Optimal Dose of Pituitrin in Laparoscopic Uterine Myomectomy: a Prospective, Double-Blinded, Randomized Controlled Trial

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Abstract

Objective: To determine the optimal effective dose pituitrin in laparoscopic myomectomy for uterine leiomyoma. Design: Prospective, double-blinded, randomized controlled trial. Setting: A tertiary women's hospital in China. Population: A total of 118 women who underwent laparoscopic myomectomy. Methods: Women were randomly divided into four groups to receive 0, 2, 4, or 6 units of pituitrin in the leiomyoma (groups 0U, 2U, 4U, and 6U, respectively). Main outcome measures: Rate of satisfactory surgical field, hemodynamic changes, total surgical time and blood loss were recorded. Results: The rate of sastisfactory surgical field was 6.7%, 72.4%, 89.7% and 93.3% in groups 0U, 2U, 4U, and 6U, respectively; it was higher in groups 2U, 4U, and 6U than group 0U, but there were no significant differences among the groups 2U, 4U, and 6U. The blood loss was higher in group 0U than that in groups 2U, 4U, and 6U (). Pituitrin was associated with a transient decrease in blood pressures and increase in heart rate in a dose-dependent fashion, with more pronounced changes in groups 4U and 6U and these groups also required higher amount of vasoactive drug to correct hemodynamic changes ($p<0.05$). Conclusions: Use low-dose pituitrin (2 units) provides a satisfactory surgical field with minimal hemodynamic changes.

Introduction

Uterine leiomyoma is the most common benign tumor in women of reproductive age with an incidence up to 70%~80%. About 20%~50% women with uterine leiomyoma are symptomatic [1, 2]. Myomectomy is the standard treatment for women who wish to preserve their uterus for fertility[3]. Surgery, however, may be associated with a risk of bleeding [4], which hampers surgical view, prolongs operating time, increase complications. Vasopressin is routinely injected in the myoma for vasoconstriction and hydroseparation[2, 5].

In parts of the world where synthetic vasopressin is not available, pituitrin, a bovine posterior pituitary extract containing vasopressin and oxytocin, is used [6, 7]. Vasopressin and oxytocin, however, have various effects on hemodynamics [9-14]. The optimal dose to achieve satisfactory view with minimal hemodynamic effects have not been documented. In 2009, Frishman suggested 1-2 units of pituitrin to achieve adequate hemostasis during myomectomy [8].

In this study, we used various doses of pituitrin (0, 2, 4, and 6 units) during laparoscopic myomectomy to characterize their surgical and hemodynamic effects in order to determine the minimal effective dose.

Methods

Participants

This was a randomized, double-blind study conducted in Women's Hospital, Zhejiang University School of Medicine from July, 2018 through December, 2018. The study was approved by Institutional Research Ethics Committee of the Women's Hospital, Zhejiang University School of Medicine (Number: 20170151) and registered at www.chictr.org.cn (registration number: ChiCTR1800017080). Informed consent was obtained in all participants. Inclusion criteria were: age 20 to 55 years, ASA I or II, with no more than three identifiable myomas by ultrasonography and the largest myoma be 10 cm or less. Exclusion criteria were: body mass index (BMI) >30kg/m^2, or major organ or systemic disease, or known allergy to bovine products.

Study protocol

In addition to standard anesthesia monitors including pulse oximetry (SpO_2) and electrocardiogram (ECG), a radial arterial line was placed for invasive blood pressure (IBP) measurement. General anesthesia was induced with intravenous (i.v.) administration of fentanyl (2-4 µg/kg), propofol (1.5-2.0 mg/kg) and cisatracurium 0.15 mg/kg. After endotracheal intubation, mechanical ventilation was established with the end-tidal CO_2 maintained between 35 and 45 mmHg. Then, anesthesia was maintained with a continuous infusion of Propofol and remifentanil. Depth of anesthesia was monitored with state Entropy (SE) and surgical pleth index (SPI). The infusion rate of propofol was adjusted to maintain SE between 40 and 60[9] and the infusion rate of remifentanil was adjusted to maintain SPI between 30˜50[10] during the operation. Muscle relaxation was maintained with cisatracurium (0.03 mg/kg) every 20-30 min.

