Original Article

# The Efficacy and Safety of Intravenous Tranexamic Acid Versus Rectal Misoprostol in Reducing Blood Loss During Abdominal Myomectomy. A Randomized Comparative Study

*Hisham Mohamed Gouda, Abdulla Hisham Muhammad Ragab and Khaled Mohamed Hussain Kholaif*

*Department of Obstetrics and Gynecology, Kasralainy, Faclty of Medicine, Cairo University, Egypt*

## ABSTRACT

**Aim:** The aim of the study is to compare the efficacy and safety of rectal Misoprostol versus IV Tranexamic acid (TXA) in reducing intraoperative blood loss during open myomectomy.

**Design:** A randomized comparative study.

**Setting:** KasrAlainy hospital Obstetrics and Gynecology department, Cairo University, Egypt, during the period from April 2021 and September 2021.

**Methods:** A total of 75 patients with uterine fibroid fulfilling the inclusion criteria were scheduled for abdominal myomectomy. Patients were randomized and allocated into one of three groups with a 1:1:1 allocation ratio. The groups were coded as A,B,C (group A for tranexamic acid ,group B for oxytocin and group C for control) (n=25 per group). In the three groups the following outcomes were reached : the estimated blood loss (EBL) during open myomectomy, need for intra and post operative blood transfusion, operative time, myomectomy time, postoperative hematocrit and hemoglobin, drop in postoperative hemoglobin , drop in hematocrit, side effects of TXA and oxytocin including and post operative stay in days.

**Interventions:** Group (A) (Tranexamic Acid group): Women received TXA as a single bolus intravenous injection of 15 mg/kg (maximum 1 g) slowly over 10 min 20 min before skin incision.

Group (B) (Misoprostol group): Women received two tablet of (200 microgram) misoprostol (Cytotec) rectally 1hr before starting of operation..

Group (C) (placebo group): Women received 500 ml saline infusion at a rate of 120 ml/h before and during the operation.

**Results:** Regarding need for intraoperative blood transfusion; statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups (no cases needed). On the other hand there was highly significant difference with control group 33 (66.0%) (p= <0.001). Also, Regarding need for postoperative blood transfusion; tranexamic acid was significantly higher than misoprostol and control groups 6 (12.0%) vs. 0 (0.0%) vs. 3 (6.0%) respectively (*p*= 0.042). Regarding intraoperative blood loss (ml); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 229.35 ± 41.05 and 225.80 ± 44.82. On the other hand there was highly significant higher intraoperative blood loss in control group 680.35 ±189.39 (*p*= <0.001). Regarding post-operative stay (days); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 1.34 ± 0.48 vs. 1.32 ± 0.47. On the other hand there was highly significant longer stay in control group 1.56 ± 0.54 (*p*= 0.030).

Regarding operation and myomectomy time (mins); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 68.50 ± 10.98 vs. 68.60 ± 10.83 and 23.38 ± 1.86 vs. 22.34 ± 1.67. On the other hand there was highly significant longer time in control group 85.70 ± 24.45 and 27.74 ± 2.93 (*p*= <0.001 and 0.001) respectively.

**Conclusion:** In women undergoing abdominal myomectomies, preoperative intravenous tranexamic acid and rectal misoprostol were very effective in reducing intraoperative blood loss, need for intra and postoperative blood transfusion, post-operative stay and operation and myomectomy time compared with placebo.

**Key Words:** Hemostasis, misoprostol, myomectomy, tranexamic acid.

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**Corresponding Author:** Hisham Mohamed Gouda, Department of Obstetrics and Gynecology, Kasralainy, Faclty of Medicine, Cairo University, Egypt, **Tel.:** +20 10906 50463, **E-mail:** hgouda183@gmail.com

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## INTRODUCTION

Uterine leiomyomas (named myomas and fibroids as well) are the most common pelvic tumor in females[1].

Short-term change in growth of uterine leiomyoma: tumor growth spurts. Fertility and sterility, 95[1], 242-246.

