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# Vaginal Misoprostol versus Bilateral Uterine Artery Ligation in Decreasing Blood Loss in Trans-Abdominal Myomectomy: A Randomized Controlled Trial

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## ABSTRACT

**Background:** Uterine leimyomas are tumors of the smooth muscles and the connective tissues of the uterus. They are considered to be the most common benign pelvic tumor affecting about 20% of women above the age of 35. The diverse symptomatology of fibroids can be attributed to size, number and location of the tumors. The common symptoms include menorrhagia, infertility, abdominal mass and pressure effects. **Aim of the Work:** The aim of this study is to compare between the effect of medical (preoperative vaginal misoprostol) and non-medical (bilateral uterine artery ligation) regarding their efficacy to decrease blood loss in trans- abdominal myomectomy. **Patients and Methods:** Prospective randomized controlled interventional clinical trial. The study was conducted in Ain Shams University Maternity Hospital, Cairo, Egypt in the period between August 2015 till December 2016. It was approved by the Ethical Research Committee, Obstetrics and Gynecology Department, Ain Shams University, Cairo, Egypt. It included 60 women recruited from those attending the outpatient gynecology clinic, seeking treatment for symptomatic uterine myomas. **Results:** The current study revealed that there was no statistically significant difference between both groups regarding operative time, blood loss and postoperative hospital stay.

**Conclusion:** A single pre-operative dose of 400 micrograms of vaginal misoprostol is as effective as uterine artery ligation in decreasing blood loss in transabdominal myomectomy. Misoprostol is a simple, cheap, fast, available and applicable tool that can be administered even an hour preoperatively. **Recommendations:** Preoperative vaginal misoprostol is an effective practical tool in decreasing blood loss in transabdominal myomectomy. Investigation of misoprostol use in larger population groups and with different dosages and administration routes, together with comparison of other methods used to reduce bleeding during myomectomy, is recommended.

**Key words:** uterine leimyoma, smooth muscles, connective tissues, vaginal misoprostol, bilateral uterine artery ligation, blood loss, transabdominal myomectomy.

## INTRODUCTION

Uterine leiomyomas are tumors of the myometrium that have a prevalence as high as 70% to 80% at the age of 50 [(1)], the etiology and prevalence seem to vary with a number of factors including age, race, and possibly geographic location. Prevalence in the United States is almost 40% in white patients and more than 60% in women of African descent in the same age group [(2)]. Leiomyomas are listed as the diagnosis for about 39% of the approximately 600,000 hysterectomies performed each year in the United States [(3)].

These benign tumors, are usually asymptomatic, and may be only detectable through ultrasound examination, or associated with a number of clinical issues including abnormal uterine bleeding (AUB) especially heavy menstrual bleeding (HMB), infertility, recurrent pregnancy loss, and complaints related to the impact of the enlarged uterus on adjacent structures in the pelvis, which are often referred to as ‘‘bulk’’ symptoms. It is generally perceived that the symptoms of HMB, infertility, and recurrent pregnancy loss largely occur as a result of lesions that distort the endometrial cavity that are therefore adjacent to the endometrium and consequently referred to as submucous leiomyomas[(3)].

Treatment options for leiomyoma vary; treatment strategies are typically individualized based on the severity of the symptoms, the size and location of the leiomyoma lesions, the patient’s age and their chronological proximity to menopause, and the patient’s desire for future fertility. The usual goal of therapy is the relief of the symptoms. The treatment options range from the use of acupuncture (ancient Chinese method) to the total removal of the uterus and its myoma contents (hysterectomy) [(4)].

Treatment of fibroids should be individualized, and symptomatology may be a decisive factor in whether or not a fibroid is removed. Myomectomy remains the gold standard for treatment for patients who wish to preserve their uteri and desire future pregnancy. The procedure can be accomplished by either



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laparotomy (through an incision into the abdomen) or laparoscopically[5].

The presence of leiomyomas in the uterus distorts normal vascular architecture, thus, the arcuate arteries may run in any axis, rather than transversely, therefore, either vertical or transverse incisions during myomectomy may transect these vessels and increase blood loss during the procedure [6].

Many interventions have been performed to reduce bleeding during myomectomy. According to Kongnyuy and Wiysonge[7] four categories of interventions can be identified:

- *Interventions on uterine arteries:* such as uterine artery embolization [8], pericervical mechanical tourniquet [9], vasopressin (natural or synthetic) [10,11], a vasoconstrictive solution of bupivacaine plus epinephrine [12]and bilateral uterine artery ligation [13].
- *Utero-tonics:* such as oxytocin [14] and misoprostol [15].
- *Myoma dissection techniques:* which include fibroid enucleation by morcellation[16] and the use of chemical dissectors such as sodium-2-mercaptoethane sulphonate (mesna) [17].
- Pharmacologic *manipulation of the coagulation cascade:* with antifibrinolytic agents such as tranexamic acid [18] and gelatin-thrombin haemostatic sealant [19].

**Aim of the Work**

The aim of the current study is to compare between the effect of medical (preoperative vaginal misoprostol) and non-medical (bilateral uterine artery ligation) regarding their efficacy to decrease blood loss in trans- abdominal myomectomy.

## PATIENTS AND METHODS

### *Study Design*

Prospective randomized controlled interventional clinical trial.

The study was conducted in Ain Shams University Maternity Hospital, Cairo, Egypt in the period between August 2015 till December 2016. It was approved by the Ethical Research Committee, Obstetrics and Gynecology Department, Ain Shams University, Cairo, Egypt.

It included 60 women recruited from those attending the outpatient gynecology clinic, seeking treatment for symptomatic uterine myomas.

