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Use of vasopressin vs epinephrine to reduce haemorrhage during myomectomy: a randomized controlled trial

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ABSTRACT

Objective: To compare the effectiveness and safety of vasopressin with epinephrine for reducing blood loss during laparoscopic myomectomy.
Study design: Sixty patients undergoing laparoscopic myomectomy were allocated at random to receive either dilute vasopressin or epinephrine into the serosal and/or overlying myometrium, and just around the myoma. The surgeon was blinded to the group allocation. Blood loss, duration of surgery, degree of surgical difficulty, postoperative pain scores and complications were compared.
Results: Patient characteristics (e.g. age, body mass index, demographic data), number of myomas, and location and size of the largest myoma were similar between the two study groups. There were no differences in operative blood loss, operative time, subjective surgical difficulty or postoperative pain between the two groups. Transient and non-serious increases in systolic and diastolic blood pressure and heart rate following intra-operative intramyometrial and/or perimyometrial injection of the vasoconstrictive agent only occurred in the epinephrine group, but the difference between the groups was not significant (13% vs 0%, $p = 0.112$). No significant postoperative complications were observed in either group.
Conclusions: Injection of dilute epinephrine before laparoscopic myomectomy was comparable to injection of dilute vasopressin in terms of operative blood loss, operative time, subjective surgical difficulty, postoperative pain and complications.

Introduction

Uterine myomas (fibroids or leiomyomas) are the most common benign tumour of the female genital tract [1], and the leading indicator for hysterectomy [2]. Although hysterectomy is the definitive treatment for myomas, myomectomy remains the 'gold-standard' treatment for women wishing to preserve their uterus and fertility [3]. However, bleeding is often a problem in myomectomy, and can result in intra-operative hypovolaemic shock, postoperative anaemia and delayed recovery.

A number of interventions have been introduced to reduce haemorrhage during myomectomy. Two categories of interventions are available: (a) vascular interventions on uterine and/or ovarian arteries, such as artery clamping, tying or embolization; and (b) pharmacological interventions, such as vasopressin, oxytocin, ergometrine, misoprostol, sulprostone or gonadotropin-releasing hormone (GnRH) agonists [4–11]. Of these, intra-operative local injection of vasopressin causing vasospasm is used most often [12,13]. A randomized controlled trial was undertaken to determine the efficacy of vasopressin compared with normal saline solution in reducing blood loss at myomectomy, and found a significant difference in mean blood loss of 500 ml ($p = 0.001$) between the groups, which correlated with the observed change in haemoglobin (1.7 vs 5.3 g/dl; $p = 0.001$) in the vasopressin and normal saline solution groups [14]. However, some serious side effects have also been reported following the use of vasopressin [15–18]. In addition, in some European countries, such as France and Italy, the use of vasopressin to reduce haemorrhage during myomectomy is prohibited because of its potential adverse effects on the cardiovascular system [15–18].

Epinephrine also induces a vasoconstrictive effect on tissues [5,19–21], and has been used during various gynaecological operations [5,22,23], endoscopic resections [24] and dermatological

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procedures [25] to reduce blood loss. However, few studies regarding the use of epinephrine in myomectomy have been undertaken [5,26]. Furthermore, a comparative study of epinephrine and vasopressin as a haemostatic agent during myomectomy has never been conducted. The aim of this study was to compare the effectiveness and safety of epinephrine with vasopressin during laparoscopic myomectomy in terms of the amount of operative blood loss, as well as the effects on operative time, surgical difficulty and complication rates.

Methods

Participants

This study was conducted prospectively between May 2013 and March 2014 in the Department of Obstetrics and Gynaecology at the CHA Gangnam Medical Centre, a high-volume centre where >400 laparoscopic myomectomies are performed each year. Women with symptomatic myomas were screened for this study. All participants underwent transvaginal and/or transabdominal ultrasonography (within 30 days preceding surgery), in which the number, size and location of myomas were assessed and recorded. Inclusion criteria were: myoma-related symptoms, such as pelvic pressure or pain, menorrhagia or infertility; not pregnant at the time of presentation (i.e. negative urine pregnancy test or last menstrual period within the last 4 weeks); and appropriate medical status for laparoscopic surgery (American Society of Anesthesiologists Physical Status Classification 1 or 2). Exclusion criteria included history of ischaemic heart disease; any pelvic abnormalities requiring concomitant surgery; presence of pedunculated subserosal or submucosal myoma as a dominant myoma; presence of a myoma with a maximal diameter of 10 cm based on pre-operative ultrasound; more than four myomas; treatment with a GnRH agonist or ulipristal acetate within 3 months preceding surgery; and inability to understand and provide written informed consent.

