

Assessment of the perioperative effect of vasopressin in patients undergoing laparoscopic myomectomy: A double-blind randomised study

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ABSTRACT

Background and Aims: Myomectomy is associated with perioperative bleeding. The aim of the study is to evaluate the effect of intramyometrial vasopressin on blood loss and the associated cardiovascular complications during myomectomy. **Methods:** The study included 194 patients classified into two groups- 1) Vasopressin group: the vasopressin was diluted as 0.1 unit/ml and 15 ml was injected by the surgeon in the plane between the myometrium and the myoma. 2) Control group: The patients received an equal amount of normal saline. The monitored parameters included the amount of blood loss, required blood transfusion, heart rate, mean arterial blood pressure, the incidence of hypertension, hypotension, bradycardia, tachycardia, electrocardiogram (ECG) changes and the blood troponin I level. **Results:** The heart rate decreased significantly in both groups, but the decrease was lower with vasopressin than the control group through the time points T3 to T5 ($P < 0.05$) The mean arterial blood pressure increased significantly in both groups, but the increase was higher with vasopressin than the control group through T3 to T5 ($P < 0.05$). The amount of blood loss decreased significantly with vasopressin than the control groups ($P = 0.001$). The number of transfused packed red blood cells was lower with vasopressin than the control group ($P = 0.001$). The incidence of hypertension, bradycardia and atrial extrasystole was higher with vasopressin than the control group ($P = 0.005$, $P = 0.012$, $P = 0.033$, respectively). **Conclusion:** Intramyometrial vasopressin decreases blood loss and blood transfusion, but it is associated with cardiovascular complications that may be serious as reported in other studies. Therefore, anaesthesiologists and gynaecologists must follow the precautions to avoid and minimise the incidence of complications with intramyometrial vasopressin.

Key words: Blood loss, bradycardia, hypertension, hypotension, laparoscopic myomectomy, tachycardia, vasopressin

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INTRODUCTION

Uterine leiomyomas (myomas or fibroids) are the most common type of pelvic tumours in women.^[1] When a uterine myoma develops, the normal anatomy of uterine blood vessels is disturbed, and the vessels run in abnormal directions. Myomectomy causes vascular damage regardless of the direction of the incision and results in severe blood loss.^[2] Vasopressin is a synthetic analogue of the anti-diuretic hormone. It causes vasoconstriction through its action on V1 receptors and anti-diuresis through V2 receptors in the kidney. Intramyometrial injection of vasopressin

causes vasoconstriction, stimulates the uterine contractions and therefore it reduces the blood loss during surgery.^[3-6] However, vasopressin was reported to be associated with severe complications such as

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bradycardia, arrhythmias, pulmonary oedema and cardiac arrest.^[7-9]

There are debates and conflicts between the surgeons and anesthesiologists regarding the risks and benefits of vasopressin and therefore, this study was conducted to evaluate the incidence of cardiovascular complications associated with the intramyometrial injection of vasopressin.

METHODS

After approval from the local ethics committee (326/2015, 14/10/2015), and obtaining written informed consent, a study was conducted on 194 patients with uterine fibroid and American Society of Anesthesiologists (ASA) physical status I and II, undergoing elective laparoscopic myomectomy through 2015-2019. The exclusion criteria were patients with ischaemic heart disease, cardiac valvular disease, hypertension, severe respiratory disease, obese patients, abnormal preoperative coagulation profiles, anti-inflammatory medications through two weeks preoperatively, severe hepatic or renal disease. The patients were randomly allocated (the concealment of allocation was done by using random numbers generated through excel) into two equal groups ($n = 97$ each): Vasopressin group: The vasopressin (Vasopressin USP, FLAGSHIP BIOTECH, USA ICL.) was prepared by dilution of 20 units vasopressin in 200 ml normal saline (0.1 unit/ml), then 15 ml was injected by the surgeon slowly after negative aspiration of blood in the plane between the myometrium and the myoma. A single injection of 15 ml was made for each myoma. Control group: The patients received an equal amount of normal saline.

