



## Research Protocol

# The Efficacy of Misoprostol plus Vasopressin versus Vasopressin Alone on Surgical Outcomes through Minimally Invasive Myomectomy: Research Protocol

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## Abstract

To compare the effect of perivascular vasopressin with a combination of rectal misoprostol plus perivascular vasopressin on blood loss reduction during minimally invasive myomectomies, a double-blind randomized clinical trial it designed to be conducted in Shiraz, Iran in 2015. The primary outcomes of the study include; blood loss during surgery and hemoglobin (Hb) drop after surgery extracting the baseline and 6-hour post-surgery serum hemoglobin levels. The secondary outcomes of the study include; duration of operation; surgical complications; post-operative complications; hemodynamic changes during surgery, administration of other uterotonic agents; and post-operative fever.

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## Introduction

Uterine fibroids or leiomyomas are benign smooth muscle tumors of uterus most common in women of late reproductive age and usually treated when turn symptomatic. Leiomyomas usually shrink after menopause, however, many women need treatment due to its complications or unpleasant symptoms such as infertility [1,2]. Hysterectomy is considered as the standard treatment of symptomatic fibroids in women who don't plan for future childbearing. Those desiring childbearing prefer to have myomectomies when possible. Laparoscopic procedures could be used both for hysterectomy and myomectomy, the latter having the advantage of preserving the childbearing function but leading to higher risks of intraoperative bleeding [3]. The bleeding risk is increased during laparoscopic myomectomy

because it is performed without first controlling the blood flow to the uterus [3]. A variety of interventions are used to reduce bleeding during myomectomy especially in laparoscopic surgery. Vasopressin has shown to have an effect on diminishing the blood loss during myomectomy [4]. However, this may not reach to a satisfying level and the evidence for its effect alone on duration of hospital stay or surgical complications is not convincing [4]. Substantial reductions in blood loss is similarly reported for vaginal misoprostol during myomectomy independently of the surgical technique applied [5]. The efficacy of the combined use of vasopressin plus misoprostol has not been well evaluated yet. The aim of this study is to compare the effect of perivascular vasopressin with a combination of rectal misoprostol plus perivascular vasopressin on blood loss reduction during minimally invasive myomectomies.

## Study design and population

Study source population includes all 18-55 year-old women referred to laparoscopy clinic of Dena and Shiraz Mother-Child Hospitals as candidates of minimally invasive myomectomy for symptomatic uterine fibroids. Leiomyoma of uterus is defined in present study according to the international classification of diseases (ICD 10) with the code D25. A parallel randomized clinical trial will be conducted to compare misoprostol plus vasopressin administration with vasopressin alone to decrease bleeding and surgical complications at minimally invasive myomectomy. The study recruitment is started in March 2016 planned for completing the enrollment by September 2106.

Inclusion criteria for enrollment of the patients are: Women with symptomatic uterine fibroids; an age range of 18-55; without any contraindication for laparoscopy, misoprostol or vasopressin; and accepting to participate in the study. The exclusion criteria are: any contraindication for laparoscopy; any contraindication for misoprostol; and any contraindication for vasopressin.

## Study sample size

A total sample size of 80 (40 for each group) is estimated to test a superiority hypothesis of comparing means of blood loss between the groups as the primary outcome of study. The estimate parameters are taken from a previous study as mean bleeding volume of 623 cc in control group versus 334 cc in trial group with a pooled standard deviation of 475 and clinical significance margin equal to 20cc assuming 95% confidence level and 80% statistical power of study [6]. Calculations were made using sampsi command in Stata version 11 statistical software package (StataCorp: College Station, Texas 77845 USA).

## The intervention protocol

The study is comprised of two parallel arms enrolling patients scheduled to undergo myomectomy. The patients in trial arm will receive 400 micro grams of rectal misoprostol by a trained nurse 60 minutes before surgical procedure. Moreover, the surgeon will do an intra-myometrial injection of 20 units of vasopressin as a 1 ml drug bolus diluted in 19 ml of normal saline before the myomectomy in these patients. The injection will be done through the surgery and prior to the myomectomy incision while the anesthesiologist closely monitors the vital signs and blood pressure. The patients in control arm will receive the placebo for rectal placebo by a trained nurse. Similarly with the trial group, the surgeon will also do an intra-myometrial injection of vasopressin in control group patients.

## Randomization and blinding

A block randomization will be applied. The random sequence will be generated using Microsoft excel as described in literature [7]. A trained nurse will assign the patients either to control or trial arm according to the generated random sequence. The same person will be responsible for rectal administration of either placebo or misoprostol 60 minutes before surgery. The patient and surgeons performing the operation will be blinded to the type of intervention procedure.

## Outcome measures and key variables

The primary outcomes of the study include; blood loss during surgery and hemoglobin (Hb) drop after surgery extracting the baseline and 6-hour post-surgery serum hemoglobin levels. The secondary outcomes of the study include; duration of operation; surgical complications; post-operative complications; hemodynamic changes during surgery, administration of other uterotonic agents; and post-operative fever.

