

Vasopressine in laparoscopic myomectomy, a review over the effectiveness, dosage and possible complications.

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Abstract: Uterine leiomyomas (myomas or fibroids) are smooth muscle tumors and are the most common type of pelvic tumors in women. Myomatous uteri have an increased number of arterioles and venules and myomectomy may involve significant blood loss.

To reduce blood loss during an laparoscopic myomectomy, gynecologic surgeons often take the preventive step of injecting a dilute solution of vasopressin intramyometrial before they start the procedure. In randomized clinical trials, injection of vasopressin has been demonstrated to reduce blood loss in several gyn surgical procedures, including myomectomy, hysterectomy, abortion, and conization.^{5,6,7}

Vasopressin is diluted with saline as 10 units of vasopressin for every 100 ml of saline. For a fibroid of about 8 cm size, 40 units of vasopressin is diluted in 400 ml of normal saline. The whole of 400 ml of this saline is injected in the myometrium. Incision is made on the uterus with just simple scissors (no energy source is required). As the uterus is cut, instead of bleeding, saline leakage takes place. This helps to keep the field clear and it is easier to get the correct plane between the fibroid and the myometrium. The separation of the fibroid is helped due to the dissection of the correct plane by the saline injection.

A persistent concern, however, is that injection of vasopressin is, occasionally, associated with bradycardia and cardiac arrest, especially if injection is made into a blood vessel inadvertently. An unresolved issue is identifying the optimal dilution and dose of vasopressin that will reduce blood loss and minimize the risk of cardiac arrest.^{9,10,11}

Keywords: *vasopressin, myomectomi, laparoscopy, hemorrhage, complications*

Objectives: *The objective of this study is to assess the effectiveness, safety dose and tolerability of vasopressin intramyometrial injection to reduce the blood loss during laparoscopic myomectomy.*

I. INTRODUCTION

Uterine leiomyomas (myomas or fibroids) are smooth muscle tumors and are the most common type of pelvic tumors in women. Myomectomy is removal of the myomas, while leaving the uterus in place.

Myomas have an increased number of arterioles and venules and myomectomy may involve significant blood loss. However, studies show that the blood loss is no greater than for hysterectomy. The average volume of blood loss during abdominal myomectomy (performed via laparotomy) is 200 to 800 mL and for laparoscopic myomectomy is 80 to 250 ml. Surgical hemorrhage may result in anemia, hypovolemia, and coagulation abnormalities.

Vascular anatomy of the uterus and leiomyomas

The ascending blood supply of the uterus is from the uterine arteries, which pass through the cardinal ligament at level of the cervicouterine junction. The descending blood supply is from the ovarian arteries, which pass through the infundibulopelvic ligaments (suspensory ligaments of the ovary) and perfuse the ovaries, fallopian tubes, and uterine cornua. The uterine and ovarian vessels anastomose to perfuse the uterus. Arcuate arteries run transversely within the uterine wall and radial arteries penetrate deeply into the myometrium.

The presence of leiomyomas in the uterus distorts normal vascular architecture. Thus, the arcuate arteries may run in any axis, rather than transversely. Thus, either vertical or transverse incisions during myomectomy may transect these vessels.

It has been the common teaching that there is a vascular pedicle at the base of each myoma, and that ligation of this pedicle will achieve hemostasis during myomectomy. However, a study using vascular corrosion casting and electron microscopy revealed that myomas are surrounded completely by a dense vascular layer supplying the myoma, which is separated from the myometrium by a narrow avascular cleft.

Bleeding can be prevented or decreased with mechanical or pharmacologic methods. One of the pharmacological methods is the myometrial injection of vasopressin before doing the myomectomy.

Vasopressin is a uterotonic in the nonpregnant uterus. Both vasopressin and oxytocin are secreted from the posterior pituitary gland. Both are napeptides that differ only in two amino acids. Vasopressin regulates

plasma volume, blood pressure, and osmolality. It causes vasoconstriction by acting through the vasopressin (V_1) receptor and exerts its antidiuretic action through the V_2 receptor in the kidney. The major mechanism by which vasopressin reduces blood loss is vasoconstriction. Vasopressin also stimulates uterine contractions by acting through myometrial V_{1a} receptors. Unlike oxytocin receptors, which are plentiful in the term uterus but far less abundant in the nonpregnant uterus, vasopressin receptors are present in the myometrium of both pregnant and nonpregnant women.