For all patients, an 18 gauge peripheral venous line was inserted and 500 ml of intravenous crystalloids was administered before surgery. Premedication with intravenous midazolam 2 mg was given 10-20 minutes before induction. After attaching the monitors [electrocardiogram (ECG), pulse oximeter, and non-invasive arterial blood pressure], the induction of anaesthesia was done for all patients by preoxygenation with 100% oxygen, intravenous fentanyl (1-2 $\mu\text{g}/\text{kg}$), etomidate (0.3 mg/kg), and atracurium (0.5 mg/kg). After tracheal intubation, anaesthesia was maintained with oxygen: air (50:50%), and sevoflurane (2-3%). An additional dose of intravenous atracurium (0.08-0.1 mg/kg) was given guided by the peripheral nerve stimulator to provide a train-of-four count zero. The

ventilation was adjusted to maintain the end-tidal PaCO_2 (30-35 mmHg). Sevoflurane concentration was adjusted to maintain the mean arterial blood pressure and heart rate within $\pm 20\%$ of the pre-induction values. Intraoperative tachycardia (heart rate >100 bpm), and systemic hypertension (systolic arterial blood pressure $>20\%$ above baseline), was managed by increasing the concentration of sevoflurane by increments of 1.0% and bolus doses of fentanyl (0.5-1 $\mu\text{g}/\text{kg}$). Intraoperative hypotension (systolic arterial blood pressure $<20\%$ below baseline) was managed by bolus doses of ephedrine (5-10 mg) and fluid administration. Bradycardia (heart rate <60 bpm) was managed by a bolus dose of atropine (0.02 mg/kg). At the end of the surgery, the sevoflurane was discontinued, and controlled ventilation with 100% oxygen was maintained until the end-tidal sevoflurane concentration was $<0.1\%$. Intravenous lidocaine (1 mg/kg) was given for all patients 2 min before the removal of the endotracheal tube to provide smooth extubation. Residual neuromuscular blockade was reversed with a combination of neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg) intravenously.

The monitored parameters included the amount of blood loss, blood transfusion (the transfusion trigger was the amount of blood loss $>20\%$ of the estimated blood volume), heart rate, mean arterial blood pressure, a continuous ECG with automatic ST-segment analysis (leads II and V), arterial oxygen saturation (SPO_2) and the end-tidal carbon dioxide (ETCO_2). The values were collected at the following timepoints; T0: preoperative value, T1: 5th minute after induction, T2: directly before intramyometrial vasopressin administration, T3: 15th minute after vasopressin administration, T4: 30th minute after vasopressin administration, T5: 45th minute after vasopressin administration, T6: 60th minute after vasopressin administration, T7: directly at the end of surgery; T8: 60th minute in the postoperative care unit. Also, the incidence of hypertension, hypotension, bradycardia, tachycardia, ECG changes and any adverse effects were documented. The blood troponin I level was checked after the 12th postoperative hour. The total amount of blood loss was assessed by measuring the amount of blood in the suction bottle and visual estimation of gauze visual analogue (surgical gauze 10 \times 10 cm).

The primary outcomes were blood loss and requirements for blood transfusion. The secondary

outcome was the safety of the study medications, as assessed by the occurrence of any cardiovascular complications (arrhythmia, hypertension, myocardial ischaemia, or pulmonary oedema).

Power analysis was performed using the Chi-square test for independent samples on the frequency of patients suffered from intraoperative bleeding because it was the main outcome variable in the present study. A pilot study was done before starting this study to assess the frequency of intraoperative bleeding with vasopressin during myomectomy. The results of the pilot study (20 patients in each group) showed that the incidence of bleeding was 30% in the vasopressin group, and 60% in the control group. Taking power 0.8, alpha error 0.05 and beta 0.2, a minimum sample size of 97 patients was calculated for each group.