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The International Federation of Gynecology and Obstetrics (FIGO) classification system for fibroid location is as follow[2].

FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age.

### *Intramural myomas (FIGO types 3, 4, and 5)*

They occur within the wall of the uterus. They may expand to the point of distorting the uterine cavity or serosal surface. Transmural fibroids are those that stretch from the serosal to the mucosal surface.

### *Submucosal Myomas in the (FIGO types 0, 1, 2)*

They originate in the myometrium just beneath the endometrium (lining of the uterine cavity). The FIGO/ European Society of Hysteroscopy classification system describes the extent of protrusion of these neoplasms into the uterine cavity, which is clinically significant in predicting the hysteroscopic outcome:

- Type 0: Completely within the endometrial cavity.
- Type 1: Myometrial extension less than 50%.
- Type 2: Myometrial extension 50% or more.

### *Subserosal myomas (FIGO type 6, 7)*

These leiomyomas arise from the myometrium on the uterus serosal surface. They can have a wide or pedunculated base intraligamentary (i.e., extending between the folds of the broad ligament).

Most myomas are small and asymptomatic, these symptoms are in relation to the size, location, and the number of tumors. Myomas can be single or numerous and vary in size from microscopic to centimeters. Fibroid symptoms could be.

Prolonged or heavy menstrual bleeding, Bulk-related symptoms, such as pelvic pressure and pain, Urinary symptoms Bowel symptoms: pressure effect of fibroids on the rectum can result in constipation , Painful menstruation: women with uterine fibroids may have dyspareunia and non-cyclic pelvic discomfort more frequently , Painful intercourse , Fibroid torsion , Infertility or obstetric complications[3-7].

Management includes expectant therapy, medical therapy (hemostatics, hormonal therapy, and analgesia), and surgical intervention ( myomectomy and hysterectomy).

There are various pharmacological and non-pharmacological methods that have been tested to control hemorrhage during myomectomy. At present, there is moderate-quality evidence that tranexamic acid and misoprostol may reduce bleeding during myomectomy.

Myomectomy is a surgical procedure that has the potential to result in severe bleeding. Tranexamic acid (TXA), a synthetic lysine-analog antifibrinolytic, was first patented in 1957, and its use has been increasing in contrast to aprotinin, a serine protease inhibitor antifibrinolytic.

Evaluated the efficacy of tranexamic acid (TXA) in decreasing blood loss during and after open myomectomy and concluded that TXA reduced blood loss during and after myomectomy[8].

Uterotonics such as misoprostol and ergometrine, cause myometrial contraction and therefore will decrease blood loss during myomectomy leading to better anatomical reconstruction of the uterus.

## AIM OF THE WORK

### *Primary outcomes*

Comparative efficacy of ontravenous Misoprostol versus Tranexamic acid in:

- Intraoperative blood loss.
- Difference between hemoglobin and hematocrit pre and 24 hrs postoperative.

### *Secondary outcome parameters*

- Operation time from skin incision to skin closure in minutes.
- Myomectomy time from first uterine incision to closure of last uterine incision in minutes.
- Postoperative hospital stay in days.
- Adverse effects of misoprostol (nausea, vomiting, diarrhea, elevated temperature >38C).
- Adverse effects of tranexamic acid (thromboembolic incidents, gastrointestinal upset in the form of nausea and vomiting).
- The need for intraoperative or postoperative blood transfusion.
- Need for massive blood transfusion An intraoperative blood transfusion will be governed by clinical condition and amount of blood loss. A postoperative blood transfusion will be indicated if the hemoglobin (Hb) concentration is <7g/dL with relevant clinical manifestations.

## MATERIALS AND METHODS

### *Type of study*

A randomized comparative study.

After approval of ethics committee, the current comparative study was conducted in Kasr Al-Ainy hospital obstetric theaters between April 2021 and September 2021. Consents were obtained from all participants.

