Effect of Intraoperative Oxytocin Infusion on Reducing the Absorption Rate of Irrigation Fluid during Hysteroscopic Myomectomy: A Novel Approach;A clinical Trial

simin Atashkhoyi[1], leila kafshdouz[1], hesam Rasoul Amini[1], and Hojjat pourfathi[1]

[1]Affiliation not available

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Abstract

Introduction: Uterine leiomyoma is one of the most common benign tumors in women. Severe bleeding and unstable hemodynamics might occur in patients undergoing hysteroscopic myomectomy due to excessive irrigation fluid absorption.The aim of this study was to evaluate the effect of Intraoperative oxytocin infusion on the absorption of irrigation fluid in patients undergoing hysteroscopic myomectomy. Methods: In a randomized double-blind clinical trial, 50 patients aged 25-45 years with American Society of Anesthesiologists (ASA) class I or II undergoing hysteroscopic myomectomy were studied. In the study group (Group O), 250 mL ringer solution containing 15 units of oxytocin was infused at rate of 125 mL/h; while, the placebo group (Group P) received 250 mL ringer solution containing 1.5 ml of normal saline was infused at rate of 125 mL/h.Intraoperative hemodynamic alterations, fluid deficit, declined hemoglobin, hematocrit, sodium and albumin levels from baseline, complications and incidence of toxicity with the administered solutions were evaluated at both intraoperative and 24 hours postoperative phases. Results: The volume of irrigation fluid (P=0.032) and volume deficit (P=0.034) were significantly lower in the Group O. The incidence of intraoperative hypotension was significantly lower in Group O compared to Group P (P=0.019). Serum hematocrit (P=0.043) and sodium (P=0.026) levels were significantly lower in Group O. Conclusion: Intraoperative infusion of oxytocin during hysteroscopic myomectomy might be associated with decreased irrigation fluid absorption and its associated complications. Therefore, this method could be used to reduce the complications caused by the absorption of large volumes of irrigation fluid during hysteroscopic myomectomy

Introduction

Uterine leiomas (fibroids) are among the most common benign tumors in 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). Myomectomy is the definitive and standard treatment of uterine myomas in the reproductive age range.Nowadays, operative hysteroscopy is commonly used for endometrial ablation, septal resection, and resection of myoma or hysterectomy (1).

In selected cases and compared to open surgery, hysteroscopy is a minimally-invasive approach with lower morbidity rate, shorter recovery time, lower costs, and fewer undesirable events (7). However, some severe complications such as uterine perforation, hemorrhage, gas or air embolism, infection, fluid overload and hyponatremia have also been reported in association with hysteroscopy (8). To perform hysteroscopy under direct vision, it is normally required to administer distension media in the uterine cavity . Glycine 1.5% is one of the low viscosity distending solutions that provides excellent visibility for the surgeon. However, absorption of large volumes of fluid during myomectomy might lead to serious complications such as volume overload and consequently hyponatremia. (9, 10). Glycine is a non-conductive, non-hemolytic and hypotonic amino acid (osmolality 200 mOsmol/L). Glycine has a plasma half-life of 85 minutes and is metabolized to ammonia and free water in the liver, which can later lead to decreased serum osmolality. In

addition, ammonia could induce coma due to its high absorption rate, despite normal electrolytes ranges. The toxicity of glycine and hyponatremia usually occurs 30-40 minutes after surgery (11). In patients under general anesthesia, hypotension and decreased arterial oxygen saturation are among the primary symptoms; pulmonary edema might occur postoperatively (12, 13). At the presence of increased intrauterine pressure, more and larger vessels in the uterus and prolonged procedure, higher volumes of fluid could be absorbed (14, 15). Several methods have been presented to prevent hysteroscopy- related hypervolemic events such as careful monitoring of volume deficit, control of irrigation pressures, preoperative reduction of endometrial thickness, and even anesthesia modifications (9). Oxytocin is a eutrotonic drug broadly used to assist starting or strengthening delivery and to reduce postpartum hemorrhage. Recent studies have demonstrated the beneficial effects of oxytocin on lowering bleeding during myomectomy (e.g. hysteroscopic, laparoscopic, and abdominal techniques) thanks to maintenance of uterine contractile force throughout the surgical procedure (10). Patients undergoing hysteroscopic myomectomy are prone to higher bleeding rates and more unstable hemodynamics following distention fluid absorption (16). Considering the lack of similar studies and high possibility of hematologic damages due to glycine absorption during hysteroscopic myomectomy, this study was designed to evaluate the effect of oxytocin infusion on the absorption rate of irrigation fluid in patients undergoing hysteroscopic myomectomy.