Data were statistically described in terms of mean \pm standard deviation (\pm SD), or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was done using the Student's *t*-test for independent samples. For comparing categorical data, a Chi-square test was performed. The exact test was used instead when the expected frequency was less than 5. *P* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program Statistical Package for the Social Science; (SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS

Table 1 shows no significant difference regarding the demographic data, haemoglobin, ASA physical status score, preoperative coagulation profiles, number and type of fibroid (*P* > 0.05).

Table 2 shows the changes in the heart rate and mean arterial blood pressure. There was no difference in the heart rate and mean arterial blood pressure either between the two groups or compared to the baseline values within the same group before and after anaesthesia induction [T0, T1, T2] (*P* > 0.05). The heart rate decreased in both groups, but the decrease was significantly lower in the vasopressin group compared to the control group and the baseline through the time points T3 to T5. Then, the heart rate returned nearly to the baseline values through T6 to T8 and the difference between the two groups

Table 1: Preoperative data of patients (mean \pm standard deviation, number, percentage)

Variables	Vasopressin group (n=97)	Control group (n=97)	<i>P</i>
Age (years)	37.30 \pm 4.70	36.68 \pm 4.13	0.330
Weight (kg)	85.42 \pm 11.60	84.80 \pm 10.50	0.696
Haemoglobin (g/dl)	12.23 \pm 1.45	11.90 \pm 1.37	0.104
ASA I: II	51:46	44:53	0.388
Number of fibroids			
Single	39	45	0.468
Multiple	58	52	0.468
Fibroid type			
Intramural	47	50	0.774
Submucosal	35	39	0.657
Subserosal	15	8	0.182
Coagulation profiles			
PT (second)	10.93 \pm 0.69	11.13 \pm 0.80	0.063
INR	1.01 \pm 0.11	1.04 \pm 0.12	0.071
aPTT (second)	39.16 \pm 5.80	40.20 \pm 5.76	0.211
Platelets($\times 10^3/\mu$ l)	285.10 \pm 80.30	294.50 \pm 84.50	0.428
BT (minute)	4.63 \pm 2.95	4.52 \pm 2.48	0.778

ASA: American Society of Anesthesiologists Physical Status Score; PT: Prothrombin time; INR: International normalised ratio; aPTT: Activated partial thromboplastin time; BT: Bleeding time

Table 2: Heart rate and mean arterial blood pressure of patients (Data are presented as mean \pm SD)

Variable	Vasopressin group (n=97)	Control group (n=97)	<i>P</i>
Heart rate (bpm)			
T0	80.48 \pm 8.30	81.21 \pm 9.13	0.560
T1	82.37 \pm 9.18	83.64 \pm 9.22	0.337
T2	81.78 \pm 10.70	83.15 \pm 9.55	0.348
T3	75.46 \pm 12.10 [†]	80.50 \pm 8.30	0.001*
T4	69.47 \pm 7.00 [†]	79.30 \pm 8.13	0.001*
T5	72.90 \pm 6.09 [†]	78.30 \pm 7.60	0.001*
T6	78.50 \pm 7.35	79.33 \pm 8.20	0.458
T7	77.33 \pm 6.39	76.94 \pm 6.47	0.673
T8	77.80 \pm 7.20	78.65 \pm 7.86	0.433
Mean arterial blood pressure (mmHg)			
T0	95.36 \pm 10.36	94.40 \pm 11.20	0.536
T1	98.50 \pm 12.90	97.85 \pm 12.40	0.720
T2	97.16 \pm 11.55	95.88 \pm 10.40	0.418
T3	108.38 \pm 15.32 [†]	101.25 \pm 12.90 [†]	0.001*
T4	110.70 \pm 16.90 [†]	102.31 \pm 13.10	0.001*
T5	113.48 \pm 16.81 [†]	101.34 \pm 12.45	0.001*
T6	100.30 \pm 11.60	97.98 \pm 10.67	0.148
T7	97.18 \pm 10.70	96.27 \pm 9.50	0.531
T8	96.49 \pm 11.85	98.10 \pm 10.35	0.314