### *Inclusion criteria*

1. Age group (18-40) years old.
2. Symptomatic myomas (heavy menstrual bleeding or abdominal / pelvic pain) candidate for abdominal myomectomy.
3. Less than 5 myomas

### *Exclusion criteria*

4. Subserousmyomas.
5. More than 5 myomas.
6. Medical disorders (for example uncontrolled hypertension, diabetes mellitus, renal or hepatic disorders).
7. Coagulation disorders or use of anticoagulant drugs.
8. Previous myomectomy.
9. Contraindications or allergy to misoprostol or Tranexamic acid.
10. Pregnancy.
11. Previous hormonal therapy (GnRH analogues).
12. Severe Anemia Hb< 7gm/dl.
13. Prisoners and mentally disabled.

### *Sample Size*

Sample size was calculated according to the following equation:

(Beth and Robert, 2004)

Where: n = required sample size,

Zα/2 = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail).

Zβ = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%) σ= is the estimate of the standard deviation in the control group=49.12 ml (Rashed RM., 2014)[9].

μ1 = mean of blood loss postoperative in the Tranexamic Acid group =470ml.

μ2 = mean blood loss postoperative in the misoprostol group=500 ml.

So, sample size was 43 women in each group with 15% as drop-out rate, the total sample size was 50 women in each group.

There are Three study groups:

**Group (A) (Tranexamic Acid group):** Twenty minutes before surgery women received TXA (amoun co. kapron ampoule is 500mg/5ml) as a single bolus intravenous injection of 15mg/kg.

A.1- (Single myoma )

A.2- (2 - 5 myomas)

**Group (B) (Misoprostol group):** Women received two tablet of (200 microgram) misoprostol (Cytotec) rectally 1hr before starting of operation.

B.1(Single myoma)

B.2(2 - 5 myomas)

**Group (C) (Placebo group):** Women received 500ml saline infusion at a rate of 120ml/h 5 minutes before and during the operation.

C.1 (Single myoma)

C.2 (2-5 myomas)

Intraoperative Blood loss was calculated by the addition of the blood volume in suction apparatus to the total weight of pads [pad count × (wet pad weight dry pad weight)]. The weight of swabs found in grams was translated to ml by using blood density (1.050g/ml)[21].

### *Informed consent was taken from patients.*

### *Methodology in details:*

### *Eligible patients in this study was subjected to*

### *Preoperative*

- Full history and examination.
- Name,age,marritalstatus,occupation,special habits.
- Medical and surgical history.
- Menstrual , obstetric and gynaecological history.
- Symptoms such as heavy menstrual bleeding and pain.
- Abdominal, vaginal and general examination (including BMI calculation).

### *Postoperative*

- Monitor Vital Signs (blood pressure, heart rate and respiratory rate).
- Estimation of Hemoglobin and haematocrite 6 hrs and 24hrs postoperatively.

## RESULTS

Regarding need for intraoperative blood transfusion; statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups (no cases needed). On the other hand there was highly significant difference with control group 33 (66.0%) ($p$= <0.001). Also, Regarding need for postoperative blood transfusion; tranexamic acid was significantly higher than misoprostol and control groups 6 (12.0%) vs. 0 (0.0%) vs. 3 (6.0%) respectively ($p$= 0.042).

Regarding intraoperative blood loss (ml); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 229.35 ± 41.05 and 225.80 ± 44.82. On the other hand there was highly significant higher intraoperative blood loss in control group 680.35 ± 189.39 ($p$= <0.001).

Regarding postoperative HB (g/dl) (6hrs post), HCT% and pulse (b/m); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 10.34±1.04vs. 10.18± 1.02, 31.15±2.98 vs. 30.19±2.51 and 81.96±7.65vs. 83.76±7.19 respectively. On the other hand there was highly significant lower postoperative HB and HCT and higher pulse rate in control group 9.64±1.08, 29.06±3.20 and 108.80±8.97 ($p$= 0.003, 0.002 and <0.001) respectively.

