Effect of Methylergonovine Infusion on Blood Loss during Laparoscopic Myomectomy

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Running title: Methylergonovine infusion and blood loss in LM

Abstract

Background: These benign tumors are the most frequent in women, with an estimated lifetime risk of 70–80% before menopause. Laparoscopic myomectomy (LM) had less postoperative discomfort, lesser
postoperative fever, and a decreased hospital stay than open myomectomy. However, control of blood loss is meanwhile a persistent challenge. Many drugs were investigated to minimize blood loss during myomectomy. Methylergonovine is used to treat postpartum uterine hemorrhage.

**Objective:** to see whether a methylergonovine peri-operative infusion may help reduce loss of blood during a laparoscopic myomectomy.

**Patients and methods:** The Obstetrics and Gynecology Department of Benha University performed this randomized controlled research. It was involved 80 patients allocated either into group A treated with methylergonovine infusion or group B receiving placebo in the form of normal saline.

**Results:** In baseline parameters, there was no substantial variation among the two groups. The length of the surgery projected intra-operative bleeding, post-operative hemoglobin, post-operative hematocrit, number of packed RBC units transfused, and postoperative hospital stay were all substantially different between the two groups. In the number of patients who need blood transfusions, there was a substantial variation. When it came to the negative effects of methylergonovine, there was no substantial difference.

**Conclusion:** During laparoscopic myomectomy, methylergonovine infusion greatly decreased loss of blood and the requirement for blood transfusions.

**Key words:** Leiomyoma, myomectomy, laparoscopy, Methylergonovine, laparoscopic myomectomy, Blood loss.

**Introduction**

Uterine myomas have been the most common benign lesions of the female genital tract before menopause, with a lifetime prevalence of 70-80%. (1).
They may cause severe morbidity, such as prolonged or heavy menstrual flow, pelvic pressure, discomfort, or infertility, and are clinically visible in up to 25% of women. (2).

The laparoscopic method is linked with reduced postoperative discomfort, a reduced risk of postoperative fever, and a reduced hospital stay as compared to standard open myomectomy. (3). Other possible benefits of the laparoscopic method have a faster recovery period and a speedier comeback to work and everyday activities. (4). Controlling blood loss during LM, on the other hand, remains a difficulty.

The incidence of hemorrhage or blood transfusion in a series of 500 or more LM ranged from 0.1 percent to 6%, with a mean intraoperative bleeding of 80–248 mL (range 20–1000 mL). (5).

Several medicinal interventions, including uterotonics such prostaglandins, misoprostol (6) and dinoprostone (7), oxytocin (8; 9) and carboprost (10), and more recently, vitamin C, have been employed to minimize loss of blood after myomectomy with varying degrees of success. (11).

Methylergonovine is used to prevent and manage uterine bleeding that might occur after delivery. It belongs to a family of drugs known as ergot alkaloids. This medication works by directly acting on the smooth muscles of the uterus, producing contractions and preventing postpartum hemorrhage (12).

The purpose of this observational research was to see whether administering methylergonovine infusion during laparoscopic myomectomy can decrease blood loss or not.

**Material and methods**

**Study design and settings:** Between the start of December 2018 and the end of December 2021, this randomized controlled trial was undertaken at Benha University's Department of Obstetrics and Gynecology in Benha, Egypt.
Sample size calculation: The sample size was calculated based on the findings of a previous study by Congzhe et al. (13), who found that with a power of 0.9 and a significant level of 0.05, 40 patients in each group were needed to achieve an inter-group mean (SD) variance of 200 mL in bleeding during laparoscopic myomectomy.

Patients: After a complete history gathering and ultrasound scanning, eighty-two participants with symptoms recurrent intramural uterine myomas (≥4) of various sizes were included. Patients with high blood pressure, cardiovascular disease, bronchial asthma, diabetes mellitus, hemorrhagic tendency, preoperative hemoglobin levels less than 10 gm/dL, body mass index greater than 35, submucosal myomas, known sensitivity to ergot alkaloids, or any contraindication to procedure or methylergonovine administration were all excluded from the study.