**P*<0.05: The comparison is significant between the two groups. [†]*P*<0.05 significant compared to the preoperative reading within the same group. T0: the preoperative value, T1: 5th min after induction, T2: directly before intramyometrial vasopressin administration, T3: 15th min after vasopressin administration, T4: 30th min after vasopressin administration, T5: 45th minute after vasopressin administration, T6: 60th min after vasopressin administration, T7: directly at the end of surgery; T8: 60th min in the postoperative care unit

was insignificant (*P* > 0.05). The mean arterial blood pressure increased in both groups, but the increase was significantly higher in the vasopressin group

compared to the control group and the baseline through the time points T3 to T5. Then, the mean arterial blood pressure returned nearly to the baseline values through T6 to T8 and the difference between the two groups was insignificant ($P > 0.05$).

Table 3 shows the intraoperative data and the outcomes in the two groups. There was no difference in the types and number of excised fibroid between the two groups ($P > 0.05$). The amount of intraoperative and postoperative blood loss decreased significantly in the vasopressin group than the control group ($P = 0.001$, $P = 0.003$ respectively). The number of patients who required blood transfusion was significantly lower with vasopressin compared to the control group ($P = 0.025$). The number of transfused packed red blood cells (P-RBC) was significantly lower with vasopressin than the control group ($P = 0.001$). As the blood transfusion was more in the control group than the vasopressin group, there was no difference in the postoperative haemoglobin level ($P = 0.152$). The amount of transfused fluids (crystalloid and Hetastarch (Hesteril)) was lower in vasopressin group

than in the control group ($P = 0.031$, $P = 0.029$, respectively). The incidence of bradycardia (heart rate $<50-60$ bpm) was higher with vasopressin than the control group ($P = 0.012$). Four cases suffered from severe bradycardia (heart rate ranges 30-40 bpm) with vasopressin and managed by atropine dose (1-1.5 mg). The number of patients who required atropine for the management of bradycardia and the required dose of atropine was higher with vasopressin than the control group ($P = 0.012$, $P = 0.001$, respectively). The incidence of atrial extrasystoles was higher with vasopressin than the control group ($P = 0.033$) without the need for medical treatment in both groups. Four cases suffered from ventricular extrasystoles with vasopressin and were managed by intravenous lidocaine 2% (0.5-1 mg/kg). The incidence of hypertension was higher in vasopressin than the control group ($P = 0.005$) and managed by increasing the sevoflurane concentration and bolus doses of fentanyl (50-100 μ g). There was no difference in the incidence of hypotension between the two groups ($P = 0.136$). The comparison of postoperative troponin I was insignificant between

Table 3: Intraoperative data and outcome of patients (mean \pm standard deviation, number, percentage)

