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Effect and Safety of Diluted Vasopressin Injection for Bleeding Control During Robot-assisted Laparoscopic Myomectomy in Reproductive Women With Uterine Fibroids: A Randomized Controlled Pilot Trial (VALENTINE Trial)

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Abstract. *Background/Aim: Vasopressin injected during myomectomy is known to effectively reduce bleeding but is sometimes associated with intraoperative vasoconstriction and hypertension due to systemic absorption. Although there is a growing preference for the use of diluted vasopressin, evidence of its effect and safety is still lacking. Patients and Methods: We performed a randomized controlled pilot trial to evaluate the effect and safety of vasopressin diluted in a constant volume during robot-assisted laparoscopic myomectomy (RALM), where a total of 39 women with uterine fibroids were randomly assigned into the following three groups (group 1, 0.2 IU/ml; group 2, 0.1 IU/ml; group 3, 0.05 IU/ml with a total of 100 ml of normal saline). The primary endpoint was to compare estimated blood loss (EBL), and the secondary endpoints were to compare postoperative value and drop ratio of hemoglobin, operation time, transfusion, hospitalization, and complications among the three groups. Results: There were no differences in the number and largest size of uterine fibroids, total weight of uterine fibroids, console time, and volumes of intravenous fluid administered during RALM among the three groups, whereas combined operation was performed more commonly in group 2 than in groups 1 and 3 (53.9% vs. 0 to 7.7%; p=0.01). The primary and secondary endpoints were also not different among the three groups. However, two patients in group 1 (15.4%) showed vasopressin-related hypertension. Conclusion: Vasopressin diluted in a volume of 100 ml showed an effective hemostatic effect and safety during RALM (Trial No. NCT04874246 in ClinicalTrial.gov).*

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Key Words: Uterine fibroids, robot-assisted laparoscopic myomectomy, vasopression, bleeding control.

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Uterine fibroids are the most common benign gynecologic condition in women, diagnosed in more than 25% of women of childbearing age. Despite its benign nature, uterine fibroids are associated with clinical symptoms, such as abnormal uterine bleeding, pain, and pressure in 25-50% of women, so there is still an ongoing clinical interest in effective treatment (1). Pharmacotherapy with non-steroidal anti-inflammatory drugs, hormonal agents, and gonadotropin-releasing hormone (GnRH) agonists is the first line of treatment for symptomatic uterine fibroids and invasive procedures, such as uterine artery embolization, or high-intensity focused ultrasound may be considered if there is a lack of response to the medical

treatment (2). However, surgical treatment, such as myomectomy or hysterectomy is ultimately chosen to control symptoms because these conservative treatments are often temporary or short-lived (3).

Especially myomectomy is considered for women of childbearing age who want to become pregnant in the future or want to preserve their uterus. Before 2000, myomectomy was mainly performed through open surgery, but since 2000, laparoscopic myomectomy has gradually expanded due to the development of surgical techniques (4). However, it is clinically important to select the right patients for laparoscopic myomectomy as the effectiveness of this procedure is influenced by the number and location of uterine fibroids and the surgeon's skill. Furthermore, the recently introduced robot-assisted laparoscopic myomectomy (RALM) is spreading rapidly around the world because it does not have these limitations and can be performed easily and comfortably by the surgeon, with reduced pain and faster recovery for the patient (5).

Nevertheless, significant bleeding from damage to the myometrium and blood vessels is common during myomectomy regardless of the surgical method, which often results in blood transfusions or, in rare cases, conversion to open surgery to try to achieve rapid hemostasis (6-8). Therefore, efforts to reduce intraoperative bleeding from surgical damage by injecting vasopressin into the subserosa of the uterus have long been practiced. However, vasopressin injected into the uterine muscle may be absorbed systemically, leading to cardiovascular adverse effects during myomectomy, and increasing surgical complications (9). Recent studies have shown that diluted vasopressin can be used to reduce the incidence of these complications, with similar hemostatic effects, but there is still a significant lack of well-designed randomized controlled trials (RCTs) on the efficacy and safety of diluted vasopressin for myomectomy. Thus, we performed this randomized controlled pilot study, "effect and safety of diluted vasopressin injection for bleeding control during robot-assisted laparoscopic myomectomy in reproductive women with uterine fibroids: a randomized controlled pilot trial (VALENTINE trial)", to evaluate whether the injection of vasopressin diluted in a constant volume is effective and safe for hemostasis during RALM.

