

BMJ Open Effect and safety of diluted vasopressin injection on bleeding during robot-assisted laparoscopic myomectomy: a protocol for a randomised controlled pilot trial

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ABSTRACT

Introduction Even though the injection of diluted vasopressin into the uterus is expected to reduce intraoperative bleeding with decreased adverse effects during robot-assisted laparoscopic myomectomy (RALM), there is a lack of relevant trials to show its effect and safety. Thus, this study was designed to compare the effect and safety of vasopressin injection on bleedings based on dilution levels of vasopressin with constant volumes during RALM.

Methods and analysis This is a randomised controlled pilot trial, where a total of 39 patients will be randomly divided into three experimental groups in a 1:1:1 ratio. All patients will be classified into the three groups based on the dilution level of vasopressin: group 1—a solution prepared by mixing 20 units of vasopressin with 100 mL of normal saline to make a total of 100 mL; group 2—a solution prepared by mixing 20 units of vasopressin with 200 mL of normal saline to make a total of 100 mL and group 3—a solution prepared by mixing 20 units of vasopressin with 400 mL of normal saline to make a total of 100 mL. During RALM, we will inject diluted vasopressin at different concentrations with a total of 100 mL. As the primary endpoint, estimated blood loss would be compared. As secondary endpoints, we will check the level of haemoglobin and haematocrit, operation time, amount of transfusion, and the period of hospitalisation. In addition, we will check other complications related to vasopressin injection.

Ethics and dissemination This pilot study has been approved by the Institutional Review Board of the Seoul National University Hospital (No. H-2011-107-1174). All potential subjects will be provided written informed consent. The results of this study will be published in peer-reviewed journals and be presented at academic conferences.

Trial registration numbers NCT04874246 and CKCT0006225.

INTRODUCTION

Uterine fibroids are the most common gynaecological tumour in women, a widespread disease found in 20%–25% of women of

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a randomised controlled pilot trial to evaluate the effect and safety of the diluted vasopressin injection during robot-assisted laparoscopic myomectomy.
- ⇒ A strength is that we will conduct this trial by using a method of keeping the injection volume constant, limiting the number of uterine fibroids and reducing the most commonly used dose of vasopressin (20 units in one ampule) proportionally, which will be helpful in investigating the haemostatic effect and relevant side effects based on the dilution levels.
- ⇒ However, a small number of patients from a single centre could underestimate the effect and safety of diluted vasopressin injection.

childbearing age or 40%–50% women over 35. Approximately 20%–50% of women with uterine fibroids show clinical symptoms and various signs depending on the number, size and location of the tumour.¹ Medical therapy, including non-steroidal anti-inflammatory drugs, gonadotropin-releasing hormone agonists or procedural therapies such as uterine artery embolisation and high-intensity focused ultrasound can be considered as a non-invasive treatment. When these methods show a temporary and subtle treatment effect, surgical intervention such as myomectomy and hysterectomy may be ultimately required to obtain a faster and more direct alleviation of relevant symptoms.

Especially, uterine fibroids causing infertility or miscarriage and symptoms such as abnormal uterine bleeding, pain and signs of rapid growth requires myomectomy for women who want to preserve the uterus or become pregnant.² Even though the laparoscopic approach depends on surgeons' preference and the location and number of

leiomyomas, robot-assisted laparoscopic myomectomy (RALM) has been an ergonomic and easier operation method that is hardly affected by surgeons' skillfulness and the location and number of them. Moreover, RALM has been popular due to shorter hospitalisation periods, faster recovery, less pain and enhanced cosmesis compared with open surgery.³ These advantages of RALM are constantly increasing the option of surgical approach as the primary treatment method for uterine leiomyomas.⁴