None of the patients received preoperative GnRH analogues or any other hormonal or nonhormonal medication to reduce myoma size or bleeding during laparoscopic myomectomy.

Randomization and allocation: Randomization was done using simple randomization based on online web-based network. Patients were allocated with 1:1 ratio in two groups 1&2. Enrolled patients were given sealed envelopes containing either letter M or S denoting the allocated group. The letter M denotes methylergonovine while S denotes saline. Study group comprised 40 patients who were treated with methylergonovine (Methergine 1m 0.2mg, ***) diluted in 1000ml of normal saline infused at a rate of ....ml/hour during operation while The control group consisted of 40 participants who received just regular saline infusions.
Intervention: Laparoscopic myomectomy

Anesthesia and Preoperative Settings: The patient was put under general anesthesia for all of the surgeries. The patients were prepped for lithotomy, and the uterine Manipulator was inserted into the uterine cavity for uterine mobilization.

Positioning of the Trocar: The closed technique was used for laparoscopic surgeries. A 10-mm scope was inserted periumbilically after pneumoperitoneum was achieved. The following three puncture sites were
created: On both sides, two 5-mm sites are located 2 cm above the anterior superior iliac supine, and a 5-mm midline port is located 3 cm above the symphysis pubis, offering an optimal laparoscopic position with a broad operational field. The surgeon stood on the patient's left side, manipulating the left lower 5-mm trocar with his right hand and the midline trocar with his left. The assistant stood on the right side, his left hand directing the camera and his right hand the right 5mm trocar.

Laparoscopic myomectomy technique: The same surgeon (HT) conducted all of the surgeries, and they were all done in the same way. Vasopressin was injected between the myometrium and the myoma capsule before excision at a dose of 20 IU/100 mL diluted saline solution to reduce the size of the blood vessels and hemorrhage.

The uterine manipulator was operated by the second assistant, who used an anteverted position for a posterior myoma and a retroverted position for an anterior myoma. The myoma was kept in a prominent location on the operating field. A monopolar needle was used to make a horizontal incision (Figure 2). The myoma was removed from its capsule using a gripping forceps, monopolar needle, and myoma screw introduced into the left upper trocar port. Dissection was aided by traction on the myoma, as well as the use of the uterine manipulator and myoma screw (Figure 3). A monopolar needle was used to complete hemostasis of the uterine bed after the myoma had been enucleated.

Depending on the depth of the hysterotomy, the uterine wall was sutured in 1 to 3 layers. A separate stitch was utilized to repair the perimetrium using a 5-mm needle holder and 2/0 Vicryl. Normally, sutures are put every 5 mm along the hysterotomy. A baseball suture was used to reconnect the serosa’s margins. The endoknife was used to remove almost all myomas from the abdominal cavity. After a full myomectomy, fibrin glue spray was employed to avoid postoperative adhesion development (Figure 4).
Follow up: We followed patients after the operation to detect any bleeding or other complications. ICU admission and postoperative hospital stay were recorded if any.

**Outcome of the study:** The projected intraoperative bleeding was the primary outcome (ml). **Secondary outcomes:** Operative time, need for blood transfusion, hospital stay, ICU admission, operative and postoperative complications and adverse effects of methylergonovine.

Blood loss was estimated using preoperative and postoperative hemoglobin and hematocrit levels (**taken 8 hours before and one hour after surgery**). We estimated Hb and Hct before operation (Hb1, Hct1) and one hour after the operation (Hb2, Hct2). We also, estimated blood loss at the operation with application of Bourke and Smith equation *(14)* which is one of the acceptable formulae to calculate the intra-operative loss of blood utilizing preoperative and post-operative hematocrit values.

\[
\text{Blood loss} = \text{Blood Volume} \times \left( \frac{\text{Hct1} - \text{Hct2}}{\text{Hct1}} \right)
\]

\[
\text{Blood Volume} = \text{Weight (Kg)} \times 70\text{ml}
\]

**Ethical issues and study registration:** The ethics committee at Benha University Faculty of Medicine examined and approved the research protocol, and all patients completed an informed consent form prior to the start of the trial.