Patients and Methods

Study design. This randomized controlled pilot study was approved by the Ministry of Food and Drug Safety, and the Institutional Review Board of Seoul National University Hospital (No. 2011-107-1174). Moreover, this trial was registered at ClinicalTrials.gov in advance (NCT04874246) and conducted according to the published protocol (10). We consecutively enrolled patients with the following criteria: age from 19 to 60 years; surgical plan of RALM for removing uterine fibroids; at least one uterine fibroid ≥5 cm; subclassification system 2 to 7 for uterine fibroids; the American Society of Anesthesiologists (ASA) physical status classification 1 or 2; Written informed consent. However, we excluded patients with pregnancy or breastfeeding after delivery; uterine fibroids >12 cm; more than five uterine fibroids; suspicious uterine malignancy; prior pelvic surgery with severe pelvic adhesion; underlying disease contraindicated to vasopressin injection. All patients were assigned into three groups in a 1:1:1 ratio using the randomization program on the website (http://randomization.com) after informed consent. The third investigator with no interest in the study (DWH) diluted vasopressin and randomized all patients without the knowledge of patients and surgeons.

Intervention. We randomly divided all patients into the following experimental groups: group 1, a solution prepared by mixing 20 IU of vasopressin with 100 ml of normal saline to make a total of 100 ml (0.2 IU/ml); group 2, a solution prepared by mixing 20 IU of vasopressin with 200 ml of normal saline to make a total of 100 ml (0.1 IU/ml); group 3, a solution prepared by mixing 20 IU of vasopressin with 400 ml of normal saline to make a total of 100 ml (0.05 IU/ml). Since the maximal number of uterine fibroids was five in this study, we injected at least 20 ml of vasopressin per uterine fibroids for a total of 100 ml according to a previous study where the minimal volume of vasopressin to be injected was 20 ml (11).

Thereafter, we conducted RALM as follows: First, we inserted trocars (Laport®, Sejong Medical, Seoul, Republic of Korea) in a row at the height of the umbilicus, and evaluated the size and location of uterine fibroid by using a laparoscopic camera inserted through the trocar; Second, we injected a total 100 ml of diluted vasopressin into the uterine subserosa layer where uterine fibroids were located, and then removed them after incision of the uterine serosa with the vessel sealer (Caiman®, Aesculap AG, Tuttlingen, Germany). Third, we repaired and enforced the defective area of the uterine muscle layer with the barbed suture: Fourth, we washed the abdominal cavity with normal saline while checking for bleeding after the removal of uterine fibroids out of the abdominal cavity; Fifth, a Jackson-Pratt drain was placed to assess for postoperative rebleeding if necessary, no hemostatic agents were used in this study.

Sample size calculation. We had difficulty calculating the number of subjects needed for the VALENTINE trial because there was a lack of reference studies with different concentrations of vasopressin under the same infusion volume. Therefore, this study was conducted as a pilot study to calculate the population for a larger randomized trial in the future. Based on the suggestion from the previous study on calculating the number of subjects in a pilot study, we planned to allocate 12 subjects per group for randomization and include a total of 36 subjects (12). With a 10% drop-out rate, we aimed to target 39 subjects.

Endpoints. As the primary endpoint, estimated blood loss (EBL) was measured as the volume collected in suction bottles without irrigation of normal saline. After the anesthesiologists checked EBL, we washed the surgical site with normal saline. As the secondary endpoints, postoperative value and drop ratio of hemoglobin, operation time, transfusion, hospitalization, and complications were assessed in the three groups. Drop ratios of hemoglobin and hematocrit were defined as (preoperative value-operative value)/preoperative value×100.