Subjects were randomized using computer-generated random number allocations into one of four groups to receive 0, 2, 4 or 6 units of pituitrin (Group 0U, Group 2U, Group 4U and Group 6U, respectively). Pituitrin (Xinbai Manufacturing Industry, Nanjing, China; Batch number: 1171102) was diluted with 0.9% normal saline to a total volume of 20 mL by a nurse who was not involved in the study. The surgeon, anesthesiologist, and other personnel in the operating room were blinded to the dose contained in the solution.

Laparoscopic procedure was performed under the intra - abdominal pressure of 12 ˜ 15 mmHg. After proper placement of camera and instruments, a 10-cm needle was inserted into myoma and the 20 mL study solution was slowly injected as the needle was gradually retracted. The surgeon was inquired if a satisfactory field was achieved within three minutes of injection.

Hemostasis was evaluated by surgeons during the operation with methods described elsewhere [11, 12]. Briefly, a visual score on the visual clarity (VS, 0-10,0: worst visual clarity; 10: optimal visual clarity) of surgical field was given by the surgeon. If surgeons reported the VAS score < 7, 2 units of pituitrin (another 6 units of pituitrin was diluted to 20 mL as additional remedial injection) was given. Upon completion of surgery, a satisfaction score (not satisfied, satisfied, very satisfied) was given by the surgeon. Surgical time and estimated blood loss were also recorded.

Invasive Systolic and diastolic blood pressures (SBP and DBP) as well as heart rate (HR) were continuously monitored throughout surgery by the anesthesia system (DoCare Anesthesia Clinical Information System, Medicalsystem® Co., Ltd, China). The baseline was defined as the mean values during the last 30 seconds before the injection of pituitrin. The maximum changes in SBP, DBP, and HR were recorded during the initial 3 minute after injection. Time for the hemodynamic variables to return to baseline was also recorded.

Hypotension, defined as a SBP below 80 mmHg or [?] 30% of the baseline, was treated with a bolus of intravenous phenylephrine 100µg. Hypertension, defined as a SBP [?] 160mmHg, was treated with a bolus of intravenous nitroglycerine 50µg.

Statistical Analysis

The primary outcome of this study was the rate of achieving a satisfactory surgical field. The sample size was calculated from a pilot study, which showed the rates in groups 0U, 2U, 4U, and 6U at 10% (0/10), 70% (7/10), 90% (9/10), and 100% (10/10), respectively. Taking into account a dropout rate of 10%, 35 patients in each group were enrolled to fulfill at 90% power to detect significant differences among groups with a two-tailed alpha value < 0.05.

Statistical analysis was performed with SPSS 19.0 software (IBM SPSS, Chicago, Illinois). Using normality plots and the Kolmogorov-Smirnov test to assess the data for normal distribution of variance. Continuous variables with normal distribution are presented as mean ± standard deviation (SD), non-normally distributed data as median and interquartile range (IQR). Variables which met normal distribution were analyzed by analysis of variance (ANOVA), non-normal distribution variables were analyzed by Kruskal-Wallis tests. A *Post-hoc*multiple comparison was performed by Bonferroni or LSD test when appropriate. Categorical data were presented as N (%), and analyzed by Chi-square (χ^2) test or Fisher's exact test. AP -value of <0.05 was considered to be statistically significant.

Results

A total of 143 subjects were screened in this study from July, 2018 to December, 2018. Three subjects were excluded, of which two did not meet inclusion criteria and one refused to participate. A total of 140 subjects were recruited in the study and were randomly assigned to various dose groups. Twenty-two subjects later dropped out from the study due to inability to insert the radial arterial catheter, failure injection of pituitrin, equipment failure, or severe intra-abdominal adhesions. A final total of 118 subjects completed the study and were included in the final analysis. Figure 1 showed the flow chart of the study.