Regarding post-operative stay (days); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 1.34±0.48vs. 1.32 ± 0.47. On the other hand there was highly significant longer stay in control group 1.56±0.54 ($p$= 0.030).

### *Post hoc pair wise comparisons*

Regarding operation and myomectomy time (mins); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 68.50±10.98vs. 68.60±10.83 and 23.38±1.86vs. 22.34±1.67. On the other hand there was highly significant longer time in control group 85.70± 24.45 and 27.74±2.93 ($p$= <0.001 and 0.001) respectively.

**Table 1:** Description of whole sample

| | | Count | % |
|---|---|---|---|
| Groups | Misoprostol group | 50 | 33.3% |
| | Tranexamic acid group | 50 | 33.3% |
| | Control Group | 50 | 33.3% |
| Need for intraoperative blood transfusion | Yes | 33 | 22.0% |
| | No | 117 | 78.0% |
| Need for post operative blood transfusion | Yes | 9 | 6.0% |
| | No | 141 | 94.0% |
| Need for massive blood transfusion | NO | 150 | 100.0% |
| Adverse effect of misoprostol | No | 150 | 100.0% |
| Number of myoma removed operatively | Single | 75 | 50.0% |
| | 2-5 | 75 | 50.0% |

**Table 2:** Mean age, BMI,estimated blood volume, comparison of preoperative HCT& HB, postoperative HCT&HB ,mean hematocrit and operative time, size and number of myomas among the patients included in the study

| | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|
| Age | 32.57 | 4.12 | 22.00 | 41.00 |
| Gravidity | 1.55 | 1.06 | 0.00 | 4.00 |
| parity | 0.93 | 0.70 | 0.00 | 3.00 |
| Number of previous Cs | 0.69 | 0.67 | 0.00 | 2.00 |
| Intraoperative Blood loss in Ml | 378.50 | 242.64 | 139.00 | 980.00 |
| Preoperative HB | 11.02 | 1.12 | 9.00 | 14.00 |
| Postoperative HB (6hrs post ) | 10.05 | 1.08 | 7.10 | 13.00 |
| Postoperative HB (next day) | 10.00 | 1.00 | 7.50 | 12.90 |
| Preoperative HCT | 32.84 | 3.27 | 27.00 | 42.00 |
| Postoperative HCT | 30.13 | 3.01 | 22.10 | 38.10 |
| Mean preoperative pulse | 81.09 | 8.57 | 60.00 | 97.00 |
| Mean post operative pulse | 91.51 | 14.62 | 65.00 | 128.00 |
| Post operative stay | 1.41 | 0.51 | 1.00 | 3.00 |
| Operation time (min) | 74.27 | 18.46 | 40.00 | 125.00 |
| Myomectomy time | 24.49 | 3.22 | 19.00 | 34.00 |
| Size of myoma by u/s in cm | 5.71 | 1.73 | 1.00 | 9.00 |
| Number of myoma removed operatively | 1.97 | 1.20 | 1.00 | 5.00 |

Table 3: Comparison between groups

| | | Misoprostol group | | Tranexamic acid group | | Control Group | | *P value* |
|---|---|---|---|---|---|---|---|---|
| | | Count | % | Count | % | Count | % | |
| Need for intraoperative blood transfusion | Yes | 0 | 0.0% | 0 | 0.0% | 33 | 66.0% | < 0.001 |
| | No | 50 | 100.0% | 50 | 100.0% | 17 | 34.0% | |
| Need for post operative blood transfusion | yes | 0 | 0.0% | 6 | 12.0% | 3 | 6.0% | 0.042 |
| | No | 50 | 100.0% | 44 | 88.0% | 47 | 94.0% | |
| Need for massive blood transfusion | No | 50 | 100.0% | 50 | 100.0% | 50 | 100.0% | ----- |
| Adverse effect of misoprostol | No | 50 | 100.0% | 50 | 100.0% | 50 | 100.0% | ----- |
| Number of myoma removed operatively | Single | 25 | 50.0% | 25 | 50.0% | 25 | 50.0% | 1 |
| | 2-5 | 25 | 50.0% | 25 | 50.0% | 25 | 50.0% | |