Several parameters will be monitored during surgery including: pulse rate, blood pressure, electrocardiographic changes, the need for blood transfusion, the need for hysterectomy or laparotomy as well as other potential complications. The blood loss is calculated measuring the suction and irrigation volume at laparoscopic myomectomy. If laparoscopic assisted myomectomy is performed bloody sponges will be counted and the attributable blood loss will be estimated and added to the volume measure through suction procedure. At the end of surgery hemovac will be inserted and the volume of drainage during the first 24 hours will also be recorded. When the drainage gets less than 50 cc/24 per hour, the hemovac will be taken out and the patient will be discharged. After the surgery, the vital signs will be recorded hourly till 4 hours and then continued each 4 hours. Any complications such as fever, transfusion and tachycardia will be recorded. The length of stay will also be recorded. A para-clinical evaluation including complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), blood urea nitrogen (BUN), creatinine and liver function test (LFT) assays will be performed. Other key variables are related to leiomyoma characteristics. A key data collection check list was developed as follows

1. Study group:  
*1-Control group: Vasopressin 2-Trial group: Misoprostol + vasopressin*
2. Demographic information:  
*Patient id, date and age*
3. Symptoms:  
*1-AUB 2-Pain 3- Pressure effect 4-Infertility 5-Others*
4. Size of the leiomyoma in ultrasound examination
5. Number of leiomyomas:  
*1, 2, 3, 4, 5, >5*
6. Leiomyoma location:  
*1-Posterior 2-anterior 3-cervical: 3 4- lateral 5-fundal 6-broad ligament*
7. Quantity of leiomyomas
8. Size of leiomyomas
9. Surgery length of time
10. Bleeding volume during the operation
11. Intraoperative administration of Methergine (methylergonovine maleate):  
*1- No 2-Yes*  
*Number of methergine doses if needed*
12. Preoperative Hb
13. Hb 6 hours after surgery
14. Hb drop
15. Length of stay
16. The drain volume:
17. Intraoperative complications

1-No complication 2-laparotomy 3-hysterectomy  
4-visceral injury

18. Postoperative complications

1-No complication 2-Fever 3-secondary surgery  
4-wound infection 5-hematuria

19. Transfusion needed:

1-No 2-Yes

20. Amount of transfusion if needed

21. Intraoperative vital signs:

1-temperature 2- blood pressure 3- pulse rate

22. Postoperative vital signs:

1-temperature 2- blood pressure 3- pulse rate

23. Type of operation:

1- Laparoscopic Myomectomy (LM)

2- Laparoscopically Assisted Myomectomy(LAM)

### Statistical analysis

The collected data will be entered into computer and analyzed using Stata version 11 statistical software package (StataCorp: College Station, Texas 77845 USA). Both descriptive and analytical methods will be applied. Means and standard deviations (SD) will be calculated for normally distributed numeric measures and median along with interquartile range will be reported for skewed distributions. Paired t test will be used for before-after comparisons and independent t test will be applied to compare the change in numeric outcome measures such as blood loss volume or Hb drop. In case the assumption for parametric tests do not hold, appropriate nonparametric tests will be used instead. If the inadequacy of randomization in controlling the confounders is suspected multivariate least squares linear regression will be used to investigate the independent effect of intervention on study primary outcomes. Leverage and influential observations will be assessed and removed if necessary. Cook's D will be calculated to check for influential observations. The linearity assumption between the regressors and regressand will be checked using scatter plots. The variance inflation factor (VIF) will be calculated for all predictors to assess multicollinearity. A VIF>10 will be considered as a sign of high multicollinearity. Considering the type of hypothesis in this study one-tailed statistical results will

be used for interpretation. A P-value <0.05 will be interpreted as statistical significance level.

### Ethical issues

The study is approved by the committee of ethics in Shiraz University of Medical Sciences under the number ir.sums.rec.1395.60. The procedure and its potential effects will be described to patients and informed consent will be taken from all the participants. They will also be informed about their freedom to decide on accepting to participate or leave at any time through the study without any restrictions to receive the healthcare they need.

### References

1. Vollenhoven BJ, Lawrence AS, Healy DL. Uterine fibroids: a clinical review. *British journal of obstetrics and gynaecology*. 1990;97(4):285-98.
2. Aboyeji AP, Ijaiya MA. Uterine fibroids: a ten-year clinical review in Ilorin, Nigeria. *Nigerian journal of medicine: journal of the National Association of Resident Doctors of Nigeria*. 2002;11(1):16-9.
3. Sami Walid M, Heaton RL. The role of laparoscopic myomectomy in the management of uterine fibroids. *Current opinion in obstetrics & gynecology*. 2011;23(4):273-7.
4. Kongnyuy EJ, Wiysonge CS. Interventions to reduce haemorrhage during myomectomy for fibroids. *The Cochrane database of systematic reviews*. 2014(8):CD005355.
5. Iavazzo C, Mamais I, Gkegkes ID. Use of misoprostol in myomectomy: a systematic review and meta-analysis. *Archives of gynecology and obstetrics*. 2015;292(6):1185-91.
6. Frederick S, Frederick J, Fletcher H, Reid M, Hardie M, Gardner W. A trial comparing the use of rectal misoprostol plus perivascular vasopressin with perivascular vasopressin alone to decrease myometrial bleeding at the time of abdominal myomectomy. *Fertility and sterility*. 2013;100(4):1044-9.
7. Asghari-Jafarabadi M, Sadeghi-Bazargani H. Randomization: Techniques and Software-aided Implementation in Medical Studies. *Journal of Clinical Research & Governance*. 2014;3(2).