests for multiple comparisons were conducted with Bonferroni adjustment, and the results are shown in Tables 4-6.

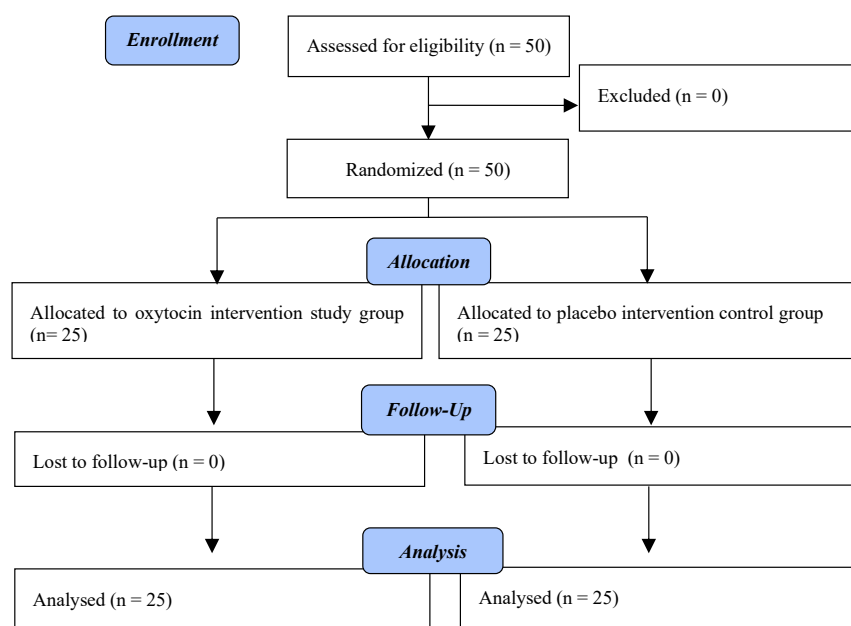


Figure 1. Flow Chart of Study.

Table 2. Comparison of Intra- and Post-operative Variables of Two Groups

Variable	Group S (n = 25)	Group P (n = 25)	P
IV fluid (mL)	1000 (475)	1000 (350)	0.930 ^a
Urine output (mL)	12 (2.00)	12 (1.00)	0.389400 ^a
Used irrigation solution (mL)	2300 (1300)	3200 (1750)	0.021 ^a
Collected irrigation solution (mL)	2050 (1225)	2700 (1450)	0.057 ^a
Deficit of irrigation solution (mL)	200 (150)	400 (200)	0.001 ^a
Hb drop (g/dL)	2 (8%)	2 (8%)	0.293 ^a
Hct drop (%)	5 (20%)	12 (48%)	0.036 ^b
Na drop (mEq/L)	4 (16%)	4 (16%)	0.026 ^b
Alb drop (g/dL)	2 (8%)	3 (12%)	0.096 ^a
Surgery time (min)	40 (17.5)	40 (16.5)	0.984 ^a
Anesthesia time (min)	53 (17.5)	50 (22)	0.838 ^a

Hb: Hemoglobin, Na: Sodium, Alb: Albumin, ml: Milliliter, Hct: Hematocrit.

Normally and non-normally distributed quantitative variables were presented as mean $\pm$ SD and median (IQR: Interquartile range), respectively. Qualitative variables were presented as No. (%). ^a Mann-Whitney; ^b χ^2 test.

Table 3. The Comparison of Perioperative Complications and Treatment of Them of Two Groups

Variable	Group S (n = 25)	Group P (n = 25)	P Value
Perioperative complications			
Hypotension (BP < 100 mm Hg)	3 (12)	6 (24)	0.269
Bradycardia (HR < 50 bpm/min)	1 (4)	2 (8)	0.552
Tachycardia	0 (0)	1 (4)	0.312
Apnea	1 (4)	0 (0)	0.312
Complication treatment			
Crystalloid	3 (12)	5 (20)	0.440
Furosemide	1 (4)	0	0.312

Data were expressed as Number (%)

Table 4. Comparison Between Study and Placebo Group for SBP, DBP, MAP and HR in Different Times Measurement