Variables		Vasopressin group (n=97)	Control group (n=97)	P
Number of fibroids	1	53	48	0.565
	2	29	37	0.288
	3	15	12	0.678
Duration of anesthesia (min)		105.30 \pm 24.45	113.70 \pm 29.40	0.031
Duration of surgery (min)		93.10 \pm 17.38	99.19 \pm 20.25	0.025
Amount of blood loss (ml)	Intraoperative	615.20 \pm 58.70	690.50 \pm 77.63	0.001
	Postoperative	152.30 \pm 47.28	174.70 \pm 58.40	0.003
Blood transfusion	Number of patients	15 (15.46%)	29 (29.89%)	0.025
	Number of P-RBC (units)	1.18 \pm 0.57	1.90 \pm 0.85	0.001
Haemoglobin (g/dl)		11.48 \pm 1.25	11.23 \pm 1.17	0.152
Fluids transfusion	Crystalloids (ml)	2540.80 \pm 520.34	2760.95 \pm 570.52	0.031
	Hesteril 6% (ml)	496.90 \pm 55.70	515.10 \pm 60.42	0.029
ECG rhythm changes	Bradycardia (HR $<60-50$ bpm)	17 (17.52%)	5 (5.15%)	0.012
	Severe bradycardia (HR $<40-30$ bpm)	4 (4.12%)	-	0.129
	Tachycardia (HR >100 bpm)	9 (9.27%)	4 (4.12%)	0.250
	Atrial extrasystole	12 (12.37%)	3 (3.09%)	0.033
	Ventricular extrasystole	4 (4.12%)	-	0.129
Atropine	Number of patients	17 (17.52%)	5 (5.15%)	0.012
	Dose (mg)	0.99 \pm 0.43	0.54 \pm 0.10	0.001
Hypertension (SAP \geq 20% above baseline)		17 (17.52%)	4 (4.12%)	0.005
Hypotension (SAP \leq 20% below baseline)		9 (9.27%)	3 (3.09%)	0.136
Arterial oxygen saturation (SPO ₂) (%)		99.20 \pm 0.21	99.18 \pm 0.22	0.992
Partial pressure of carbon dioxide (PaCO ₂)(mmHg)		35.73 \pm 3.25	35.54 \pm 3.42	0.692
Troponin I (ng/ml)		0.41 \pm 0.06	0.40 \pm 0.08	0.325
Myocardial infarction		-	-	-
Pulmonary oedema		-	-	-
Congestive heart failure		-	-	-
Cardiac arrest		-	-	-
Mortality		-	-	-

* $P < 0.05$ significant comparison between the two groups. SAP : Systolic arterial blood pressure; HR : Heart rate. P-RBC : Packed- red blood cells; ECG:Electrocardiogram

the two groups ($P = 0.325$). There was no incidence of myocardial infarction, pulmonary oedema, congestive heart failure, cardiac arrest, or mortality in any of the two groups ($P > 0.05$).

DISCUSSION

The changes in heart rate and blood pressure after intramyometrial vasopressin injection may be related to the systemic absorption of vasopressin especially during the surgical excisions of the fibroid and not related to the direct intravascular injection; first, the vasopressin was injected after negative blood aspiration during injection and second, these changes did not happen during vasopressin injection but after 10 minutes of vasopressin injection in most of the cases.

The injection of diluted vasopressin into the plane between the myoma and myometrium leads to vasoconstriction of the feeding vessels (capillaries, small arterioles and venules) for 45-60 min which is usually sufficient for the myometrial suturing to be completed and therefore reducing the blood flow to the myoma and decreasing the blood loss during the excision of the myoma.^[10-12]

The present study showed that intramyometrial vasopressin decreased significantly the blood loss and blood transfusion during myomectomy. It was associated with mild cardiovascular adverse effects such as bradycardia, hypertension, atrial and ventricular arrhythmias. The cardiovascular adverse effects were managed properly by medications. Only four cases suffered from severe bradycardia with vasopressin and responded well to atropine. There was no cardiac arrest or the need for cardiopulmonary resuscitation.

The results of the present study correlate with the findings of other studies. Protopapas *et al.*^[13] compared vasopressin (20 units, 0.2 unit/ml) in 100 patients with 50 patients without vasopressin during laparoscopic myomectomy. The blood loss and the requirement for blood transfusion decreased significantly with vasopressin compared to the control group without serious cardiovascular adverse events. Thiek *et al.*^[14] found that vasopressin decreased significantly the blood loss and blood transfusion during myomectomy in 35 patients compared to the control group without cardiovascular complications. Kimura *et al.*^[8] showed a mild elevation in systolic blood pressure (10–20 mmHg)

and a mild decrease in heart rate (5–15 bpm) in ~60% of the patients without the requirement for medical treatment. Only one patient experienced significant bradycardia (45 bpm), which was managed by intravenous atropine. Fletcher *et al.*^[15] reported that vasopressin (20 units, 1 unit/ml) decreased the blood loss during myomectomy in 26 patients without significant cardiovascular complications and the findings were shown by other studies.^[16,17]