Patients demographic details and surgical parameters

The demographic details and surgical parameters of the patients were shown in Table 1. All groups were comparable in terms of demographic and surgical parameters among the groups (P ¿0.05).

As shown in Table 2, the rate of achieving a satisfactory surgical was higher in groups 2U, 4U and 6U than that in group 0U (6.7% *vs*72.4%, 89.7%, 93.3%; $P < 0.01$), however, no significant differences were found among the groups 2U, 4U and 6U ($P > 0.05$). Similarly, visual clarify in groups 2U, 4U, and 6U was higher than in group 0U ($P < 0.01$). There were no significant differences in visual clarify among groups 2U, 4U, and 6U ($P > 0.05$). The amount of blood loss was higher in group 0U than that in the groups 2U, 4U, and 6U ($P< 0.01$), whereas, no significant differences were found among the groups 2U, 4U and 6U ($P >$ 0.05). Compared with group 2U, 4U, and 6U, more patients in group 0U requires supplemental pituitrin (P < 0.01). There was no significant difference among the groups 2U, 4U, and 6U in the need to supplement pituitrin ($P > 0.05$). No significant difference surgical time noted among all groups. No severe adverse events occurred during the study.

Perioperative hemodynamics changes

Hemodynamic changes associated pituitrin injections are presented in Figure 2 (A-B-C). There was a biphasic change in SBP and DBP in groups 2U, 4U, and 6U, with an initial decrease within three minutes of injection, followed by increase afterwards. The maximum decrease in SBP in groups 0U, 2U, 4U, and 6U were 2.0 ± 3.6%, 28.9 ± 13.1%, 35.7 ± 6.2%, and 36.8 ±6 .6%, respectively; the maximum decrease in DBP were 2.0 ± 4.4%, 28.2 ± 13.2%, 34.1 ± 6.9%, and 35.2 ± 5.5%, respectively. The maximum decrease in SBP and DBP were greater in groups 2U, 4U, and 6U than in group 0U ($P < 0.01$). The decrease in SBP and DBP in other groups appeared dose-dependent ($P < 0.05$, Table 3).

A transient increase in HR in groups 2U, 4U, and 6U after injection were noted. The maximum increase in HR in groups 0U, 2U, 4U, and 6U were 2.7 ± 7.6%, 11.9 ± 8.4%, 19.3 ± 13.6%, and 23.2 ± 13.8%, respectively. The effect of pituitrin on HR also appeared to be dose-dependent ($P < 0.05$, Table 3).

The timing of the maximum effect was similar among the groups ($P< 0.762$), whereas the time to return to baseline was shorter in group 2U than in other groups ($P < 0.05$). The total nitroglycerin consumption in group 4U and group 6U was significantly higher than in group 0U and group 2U ($P < 0.05$, Table 3).

Discussion

Vasopressin is widely used to reduce blood loss and help demarcate the tumors in myomectomy.[13, 14] Where vasopressin is not available, use of pituitrin may be the only choice.

Responses to vasopressin and pituitrin are very different. Shimanuki et al.[15] showed myometrial injection of vasopressin (total dose = 4 units) was associated with increases in systolic and diastolic blood pressures and decreases in heart rate. Butala et al.[16] reported severe vasospasm and bradycardia after injection of vasopressin. In this study, we observed a biphasic pattern in blood pressures – an initial decrease followed by a subsequent increase in both SBP and DBP. The increase in HR appeared to be monophasic and dose-dependent.

