Intra-myometrial injection of carbetocin versus vasopressin for reduction of blood loss in myomectomy operations

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Abstract

Background: There are various contemporary therapies for uterine fibroids, but surgical resection—including hysterectomy and myomectomy—remains the primary method. This study compared the effectiveness of intramyometrial carbetocin injection versus vasopressin for reducing blood loss in myomectomy instances.

Methods: This randomized, comparative clinical trial was performed on 60 female patients undergoing myomectomy with uterine fibroids, abnormal vaginal bleeding, chronic pelvic pain, pressure symptoms, or reproductive abnormalities and pre-operative hemoglobin levels > 10 g/dL. Three identical groups of patients were formed (N=20): Control group: No medications. Carbetocin group: Using 100 µg carbetocin. Vasopressin group: using 20 units vasopressin.

Results: In comparison to the other two groups, controls (881.25 ml) experienced a significant rise in overall blood loss (760 and 698 ml in the carbetocin and vasopressin groups respectively). Only two cases—one each in the carbetocin and vasopressin groups—required hysterectomy. Hemoglobin and hematocrit levels were significantly less in control group (9.15 gm/dl) than in the two treatment groups (9.61 and 10.05 gm/dl for carbetocin and vasopressin, respectively).

Conclusions: Both vasopressin and carbetocin are safe and efficacious in decreasing bleeding after myomectomy.

Keywords: Carbetocin, vasopressin, intra-myometrial, blood loss, myomectomy

Introduction

The most prevalent benign tumours in women are uterine leiomyomas, which develop from myometrial smooth muscle cells. These tumours develop during the reproductive cycle and are estrogen-dependent [1]. Incidence of roughly 70% among general population. In between 20 and 40% of women with fibroids, there are noticeable symptoms and they seek gynaecological care but the exact extent of their occurrence is certainly underestimated [2]. Women who do not want to have further children should have a hysterectomy, whereas those who want to retain their fertility should have a myomectomy [3].

A minimum access technique called the laparoscopic approach was created to lessen damage to abdominal wall and to promote a speedy recovery for the patient after surgery. Transcervical hysteroscopic resection is a suitable alternative for patients with submucous myomas since it benefits both the patient and the doctor [4].

One of the major problems that can cause considerable morbidity and mortality during myomectomy is bleeding. Gynecologic surgeons continue to face a significant challenge as a result of improvements in preventing excessive bleeding during the treatment. For this procedure, a number of measures have been devised to prevent hemorrhage such as dissection and embolization of uterine artery [5], using mechanical tourniquets and uterotonic drugs including misoprostol, oxytocin, carbetocin, and ergometrine [6].

An artificial long-acting oxytocin analogue is carbetocin. Its half-life in the bloodstream is 85 to 100 minutes, which is ten times longer than oxytocin's. It acts quickly and for a long time [7]. Carbetocin causes rhythmic contractions in the uterus by acting on the uterine oxytocin receptors, which can raise both the frequency and tone of current contractions [8].
In comparison to a single intramuscular dose of oxytocin, the effect of IV or IM injection lasted 60 to 120 min longer. To make it simple to locate and remove the tumour that was protruding from the uterine surface during surgery, smooth muscles of uterus were modified to contract. Vasopressin is mainly an antidiuretic hormone that is released in reaction to rises in plasma osmolality or falls in blood volume. It works on V1 receptors at higher concentrations, causing generalized constriction of most blood arteries, including the coronary vasculature.

Each fibroid’s planned uterine incision location is given a shot of vasopressin to stop blood loss. Vasopressin works by tightening smooth muscle lining the venules, capillaries, and tiny arterioles. Vasopressin myomectomy is much less invasive than placebo myomectomy (299 ml less), and it is less invasive than or equivalent to using a uterine artery tourniquet. This study compared the effectiveness of intra-myometrial injections of carbetocin and vasopressin for reducing blood loss during myomectomy procedures.