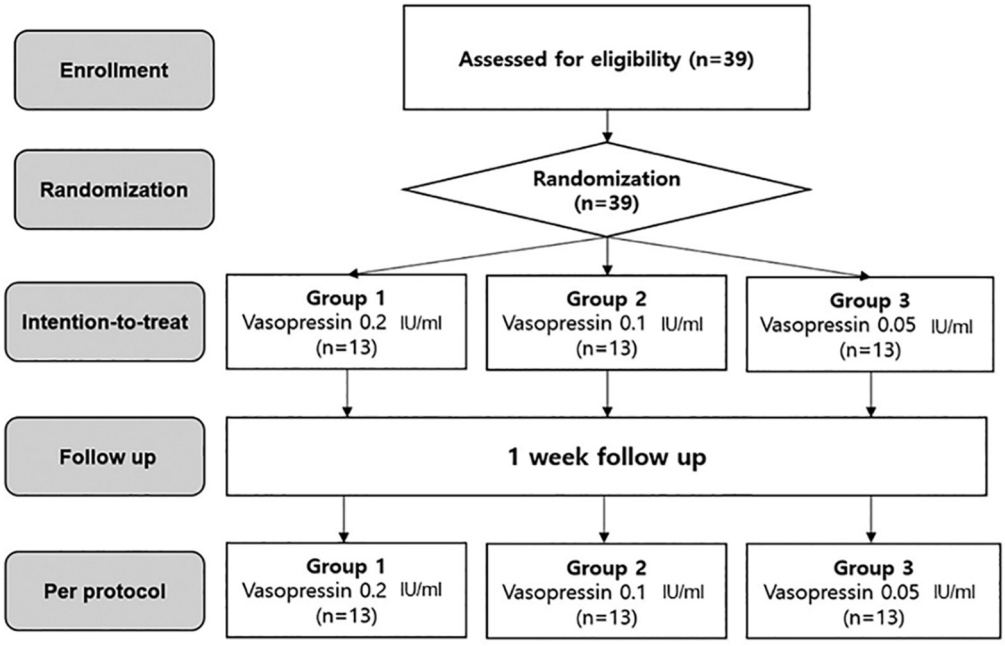

Figure 1. *Flow diagram of this randomized controlled pilot trial.*

Table I. *Baseline characteristics.*

Characteristics	Group 1 (n=13)	Group 2 (n=13)	Group 3 (n=13)	*p*-Value
Age (median, range, y)	42 (30, 46)	39 (32, 49)	37 (26, 49)	0.43
Body mass index (median, range, kg/m^2)	23.5 (18.6, 34.1)	21.1 (18.3, 28.6)	21.5 (18.7, 25.3)	0.07
Parity (median, range)	0 (0, 2)	0 (0, 4)	1 (1, 3)	0.75
ASA physical status (n, %)				0.39
1	2 (15.4)	5 (38.5)	3 (23.1)	
2	11 (84.6)	8 (61.5)	10 (76.9)	
Diagnostic methods for uterine fibroids (n, %)				0.72
Ultrasonography	4 (30.8)	3 (23.1)	4 (30.8)	
Magnetic resonance imaging	9 (69.2)	10 (79.9)	9 (69.2)	
The largest size of uterine fibroids on preoperative images (median, range, cm)	8 (5-12)	8 (5-11)	9 (4-11.3)	0.232
The number of uterine fibroids on preoperative images (median, range)	2 (1-5)	1 (1-5)	1 (1-3)	0.861
Preoperative hemoglobin (median, range, g/dl)	12 (10.1, 14.1)	12.8 (11.2, 14.9)	12.7 (9.9, 14.5)	0.29
Prior use of GnRH agonist (n, %)	4 (30.8)	5 (38.5)	4 (30.8)	0.92
Prior abdominal surgery (n, %)	0 (0, 1)	0 (0, 2)	0 (0, 2)	0.15

ASA: American Society of Anesthesiologists; GnRH: gonadotropin-releasing hormone.

Statistical methods. Dichotomous data are shown with number and percentage and compared by using the chi-square or Fisher's exact test among the three groups. Continuous data are presented with median value and range and compared by using the Kruskal-Wallis H test. We used SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA) and a $p<0.06$ was considered statistically significant.