Study protocol

Subjects were assigned at random to the vasopressin or epinephrine group in a 1:1 ratio using a random permuted-block algorithm via an interactive Web-based response system (http://www.randomization.com). The study coordinator, who was not involved in the randomization procedure, prepared all sequentially numbered, opaque, sealed envelopes containing the assigned intervention to ensure that the sequence was concealed. Randomization took place when a circulating nurse telephoned the coordinating centre just before general anaesthesia on the day of surgery. The surgeon was blinded to group allocation. The protocol was approved by the institutional review board and registered with ClinicalTrials.gov (NCT01861015). The study was performed in accordance with the protocol, and all subjects provided signed informed consent before participation.

A single surgeon (T. Song) performed all laparoscopic myomectomies using a 10-mm umbilical trocar and three ancillary 5-mm trocars. To reduce blood loss, only the haemostatic agent (either epinephrine or vasopressin) assigned was injected into the serosal and/or myometrium overlying the myoma before the uterine incision. In the epinephrine group, dilute epinephrine {0.5 mg of epinephrine (1/2 vial of 1 mg/ml concentration) in 50 ml of saline solution [26]} was used, taking care to use no more than 20 ml of solution per subject. In the vasopressin group, dilute vasopressin (5 units in 50 ml of saline solution) was used, taking care to inject no more than 20 ml of solution per subject. During injection, careful electrocardiographic monitoring was used to detect arrhythmias. The surgical technique of laparoscopic myomectomy has been reported in detail elsewhere [27,28].

Systolic and diastolic blood pressure and heart rate were measured accurately, and an electrocardiogram was performed in each subject 5 min before and after the injection of epinephrine or vasopressin. Total operative time was defined as the time from skin incision to skin closure. The times required to perform each phase were measured and calculated with a digital time counter: entry time (defined as the time from the start of skin incision until the start of epinephrine or vasopressin administration); enucleation time of all myomas; suturing time of all uterine wall defects; morcellation time; haemostasis time (defined as the time from removal of the morcellator until confirmation of haemostasis and washing of the pelvic cavity); and skin closure time. The volume of operative blood loss was calculated by adding the blood aspirated to the weight of the gauzes used during surgery. At the end of each surgical procedure, the degree of total surgical difficulty, enucleation difficulty and suturing difficulty were evaluated by the surgeon using a visual analogue scale (VAS) varying from 1 (very low difficulty) to 10 (very high difficulty), as described by Vassiliou et al. [29]. Postoperative pain assessments were performed using a VAS at 12, 24 and 48 h after surgery by several independent assessors. The scale was presented as a 10-cm line with verbal descriptors ranging from 'no pain' to 'pain as bad as it could be'. In both study groups, blood samples were taken within 24 h after surgery, and change in haemoglobin level was defined as the difference between pre-operative haemoglobin and haemoglobin on the first postoperative day. The subjects were discharged from the hospital after bowel activity restoration, ambulation, lack of postoperative fever and no need for narcotic analgesics. Length of hospital stay was defined as the number of days from surgery to discharge. All intra- and postoperative complications arising within 30 days of surgery were recorded. All subjects were seen for follow-up assessments 1 week and 1 month after surgery.

Outcome measures and sample size

The primary outcome measure was operative blood loss. Secondary outcomes included operative time, subjective surgical difficulty, postoperative pain score and complication rate.

The sample size was determined with reference to operative blood loss as the primary outcome measure. To ensure that the study was designed with a power of at least 0.80 at a significance level of 0.05, a retrospective chart review of patients who underwent laparoscopic myomectomy using dilute vasopressin injection was performed. The mean blood loss in a sample of 50 patients was 175.2 [standard deviation (SD) 47.0] ml. Allowing for a 5% dropout rate, it was estimated that 30 subjects would be needed in each group to detect a 20% difference in operative blood loss, which would be considered clinically significant between the two groups. No interim analysis was planned or performed.

Statistical analysis

Statistical Package for the Social Sciences Version 13.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data are presented as mean (SD) or median [range] for quantitative variables, and frequency (%) for qualitative variables. All analyses were performed according to the intention-to-treat principle. The baseline clinical characteristics, and primary and secondary outcomes of the two groups were compared using Student's *t*-test or Mann–Whitney test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables, as appropriate. $p < 0.05$ was considered to indicate statistical significance.