### Patients and Methods

This randomized comparative clinical study was performed on 60 female patients aged from 18 to 35 years old, with clinical criteria of uterine fibroid (intramural - not exceeding 12 weeks gestation), excessive vaginal bleeding, chronic pelvic pain, pressure symptoms or reproductive disorders with pre-operative hemoglobin >10 g/dl. The study was done from December 2019 to February 202 after approval from Ethical Committee Tanta University Hospitals. Every patient signed an informed consent form. Exclusion criteria were presence of hypertension, post-menopausal women, bleeding/clotting disorders, receiving anticoagulant, chronic use of NSAIDs or antiplatelet, a history of gynecological malignancy, previous abdominal myomectomy, family history of venous thrombo-embolism, venous thromboembolism and active liver, kidney or cardiovascular diseases.

Patients were further divided in to three equal groups (N = 20): group I: (Carbetocin group): carbetocin was used to control bleeding during myomectomy, group II: (vasopressin group): Vasopressin was used to control bleeding during myomectomy and group III (control group) myomectomy was done without use of medication.

All patients were subjected to: Transvaginal and/or abdominal ultrasound to estimate the fibroids and complete blood count (CBC) to determine hemoglobin and hematocrite.

**Procedure:** Pfannenstiel skin incision was done to remove the myoma. Incision of anterior abdominal wall in layers. The leiomyomas can be found by palpating the uterus.

**For control group:** Myomectomy was done without utilizing medication.

**For Carbetocin group:** A preparation of 100 μg carbetocin (PapaL; Ferring Pharmaceutical, Copenhagen, Denmark) diluted within 10 cm saline (0.9%) in sterile syringe was injected intramurally 1-2 cm away from margins of myoma all around just before uterine incision for myoma extraction.

**For Vasopressin group:** 15-20 ml preparation made of (20 units vasopressin Vasmed diluted in 200 ml normal saline) in sterile syringe injected intramurally, 1 to 2 cm away from the myoma's margins on all sides prior to uterine incision for myoma removal.

In order to prevent intravascular injection, the surgeon would remove the syringe's plunger and look for blood. Prior to the injection, the anesthesiologist was always informed. Myomas must be removed by extending down from a midline uterine incision that has been carefully planned and placed. Uterine incision encompassing the entire fibroid pseudo capsule and myometrium. Once the myoma has been identified, make an incision through the least vascular plane that is just deep enough to access capsule. Once the myoma has been detected, this incision can be extended just deep enough to reach the capsule, which is the least vascular plane. Surgeons use Allis clamps to pull the myometrial borders apart once the myoma is plainly visible and bulging. The myomas are then unchelated by being held in place with a towel clamp or single-tooth tenaculum. Typically, back of an empty knife handle or a sponge are used to bluntly slice the plane between myometrium and myoma. Layers of sutures are used to close the uterine abnormalities. For the tissue to be approximated and hemostasis to be achieved, two layers may be required if myometrial defect is deep (> 2 cm). In our investigation, the myometrium was sutured with a size 0 polyglaactin 910 (Vicryl™) suture. We employed size 2-0 polydioxanone (PDS™) running sutures to seal the serosa.

**Blood loss assessment** procedures for determining weight or saturation that involve deducting dry weight of absorbent materials (pads, sponges, etc.) from the weight of materials that contain blood and through conversion. The amount of blood in the materials and the amount of blood drawn out by suction machine are both measured in terms of 1 gm weight = 1 ml. Additionally, the amount of blood loss includes any aspirated blood from the field that may have been present.

CBC was performed twice: Right before the operation and 24 hours later. Time from the point of skin incision to point of skin suturing is calculated intraoperatively in minutes. A few days following the procedure, a postoperative hospital stay was noted. The primary outcome was an estimate of blood loss during surgery. The secondary outcomes were intra-operative events, time of operation and postoperative stay, hemoglobin and hematocrit levels before and 24 h after operation and urinary output.

**Statistical analysis** SPSS v26 was employed to conduct statistical analysis (IBM Inc., Chicago, IL, USA). ANOVA (F) test with a post hoc (Tukey) comparison was employed to determine quantitative variables across the three groups after they were described as mean and standard deviation (SD). Chi-square test was utilized to examine qualitative variables, which were provided as frequency and percentage (%). In order to be statistically significant, a two-tailed P value < 0.05 was required.