The biphasic responses in blood pressures and the increase in HR may be related to the two physiologically active components in pituitrin: vasopressin and oxytocin[6]. These agents bind to different receptors in the myometrium as well as vascular smooth muscles. Binding of vasopressin to the V_1 receptors promotes the contraction of vascular smooth muscles, resulting in peripheral vasoconstriction and increased blood pressure.[17-20]. Oxytocin receptors are expressed on the surface of endothelial cells [21]. Activation of the oxytocin receptor increases concentration of intracellular Ca^{2+}, forming Ca-calmodulin which increase constitutive endothelial nitric oxide synthase (*eNOS*) activity. The increase of *eNOS* activity will promote release of nitric oxide (NO), leading to vascular relaxation [17, 18]. The overall effect of pituitrin appears to be dependent on the timing and concentration the two opposing substances in the compound. As the half-life of vasopressin (20 to 30min) is longer than oxytocin (3 to 4min) [5, 22], the increase in blood pressures are more sustained than the initial decrease.

With stronger vascular effects from vasopressin than oxytocin, severe hypertension may require treatment. As the duration of the effects from vasopressin may not be predictable, and short-acting vasoactive drugs may not always be available, it is prudent to choose a dose that offers a satisfactory surgical field with minimal systemic effects.

Several previous literatures reported the ideal dosage of vasopressin and how to use vasopressin in myomectomy procedure [5, 13, 23]. However, the optimal dosage of pituitrin in myomectomy has still not been determined, which is one of the most important issue clinical doctors are concerned. Therefore, we investigated the effects of four different doses of pituitrin injected into myoma in myomectomy procedure on surgical field quality, blood loss, hemodynamic, etc. in order to find out an optimal pituitrin dosage in myomectomy.

In our study, we did not find remarkable differences among the group 2U, group 4U, and 6U in the surgical field quality. In group 0U, most women required supplemental dosing but few in the 2U needed it. There were no surgical benefits in using more than 2 units of pituitrin. Similarly, 2 units of pituitrin could significant produce less blood loss than 0 unit of pituitrin and increase the dosage of pituitrin more than 2 units did not decrease the blood loss further.

There are some limitations to this study. First, we did not include patients with more than 3 myomas or diameters of myomas exceeding 10 cm. The result of the dosage of pituitrin required in myomectomy could not be appropriate for all patients. Second, the exact proportions of these two components (vasopressin and oxytocin) in pituitrin were not known. A preparation from a different batch or vendor may show different results.

In summary, 2 units of pituitrin was adequate for a satisfactory surgical field during laparoscopic uterine myomectomy. There is a biphasic response in blood pressures to pituitrin injection. Higher doses of pituitrin are associated with more pronounced hemodynamic effects with few additional surgical benefits.

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Disclosure of interests

All authors declare no conflict interests.

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Details of Ethics Approval

The study was approved by Institutional Research Ethics Committee of the Women's Hospital, Zhejiang University School of Medicine (Number: 20170151)

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Table 1. Patients demographic data and surgical data of the study.

	Group 0U (n=30)	Group 2U (n=29)	Group 4U (n=29)	Group 6U (n=30)	P-value
Age (years)	39.2±6.9	41.2±5.4	39.8±5.8	41.2±6.9	0.507
BMI (kg/m^2)	22.7±2.5	22.6±2.8	22.0±2.5	23.0±2.5	0.497
ASA grade					0.482
I	26 (86.7%)	25 (86.2%)	28 (96.6%)	28 (93.3%)	
II	4 (13.3%)	4 (13.8%)	1 (3.4%)	2 (6.7%)	
Number of myomas	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.774
Location of the largest myomas					0.691
Anterior	14 (46.7%)	14 (48.3%)	13 (44.8%)	9 (30.0%)	
Posterior	9 (30%)	9 (31%)	12 (41.4%)	13 (43.3%)	
Lateral and fundal	7 (23.3%)	6 (20.7%)	4 (13.8%)	8 (26.7%)	
Diameter of the largest myoma (cm)	6.9±0.9	6.5±1.1	6.2±1.1	6.7±1.6	0.213
Duration of injection (sec)	32.5±8.2	33.6±6.7	33.1±9.5	31.7±7.3	0.570

Data were presented as Mean ± SD, Median (IQR) or n (%); SD, standard deviation; IQR, interquartile range.