### *Inclusion criteria*

- Age (20 - 40) years.
- A total number of ≤ 5 symptomatic uterine myomas, presented with either:
  - Abnormal uterine bleeding (menorrhagia and/or metrorrhagia).
  - Pain (dull aching lower abdominal pain and/or dysmenorrhea).
  - Pressure symptoms (dysparunia, dysuria, dyschazia and/or backache).
  - Progressive abdominal enlargement (abdominal swelling).
- All myomas were classified as subserous or intramural by ultrasound, whereas the maximum diameter of the largest fibroid was >4cm and <10 cm.

### *Exclusion criteria*

- Virgin patients.
- Obesity (BMI >30 kg/m$^2$).
- Patients with positive pregnancy test.
- Patients who received pre-operative hormonal therapy (such as a GnRH analogue).
- Patients known to be allergic to prostaglandin preparations.
- Cardiac, pulmonary, endocrine or hematological disease (including anemia; hemoglobin level < 10 gm/dl).
- Patients diagnosed as having submucous, cervical, supracervical, broad ligamentray and pedunculated myomas.
- Patients presented by or with suspected malignant gynecological disease.
- Any associated pelvic pathology other than uterine myomas.
- Patients with contraindication to general anaethesia.

After enrollment, an informed written consent was taken from all participants before recruitment in the study, and after explaining the purpose, possible risks and complications of different study procedures (including possibility of blood transfusion and the possible need for hysterectomy).

**Prior to surgery all included women were subjected to the following:**

- History taking with particular emphasis on past medical, surgical and menstrual history.
- Examination:
  - 1. General examination:
    - The patient's general condition (e.g. chronic fatigue may be present in anemic patients).
    - Body mass index (BMI) measured in kg/m$^2$.
    - Vital colors: Color of complexion and mucous membranes of lips and conjunctiva (e.g. Pallor may be present in anemic patients).

- Presence of orthopnea (mechanical effect of large fibroids) or dyspnea (as a symptom of anemia).
- Vital data: Measuring of peripheral pulse and arterial blood pressure.
- 2. Abdominal examination:
- *Inspection* of abdominal enlargement, scars of previous operations and presence of stretch marks.
- *Palpation* of the abdomen.
- 3. Local examination: using Cusco speculum, PV examination and bimanual examination.
- 2D Ultrasonography was carried out using trans-abdominal and trans-vaginal probe of Sonoace R5® device by Samsung Medison to confirm the exact site, size and number of uterine fibroids and to exclude any associated pelvic pathology.
- Venous blood samples for the assessment of Hemoglobin (Hb) and hematocrit levels were withdrawn before the operation for each case.
- Other venous blood samples were withdrawn for the assessment of kidney functions (serum creatinine level), liver functions (ALT), coagulation profile (PT, PTT, INR) and viral markers (HBVs Ag and HCV antibody), as a part of anaesthetic workup.

**Methods of randomization:**

To ensure that every patient who fulfilled the inclusion criteria had the chance of participation, randomization was guided by table of random numbers using a computer based program (www.randomization.com).

**Allocation concealment:**

Sixty sequentially numbered, opaque, sealed envelopes were used, each envelope carried a number, and each envelope enclosed a paper with a letter (A or B) whereas:

- Letter A represents the misoprostol group.
- Letter B represents the bilateral uterine artery ligation.

One day before the operation each patient randomly picked an envelope carrying a number, so that patients were not aware of the assignment (single blind technique), and the procedure used to decrease blood loss during the operation was applied according to the letter enclosed (A or B) guided by the computer based randomization table.

The patients were randomly assigned to one of the two parallel groups:

- **Group A:** patients received 400 microgram prostaglandin E2 analogue misoprostol (2 tablets of Misotac® by SIGMA pharmaceutical industries, Alexandria, Egypt) in posterior vaginal fornix, using a lubricant K-Y jel, 1 hour before the surgery [(15)]and the patient was asked to stay in bed for 30 minutes after insertion of the vaginal misoprostol.
- **Group B:** bilateral ascending uterine artery ligation was performed (without cutting) at the level of uterine isthmus with 2/0 vicryl suture (Egysorb®). The uterus was pulled up, so as the thumb was placed anteriorly and the rest of the fingers posteriorly, to expose the lower part of the broad ligament. In this technique, a large curved round needle sized 40mm, ½ curved with a No. 2/0 vicryl suture was directed from anterior to posterior through the myometrium, approximately 1 to 2 cm medial to the broad ligament. The suture then was directed posterior to anterior through an avascular space in the broad ligament, close to the lateral border of the uterus, and was tied. This suture was done bilaterally [(20)].

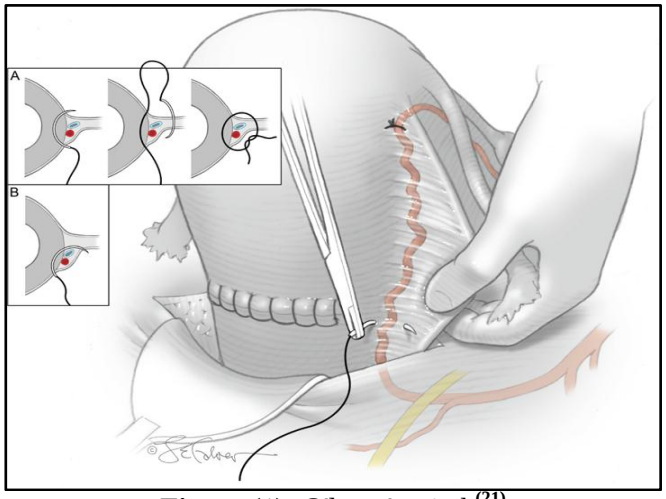


**Figure (**1**):** O'leary's stitch[(21)]

**Steps of the procedure:**

**1. General anaesthesia:**

- $O_2$ mask followed by inhalational anesthesia (Isoflurane®).
- Intravenous anesthetics:
  - Induction of anesthesia (Intraval®).
  - Muscle relaxant (Trachium®) (intubating dose).
  - Analgesics (Fentanyl®or Morphine ®).
- Endotracheal intubation (using a tube of appropriate size).