**Results:** The demographic data variables were comparable between the three studied groups (*p*>0.05). No discernible variations in myoma size or type were found amongst the three study groups (*p*>0.05).
Between the three groups, there was a non-significant variation in operational time (p=0.646). In comparison to the carbetocin and vasopressin groups (321.25 and 263.75 ml correspondingly, respectively, with a p-value of 0.001), quantity of blood in the suction jar increased significantly in control group (417.5 ml). The total volume of blood loss was significantly greater in the control group (881.25 ml) than in the other two groups (760 and 698 ml, respectively, in the carbetocin and vasopressin groups, p<0.001). When contrasted to carbetocin group, post-hoc analysis showed that vasopressin group saw significantly less blood loss (p=0.015).

Table 1: Comparison between study groups as regard demographic data and type, size of myoma

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N= 20)</th>
<th>Carbetocin Group (N = 20)</th>
<th>Vasopressin Group (N= 20)</th>
<th>P</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.90±3.7</td>
<td>28.05±4.084</td>
<td>29.55±3.88</td>
<td>0.481</td>
<td>1</td>
<td>1</td>
<td>0.689</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.74±2.2</td>
<td>26.58±2.630</td>
<td>26.89±2.35</td>
<td>0.308</td>
<td>0.833</td>
<td>0.419</td>
<td>1</td>
</tr>
<tr>
<td>Parity</td>
<td>2 or less</td>
<td>70.00±(14)</td>
<td>85.00±(17)</td>
<td>0.129</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>3 or more</td>
<td>30.00±(6)</td>
<td>15.00±(3)</td>
<td>5.00</td>
<td>10.00</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Type Subserousintramural</td>
<td>45.00± (9)</td>
<td>30.00± (6)</td>
<td>20.00± (4)</td>
<td>0.231</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>5.12±1.343</td>
<td>4.94±4.178</td>
<td>4.72±1.624</td>
<td>0.703</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are displayed as mean ± standard or frequency (%). BMI: Body mass index. P is significant when < 0.05. P1: Control group and Carbetocin group. P2: Control group and Vasopressin group. P3: Carbetocin group and Vasopressin group.

Table 2: Duration of surgery and amount of blood loss in both groups

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N= 20)</th>
<th>Carbetocin Group (N = 20)</th>
<th>Vasopressin Group (N= 20)</th>
<th>P</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative duration (minutes)</td>
<td>94.75±11.751</td>
<td>94.00± 13.139</td>
<td>91.25 ± 12.341</td>
<td>0.646</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blood in suction jar (ml)</td>
<td>417.50±59.105</td>
<td>321.25 ± 43.130</td>
<td>263.75 ± 46.222</td>
<td>&lt; 0.001**</td>
<td>&lt; 0.001**</td>
<td>&lt; 0.001**</td>
<td>0.002*</td>
</tr>
<tr>
<td>Estimated Blood Loss (ml)</td>
<td>881.25±68.365</td>
<td>760.00 ± 53.435</td>
<td>698.75±75.426</td>
<td>&lt; 0.001**</td>
<td>&lt; 0.001**</td>
<td>&lt; 0.001**</td>
<td>0.015*</td>
</tr>
</tbody>
</table>

Data are shown as mean ± standard deviation. * Significant. **Highly Significant. P is significant when < 0.05. P1: Control group and Carbetocin group. P2: Control group and Vasopressin group. P3: Carbetocin group and Vasopressin group.

Table 3: Basal and post-operative hemoglobin and hematocrit values in both groups