**Table 4:** comparison between all groups regarding Regarding intraoperative blood loss (ml)

| | Groups | | | | | | *P value* |
|---|---|---|---|---|---|---|---|
| | Misoprostol group | | Tranexamic acid group | | Control Group | | |
| | Mean | SD | Mean | SD | Mean | SD | |
| Age | 31.72 | 4.66 | 32.18 | 3.63 | 33.82 | 3.76 | 0.026 |
| Gravidity | 1.88 | 1.02 | 1.78 | 1.02 | 0.98 | 0.91 | < 0.001 |
| parity | 1.04 | 0.57 | 0.90 | 0.68 | 0.86 | 0.83 | 0.406 |
| Number of previous Cs | 0.80 | 0.61 | 0.66 | 0.69 | 0.62 | 0.70 | 0.367 |
| Intraoperative Blood loss in Ml | 229.35 | 41.05 | 225.80 | 44.82 | 680.35 | 189.39 | < 0.001 |
| Preoperative HB | 10.77 | 1.10 | 10.63 | 0.94 | 11.67 | 1.03 | < 0.001 |
| Postoperative HB (6hrs post ) | 10.34 | 1.04 | 10.18 | 1.02 | 9.64 | 1.08 | 0.003 |
| Postoperative HB (next day) | 10.20 | 1.01 | 10.02 | 0.85 | 9.78 | 1.09 | 0.111 |
| Preoperative HCT | 31.99 | 3.04 | 31.59 | 2.62 | 34.93 | 3.10 | < 0.001 |
| Postoperative HCT | 31.15 | 2.98 | 30.19 | 2.51 | 29.06 | 3.20 | 0.002 |

**Table 5:** comparison between all groups regarding Regarding postoperative HB (g/dl) (6hrs post), HCT% and pulse (b/m)

| | | Misoprostol group | Tranexamic acid group | Control Group |
|---|---|---|---|---|
| Age | Misoprostol group | | 1.000 | 0.031 |
| | Tranexamic acid group | 1.000 | | 0.133 |
| | Control Group | 0.031 | 0.133 | |
| Gravidity | Misoprostol group | | 1.000 | < 0.001 |
| | Tranexamic acid group | 1.000 | | < 0.001 |
| | Control Group | < 0.001 | < 0.001 | |
| Intraoperative Blood loss in Ml | Misoprostol group | | 1.000 | < 0.001 |
| | Tranexamic acid group | 1.000 | | < 0.001 |
| | Control Group | < 0.001 | < 0.001 | |
| Preoperative HB | Misoprostol group | | 1.000 | < 0.001 |
| | Tranexamic acid group | 1.000 | | < 0.001 |
| | Control Group | < 0.001 | < 0.001 | |
| Postoperative HB (6hrs post ) | Misoprostol group | | 1.000 | 0.003 |
| | Tranexamic acid group | 1.000 | | 0.033 |
| | Control Group | 0.003 | 0.033 | |
| Preoperative HCT | Misoprostol group | | 1.000 | < 0.001 |
| | Tranexamic acid group | 1.000 | | < 0.001 |
| | Control Group | < 0.001 | < 0.001 | |
| Postoperative HCT | Misoprostol group | | 0.307 | 0.001 |
| | Tranexamic acid group | 0.307 | | 0.164 |
| | Control Group | 0.001 | 0.164 | |