ASA, American Society of Anesthesiologists; BMI, body mass index.

Table 2. Evaluation of the hemostasis efficacy and duration of surgery among the groups.

	Group 0U (n=30)	Group 2U (n=29)	Group 4U (n=29)	Group 6U (n=30)	p-value
Satisfactory surgical field, n(%)	2 (6.7)	21 (72.4) *	26 (89.7) *	28 (93.3) *	< 0.001
Visual clarify score	3(2-4)	8(6-9) *	9(8-9) *	9(8-10) *	< 0.001
Number cases requiring supplement pituitrin, n(%)	28 (93.3)	3 (10.3) *	0 (0) *	0 (0) *	< 0.001
Blood loss (ml)	145 [117-175]	100 [50-150] *	100 [50-125] *	95 [67-125]*	< 0.001
Surgical time (min)	69[57-98.5]	89[70.5-105.5]	78[57.8-108.5]	84[71-107]	0.224

Data were presented as Median (IQR) or n (%).

*$P < 0.01$ compared with group 0U.

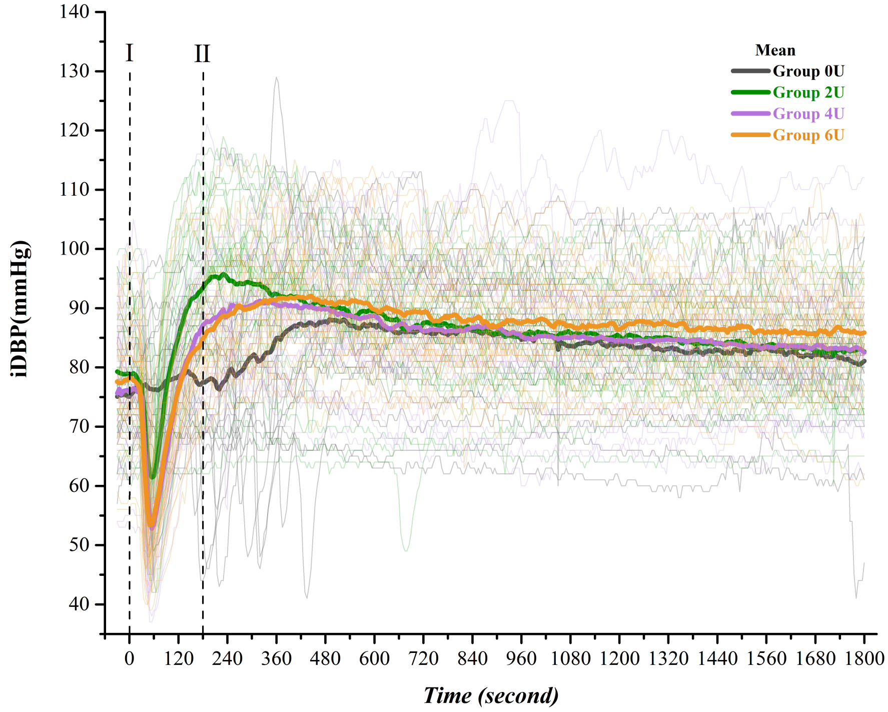
Table 3. Comparison of hemodynamic parameters and nitroglycerin consumption among the groups during the intraoperative period.