**2. Pre anesthetic medication:**

- Antibiotic prophylaxis was given as a single dose of intravenous 1st generation cephalosporins (Cefazoline®) 2gm taken 30 to 60 minutes before skin incision and the dose was repeated if the operation lasted for more than 3 hours or blood loss was more than 1500 cc[(22)].
- Cephalosporins were replaced by Ampicillin/Sulbactam in case of cephalosporin hypersensitivity [(23)].

**3. Surgical procedure:**

- Patients were placed in dorsal lithotomy position followed by urinary catheterization - after general anaesthesia- surgical sterilization and toweling.
- Trans-abdominal myomectomy was performed by the same team of skilled lecturers in obstetrics and gynecology in all patients (to avoid any bias related to surgical skills) according to the standard technique through transverse lower abdominal incision (Pfannensteil incision). Surgical techniques which reduce intra-operative blood loss were applied as much as possible as follows: (uterine incision) [(24)].
  - Midline vertical anterior incisions.
  - All myomas were enucleated through a single incision.
  - New incisions were not opened except after closing the old ones.
- Post-operative venous blood samples of hemoglobin and hematocrit levels were withdrawn from patients after 24 hours to avoid wrong results due to hemodilution by intravenous fluids in the first 24 hours.
- Linen towels used in the operation were weighed (in grams) before the procedure using a highly accurate digital balance.
- After the operation, the linen towels (which were used in drying blood from the operative field after opening of the rectus sheath) were re-weighed using the same balance, and the difference in weight between dry and soaked linen towels was calculated.
- Blood loss collected by the suction bottle was equal to the difference in weight between clean empty and full suction bottle container using the same digital balance in grams.
- The digital balance was calibrated daily and before each measurement, and weighing the used towels and suction bottle container was done twice in the same setting and the average of the two measurements was taken; so as to minimize possible errors.
- The used towels and suction bottle container were weighed as soon as possible after contamination with blood so that the loss by evaporation was minimized.
- Peritoneal irrigation with warm saline during or after the operation or the use of saline wet towels was avoided so as not to change in the weight of the used towels.

**Therefore; blood loss during the operation was calculated as follows:**

1. Difference in weight of suction bottle containers (in grams) **(A)** (weight of full suction bottle container - weight of empty suction bottle container).
2. Difference in weight of linen towels (in grams) **(B)** (weight of soaked linen towels - weight of dry linen towels).

**So blood loss during operation (gm) = (A + B)**

- All the patients received non-steroidal anti-inflammatory preparation in the form of (Diclofenac sodium®) 75mg IM (one ampoule) (Produced by: NOVARTIS PHARMA S.A.E. Cairo, under license from: Novartis Pharma AG, Basle, Switzerland)immediately postoperative then one ampoule 12 hours postoperative.
- The patients were followed up in the ward, their vital data and post-surgical complications (if present) were recorded till being discharged from hospital.
- **Primary outcome**:
  - Estimated intra-operative blood loss measured in milliliters.
- **Secondary outcomes:**
  - *The need for intra-operative blood transfusion:*

(It was indicated when intra-operative blood loss exceeds 15% of the patient's estimated blood volume, which is equal to the patient's weight in ilograms multiplied by 10) [(25)]**.** Blood transfusion was guided by measuring allowable blood loss [(26)].

- *The need for conversion from myomectomy to hysterectomy:*

(It was indicated when there was uncontrolled intra-operative hemorrhage affecting the patient's vital signs and not responsive to conservative measures, or when it was impossible to reconstruct the uterus because of the many defects left by the removal of multiple fibroids).

- *Intra-operative or post-operative complications:*

(E.g. Bladder injury, hematoma formation, post-operative fever; temperature >38°C within 24 hours after surgery).

- *Operative time measured in minutes:*

(It was measured from the start of skin incision till skin closure).

- *Difference between Pre and post-operative hemoglobin and hematocrit levels:*

(Postoperative hemoglobin and hematocrit levels were measured 24 hours after the operation via a venous blood sample).

- *Duration of hospital stay in days:*

(Decision of discharging the patient from hospital was taken by the surgeon who performed the operation based on patient's wellbeing, i.e. easy ambulation, absence of anemia clinically and by measuring hemoglobin level, bowel motility and presence of clean and dry wound).

- Shifting from applying method of decreasing blood loss intra-operatively to another alternative method, addition of another method and (or) conversion from myomectomy to hysterectomy was justified and explained by the senior surgeon.

***Elimination of bias***

- Laboratory samples were done in the same laboratory preoperative and postoperative.
- All the towels used in the operation were similar in material, and almost of same size and weight.
- All suction bottles used in the operation were of the same trade mark and their containers were equal in weight.
- The scale used in weighing the used towels preoperative and postoperative was the same and was calibrated before use in each time.
- Weighing towels and suction bottle containers were done by the same person.

The study was done after approval of ethical board of Al-Azhar university and an informed written consent was taken from each participant in the study.