**Statistical analysis:** IBM SPSS version 22.0 was used to analyze computer-generated data. To express quantitative data, percentages and numbers were employed. Before utilizing the median in nonparametric analysis or the interquartile range in parametric analysis, it was required to perform Kolmogorov-Smirnov tests to ensure that the data were normal. We used the *(0.05)* significance threshold to establish the significance of the findings. The Chi-Square test is used to compare two or
more groups. The Monte Carlo test may be used to adjust for any number of cells with a count less than 5. Fischer Chi-Square adjustment was applied to 2*2 tables when at least a quarter of cells had a count of less than 5.

Figure (2): Incision of uterine surface.

Figure (3): Dissecting the myoma from myometrium after methergine
Figure (4): After complete myomectomy

Results

Table (1): Patients basal features.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n=40)</th>
<th>Control group (n=40)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>32.5 (2.5)</td>
<td>31.4 (2.3)</td>
<td>&gt;0.05²</td>
</tr>
<tr>
<td>BMI</td>
<td>26.9 (5.9)</td>
<td>27.3 (7.2)</td>
<td>&gt;0.05²</td>
</tr>
<tr>
<td>Uterine Size (Week)</td>
<td>15.6 (0.8)</td>
<td>15.3 (0.5)</td>
<td>&gt;0.05²</td>
</tr>
<tr>
<td>Measurement of the largest</td>
<td></td>
<td></td>
<td>&gt;0.5³</td>
</tr>
<tr>
<td>Fibroid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
As demonstrated in table (1), there was no substantial variance in basal features among the two groups.

**Table (2): Preoperative details**

<table>
<thead>
<tr>
<th></th>
<th>Cases (N=40)</th>
<th>Controls (N=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation Duration (min)</td>
<td>100.3 (20.5)</td>
<td>145.5 (13.6)</td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Estimated intra-operative blood loss (ml)</td>
<td>220.8 (45.6)</td>
<td>440.3 (58.9)</td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of removed myomas</td>
<td>6.7 (2.6)</td>
<td>6.2 (2.1)</td>
<td>&gt;0.05&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pre-operative Hemoglobin (gm%)</td>
<td>13.2 (0.8)</td>
<td>13.5 (1.1)</td>
<td>&gt;0.05&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Post-operative Hemoglobin (gm%)</td>
<td>12.6 (0.5)</td>
<td>10.6 (0.6)</td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pre-operative Hematocrit (%)</td>
<td>39.5 (0.4)</td>
<td>38.8 (0.8)</td>
<td>&gt;0.05&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Post-operative Hematocrit (%)</td>
<td>35.9 (0.6)</td>
<td>31.2 (0.3)</td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of patients needed blood transfusion</td>
<td>4 (10%)</td>
<td>16 (40%)</td>
<td>&lt;0.5&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of packed RBCs units transfused</td>
<td>2.1 (0.2)</td>
<td>3.5 (0.6)</td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Postoperative hospital stay (days)</td>
<td>1.9 (0.1)</td>
<td>3.6 (0.2)</td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Admission to Intensive care unit</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

1: Fisher’s exact test  | 3: chi square test

P > 0.05: No substantial difference.
P< 0.05: substantial difference.

P< 0.001: High substantial difference.

The length of surgery evaluated intra-operative bleeding, post-operative hemoglobin, post-operative hematocrit, number of packaged RBC units transfused, and post-operative hospital stay were all substantially differ comparing the two groups. In the number of patients who need blood transfusions, there was a substantial variation. The number of myomas excised, pre-operative hemoglobin level, and pre-operative hematocrit value, however, did not vary significantly as shown in table (2).

**Table (3): Adverse effects of methylergonovine administration**

<table>
<thead>
<tr>
<th></th>
<th>Cases (N=40)</th>
<th>Controls (N=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in blood pressure</td>
<td>5 (12.5%)</td>
<td>3 (7.5%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>7 (17.5%)</td>
<td>5 (12.5%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Difficult breathing</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

3: chi square test.

P> 0.05: No substantial difference.

There was no substantial difference regarding Adverse effects of methylergonovine administration (Changes in blood pressure, nausea and vomiting) as shown in table (3).