There are some of cases reports with serious complications such as bradycardia, cardiovascular collapse, pulmonary oedema and death with the use of intramyometrial vasopressin during myomectomy. Hobo *et al.*^[9] reported a case of sudden cardiac arrest after intramyometrial vasopressin (11.2 units, 0.2 unit/ml) and the same complication was described by Nerurkar *et al.*^[18] Hung *et al.*^[19] reported two cases of bradycardia followed by cardiac arrest and pulmonary oedema with intramyometrial vasopressin (12-20 units, 2 unit/ml) and similar complications were described by other studies.^[20,21] Severe hypotension was described by Nezhat *et al.*,^[6] and Chilkoti *et al.*^[22] Deschamps *et al.*^[23] described severe bradycardia and atrioventricular block with bigemini after injecting 3 units of intramyometrial vasopressin.

Kitamura *et al.*^[8] in a case report, described after vasopressin injection (7.9 units, 0.2 unit/ml) during laparoscopic myomectomy severe hypotension, bradycardia in addition to ST-segment depression and premature ventricular contractions in the ECG and the same findings were described by Lurie *et al.*^[24] Lee *et al.*^[25] reported a case of severe bradycardia (26 bpm) followed by cardiac arrest after intramyometrial injection of vasopressin (20 units, 0.5 unit/ml) and the heart recovered completely after atropine administration. Kabade *et al.*^[26] reported a case of bradycardia, severe hypotension, cardiac arrest after intramyometrial vasopressin (8 units, 0.2 unit/ml). After resuscitation, the patient recovered, but the haemodynamics was severely unstable even with inotropic support, and the echocardiography showed severe deterioration in the ejection fraction compared to the preoperative echocardiography. The patient died on the 4th postoperative day.

The possible causes of these complications may be related to the severe vasopressin induced hypertension, severe bradycardia and cardiac arrest as a result of large dose or accidental intravascular administration. The vasoconstrictive effect of vasopressin causes coronary

artery vasospasm that causes cardiac ischaemia, infarction and arrest.^[12,27-29]

We reviewed many studies on intramyometrial vasopressin, but we could not find any definite dose or concentration which is associated with serious cardiovascular complications, as the serious cardiovascular adverse events often occurred with higher doses and concentration and also, there were complications with lower doses (3–11 units)^[6,7,12,20,23,28] and concentration (0.1 unit/ml).^[30] So, there are some precautions to avoid and minimise the incidence of cardiovascular complications of vasopressin by giving a small diluted dose (total dose <5 units, 0.1 unit/ml), avoiding the intravascular injection and avoiding the drug in those with cardiovascular diseases, and careful observations of the heart rate, blood pressure, and ECG during and after the vasopressin injection in addition to the proper selection of patients.^[7,8,13,29-31] This can be supported by using vasopressin as a very slow infusion in the management of refractory hypotension without cardiovascular complications.^[32] Also, it is better to avoid vasopressin in smokers due to the possible synergistic effect of nicotine and vasopressin on vasoconstriction. It must be balanced between the benefits and risks of vasopressin administration during myoma excision to avoid exposure of the patients to severe complications.

The use of intramyometrial vasopressin to decrease blood loss during myomectomy has not been approved by the United States Food and Drug Administration but still, it has been used commonly in clinical practice.

There are some limitations in the present study. First, the study was done in a single centre, and secondly, the small sample size.

CONCLUSION

The use of intramyometrial vasopressin decreases blood loss and blood transfusion, but it is associated with cardiovascular complications that may be serious as reported in other studies. Therefore, anaesthesiologists and gynaecologists must follow the precautions to avoid and minimise the incidence of cardiovascular complications associated with intramyometrial vasopressin.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the

patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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