Group	DBP		SBP		MAP		HR	
	Study Group	Placebo Group	Study Group	Placebo Group	Study Group	Placebo Group	Study Group	Placebo Group
Time								
Baseline	80.52 $\pm$ 11.38	82.52 $\pm$ 11.61	128.08 $\pm$ 11.40	129.32 $\pm$ 10.87	97.08 $\pm$ 10.38	101.28 $\pm$ 13.03	96.00 $\pm$ 19.91	98.28 $\pm$ 18.25
5	76.92 $\pm$ 14.04	68.96 $\pm$ 13.36	121.52 $\pm$ 15.58	115.36 $\pm$ 19.76	92.56 $\pm$ 15.26	85.20 $\pm$ 16.03	89.04 $\pm$ 16.48	96.88 $\pm$ 21.96
10	79.20 $\pm$ 12.16	68.32 $\pm$ 13.70	121.64 $\pm$ 15.53	110.64 $\pm$ 14.42	93.68 $\pm$ 12.97	81.64 $\pm$ 12.89	86.28 $\pm$ 13.01	91.56 $\pm$ 18.64
20	78.84 $\pm$ 16.55	70.52 $\pm$ 16.48	121.56 $\pm$ 15.67	113.80 $\pm$ 17.31	93.96 $\pm$ 16.86	85.48 $\pm$ 19.59	84.76 $\pm$ 11.75	83.92 $\pm$ 20.65
30	80.44 $\pm$ 15.93	70.84 $\pm$ 16.50	121.16 $\pm$ 15.20	113.32 $\pm$ 12.93	97.48 $\pm$ 16.47	87.96 $\pm$ 14.77	86.56 $\pm$ 13.66	82.88 $\pm$ 18.81
60	78.20 $\pm$ 14.76	69.92 $\pm$ 16.22	121.20 $\pm$ 13.15	115.16 $\pm$ 15.82	92.88 $\pm$ 13.65	87.44 $\pm$ 14.83	82.52 $\pm$ 14.45	86.24 $\pm$ 13.89
End	78.60 $\pm$ 11.65	71.88 $\pm$ 12.29	121.24 $\pm$ 9.46	117.16 $\pm$ 10.94	93.76 $\pm$ 11.34	89.56 $\pm$ 11.31	82.48 $\pm$ 12.25	84.52 $\pm$ 13.60
PACU	75.88 $\pm$ 9.40	71.00 $\pm$ 14.55	117.52 $\pm$ 9.19	113.84 $\pm$ 11.57	90.84 $\pm$ 9.33	87.64 $\pm$ 12.34	81.32 $\pm$ 13.84	86.28 $\pm$ 14.93
P value								
Time	0.287		<0.001		0.076		<0.001	
Group	0.007		0.030		0.027		0.648	
Time $\times$ Group	0.828		0.272		0.326		0.331	

Repeated measurement analyses were conducted using SPSS version 26.

Discussion

To our knowledge, this is the first study to evaluate the impact of oxytocin infusion on the rate of irrigation fluid absorption during hysteroscopic myomectomy. We believe that this technique might be usefully employed in women with hysteroscopic myomectomy. In the present study, the amount of absorbed and collected media fluid and the lack of it in the study group were significantly

lower than in the placebo group.

Oxytocin receptors are found in myometrium and fibroid tissues (17). Oxytocin elicits prostaglandin release (19), decreasing uterine perfusion (18). Increased uterine contractility directly impacts the vascular architecture of the uterus, decreasing blood flow to the arteries and fibroids (12, 19).

Uterine myomectomy and polypectomy are

Table 5. Pairwise Comparisons for SBP in Different Times Measurement

(J) Time	(I) Time				
	Mean difference (I-J)	Std. Error	P value	95% Confidence Interval for Difference ^a	
				Lower Bound	Upper Bound
1					
2	10.260*	2.312	0.001	2.613	17.907
3	12.560*	2.079	< 0.001	5.682	19.438
4	11.020*	2.425	0.001	2.996	19.044
5	11.460*	2.448	0.001	3.361	19.559
6	10.520*	2.575	0.005	2.002	19.038
7	9.500*	1.785	< 0.001	3.594	15.406
8	13.020*	1.756	< 0.001	7.209	18.831
2					
3	2.300	2.175	1.000	-4.896	9.496
4	.760	2.855	1.000	-8.685	10.205
5	1.200	3.125	1.000	-9.139	11.539
6	.260	3.241	1.000	-10.461	10.981
7	-.760	2.783	1.000	-9.966	8.446
8	2.760	2.790	1.000	-6.469	11.989
3					
4	-1.540	2.239	1.000	-8.947	5.867
5	-1.100	2.260	1.000	-8.575	6.375
6	-2.040	2.458	1.000	-10.171	6.091
7	-3.060	2.278	1.000	-10.596	4.476
8	0.460	2.253	1.000	-6.992	7.912
4					
5	0.440	1.892	1.000	-5.819	6.699
6	-.500	1.983	1.000	-7.059	6.059
7	-1.520	2.108	1.000	-8.492	5.452
8	2.000	2.420	1.000	-6.006	10.006
5					
6	-0.940	1.818	1.000	-6.954	5.074
7	-1.960	1.660	1.000	-7.452	3.532
8	1.560	2.012	1.000	-5.096	8.216
6					
7	-1.020	1.842	1.000	-7.113	5.073
8	2.500	2.021	1.000	-4.186	9.186
7					
8	3.520	1.344	0.329	-0.926	7.966

* The mean difference is significant at the 0.05 level.

^a Adjustment for multiple comparisons: Bonferroni.

among popular conventional and minimally invasive gynecological procedures in hysteroscopy (20). Despite numerous advantages of the hysteroscopic, absorption of irrigation fluid is one of the complications leading to hypervolemia in 3-6% of women (21). 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 (22). 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 (23). Intravasation of the fluid is the most serious complication. Glycine overload

resulted in electrolyte abnormalities (hyponatremia, hypoproteinemia, and low hematocrit) (23).