II. USAGE AND DOSAGE

Vasopressin is diluted with saline as 10 units of vasopressin for every 100 ml of saline. For a fibroid of about 8 cm size, 40 units of vasopressin is diluted in 400 ml of normal saline. The whole of 400 ml of this saline is injected in the myometrium. Using a 10-ml syringe and a laparoscopic injection needle, from the 5 mm port, the injection needle is inserted between the uterus and the myoma. Needle is inserted to a depth of about 2.5 cm. Single insertion is sufficient in most cases. If needed, position of the needle may be changed once. Multiple sites will cause the injected saline to ooze out from the previous punctures. As the effect of aquadissection with saline and vasopressin is achieved, the color of uterus changes from pink to white or marble like appearance. Incision is made on the uterus with just simple scissors; no energy source is required.

As the uterus is cut, instead of bleeding, saline leakage takes place. This helps to keep the field clear and it is easier to get the correct plane between the fibroid and the myometrium. The separation of the fibroid is helped due to the dissection of the correct plane by the saline injection. For enucleation of fibroid, traction is given with a myoma screw and countertraction given with a suction cannula or a toothed needle holder.

III. MATERIALS AND METHODS

As according to R. Modi¹, in a total of 157 patients with fibroid, who underwent laparoscopic myomectomy and vasopressin and saline aquadissection technique was used, it was found that the blood loss ranged from 20 to 250 ml. The operating time was 50-100 mins. No hemorrhagic complication occurred in any patient during surgery or postoperatively. In none of the cases, blood transfusion was required during or after surgery. There was neither any bowel or bladder injury nor any anesthetic complication. None of the patients required readmission or any repeat surgical or medical intervention postoperatively.

As a routine, transvaginal sonography was done after 3 months of surgery which revealed normal sized uterus with no collection or hematoma. Four of the myomectomy patients conceived and delivered by cesarean section. No adhesions were found on the myomectomy scar.

As according to E.J. Kongnyuy², who made a systematic review of 12 randomised controlled trials with 674 participants on different methods of reducing hemorrhage during myomectomy, significant reduction of intraoperative blood loss (298.72 ml) was noted when vasopressin is injected into the uterine muscles overlying the myoma during myomectomy. He concluded that blood loss was significantly lower with vasopressin vs placebo. (One of the studies used natural vasopressin, while the other study used ornithine vasopressin – ornipressin – a synthetic analogue of vasopressin).

As according to the study of F. Frederic³, the use of vasopressin resulted in median blood loss of 225 ml (range 150-400 ml) compared with 675 ml (range 500-800 ml) in the placebo group. The vasopressin group had a correspondingly lower fall in haemoglobin level (median 1.7 g/dl vs 5.3 g/dl) and haematocrit (median 5% vs 13%) compared with the controls. Fifty percent of the placebo group had blood transfusions compared with none in the vasopressin group ($P = 0.03$).

As according to T. Kimura⁴, in a non-randomized study in a total of 84 patients, to whom was applied intraoperative myometrial vasopressin injection during myomectomy, was found that vasopressin injection significantly reduced the intraoperative blood loss and postoperative hemoglobin fall in patients without and with GnRH agonist pretreatment. No serious complications occurred on account of the vasopressin injection. He concluded that intraoperative vasopressin injection is effective even in GnRH agonist-pretreated myomectomies.

IV. THE ADVANTAGES

- The vasopressin injected causes vasoconstriction of myometrial vessels, which helps to hold the saline within the myometrium for a period of about 45-60 min which is sufficient for the myometrial suturing to be completed.
- The saline and vasopressin solution follows the path of least resistance and enters the plane between the myometrium and the myoma, which helps in enucleation of myoma. This is called aquadissection.
- Myomectomy does not require energy source; only simple scissors are used to cut the myometrium. Neither a monopolar hook nor a harmonic is used. As no energy source is used for cutting or coagulation, no dead or scarred tissue is left behind. Thus, there is better tissue healing, better scar integrity and less chances of scar dehiscence.