Since myomectomy sometimes leads to significant bleeding that necessitates blood transfusion, vasopressin injection into the subserosa of the uterus can be an option to reduce myometrial bleeding. Vasopressin has been used as a haemostatic agent for over 50 years in various gynaecological surgeries such as cervical conisation, hysterectomy and myomectomy, which has been shown to be effective in reducing blood loss in many surgical fields.^{5,6} Labelled indications of vasopressin are the treatment of central diabetes insipidus, vasodilatory shock and variceal bleeding,^{7,8} whereas it is used as an off-label drug during myomectomy. Although vasopressin induces uterine contraction and thereby decreased blood loss, transfusion and operative time,⁹ it can cause general hypotension and severe vasoconstriction within 2 or 3 min when vasopressin is injected into the muscular layer of the uterus, it can cause.¹⁰ Typically, these changes return to normal after 15–25 min, but they can also have a fatal effect on the patient. Their severe complications mainly affect cardiopulmonary function, such as sudden cardiac arrest starting with bradycardia or acrotism, pulmonary oedema and myocardial infarction.^{11–13}

Thus, recent studies showed the potential that diluted vasopressin injection might also have a similar haemostatic effect,^{14–16} but there is still a lack of well-designed trial to show the effect and safety of diluted vasopressin injection because of different doses and volumes of vasopressin and various numbers of uterine fibroids.

Therefore, we will perform this randomised pilot study to evaluate whether the diluted vasopressin injection with the constant volume is effective and safe for haemostasis during RALM. These findings of this study will help calculate the appropriate number of subjects for relevant clinical trials in the future.

METHODS AND ANALYSIS

Study design

A flow chart of this study is depicted in [figure 1](#). This study is a single-centre, randomised controlled pilot trial approved by the Ministry of Food and Drug Safety and Institutional Review Board of Seoul National University Hospital. The study will follow the principles of the Declaration of Helsinki. The study conforms to the Standard Protocol Recommendations for Interventional Trials 2013 Statement,¹⁷ and the results will be reported according to the Consolidated Standards of Reporting Trials Statement extension for trials.¹⁸

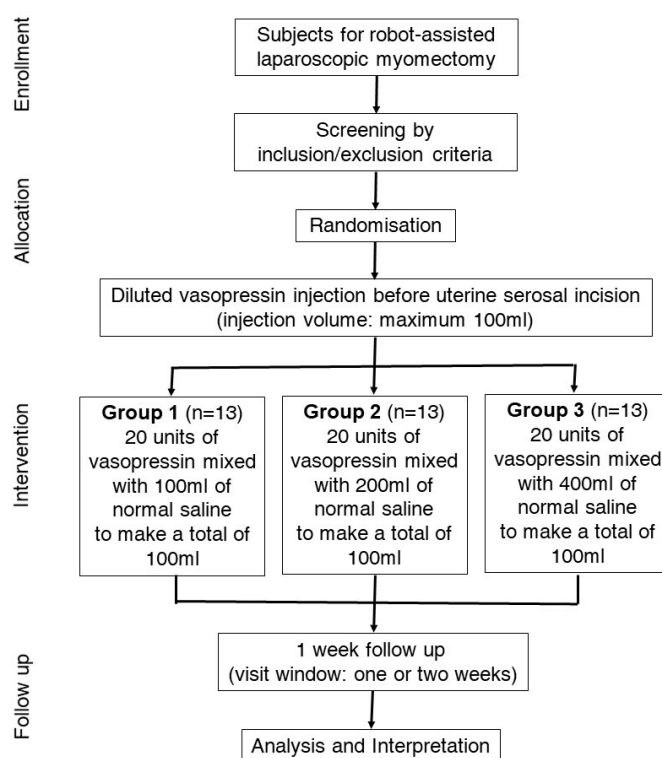


Figure 1 Flow diagram of the study.

Participants who meet the inclusion and exclusion criteria will be enrolled from August 2021 to December 2022. This study has been registered in the clinicaltrials.gov (No. NCT04874246) and the Clinical Research Information Service operated by Korea Centers for Disease Control and Prevention (No. KCT0006225).

STUDY POPULATION

It is intended for patients with leiomyomas diagnosed by an imaging test (pelvic ultrasound, CT, MRI, etc). All three tests do not need to be performed, and they can be replaced if the diagnosis is confirmed with just one test. Only participants who voluntarily agree with the contents of this study will be enrolled, and written consent will be obtained from all participants with the following criteria.