Methods and materials

The present study was conducted on 50 women aged 25-45 years old with physical status of I or II based on American Society of Anesthesiologists (ASA) classification who were scheduled for hysteroscopic myomectomy. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.799) and registered in IRCT (IRCT20160103025821N5). Written informed consent was obtained from patients. In order to identify sample size and due to lack of similar studies, 15 pilot patients in each group were assessed at first. Final sample size was calculated based on the comparison of irrigation fluid in tow groups and consequently 25 cases were calculated for each group. Later, these 50 patients were randomly allocated into two study groups based on easy sampling method and the order of referral using randomized online Rand list software. The primary outcome of the study was lack of irrigation fluid. Inclusion criteria were as follows: presence of uterine sub-mucosal myomas, hysteroscopic myomectomy, and resection immediately after menstruation. Patients scheduled for either diagnostic or operative hysteroscopy for endometrial or uterine resection, abdominal myomectomy, large uterine myoma (uterus greater than 14 weeks of gestation), sub-serousal myomas, uterine prolapse, pelvic inflammation, or pelvic inflammatory disease were excluded. Prior to the operation, intravenous line was placed for all patients and routine monitoring including non-invasive blood pressure (NIBP), electrocardiography (ECG), and pulseoximetry were established for all patients. The case group (Group O, n=25) received 15 units of oxytocin (10 µ /mL/amp) (oxy TIP; Rasht Iran Pharmaceutical Co.) - plus 250 mL ringer solution at the rate of 125 mL / h. In the control group (Group P, n=25), 1.5 ml of normal saline was added to the same volume of Ringer's solution and administered at the same rate. Infusion of the solutions was immediately started after the induction of general anesthesia and discontinued at the end of procedure. Another IV cannula and also a Foley catheter were placed to obtain blood samples and to monitor urine output, respectively. General anesthesia after standardized pre- oxygenation was induced using midazolam 0.03 mg/kg, remifentanil 1 µg/kg and propofol 1.2-1.5 mg/kg and later appropriate size LMA was replaced, based on the recommendations of the manufacturer. Anesthesia was maintained using total intravenous anesthesia (TIVA: propofol infusion 50-100 ug/kg/min and remifentanil 0.1-1 µg/kg /min, respectively). Later, patients were placed in lithotomy position and hysteroscopist started the procedure by 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 mmHg using Hysterometer flow monitoring. The amount of irrigated fluid and total volume of the collected fluid including fluid in the canister and sources of spill was recorded. 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 minutes intervals until patient was discharged from PACU. Bradycardia (HR $<$ 50 min/min),

hypotension (SBP < 100 mmHg) 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 obtained before and after the procedure to measure hemoglobin (Hb), hematocrit (Hct), and serum sodium and albumin levels. Complications of administered solutions (hypotension, tachycardia, and bradycardia and ST depression), glycine toxicity and hypothermia (hypotension, arterial oxygen saturation, pulmonary edema, etc.) were evaluated intraoperatively and until 24 hours postoperatively. All participants (i.e. patients, anesthesiologist, surgeon, and the assistant of anesthesiology) were unaware of the studied solution. The anesthesiologist was responsible for preparing solutions, anesthesia, and the patients' monitoring. Data were analyzed using SPSS V.23 statistical software by descriptive statistics (mean ±SD) and independent t-test to compare the means of two groups. The normal distribution of data was evaluated using Kolmogorov-Smirnov test. P-value less than 0.05 was considered statistically significant.

Results

There was no statistically significant difference between two groups in terms of patient demographic characteristics (Table1). The comparison of the hemodynamic status of the patients during the procedure showed that the values SBP, DBP, MAP and HR were significantly lower in Group O than Group P (Figure 1). Table 2 represents the volume of injected and collected irrigation fluid, the lack of its volume during the procedure; and declining of serum hematocrit and sodium level at the end of surgery were lower in Group O ($p<0.05$). Table 3 presents the perioperative complications and their management. which occurred in 14 cases. The most common complication was hypotension during the procedure (18%) (3 and 6 cases in Groups O and P, respectively) ($p=0.019$). The most common undesirable effect of treatment was related to crystalloids (16%) ($p=0.018$). The values for other variables are presented in table 3.