- Enucleation of myoma is easy as the saline and vasopressin solution partially dissects the myoma-myometrial interface.
- Reduced chances of endometrial avulsion; in cases of intramural myomas with a submucous component, the incidence of avulsion of endometrium is minimized. The saline-vasopressin solution enters the plane between the myoma and endometrium and pushes the endometrium down and away and thus the myoma is easily peeled off.
- Reduced blood loss: Usually 300-400 ml of blood loss may be seen during a myomectomy, but with the use of aquadissection technique, this figure is reduced to less than 100 ml which holds a lot of significance for both patient and surgeon¹.
- Easy suturing of myometrial defect: as the field is very clear due to almost no bleeding, myometrial defect closure becomes very convenient, and the surgeon need not hurry to place the sutures for hemostatic purpose.

V. POSSIBLE COMPLICATIONS

Occasionally, there is associated bradycardia and/or cardiac arrest ^{9,10,11}

In gynecologic surgery, bradycardia with subsequent cardiac arrest is a frightful and shocking development.

As according to Hobo R., during a laparoscopic myomectomy, where 11.2 units of vasopressin was injected into the myometrium at a dilution of 0.2 units/mL, two minutes after injection, the patient's heart rate fell to 58 bpm, then to 35 bpm; cardiac arrest followed—all in 5 minutes.²

The patient was given 1 mg epinephrine, 0.5 mg of atropine, and 100% oxygen; chest compressions were initiated. Effective cardiac activity was reestablished. The heart rate was initially measured at 150 bpm; blood pressure, 220/140 mm Hg. Both vital signs gradually returned to normal range. The surgical procedure was discontinued.

In another case report by Kitamura et al ⁴, vasopressin injection for laparoscopic myomectomy caused sudden fall in blood pressure and heart rate. ECG showed ST segment depression and premature ventricular contractions. Patient was administered nicorandil 3 mg followed by continuous infusion at a rate of 3 mg/hr, and lidocaine 60 mg, intravenously. The ST depression and premature ventricular contraction disappeared immediately.

What might have caused these events?

Intramyoetrial injection may cause increase in blood concentration of vasopressin and therefore an increase in blood pressure. It's thought that this vasopressin-induced increase in blood pressure causes a vagal-mediated decrease in the heart rate. The vasoconstrictive effects of vasopressin may, simultaneously, cause coronary artery vasospasm, resulting in decreased cardiac output and cardiac ischemia.

P.S. In many of the case reports of vasopressin-induced bradycardia and cardiac arrest, the dose of vasopressin administered, as in the case just described, exceeded 5 units (5-11 UI),- or the vasopressin was injected into a vessel unintentionally.

VI. DISCUSSION

- The main concern with the use of vasopressin is that it causes sudden rise in blood pressure, if it is accidentally injected directly into a blood vessel. This complication can be avoided by simply aspirating before injecting.
- There are concerns regarding the cardiac effect of vasopressin. Myocardial vessel constriction may mimic transient myocardial ischemia. This will manifest as ST segment depression on ECG monitoring ¹². This may last for up to 20 min, till the effect of vasopressin wears off. However, ECG changes were not seen intraoperatively with the use of vasopressin at most of the studies. Sometimes, severe transient peripheral vasoconstriction occurs with the use of vasopressin. In this case, pulse oximeter may not show proper reading for a short period ⁸.
- If we only use 400 ml of saline without vasopressin, then the effect of hemostasis will only be effective for 5-10 min, during which time it is washed out from the tissues and bleeding starts while the surgery is still on.

Recommended dosage and administration:

The optimal dose and dilution of vasopressin continues to be controversial:

- **Solution** - Dilute the vasopressin in the range of 0.1 to 0.2 U/mL. Avoid concentrations >1 U/mL.
- **Vital signs** - Alert the anesthesiologist and the surgical team before you inject vasopressin, so that they are vigilant for changes in vital signs. Don't inject if vital signs are unstable.