**Table 6:** Comparison between all groups Regarding post-operative stay (days)

| | Groups | | | | | | *P value* |
|---|---|---|---|---|---|---|---|
| | Misoprostol group | | Tranexamic acid group | | Control Group | | |
| | Mean | SD | Mean | SD | Mean | SD | |
| Mean preoperative pulse | 82.12 | 6.69 | 81.56 | 7.70 | 79.60 | 10.75 | 0.305 |
| Mean post operative pulse | 81.96 | 7.65 | 83.76 | 7.19 | 108.80 | 8.97 | < 0.001 |
| Post operative stay | 1.34 | 0.48 | 1.32 | 0.47 | 1.56 | 0.54 | 0.030 |
| Operation time (min) | 68.50 | 10.98 | 68.60 | 10.83 | 85.70 | 24.45 | < 0.001 |
| Myomectomy time | 23.38 | 1.86 | 22.34 | 1.67 | 27.74 | 2.93 | < 0.001 |
| Size of myoma by u/s in cm | 5.74 | 1.55 | 6.14 | 1.50 | 5.26 | 2.02 | 0.038 |
| Number of myoma removed operatively | 1.94 | 1.11 | 2.02 | 1.24 | 1.94 | 1.25 | 0.929 |

**Table 7:** comparison between all groups Regarding operation and myomectomy time

| | | Misoprostol group | Tranexamic acid group | Control Group |
|---|---|---|---|---|
| Mean post operative pulse | Misoprostol group | | 0.783 | < 0.001 |
| | Tranexamic acid group | 0.783 | | < 0.001 |
| | Control Group | < 0.001 | < 0.001 | |
| Operation time (min) | Misoprostol group | | 1.000 | < 0.001 |
| | Tranexamic acid group | 1.000 | | < 0.001 |
| | Control Group | < 0.001 | < 0.001 | |
| Myomectomy time | Misoprostol group | | 0.063 | < 0.001 |
| | Tranexamic acid group | 0.063 | | < 0.001 |
| | Control Group | < 0.001 | < 0.001 | |
| Size of myoma by u/s in cm | Misoprostol group | | 0.730 | 0.485 |
| | Tranexamic acid group | 0.730 | | 0.033 |
| | Control Group | 0.485 | 0.033 | |

## DISCUSSION

Methods of reducing hemorrhage during myomectomy include the use of intraoperative maneuvers such as; uterine and/or ovarian artery ligation, and use of drugs such as vaginal misoprostol, intravenous tranexamic acid or oxytocin, etc. However, the best intervention to reduce blood loss during myomectomy is still debatable[10].

This randomized comparative clinical trial was conducted at Kasr Al-Ainy hospital "obstetric theaters" between April 2021 and September 2021to compare the efficacy and safety of intravenous tranexamic acid versus rectal misoprostol before abdominal myomectomy in reducing intraoperative blood loss during abdominal myomectomy. A total of 150 female patients with symptomatic myoma indicated for abdominal myomectomy or candidate for and choosing it as surgical management option were enrolled and divided into 3 groups; group A received 1gm tranexamic acid slowly intravenous over a minute before skin incision, group B received 400 micrograms of misoprostol rectally one hour preoperatively and group C (placebo group) received 500 ml saline infusion at a rate of 120ml/h 5 minutes before and during the operation.

Regarding intraoperative blood loss (ml); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 229.35±41.05 and 225.80±44.82. On the other hand there was highly significant higher intraoperative blood loss in control group 680.35 ± 189.39 ($p$= <0.001).

Regarding need for intraoperative blood transfusion; statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups (no cases needed). On the other hand there was highly significant difference with control group 33 (66.0%) ($p$= <0.001). Also, regarding need for postoperative blood transfusion; tranexamic acid was significantly higher than misoprostol and control groups 6 (12.0%) vs. 0 (0.0%) vs. 3 (6.0%) respectively ($p$= 0.042).

Regarding postoperative HB (g/dl) (6hrs post), HCT% and pulse (b/m); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 10.34±1.04vs. 10.18± 1.02, 31.15±2.98 vs. 30.19± 2.51 and 81.96± 7.65 vs. 83.76±7.19 respectively. On the other hand there was highly significant lower postoperative HB and HCT and higher pulse rate in control group 9.64±1.08, 29.06±3.20 and 108.80±8.97 ($p$= 0.003, 0.002 and <0.001) respectively.