**RESULTS**

The mean *age* of study population was 35.35 years, with range (20–40); whereas 42 patients (70%) were ≥35 years old and 18 patients (30%) were <35 years old.

The mean *BMI* of the study population was 28.35 kg/m$^2$, with range (23–30); whereas the BMI of 55 patients (91.7%) was ≥ 26 kg/m$^2$, and 5 patients (8.3%) with a BMI <26 kg/m$^2$.

22 patients (36.7%) were of a *dark race* (born or live in Upper Egypt or other African countries), and 38 patients (63.3%) were not of a dark race.

**Table (1):** Age, body mass index (BMI) and race among the study population*:*

| | | **Number (total = 60)** | **%** |
|---|---|---|---|
| **Age (yrs) (range)**<br>**Mean ± SD** | | 20 – 40<br>35.35 ± 4.87 | |
| < 35 yrs | | 18 | 30% |
| ≥ 35 yrs | | 42 | 70% |
| **BMI (kg/m$^2$) (range)**<br>**Mean ± SD** | | 23 – 30<br>28.35 ± 1.81 | |
| < 26kg/m$^2$ | | 5 | 8.3% |
| ≥ 26 kg/m$^2$ | | 55 | 91.7% |
| **Dark Race** | **No** | 38 | 63.3% |
| | **Yes** | 22 | 36.7% |

In the current study, 48 patients (80%) were nonsmokers and 12 (20%) patients were smokers, 46 patients (76.7%) didn't use COC as hormonal contraception and 14 patients (23.3%) were COC users and 25 patients (41.7%) didn't conceive before and 35 patients (58.3%) conceived before.

**Table (2): Smoking, use of COC as hormonal contraception and gravidity in the study population:**

| | | N | % |
|---|---|---|---|
| **Smoking** | **No** | 48 | 80.0% |
| | **Yes** | 12 | 20.0% |
| **COC use as hormonal contraception** | **No** | 46 | 76.7% |
| | **Yes** | 14 | 23.3% |
| **Gravidity** | **No** | 25 | 41.7% |
| | **Yes** | 35 | 58.3% |

As regard the *myoma site*, 43 patients (71.7%) had interstitial uterine myoma, 12 patients (20%) were presented by subserous uterine myoma and 5 patients (8.3%) had mixed uterine myomas.

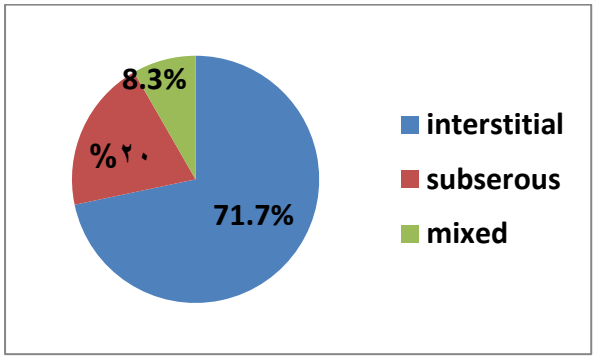


**Figure (2):**Myoma site among study population

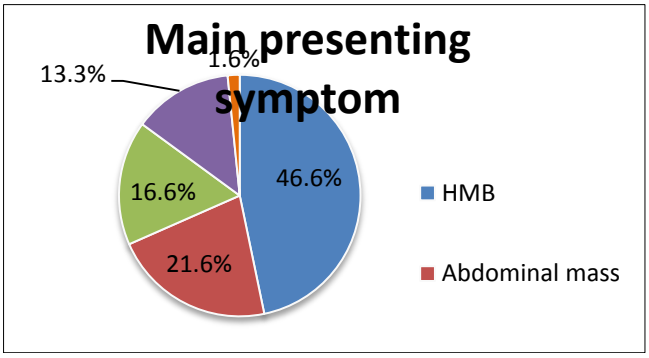


**Figure (3):** The main presenting symptom among the study population

*The main presenting symptom* in the study population was heavy menstrual bleeding (HMB) in 28 patients (46.6%), abdominal mass in 13 patients (21.6%), abdominal pain in 10 patients (16.6%), primary or secondary infertility in 8 patients (13.3%) and pressure symptoms in only 1 patient (1.6%) (**figure 3**).

The results showed that there was no significant difference between both groups regarding *hemoglobin level, hematocrit level, towels' weight and suction bottle weight pre and postoperative* (**table 3**).

**Table (3):** Comparison between both groups regarding hemoglobin level, hematocrit level, Towels' weight and suction bottle weight pre and postoperative:

| | | BilatUt. A. ligation | | Vaginal Misoprostol | | t test | |
|---|---|---|---|---|---|---|---|
| | | Mean/Median | SD/IQR | Mean/Median | SD/IQR | p value | sig. |
| **HB (gm/dl)** | **Preoperative** | 11.35 | 0.89 | 11.32 | 1.10 | 0.918 | NS |
| | **Postoperative** | 9.75 | 1.26 | 9.89 | 1.34 | 0.678 | NS |
| | **% of change** | 14.00 | 9.45 | 12.65 | 8.59 | 0.565 | NS |
| **HCT (%)** | **Preoperative** | 34.22 | 2.55 | 34.37 | 2.80 | 0.836 | NS |
| | **Postoperative** | 30.21 | 3.49 | 30.74 | 3.66 | 0.571 | NS |
| | **% of change** | 71.50 | 3.04 | 71.22 | 3.12 | 0.724 | NS |
| **Towels' Weight (gm)** | **Preoperative** | 333.30 | 4.07 | 334.20 | 4.56 | 0.423 | NS |
| | **Postoperative** | 591.67 | 186.31 | 614.40 | 312.07 | 0.733 | NS |
| | **Change** | 176.5 ■ | 118-409 ▲ | 133 ■ | 109-405 ▲ | 0.344* | NS |
| **Suction Bottle weight (gm)** | **Preoperative** | 663.00 | 2.45 | 662.80 | 3.06 | 0.781 | NS |
| | **Postoperative** | 843.07 | 163.15 | 830.00 | 170.83 | 0.763 | NS |
| | **Change** | 141■ | 26-79 ▲ | 107 ■ | 69-140 ▲ | 0.416* | NS |