- **Insufflation** - The pneumoperitoneum necessary for laparoscopic surgery may increase the risk of bradycardia.¹ The combined pneumoperitoneum and intravascular injection of vasopressin is likely to increase the risk of cardiovascular changes.
- **Injection** - Double-check that you are not injecting into a blood vessel by carefully testing the results of negative aspiration applied to the syringe.
- **Dosage** - Don't exceed a total dosage of approximately 5 units. Using a solution of 0.1 U/mL, the maximum injection is 50 mL.
- **Repeat dose** - Vasopressin has a relatively short half-life in circulation. Repeat injection, 45 to 60 minutes after the first one, may be safe.
- **Nicotine** - If your patient smokes or uses a nicotine replacement medication, be especially cautious about the possible synergistic effect that nicotine plus vasopressin may have on vasoconstriction.
- **Cardiovascular pitfalls** - Be cautious about using vasopressin in a patient who has established coronary artery or myocardial disease.

Vasopressin in other gynecological procedures: Clinical trials have shown that vasopressin is effective in reducing blood loss during other gynecologic surgical procedures. Three studies of interest looked at:

1. Pregnancy termination (Schultz KF) - 337 pregnant women undergoing termination of pregnancy were randomized to preprocedure injection into the cervix of either 20 mL of 1% mepivacaine solution or 4 units of vasopressin diluted (at 0.2 U/mL) in 1% mepivacaine. For women at 19 weeks' gestation, or later, measured mean blood loss was 400 mL in the mepivacaine group and 179 mL in the vasopressin-mepivacaine group.⁷
2. Excision of ovarian endometrioma (Saeki A.) -- At this study they counted the number of pinpoint bipolar coagulations on the normal ovarian cortex that were required from the beginning of stripping until hemostasis had been achieved, as well as the times required to achieve hemostasis. The first group of patients underwent an ordinary laparoscopic cystectomy without injection, the second group had laparoscopic cystectomy with injection of saline solution, and the third group had laparoscopic cystectomy with the injection of vasopressin directly to the ovarian cortex. The group with the vasopressin injection technique required significantly fewer coagulation events to achieve hemostasis, as compared with the group receiving an ordinary cystectomy. So, the vasopressin injection technique reduces the use of coagulation, and in such a way it increases the possibility of protecting ovarian reserves.⁶
3. Conization of the cervix (Sabol ED) - Ninety-two women undergoing conization were randomized to injection of saline or ≤ 3 units of vasopressin diluted in saline (0.1 U/mL) into the cervix. Blood loss averaged 136 mL in the saline group and 35 mL in the vasopressin-saline group.⁵

VII. CONCLUSION

The results indicate that vasopressin is effective in preventing blood loss and reducing the need for blood transfusion during myomectomy.

Safe use of vasopressin depends upon the surgeon's knowledge of its pharmacodynamics and use of safe practices. Care should be taken to avoid intravascular injection; before injecting, the surgeon should pull back on the plunger of the syringe to check for blood. However, complications may result even if intravascular injection does not occur. The maximal safe dose of vasopressin is not well established. Cardiovascular complications following intramyometrial injection have been reported in isolated cases with total vasopressin doses ranging from 5 to 11 units. A classic prospective cohort study found no cardiovascular complication in 13 women undergoing myomectomy who received a maximum of 4 units of intramyometrial vasopressin. An upper limit of a cumulative total vasopressin dose per procedure of 4 to 6 units has been proposed. Use of a dilute solution helps to limit the total dose. For example, if we dilute 20 units of vasopressin in 100 ml of saline; 4 to 6 units of vasopressin is equal to 20 to 30 mL of this solution.

The half-life of intramuscular vasopressin is 10 to 20 minutes and the duration of action is two to eight hours.

There are few data about combining use of vasopressin with other measures. The only randomized trial to address this issue included 105 women who underwent laparoscopic myomectomy and were assigned to one of three groups: vasopressin combined with ligation of the myoma pedicle with a loop of suture, vasopressin alone, or no vasopressin or loop ligation. Blood loss was significantly lower with combined use of vasopressin/loop ligation compared with vasopressin alone (59 versus 224 mL); both treatment groups had a significantly lower blood loss than the group that was not treated with either vasopressin or loop ligation (no treatment group: 364 mL). Ligation of the myoma pedicle merits further study.¹⁵

Vasopressin use during myomectomy has been associated with rare cases of bradycardia, cardiovascular collapse, and death.^{9,10,11} Vasopressin use may be contraindicated in women with medical comorbidities (eg,

cardiovascular, vascular, or renal disease). The use of vasopressin to decrease blood loss during myomectomy has not been approved by the United States Food and Drug Association.

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