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N = 20)</th>
<th>Carbetocin Group (N = 20)</th>
<th>Vasopressin Group (N = 20)</th>
<th>P</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal HB (gm/dl)</td>
<td>11.11±0.371</td>
<td>11.23±0.609</td>
<td>11.32±0.739</td>
<td>0.643</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative HB (gm/dl)</td>
<td>9.15±0.622</td>
<td>9.61±0.525</td>
<td>10.05±0.512</td>
<td>&lt; 0.001**</td>
<td>0.036*</td>
<td>&lt; 0.001**</td>
<td>0.042*</td>
</tr>
<tr>
<td>HB change (gm)</td>
<td>-196.0±2.444</td>
<td>-1.62±0.202</td>
<td>-127.0±0.399</td>
<td>&lt; 0.001**</td>
<td>0.002*</td>
<td>&lt; 0.001**</td>
<td>0.001*</td>
</tr>
<tr>
<td>Basal RTC (%)</td>
<td>32.95±1.710</td>
<td>31.17±1.787</td>
<td>47.14±61.942</td>
<td>0.363</td>
<td>1</td>
<td>0.645</td>
<td>0.666</td>
</tr>
<tr>
<td>Postoperative HTC (%)</td>
<td>28.05±1.498</td>
<td>29.70±1.702</td>
<td>31.12±1.495</td>
<td>&lt; 0.001**</td>
<td>0.005*</td>
<td>&lt; 0.001**</td>
<td>0.017*</td>
</tr>
<tr>
<td>HTC change (%)</td>
<td>-4.90±0.465</td>
<td>-3.47±0.265</td>
<td>-2.07±0.622</td>
<td>&lt; 0.001**</td>
<td>&lt; 0.001**</td>
<td>&lt; 0.001**</td>
<td>&lt; 0.001**</td>
</tr>
</tbody>
</table>

Data are displayed as mean ± standard deviation. HB: hemoglobin. HTC: Haematocrit. *Significant. **Highly Significant P is significant when < 0.05. P1: Control group and Carbetocin group. P2: Control group and Vasopressin group. P3: Carbetocin group and Vasopressin group. Only three (15%) of the controls required blood transfusions, but none of the cases in the other two groups did. However, statistical analysis found no discernible difference (p>0.05) in that parameter between the three groups.

Hysterectomy and duration of hospitalization There was no significant variation between the three groups (p=0.596), (p=0.621) respectively.

Table 4: Need for blood transfusion, additional oxytocic and total hospital stay

<table>
<thead>
<tr>
<th></th>
<th>Control Group (N = 20)</th>
<th>Carbetocin Group (N = 20)</th>
<th>Vasopressin Group (N = 20)</th>
<th>P</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for transfusion</td>
<td>15.0±5 (3)</td>
<td>0.0±0 (0)</td>
<td>0.0±0 (0)</td>
<td>0.100</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Need for Hysterectomy</td>
<td>0.0±0 (0)</td>
<td>5.0±1 (1)</td>
<td>5.0±1 (1)</td>
<td>0.596</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hospital stays (hours)</td>
<td>33.00±9.437</td>
<td>30.60±9.110</td>
<td>30.60±8.236</td>
<td>0.621</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion

The most prevalent type of good-risk tumours which impact women who are of reproductive age is uterine fibroids. There are various contemporary therapies for uterine fibroids, but surgical resection—including hysterectomy and myomectomy—remains the primary method [11]. When number and size of leiomyomas preclude any alternative surgical route of the surgery, myomectomy continues to be the primary option with excellent results in regard to fertility preservation and symptom relief [12]. Regarding the age of included patients there was no significant
In the current study, the included fibroid lesions were with no significant variation between the three study groups. Another study carried out by Sallam and Shady [12] reported greater size range. Other authors reported lower size range [14]. In the present research, there was no significant variation between our three study groups concerning most of the preoperative demographic and clinical variables. In our study, carbetocin administration led to a significant decrease in blood loss compared to controls (p<0.001).

Man and his associates [15] confirmed the previous findings, with a significant variation (p<0.001). In the same context, a study confirmed by Sallam and Shady, et al. [12] showed blood loss during surgery with a significant variation (p<0.001). All the previous studies agree with our findings concerning effectiveness of carbetocin in minimizing bleeding during myomectomy.

In the current study, no significant variation was noted between carbetocin and control groups concerning the requirement for blood transfusion (p>0.05), although it was required for 3 controls (15%) compared to 0 cases in the carbetocin group. In line with our findings, Gad Allah, and his associates [16] also reported no significant variation between carbetocin and control groups regarding requirement for blood transfusions (p=0.09). Contrarily, Sallam and Shady, et al. [12] reported that the intravenous administration of carbetocin during myomectomy operations led to a significant decrease in requirement for blood transfusions (p<0.001).