NS= non-significant, * Mann-Whitney test, **■ Median, ▲ IQR (Interquartile range)**

The results showed that there was no significant difference between both groups regarding *blood loss,operative time* and *postoperative hospital stay* (table 4) and (figures 4,5,6).

**Among the bilateral uterine artery ligation group:**

The intraoperative *blood loss* in 21 patients was ≤ 500 mL, while it exceeded 500 mL in the rest of patients; the maximum blood loss was in 2 patients; 1353 mL & 1256 mL due to excision of 4 interistial myomas & occurrence of broad ligamentary hematoma respectively and both patients received 2 units of packed RBCs.

As for the *operative time*, the operation lasted for ≤ 80 min in 20 patients, and it exceeded 80 min in the rest of the patients; 2 patients had the longest operative time; 120 min and 155 min due to occurrence of broad ligamentary hematoma and urinary bladder injury (in a para 4 c.s. patient) respectively.

Regarding the *postoperative hospital stay*, 23 patients were discharged after 1 day postoperatively, while only 7 patients were discharged after a period more than 1 day (the longest duration was 4 days in one patient who was complicated by urinary bladder injury).

**Among the vaginal misoprostol group:**

The intraoperative *blood loss* in 22 patients was ≤ 500 mL, while it exceeded 500 mL in the rest of patients; the maximum blood loss was in 3 patients; 1649 mL, 1618 mL & 1228 mL due to excision of 5 mixed non adjacent myomas of different sizes with 2 uterine incisions, 3 interstitial myomas (in a para 3 c.s. patient with extensive adhesions) & one huge interstitial myoma measuring 10 x10 cm respectively. The first patient received 4 units of packed RBCs.

As for the *operative time*, in 25 patients the operation lasted for ≤ 80 min and it exceeded 80 min in the rest of the patients; the longest operative duration was in 1 patient which lasted for 180 min due to excision of 5 mixed non adjacent myomas.

Regarding the *postoperative hospital stay*, 22 patients were discharged after 1 day postoperatively, while only 8 patients were discharged after a period more than 1 day; the longest was 5 days in 2 patients. The 1st patient had delayed bowel motility & received 4 units of packed RBCs while the 2nd patient was complicated by wound seroma & needed frequent wound dressing.

**Table (4): Comparison between both groups regarding blood loss, operative time and postoperative hospital stay:**

| | Bilat Ut. A. ligation | | Vaginal Misoprostol | | t-test | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p value | sig. |
| **Blood Loss (ml)** | 438.43 | 124.79 | 447.40 | 133.32 | 0.928 | NS |
| **Operative time (min)** | 81.33 | 21.09 | 80.83 | 24.25 | 0.932 | NS |
| **Postoperative Hospital stay (days)** | 1.43 | 0.82 | 1.50 | 1.07 | 0.788 | NS |

NS= non-significant.