Administration of oxytocin during myomectomy did not reduce preoperative blood loss (24). 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 (25). Oxytocin receptors in the uterus and fibroid tissue lead to contractile prostaglandins synthesis and release (26). Oxytocin infusion was associated with a significantly decreased intraoperative blood loss and glycine deficit (27).

In the present study, the amount of injected and collected media fluid and its deficit were significantly lower in the oxytocin group. Also, the rate of decreased

Table 6. Pairwise Comparisons for Heart Rate

(J) Factor1	(I) Factor1				
	Mean difference (I-J)	Std. Error	P value	95% Confidence Interval for Difference ^b	
				Lower Bound	Upper Bound
1					
2	4.180	2.504	1.000	-4.104	12.464
3	8.220	3.177	0.357	-2.291	18.731
4	12.800*	2.933	0.002	3.096	22.504
5	12.420*	2.850	0.002	2.992	21.848
6	12.760*	2.889	0.002	3.201	22.319
7	13.640*	2.728	< 0.001	4.615	22.665
8	13.340*	3.051	0.002	3.249	23.431
2					
3	4.040	2.254	1.000	-3.416	11.496
4	8.620	2.827	0.104	-0.733	17.973
5	8.240*	2.488	0.050	0.008	16.472
6	8.580	2.665	0.064	-0.235	17.395
7	9.460*	2.694	0.027	0.548	18.372
8	9.160*	2.648	0.032	0.401	17.919
3					
4	4.580	2.126	1.000	-2.453	11.613
5	4.200	1.791	0.649	-1.724	10.124
6	4.540	2.054	0.893	-2.255	11.335
7	5.420	2.055	0.315	-1.379	12.219
8	5.120	2.151	0.597	-1.996	12.236
4					
5	-0.380	2.065	1.000	-7.211	6.451
6	-0.040	2.002	1.000	-6.663	6.583
7	0.840	2.181	1.000	-6.373	8.053
8	0.540	2.408	1.000	-7.427	8.507
5					
6	0.340	1.863	1.000	-5.823	6.503
7	1.220	2.355	1.000	-6.571	9.011
8	0.920	2.462	1.000	-7.223	9.063
6					
7	0.880	1.421	1.000	-3.820	5.580
8	0.580	1.722	1.000	-5.116	6.276
7					
8	-0.300	1.462	1.000	-5.136	4.536

* The mean difference is significant at the 0.05 level.

^a Adjustment for multiple comparisons: Bonferroni.

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 (16).

In hysteroscopic surgeries, >2 L fluid could overload in 1% of women. These women showed a more pronounced postoperative decrease in serum sodium and a more significant glycine deficit than women without nausea. The postoperative decrease in serum sodium correlated significantly to the glycine deficit (28). Our study demonstrated that serum sodium decrease was

not different between the groups. Recently conducted randomized studies comparing monopolar and bipolar transurethral resection, demonstrating that the decline in postoperative serum sodium was significantly less in the bipolar group compared to the monopolar group and that bipolar equipment was as effective as monopolar equipment (29). However, none of these issues were observed among the women who participated in our research. The small sample size of our randomized experiment may explain why there were no problems.

In our study, the evaluation of hemodynamic variables showed that oxytocin infusion modulation of systolic, diastolic, MAP, and HR in women undergoing hysteroscopic myomectomy. Intraoperative blood loss could lead to hemodynamic alterations, and up to 5% of women undergoing hysteroscopic myomectomy might

require blood transfusion (14, 30). In our study, the frequency of hypotension in women receiving oxytocin did not show any significant differences between the placebo group. Whereas studies showed that oxytocin's most common side effects were hypotension, tachyarrhythmias, and hyponatremia (31). 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.

Limitations of the Study

The study was a double-blinded, randomized controlled design. The limitation of this study includes those elderly women and those with ASA grade III or higher who were not evaluated in our study. Because age and underlying diseases might affect respiratory mechanics, arterial oxygen saturation, and other outcomes, it is recommended to survey hysteroscopic surgery in elderly women and those with higher ASA classes. We didn't utilize large dosages of oxytocin since there isn't enough data to support their safety.

Conclusions

Complications during diagnostic hysteroscopy are common. Intraoperative oxytocin infusion in hysteroscopic myomectomy could be used to decrease the absorption of irrigation fluid during hysteroscopic myomectomy. More studies with varied dosages and methods are needed to validate these findings.

Authors' Contribution

HA and SA conceived the idea for the review and its structure, reviewed literature and drafted the manuscript. HP participate in the review of the literature and drafting the manuscript. HP and LK participated in the drafting of the manuscript. LK prepared histopathological figures for publication and draft the manuscript. All authors approved the final version of the manuscript.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran approved the study proposal (code: IR.TBZMED.REC.1397.799), and it was registered in Iranian Registry of Clinical Trials (identifier: IRCT20160103025821N5). All women enrolled to this study signed a written informed form.

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