Inclusion criteria

1. Age: 19–60 years.
2. Surgical plan of RALM for uterine fibroids.
3. At least one uterine fibroid ≥ 5 cm.
4. Subclassification system 2–7 for uterine fibroids.
5. The American Society of Anaesthesiologists Physical Status classification 1 or 2.
6. Written informed consent.

Exclusion criteria

1. Pregnancy or breast feeding.
2. Uterine fibroids >12 cm.
3. More than five uterine fibroids.
4. Suspicious uterine malignancy.
5. A history of pelvic surgery with severe pelvic adhesion.

- Underlying diseases contraindicated to vasopressin injection.

Randomisation and blinding

Patients will be assigned into three groups in a 1:1:1 ratio using the randomisation programme on the website (<http://randomization.com>) after informed consent. The third investigator with no interest in the study (YK) will dilute vasopressin and randomise all patients without the knowledge of patients and surgeons.

Interventions

All patients will be randomly divided into three experimental groups: group 1—a solution prepared by mixing 20 units of vasopressin with 100 mL of normal saline to make a total of 100 mL; group 2—a solution prepared by mixing 20 units of vasopressin with 200 mL of normal saline to make a total of 100 mL and group 3—a solution prepared by mixing 20 units of vasopressin with 400 mL of normal saline to make a total of 100 mL.

The evidence for setting the upper limit dosage in 20 units of vasopressin is based on previous relevant studies,^{19–22} where 20 units of vasopressin were diluted in 20 mL of normal saline solution. On the other hand, other studies used a more diluted concentration than these (20 units of vasopressin diluted in 1000 mL of normal saline).^{14 15} Considering insufficient evidence of proper dilution doses of vasopressin and its volume, we will use the three popular diluted vasopressin solutions with a total of 100 mL in this trial, based on the results of previous studies that have proven their effectiveness. Since the maximal number of uterine fibroids is five in this study and the minimal volume of vasopressin to be injected has been reported to be 20 mL in previous reports,¹⁶ we will inject at least 20 mL of vasopressin per uterine fibroid for a total of 100 mL.

Surgical procedures

Surgical procedures for RALM are as follows.

- After trocars are inserted in a row at the height of the navel, a laparoscopic camera is inserted to determine the location of uterine fibroids. If the camera trocar insertion to the navel is challenging, it can be inserted above the navel. As a convenience, two or three additional trocars are inserted in the position where uterine fibroids can be removed and sutured more easily while looking through the camera.
- Diluted vasopressin is injected into the uterine subserosal area (the lower part of the uterine serosa and the subcapsule of fibroids) where uterine fibroids are located.
- After the uterine serosa incision is made, uterine fibroids are removed.
- Sutures of the defective part of the uterine muscle layer are enforced with the barbed suture.
- The abdominal cavity is washed with normal saline while checking for bleeding.

- Removal of uterine fibroids out of the abdominal cavity.
- After the operation, tranexamic acid can be administered up to the second day for bleeding control.

OUTCOME MEASURES

As the primary endpoint, estimated blood loss (EBL) would be compared among the three groups. Since it is not a laparotomy, it is expected that there will be no loss of bleeding that is absorbed by gauze. So, EBL will be measured as a volume collected in suction bottles without irrigation of normal saline. After the anesthesiologist will check the volume, we will wash the surgical site with normal saline. As secondary endpoints, haemoglobin and haematocrit levels, operation time, the amount of transfusion, and the length of hospital stay will be assessed. In addition, side effects related to vasopressin injection will also be checked, and all other possible adverse events, including reoperation, within 4 weeks will be analysed.

Data and safety monitoring

After obtaining informed consent from the participants, the collected data and adverse events will be documented in the case report forms. All patients will not be excluded after informed consent if they do not withdraw their consent. The data and safety monitoring board members (SL, GWY and GS) will monitor the registration of participants, intervention allocation, reasons for withdrawal, adverse events and violation of initial protocol. All members are independent of the sponsor and competing interests.