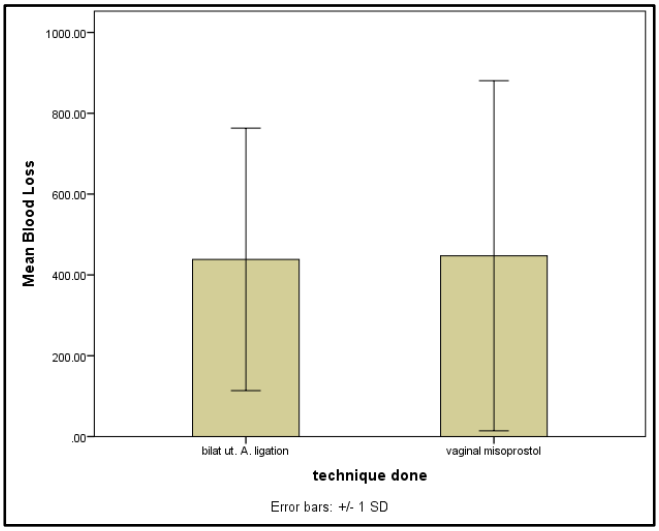


**Figure (4):** Comparison between both groups regarding mean blood loss.

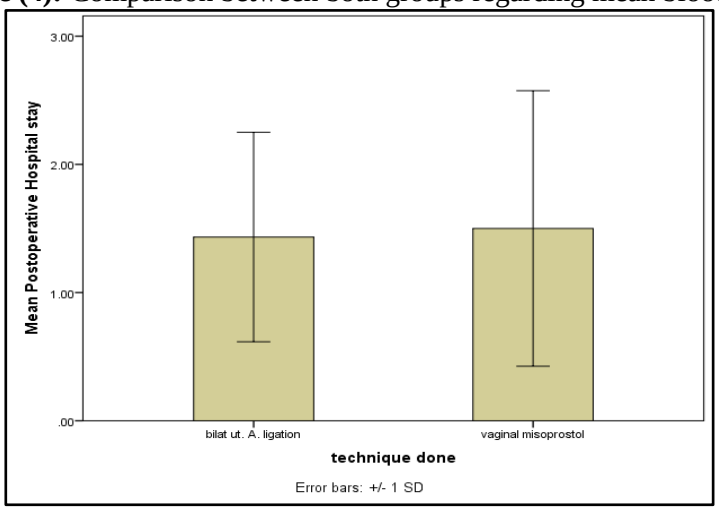


**Figure (5):** Comparison between both groups regarding mean post-operative hospital stay.

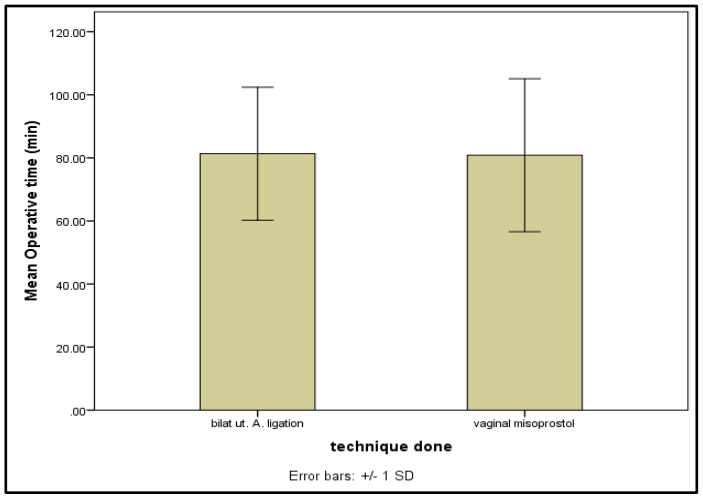


**Figure (6):** Comparison between both groups regarding mean operative time.

The results showed that there was no significant difference between the two groups regarding intra and postoperative blood transfusion, postoperative parentral iron transfusion, postoperative wound infection, postoperative nausea and vomiting, postoperative fever and other complications.

Other postoperative complications included *postoperative wound infection (seroma)* in only 1 patient and was in the misoprostol group, *delayed bowel motility* in 3 patients, and were all in the vaginal misoprostol group, *urinary bladder injury* in 1 patient and was in the bilateral uterine A. ligation group, *broad ligamentary hematoma* in only 1 patient (managed conservatively) and was in the bilateral uterine A. ligation group and no patients needed *conversion from myomectomy to hysterectomy* (table 5) and (figure 7).

**Table (5): Comparison between both groups regarding intra and postoperative complications:**

| | | BilatUt. A. ligation | | Vaginal Misoprostol | | Chi square | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | value | sig. |
| **Intra or Post-operative blood transfusion** | **No** | 23 | 76.7% | 27 | 90.0% | 0.166 | NS |
| | **Yes** | 7 | 23.3% | 3 | 10.0% | | |
| **Postoperative parentral iron transfusion** | **No** | 25 | 83.3% | 29 | 96.7% | 0.195 | NS |
| | **Yes** | 5 | 16.7% | 1 | 3.3% | | |
| **Postoperative wound infection** | **No** | 30 | 100 % | 29 | 96.7% | 1 | NS |
| | **Yes** | 0 | 0% | 1 | 3.3% | | |
| **Postoperative nausea and vomiting** | **No** | 18 | 60 % | 17 | 58.6% | 0.914 | NS |
| | **Yes** | 12 | 40% | 12 | 41.4% | | |
| **Postoperative fever** | **No** | 21 | 70% | 18 | 60.0% | 0.417 | NS |
| | **Yes** | 9 | 30% | 12 | 40.0% | | |
| **Other Postoperative complications** | **No** | 28 | 93% | 26 | 86.7% | 0.671 | NS |
| | **Yes** | 2 | 6.7% | 4 | 13.3% | | |

NS= non-significant.

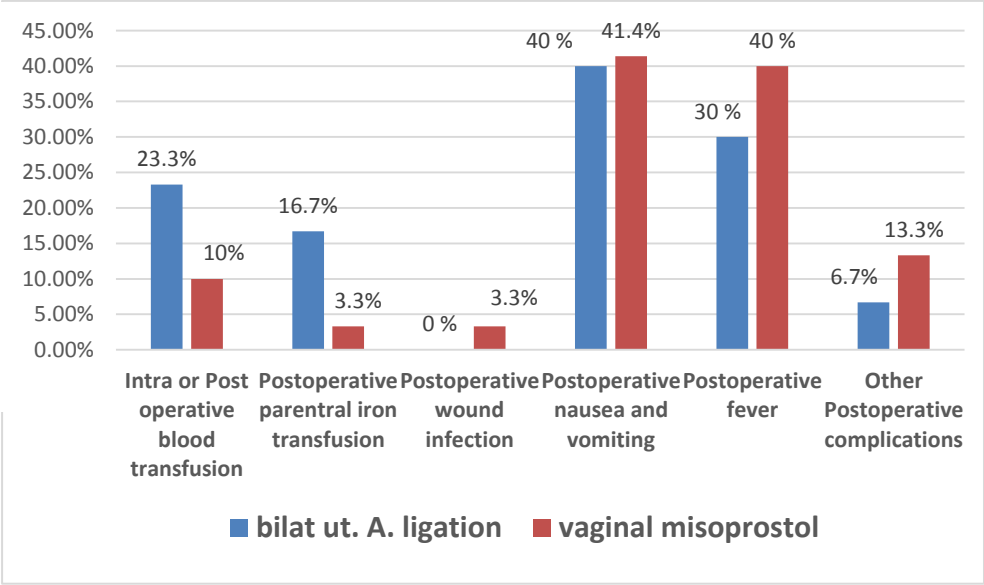


**Figure (7):** Comparison between both groups regarding intra and postoperative complications.

## DISCUSSION

The *primary outcome* of this study was to compare the intraoperative blood loss in the two groups (vaginal misoprostol versus bilateral uterine artery ligation group). Other *secondary outcomes* were also compared including: the need for intraoperative blood transfusion, the need for conversion from myomectomy to hysterectomy, operative time in minutes, intraoperative and postoperative complications, difference between pre and post-operative hemoglobin and hematocrit levels and duration of hospital stay in days.