Results

A total of 39 patients were enrolled from August 2021 to August 2022, of which 13 were randomized to each of the three groups. No patients dropped out at the outpatient clinic one week after discharge (Figure 1). Table I depicts the

Table II. *Operative outcomes*.

Characteristics	Group 1 (n=13)	Group 2 (n=13)	Group 3 (n=13)	*p*-Value
The number of uterine fibroids (median, range)	2 (1-5)	2 (1-10)	2 (1-4)	0.63
The largest size of uterine fibroids (cm, median, range)	8 (6-12)	8 (5-11)	9 (7-11)	0.79
Total weights of uterine fibroids (median, range, g)	173 (47-570)	224 (60-547)	193 (53-399)	0.98
Combined operation (n, %)				0.01
Ovarian cystectomy	1 (7.7)	6 (46.2)	0	
Hysteroscopic endometrial polypectomy	0	1 (7.7)	0	
Console time (median, range, mins)	86 (35-135)	90 (45-145)	80 (10-160)	0.21
Volumes of intravenous fluid administered during surgery (median, range, ml)	950 (550-1,400)	850 (250-2,170)	950 (400-1,700)	0.69

Table III. *Primary and secondary endpoints*.

Characteristics	Group 1 (n=13)	Group 2 (n=13)	Group 3 (n=13)	*p*-Value
Primary endpoint				
Estimated blood loss (median, range, ml)	110 (0, 860)	200 (40, 490)	100 (0, 640)	0.51
Secondary endpoints				
Postoperative Hb (median, range, g/dl)	9.8 (9-12.8)	10.3 (8-12)	10 (8.4, 12.3)	0.93
Hemoglobin drop ratio (median, range, %)	13.5 (7.8, 31.2)	19.6 (5.2, 31.6)	18.6 (6.5, 36.6)	0.21
Operation time (median, range, min)	155 (100-217)	150 (80-235)	145 (60-245)	0.54
Transfusion (n, %)				
Intraoperative	0 (0)	0 (0)	0 (0)	-
Postoperative	0 (0)	1 (7.7)	1 (7.7)	0.34
Hospitalization (median, range, d)	3 (3, 9)	3 (3, 7)	3 (3, 4)	0.23
Complications (n, %)				
Intraoperative				
Vasopressin-related hypertension	2 (15.4)	0 (0)	0 (0)	0.12
Bowel injury	1 (7.7)	0 (0)	0 (0)	0.36
Postoperative				
Ileus 1 (7.7)	0 (0)	(0)	0.36	

baseline characteristics of the three groups of patients. There were no differences in age, body mass index, parity, ASA physical status, diagnostic methods for uterine fibroids, the largest size and number of uterine fibroids, preoperative level of hemoglobin, prior use of GnRH agonist, and prior abdominal surgery.

In terms of operative outcomes, there were no differences in the number and largest size of uterine fibroids, total weight of uterine fibroids, console time, and volumes of intravenous fluid administered during RALM. However, a combined operation, such as ovarian cystectomy or hysteroscopic endometrial polypectomy was performed more commonly in group 2 than in groups 1 and 3 (Table II).

Regarding the primary endpoint, EBL did not differ among the three groups. Furthermore, there were no differences in secondary endpoints, such as postoperative hemoglobin level and drop ratio of hemoglobin, operation time, transfusion, hospitalization, and complications among the three groups. However, two patients in group 1 (15.4%) showed vasopressin-related hypertension, and one (7.7%) underwent small bowel resection and anastomosis because of small bowel injury during the morcellation of uterine fibroids (Table III).

Discussion

The VALENTINE trial is meaningful because it is the first randomized controlled pilot trial to evaluate the efficacy and safety of diluted concentrations of vasopressin at the same infusion volume in reducing EBL during RALM. A literature review identified only one RCT that evaluated the efficacy and safety of dilute vasopressin during myomectomy, which compared EBL between the following two groups: 10 IU in 200 ml of normal saline and 10 IU in 30 ml of normal saline. As a result, both diluted and concentrated vasopressin solutions showed comparable efficacy and safety for hemostasis, and similar outcomes including transfusion (2.6%) and complications (12.5%) like the VALENTINE

trial (13). Especially, this study showed that vasopressin was effective in controlling bleeding during RALN despite being administered in half the volume while keeping the lowest concentration the same as in the previous study (0.05 IU/ml).