Our findings revealed comparable operative time between carbetocin and control groups (P = 1). The results obtained by Lotfy, et al. [17] negated that carbetocin administration had a significant impact on operative time, with no significant variation on statistical analysis (P = 1). This coincides with our findings. Meanwhile, Man, et al. [15] showed a reduced operating time in their study group (carbetocin). (p=0.002).

In the current study, basal hemoglobin and hematocrit levels were comparable between the carbetocin and control groups. Nevertheless, after operation, the carbetocin group expressed greater values of both parameters compared to controls (p<0.05). Additionally, the decrease in these two parameters was more significant in controls. In line with our findings, Gad Allah, et al. [16] reported a substantial drop in both hemoglobin and hematocrit values after myomectomy in controls contrasted to carbetocin group (p = 0.02 and 0.03 respectively).

In the same context, Lotfy, et al. [17] reported a decrease in both hemoglobin and hematocrit. The decrease was significantly less in patients who obtained IV carbetocin.

In the current study, administration of carbetocin did not substantially impact length of hospitalization contrasted to controls (30.60 vs. 33 hours respectively – P = 1). Another study carried by Gad Allah, et al. [16] also negated any significant variation between controls and carbetocin groups regarding hospitalization period (p=0.850). Moreover, Sallam and Shady, et al. [12] reported no significant impact of carbetocin administration on the duration of hospitalization (p=0.514). On the other hand, Man, et al. [15] reported a significant prolongation of hospitalization in controls compared to the group received intramyometrial carbetocin (p<0.001).

Both pregnant and non-pregnant women's myometriums contain vasopressin receptors. A recent investigation by Elgendy et al. confirmed our findings. [18] Vasopressin group demonstrated a significantly less intraoperative blood loss (p<0.001) than control group. Also, Isah, et al. [19] confirmed the previous findings. Furthermore, a trial carried by Kongnyuy and Wiysonge [20] demonstrate that usage of vasopressin considerably decreases blood loss during myomectomy contrasted to placebo (299 mL less) and is less effective than or similar to applying a tourniquet to the uterine artery.

Our findings revealed that vasopressin administration did not lead to significant changes in operative time (p>0.05). Wong et al. [14] also reported that intra-myometrial injection of vasopressin did not significantly affect operative time. In the current study, the vasopressin group exhibited significantly less changes in hemoglobin and hematocrit values after operation, compared to controls (p<0.001). Like our findings, Elgendy, et al. [18] reported that preoperative hemoglobin and hematocrit values were statistically comparable between the vasopressin and control groups (p>0.05). However, post-operative values of the same two parameters exhibited a significant decrease in control group (p<0.001). In the same context, Isah, et al. [19] reported that the vasopressin group had a greater mean postoperative hematocrit than placebo group. These outcomes are consistent with those of additional investigations conducted by Frederick et al. and Kimura et al. [21, 22] found that participants in placebo group saw a greater drop in hematocrit than those in vasopressin group. In the current study, vasopressin administration failed to significantly affect the requirement for blood transfusion (p>0.05). Saha et al. [23] also negated that intra-myometrial vasopressin had a significant impact on blood transfusion rates. Conversely, a previous Egyptian study carried by Elgendy, et al. [18] reported that no transfusions were necessary in vasopressin group while 30% of control group required blood transfusions. Besides, Isah et al. [19] reported a significant variation between two groups (p<0.001). However, LaMorte, et al. [24] found that women who got pitressin and/or vasopressin had a greater rate of blood transfusion (28 %) than women who did not get any preventative hemostatic care. In the current study, the length of hospitalization was comparable between vasopressin and control groups (P = 1). The study done by Song, et al. [25] noted no significant variation in the duration of hospitalization between intra-myometrial vasopressin and epinephrine when used to decrease bleeding during myomectomy.

Limitations: Single center study, small sample size and future research should be undertaken with additional cases from various surgery centres.

Conclusions:
Both vasopressin and carbetocin are safe and effective in cutting down on myomectomy-related blood loss. However, the former drug was superior to the latter. More studies should be conducted to estimate the best one that will achieve the least amount of blood loss.

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Conflict of Interest: Nil

References:
1. Drayer SM, Catherino WH. Prevalence, morbidity, and