Discussion

To the best of our knowledge, this study is the first to evaluate the effects of oxytocin infusion on the absorption rate of irrigation fluid during hysteroscopic myomectomy. We believe that this technique might be usefully employed in patients with hysteroscopic myomectomy. In the present study the amount of absorbed and collected media fluid in case group were significantly lower than control group.

Oxytocin receptors are found in myometrium and fibroid tissues(17).Oxytocin elicits prostaglandins release(18) which in turn decreases uterine perfusion(19). Increased uterine contractility directly affects uterine vascular structures, decreasing blood supply to the arteries and fibroids (20, 21).

Uterine myomectomy and polypectomy are among popular conventional and minimally invasive gynecological procedures in hysteroscopy (22). Despite numerous advantages of the hysteroscopic, absorption of irrigation fluid is one of the complications that can lead to hypervolemia in 3 to 6% of patients (23). Hypotonic solutions, which include 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 (24).

In our study, the evaluation of hemodynamic variables showed that the use of oxytocin infusion resulted in modulation of systolic, diastolic, MAP and HR in patients undergoing hysteroscopic myomectomy. Intraoperative blood loss could lead to hemodynamic alterations and up to 5% of patients undergoing hysteroscopic myomectomy might require blood transfusion (15, 25). According to recent studies, it has been observed that oxytocin, thanks to its vasoconstrictor properties in the uterine arteries, reduces intraoperative bleeding and hence, less hemodynamic changes are .Thus, the amount of injected and collected media fluid and its deficit were significantly lower in oxytocin receiving group. In addition, the rate of decreased serum hematocrit and sodium level after surgery was significantly lower than control group. Bradley et al reported that intravascular absorption of irrigation solution, which might occur during hysteroscopic surgeries through vasculature or fallopian tubes opening into the peritoneum, could result in hypertension or other hemodynamic imbalances, hematological disorders, pulmonary edema, increased intracranial pressure (ICP)and even

organ failure(26). Istre et al reported that absorption of irrigating solution may be associated with serious complications during hysteroscopic surgery(27). Oxytocin targets special receptors in the uterus and fibroid tissue, leading to the synthesis and release of contractile prostaglandins. Increased uterine contractility has direct effect on the structure of uterus and reduces both arterial and venous blood flow which in turn leads to decreased absorption of fluid through the open vessels during surgery (28). On the other hand, it also results in decreased blood loss as reported by Atashkhoei et al. (28). In our study, the frequency of hypotension in patients receiving oxytocin was significantly lower than control group. Whereas Langesaeter et al. reported that the most common side effects of oxytocin were hypotension, tachyarrhythmias, and hyponatremia (29). It seems that few side effects in the present study might to be due to the low dose of oxytocin used as well as the low sample size.

Conclusion

Intraoperative oxytocin infusion in hysteroscopic myomectomy could decrease the absorption of irrigation fluid and therefore it could be used to reduce the complications caused by excessive absorption of large volumes of irrigation fluid during hysteroscopic myomectomy.

Limitations

Elderly patients and those with ASA grade III or higher were not evaluated in our study. Considering the fact that age and underlying diseases might affect respiratory mechanics, arterial oxygen saturation and other outcomes, it is recommended to survey hysteroscopic surgery in elderly patients and those with higher ASA classes as well.

Conflict of interest

The authors stated that they had no conflict of interest.

Details of ethics approval

The study was approved by the Research Ethical Board of Tabriz University of Medical Sciences (IRCT20160103025821N5).

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Contribution to authorship

HP and SA contributed to the concept and planned the study frame, and they were responsible for the preoperative visit and premedication. HA prepared the two blocked randomization lists of the patients with online software.According to the randomisation list, SA prepared the study solution and, except SA, all other authors were blinded to the treatment solution until the end of study. HA was responsible for blind data collection and recording. HP with the consult of a social medicine specialist had the responsibility of data analysing, continuous study progress monitoring and managing study methodology. SF and HP (anaesthesiologists) responsible for anaesthetic and surgical management of the patients during the study, respectively. LK prepared the manuscript for publication. All authors reviewed and approved the final version of the manuscript.

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