SAMPLE SIZE

Since this study is conducted as a pilot study, we did not separately calculate the sample size. The present pilot study examines the feasibility of a full randomised clinical trial of proper dilution level of vasopressin for RALM and determines the effect size for further large-scale studies. Based on a previous report, we plan to allocate 12 subjects per group for randomisation, and a total of 36 subjects are required.²³ With a 10% drop-out rate and 1 subject per group, we aim to target 39 subjects.

Statistical methods

For the statistical analyses, we will use SPSS software V.25.0 (SPSS). Measurement data will be described in mean and SD or median and IQR, and categorical variables as number and percentage. The difference in blood loss between the three groups was analysed using the Kruskal-Wallis H test. The incidence of side effects between each group is compared and evaluated using the χ^2 test or Fisher's exact test. A $p < 0.05$ is considered statistically significant.

Ethics and dissemination

The Institutional Review Board has approved this pilot study of the Seoul National University Hospital (No.



H-2011-107-1174). The current protocol version is 1.3. Even though vasopressin has already been approved for marketing and is used in clinical practice, the use of vasopressin to reduce bleeding in myomectomy has not been approved up to now. Thus, this clinical trial has been separately approved by the Korean Ministry of Food and Drug Safety (No. 33696).

The confidentiality of personal information will be protected. All of the personal identification information will be deleted. Each participant is assigned a study identification number at enrolment. Data will be handled by the study identification number. Before participation, patients will receive detailed information about the purpose and possible consequences of the trial. Written informed consent will be obtained from each participant before enrolment by the investigators. Finally, the results of this study will be published in peer-reviewed journals and be presented at academic conferences.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

DISCUSSION

This trial is a randomised controlled pilot study to determine the range of an effective and safe dilution concentration of vasopressin during RALM. Although some studies showed the effect and safety of diluted vasopressin injection during myomectomy,^{14 15} Injected volumes were not constant, which could act as a bias because only injection of normal saline showed comparable operative outcomes, including operation time and hospitalisation period.²⁴ Thus, we could not find adequate references to calculate the sample size for a relevant randomised controlled trial, and decided to conduct a randomised controlled pilot trial alternatively.

The strength of this study is that we will conduct a well-designed trial, where we will keep the injection volume constant, limit the number of uterine fibroids (≤ 5) and reduce the most commonly used dose of vasopressin (20 units in one ample) proportionally. The results will be helpful in investigating the haemostatic effect and relevant side effects based on the dilution levels and estimating the sample size for the future trial. However, a small number of patients from a single centre could underestimate the effect and safety of diluted vasopressin injection because of insufficient power. Moreover, the number of uterine leiomyomas or the presence of intra-abdominal adhesion could act as a bias in calculating the amount of blood loss.

In previous studies, diluted vasopressin injection showed comparable blood loss, EBL, haematocrit difference and hospitalisation period to concentrated injection with no differences in rates of the laparoscopic approach, locations and weights of fibroids, suture types and transfusion during myomectomy.^{14 15} Compared with previous

studies, we will use only RALM with barbed suture, which will control external factors because we can minimise the influence of surgeons' skillfulness on outcomes of this study through an ergonomic and minimally invasive approach. Conclusively, this study is believed to be an important opportunity to prospectively investigate the appropriate and safe concentration of diluted vasopressin used during RALM and examine-related adverse events.

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Contributors HSK conceived the idea and supervised all the procedures of this trial. E.J.L. wrote the initial manuscript and conducted this protocol. S.L., G.W.Y. and G.S. edited the first manuscript. S.J.P., Y.K. and H.L. provided input and revision on the protocol. All authors approved the final version for submission and the revised manuscript.

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Competing interests HSK, the corresponding author received research support from the MEDITECH INFRAMED Corp. (Seoul, Republic of Korea). Moreover, he is the Chief Executive Officer (CEO) in Dreampac Corp. (Wonju, Republic of Korea), and the Chief Financial Officer (CFO) in Precision Medicine for Peritoneal Metastasis Corp. (Wonju, Republic of Korea). No other authors has reported a potential conflict of interest relevant to this article.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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