Till the time being there were no studies comparing the use of vaginal misoprostol versus bilateral uterine artery ligation in decreasing blood loss in trans- abdominal myomectomy, yet there are studies comparing the use of vaginal misoprostol versus placebo [15,27,28], rectal misoprostol versus placebo [29], single versus double dose misoprostol [30], uterine artery ligation during abdominal myomectomy versus traditional myomectomy (without uterine artery ligation or occlusion) [31] and uterine artery ligation versus pericervical mechanical tourniquet [32].

In the current study the mean intraoperative blood loss in the misoprostol group was 447.40 ml ± 433.32 and 438.43 ml ± 324.79 in the bilateral uterine artery ligation group. There was no statistically significant difference between both groups regarding estimated intraoperative blood loss. However, in other studies there was statistically significant difference in blood loss when misoprostol was used versus placebo, or when bilateral uterine arteries were ligated intraoperatively versus non ligation.

In a study by Iavazzo *et al*.[27], 284 patients undergoing abdominal myomectomy were included in the study, where 142 patients received 400 microgram misoprostol vaginally and the other 142 patients received a vaginal placebo tablet. The mean estimated blood loss was 347.5 mL in the misoprostol group, while at the placebo group was 539.3 mL, and this agrees with the present study and makes misoprostol an effective tool to decrease blood loss intraoperatively. Similar results were reported in other studies [28,30].

In another study by Abdel-Hafeez[29], 50 women undergoing abdominal myomectomy for symptomatic uterine leiomyomas were randomly assigned to receive a single dose of pre-operative of rectal 400 micrograms misoprostol (n = 25) or placebo (n = 25) 1 h before the operation. The primary outcome was intraoperative blood loss. Intra-operative blood loss was significantly lower in those women randomized to receive rectal misoprostol versus the placebo group (574±194.8 mL vs. 874±171.5 mL), which match the results of the current study.

This observation is in accord with the results of study reported by Celik and Sapmaz[15] in which 25 women underwent abdominal myomectomy, 13 in the study group were given a single dose 400 micrograms of vaginal misoprostol, and 12 patients in the control group were given placebo. Misoprostol led to reduction in blood loss of 149 mL in the study group. This finding is also consistent with that of Kalogiannidis et al.,[33] in which 67 menstruating women with three or less myomas of a maximum diameter of 90 mm, scheduled for minimally invasive (laparoscopic) myomectomy. The average blood loss was significantly higher in the placebo group (217±74 mL) versus misoprostol group (126±41 mL). Misoprostol led to a reduction in blood loss of 91 mL. Blood loss was much lower in both the study and control group of Kalogiannidis *et al*.[33]than the present study, possibly due to laparoscopic approach of the procedure.

In a study by Saeed Al borzi *et al*.[34], 152 women with symptomatic uterine myomas necessitating surgical intervention who wished to retain their uteri were enrolled in the study, where 65 underwent laparoscopic uterine artery ligation and myomectomy (experimental group) and 87 received laparoscopic myomectomy only (control group). The average operating time and blood loss were 112 ± 18 minutes and 173 ± 91 mL for the experimental group and 95 ± 14 minutes and 402 ± 131 mL for the control group, respectively (statistically significant). Similar results were achieved by Liu et al.,[35]. Both studies agree with the results of the present study except that blood loss in laparoscopic approach was much less than the abdominal approach.

However, in a study by Ji Hae Bae *et al*.[31], 51 patients (56.6%) underwent laparoscopic myomectomy with uterine artery ligation (group A), and 39 patients (43.3%) underwent laparoscopic myomectomy alone (group B), there was no significant difference between the two groups with respect to

intraoperative blood loss, which matches the results of the present study.

In a study by Adel Saad Helal *et al.*[32] a total of 103 patients undergoing myomectomy were randomly allocated to undergo preliminary uterine artery ligation (52 patients) or pericervical tourniquet (51 patients). The primary outcome measure was estimated blood loss. Operative blood loss was significantly less with uterine artery ligation compared with tourniquet (433.80 ± 285.21 vs. 823.23 ± 237.33 mL, P 0.001). This result is in agreement with other studies [35,36,37], which have reported the benefit of uterine artery ligation in reducing blood loss during myomectomy. Other studies by Celik and Sapmaz[15] have reported that bilateral ascending uterine artery ligation and tourniquet have a similar outcome for intraoperative blood loss in abdominal myomectomy.

In the current study, the mean operative time in the misoprostol group was 80.83 min and 81.33 min in the bilateral uterine A. ligation group. There was no statistically significant difference between both groups regarding operative time.

In the study of Iavazzo *et al.*[27],there was no statistically significant difference regarding operative time between the use of vaginal misoprostol and vaginal suppository placebo. The mean difference was 6.24 min per operation [95 % confidence intervals (CI) which agrees with the results of the current study.

In a study by Ji Hae Bae *et al.*[31]**,** the mean operating time was 100.0 ± 33.8 minutes in the uterine artery ligation group and 90.0 ± 37.1 minutes in the traditional myomectomy group, which makes uterine artery ligation more time consuming. Similar findings were reported by Saeed Al borzi *et al.* [34]**.**

In the current study, the mean postoperative hospital stay in the misoprostol group was 1.5 days versus 1.43 days in the ligation group; there was no statistically significant difference between both groups regarding postoperative hospital stay.