Vasopressin is a hemostatic agent used in gynecologic surgeries for over 50 years, and has been shown to effectively reduce bleeding, helping to clear the surgical field (14). In general, the licensed indication for vasopressin is the treatment of variceal bleeding, central diabetes insipidus, and vasodilatory shock, whereas it is used off-label for hemostasis during surgery in most countries (15, 16). However, systemic absorption of injected vasopressin during myomectomy can result in severe vasoconstriction leading to hypertension within 2 to 3 minutes, which usually returns to normal after 15 to 25 minutes with conservative management (9). In addition, it can lead to serious cardiopulmonary events including cardiac arrest, myocardial infarction, bradycardia, and pulmonary edema in rare cases, therefore, there is a clinical unmet need to use lower concentrations of vasopressin for bleeding control during benign surgeries such as myomectomy (10, 17).

The VALENTINE trial suggests that diluted vasopressin, when infused in the same volume, may be just as hemostatic as concentrated vasopressin, with comparable surgical outcomes. Although there was no statistical difference, vasopressin-related hypertension occurred intraoperatively when the highest concentration of vasopressin was infused (0.2 IU/ml). With proper handling by the anesthesiologist, there were no major problems during and after surgery, but this could be considered a significant increase in complications in a large RCT with more than 100 patients in each arm ($p<0.01$). Therefore, with these results, we would like to emphasize the importance of using vasopressin in as low a concentration as possible to reduce unnecessary complications.

This study has the following limitations: First, the experience of the surgeon performing the RALM may be a confounding factor. However, in this study, three gynecologic surgeons (SJP, EJL and HSK) who had completed a gynecologic fellowship program and had performed open and laparoscopic myomectomy for more than three years performed conventional RALM with four trocars and barbed suture, so it is not expected that the difference in surgical technique is significant; Second, we did not establish a control group with no treatment for hemostasis as a comparison. Since vasopressin is already known to be effective for hemostasis during myomectomy, a control group without the treatment could not be established in this study because it would have raised issues related to human subjects' risk of harm in the design phase (18). As an alternative, it is considered preferable to establish a control group in future trials using other methods of hemostasis, such as tourniquets and rectal misoprostol (14, 19): Third, the number of subjects was too small to generalize the results of this study despite being a randomized controlled pilot trial. We believe that the results of the future large-scale RCT can be generalized if the appropriate number of subjects is calculated from the VALENITEIN trial.

Conclusion

This VALENTINE trial comparing the hemostatic effect and safety of three different concentrations of vasopressin (0.2 IU/ml, 0.1 IU/ml, and 0.05 IU/ml) in a volume of 100 ml of normal saline showed comparable outcomes among the three different concentrations. However, the highest concentration of vasopressin (0.2 IU/ml) was associated with a 15.4% incidence of unnecessary intraoperative hypertension, suggesting that dilution of vasopressin to 0.05 IU/ml may be both effective and safe for hemostasis during RALM.

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Prior Presentation

For this research, we received the best oral presentation award (JWL) at the 1st Annual Congress of the Society of Korean Robot Gynecologic Surgery held on November 5, 2022, in Daegu, Republic of Korea.

Conflicts of Interest

SJP and HSK are the Chief Technology Officer and Chief Executive Officer of Dreampac Corporation (Wonju, Republic of Korea). Moreover, SL and GWP are the Chief Executive Officer and a director of Precision Medicine for Peritoneal Metastasis Corporative (Wonju, Republic of Korea). The other Authors declare no conflict of interest in relation to this study.

Authors' Contributions

EJL and HSK designed this study, and SJP, EJL, and HSK performed RALM after DWH randomly assigned all subjects. SJP, JWL, EJL, and HSK collected the data, and SJP, JWL, DWH, SL, GWY, and GS analyzed them. The first draft was written by SJP, JWL, EJL, and HSK. All Authors read and approved the final manuscript. The final version of this manuscript was revised by EJL and HSK.

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