	Group 0U (n=30)	Group 2U (n=29)	Group 4U (n=29)	Group 6U (n=30)	*P*-value
Baseline SBP (mmHg)	125.2±11.4	132.1±14.4	125.8±15.9	131.0±18.3	0.251
Baseline DBP (mmHg)	75.3±7.7	79.0±10.1	75.9±10.8	77.7±10.7	0.540
Baseline HR (bpm)	67.3±12.1	68.9±12.2	69.0±9.7	69.0±9.8	0.937
Lowest SBP (mmHg)	122.7±12.2	93.4±16.7	80.7±12.3	82.5±12.8	<0.001
Lowesst DBP (mmHg)	73.8±8.5	56.3±11.2	49.9±8.2	50.1±7.0	<0.001
Highest HR (bpm)	68.7±10.6	76.9±12.8	82.0±11.2	84.7±12.6	<0.001
Maximum decrease in SBP (%)	2.0±3.6	28.9±13.1*	35.7±6.2*	36.8±6.6*	<0.001
Maximum decrease in DBP (%)	2.0±4.4	28.2±13.2*	34.1±6.9*	35.2±5.5*	<0.001
Maximum increase in HR (%)	2.7±7.6	11.9±8.4	19.3±13.6*	23.2±13.8*	<0.001
Timing of maximum effect (s)	40 (12.5-122.5)	50 (50-62.5)	55 (50-60)	55 (50-55)	0.762
Time to return to baseline (s)	N/A	109.5±29.0	146.7±34.4	174.7±79.1	<0.001
Total NTG consumption (ug)	80 (0-112.5)	100 (0-425)	500 (25-1200) *	750 (100-1525) *	<0.001

Data were presented as Mean ± SD or Median (IQR) appropriately.

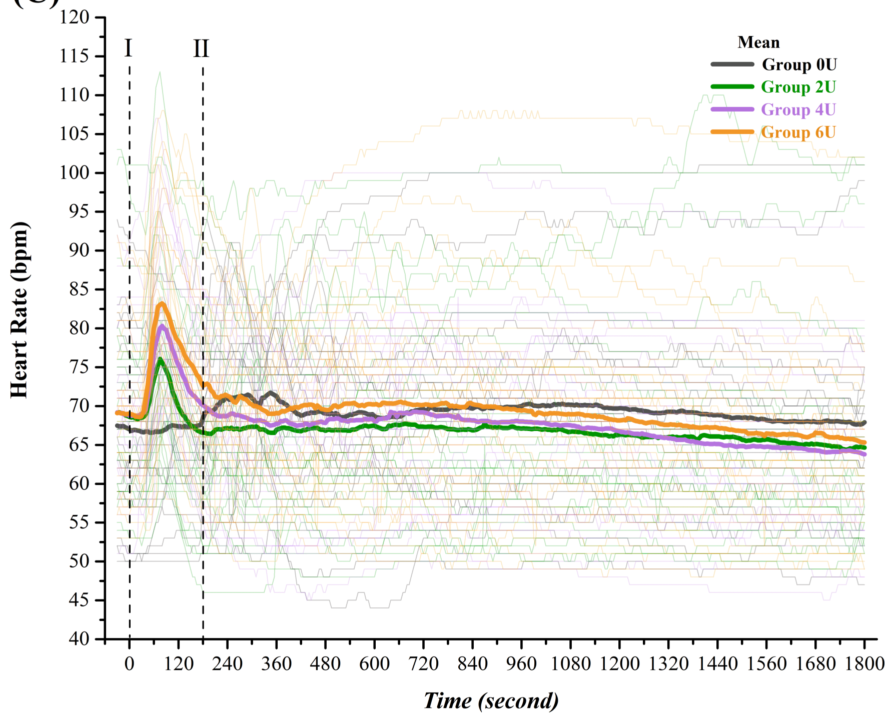
*$P < 0.01$ compared with the group 0U;$^{P<0.05comparedwiththegroup2U}$;$^{P<0.05comparedwithbaselinelevel}$.‘N/A’ represents not available; ‘NT

(B)



iDBP(mmHg)
Time (second)
I
II
Mean
Group 0U
Group 2U
Group 4U
Group 6U

(C)



Heart Rate (bpm)
Time (second)
I
II
Mean
Group 0U
Group 2U
Group 4U
Group 6U