**Discussion**

This research found that intravenous Methylergonovine infusion dramatically decreased blood loss during laparoscopic myomectomy, resulting in fewer patients needing blood transfusions and a shorter hospital stay after surgery. Throughout myomectomy, methylergonovine infusion had no significant side
effects that required attention, such as blood pressure fluctuations, nausea and vomiting, chest discomfort, or difficulty breathing.

There was a substantial difference regarding the number of patients who needed blood transfusions. Only 4% of the case group needed blood transfusions, while 40% of the control group needed blood transfusions. According to previous findings, roughly 20–30% of patients having myomectomy needed blood transfusions. (15; 16).

The effect of methylergonovine on uterine contractility in a non-pregnant uterus was previously studied in an observational study comparing the pharmacokinetics and pharmacodynamics features of oral versus intravenous methylergometrine on uterine motility throughout menstruation, which discovered that after intravenous infusion, a rapid increase in the frequency and basal tone of uterine contractions took place with a decrease in their amplitude, which lasted (17).

There was no substantial variance regarding the number of removed myomas. However, Asgari et al., 2021 (16) reported a highly substantial variance between the two included groups. According to randomization, there must be no difference in the myomas that need to be removed.

Operative duration mean reached up to 145.5 minutes in control groups. Similar data were found in Asgari et al., 2021 (16), where it reached up to 140 minutes. In our clinical trial, there was no substantial variance in complication occurrence. The same was reported by Dawood et al. (2018). (18)

There was no substantial variance regarding hemoglobin level preoperatively; however, postoperative hemoglobin level showed a substantial variance between the two groups. The same was reported by (Podzolkova et al., 2020) (19).
Most similar study was conducted by Frass et al., 2019 (20) utilizing ergometrine and concluded that, the median loss of blood during surgery was 110.8±68.9 ml for the Ergometrine treated group and 490.6 ± 86.4 ml for the control group (P<0.001). Similar to our study as we reported Estimated intra-operative blood loss men to be 220 in Methylergonovine group with SD of 45.6 ml and it reached up to 440.3 ml with SD of 58.9 in controls (P<0.001).

Seven patients (17.9%) in the control group required intraoperative blood transfusions. In the control group, 7 patients (17.9%) required intraoperative blood transfusion. our study differ with their results as 10% of cases group needed blood transfusion and 40% of controls needed blood transfusion.

The median decline of hemoglobin level was 1 ± 0.237 for the treated group vs 1.9 ± 0.397 for the control group. The median decline of hemoglobin level was similar in treated group in our study however it was much more in controls as it reached mean of 3 with SD of 0.5 gm%.

The Ergometrine group’s postoperative hospital stay was 2.7 ±1.1 days, whereas the control group was 4.1 ± 1.3 days (P <0.001). The duration of post-operative hospital stay in our research was shorter in the treated group, with a median of just 1.9 days and an SD of 0.1. In addition, there was a substantial variance in postoperative hospital stay between the two groups (P <0.001).

Only 3/40 (7.5%) of patients in the experimental group needed blood transfusion, compared to 12/42 (28.6%) in the control group, similar to our results in Dawood et al., (21) research on abdominal myomectomy. They found that infusing Methylergonovine during abdominal myomectomy decreased bleeding and the requirement for blood transfusions considerably. According to previous research, roughly 20-30% of patients having myomectomy needed blood transfusions. (22; 23).

Misoprostol, bupivacaine plus epinephrine, tranexamic acid, gelatin-thrombin matrix, a peri-cervical tourniquet, vitamin c, dinoprostone, loop ligation, and a fibrin sealant patch were found to decrease loss
of blood during myomectomy in a previous Cochrane review, while oxytocin, morcellation, and temporary clipping of the uterine (24). Although previously debunked by a Cochrane review, the use of intravenous oxytocin infusions to reduce bleeding in laparoscopic myomectomy has been thoroughly investigated in recent years with proven effectiveness. (25; 26).

**Conclusion:** During laparoscopic myomectomy, methylergonovine infusion greatly decreased loss of blood and the requirement for blood transfusion.
References