Abdel-Hafeez *et al.* [29], reported that there was no statistically significant difference between the misoprostol group and the placebo group regarding postoperative hospital stay (3.33±0.49 in both groups)**.** Similar findings were documented by ***Ragab et al.*** [30]. These results agree with the current study.

In the current study, 10 patients required blood transfusion (16.7%); whereas 3 patients were in the misoprostol group and 7 patients were in the bilateral uterine A. ligation group, yet, no statistically significant difference between both groups was found.

In the study by Abdel-Hafeez *et al.*[29], there was no significant difference in the need for the blood transfusion between groups (misoprostol versus placebo),which matches the results of the present study. This result differs from those of Celik and Sapmaz, [15] and Shokeir et al.,[38]who found that blood transfusion was significantly greater in the control (placebo) group.

In the current study there was no statistically significant difference between both groups regarding change in pre-operative and postoperative haemoglobin and change in pre-operative and postoperative haematocrit.

The results of the current study differ from the study by Abdel-Hafeez et al. [29], in which the change in haemoglobin and haematocrit was significantly lower in the misoprostol group than the placebo group. These results are consistent with those reported by Celik and Sapmaz[15]and Kalogiannidis *et al.*[33].

Ji Hae Bae et al.,[31] reported that there were no significant differences between the two groups (ligation versus non ligation group) regarding change in pre-operative and postoperative haemoglobin and change in pre-operative and postoperative haematocrit, which match the results of the current study.

In the current study, 24 patients had postoperative nausea and vomiting (40.7%); whereas 12 patients were in the bilateral uterine A. ligation group and 12 patients were in the misoprostol group and 21 patients had postoperative fever (35%); whereas 9 patients were in the bilateral uterine A. ligation group and 12 patients were in the misoprostol group. There was no significant difference between both groups regarding postoperative nausea and vomiting and febrile morbidity.

Abdel-Hafeez *et al.* [29] reported that there was no significant difference between the two groups (misoprostol versus placebo) as regards postoperative febrile morbidity and other misoprostol side effects (e.g. diarrhea, nausea). This may be explained by the single-dose administration of misoprostol or the use of regular IV paracetamol in the first 24 hours

postoperatively which may mask the febrile episodes. Similar findings were reported by Ragab *et al.*[30]**.** Both studies agree with the results of the current study.

The most common side effects of using misoprostol include chills, nausea and vomiting, headache and vertigo, hypertension, abdominal pain, diarrhea which are not associated with either the dosage or route of administration. Usually, all these side effects were found in 90-min post administration. The ideal dosage and route of administration need to be clarified. However, it is shown that oral misoprostol reaches its peak concentration in the plasma earlier compared to vaginal route [39,40].

Ji Hae Bae *et al.*[31] and Shokeir *et al.*[38]reported that there was no difference between the two groups (ligation versus non ligation group) regarding postoperative fever and this agrees with the results of the present study.

Febrile morbidity is frequently encountered following myomectomies. The main cause of postoperative fever may have been remaining blood clots in the abdomen or hematoma formation in the myometrium [41].

In the current study, only 1 patient had postoperative wound infection (seroma), and was in the misoprostol group, 3 patients had delayed bowel motility, and were all in the vaginal misoprostol group, only 1 patient had urinary bladder injury and was in the bilateral uterine A. ligation group, only 1 patient had broad ligamentary hematoma, which was managed conservatively and was in the bilateral uterine A. ligation group and no patients needed conversion from myomectomy to hysterectomy. There was no significant difference between both groups regarding postoperative wound infection, postoperative nausea and vomiting, and other postoperative complications.

## CONCLUSION

A single pre-operative dose of 400 micrograms of vaginal misoprostol is as effective as uterine artery ligation in decreasing blood loss in transabdominal myomectomy. Misoprostol is a simple, cheap, fast, available and applicable tool that can be administered even an hour preoperatively. It is characterized by thermo and light stability and can achieve a shelf-life of several years even in tropical climate. It is independent of any blood pressure and is not related to any bronchoconstrictive action to the lungs. Misoprostol has side effects which are usually tolerable and found in 90-min post administration and are dose dependent. So, misoprostol is preferred in hospitals with low resources and non-availability of blood transfusions.

However, bilateral uterine artery ligation is also effective in decreasing blood loss intraoperatively, but needs skilled operative technique.

Therefore, the choice between application of both techniques is left to the surgeon's surgical capabilities and preference.

**Limitations:**

The current study had some limitations. *Firstly*, it was a single center study. *Secondly*, only one route of misoprostol was evaluated (vaginal route). *Thirdly*, operative time was falsely prolonged in some patients as it was measured from the start of skin incision till skin closure, and this wasn't the actual operative time; as in some patients there was waste of time in entering the abdomen (as in patients with adhesions). Therefore, operative time should have been measured after entering the peritoneal cavity till peritoneal closure. *Fourthly*, the variation range in myoma number, size and site should have been narrowed as it markedly affected the results regarding blood loss and operative time. And *finally*, increasing the sample size of the study population could have given more representative and more accurate results.

## RECOMMENDATIONS

Preoperative vaginal misoprostol is an effective practical tool in decreasing blood loss in transabdominal myomectomy. Investigation of misoprostol use in larger population groups and with different dosages and administration routes, together with comparison of other methods used to reduce bleeding during myomectomy, is recommended.

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