Regarding post-operative stay (days); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 1.34±0.48 vs. 1.32± 0.47. On the other hand there was highly significant longer stay in control group 1.56±0.54 ($p$= 0.030).

Regarding operation and myomectomy time (mins); statistical analysis of current results showed that there was no significant difference between tranexamic acid and misoprostol groups 68.50±10.98vs. 68.60±10.83 and 23.38±1.86 vs. 22.34±1.67. On the other hand there was highly significant longer time in control group 85.70±24.45 and 27.74±2.93 ($p$= <0.001 and 0.001) respectively.

Current study disagreed with Caglar and his colleagues who stated that no additional benefit of intravenous infusion of tranexamic acid was found. Tranexamic acid does not seem to be a useful adjunct in myomectomy if given according to the described protocol in this study. This disagreement might be due to different douse of tranexamic acid. On the other side, current study agreed with Caglar and his colleagues who stated that statistically significant differences were found between the two groups when compared for postoperative and total blood loss and duration of surgery ($p < 0.01$, $p = 0.03$ and $p = 0.03$, respectively) (Caglar *et al*., 2008)[11].

Current study was against Kongnyuy and WiysongeIntervention Review who stated that there was limited evidences that misoprostol and tranexamic acid reduces bleeding during myomectomy. Only randomized controlled trials (RCTs) that compared the use of interventions to reduce blood loss during myomectomy to placebo or no treatment were included. Regarding misoprostol versus placebo, there was no evidence of effect on the need for blood transfusion (OR 0.36, 95% CI 0.05 to 2.50) and duration of hospital stay (MD 0.00 days, 95% CI-0.82 to 0.82). Regarding tranexamic acid versus placebo, intravenous infusion of tranexamic acid but did not reduce the need for blood transfusion (OR 1.71, 95% CI 0.68 to 4.30) and did not change postoperative haemoglobin levels (MD 0.21 g/dl, 95% CI-0.36 to 0.78) or haematocrit (MD 1.00%, 95%CI 0.43 to 2.43). These differences might be due to different study populations and routes of interventions[12].

On the other hand, current study agreed with Kongnyuy and WiysongeIntervention Review who stated that regarding misoprostol versus placebo, misoprostol significantly reduced blood loss (1 trial with 25 participants: MD 149.00 ml, 95% CI -229.24 to -68.76), shortened duration of surgery (MD - 9.50 min, 95% CI -15.90 to -3.10) (Analysis 64 5.2), and increased postoperative haemoglobin (MD 0.80g/dl, 95%CI 0.33 to 1.27). Regarding tranexamic acid versus placebo, intravenous infusion of tranexamic acid reduced blood loss during myomectomy (1 trial with 100 participants: MD -243ml, 95% CI -460.02 to -25.98) and shortened the duration of surgery (MD -11 min, 95% CI -21.09 to -0.91)[12].

Current study was in line with Wang and his colleagues who performed "a meta-analysis of randomized controlled trials" and stated that intravenous administration of TXA in open myomectomy was associated with significantly reduced total blood loss, postoperative hemoglobin decline, duration of surgery, and transfusion requirements. This systematic search was performed in Medline (1966–2017.03), PubMed (1966–2017.03), Embase (1980–2017.03), ScienceDirect (1985–2017.03,) and the Cochrane Library[13].

Finally, current study corresponded with Wali and his colleagues who performed "a recent systematic review and meta-analysis of randomized control trials" and stated that moderate- to high-quality studies have established that misoprostol minimizes blood loss and need for blood transfusion at open myomectomy. This low-cost and readily available drug should be routinely administered prior to open myomectomy to improve clinical outcomes. Eight studies were included with a total of 385 patients, of which 192 received misoprostol. The included studies were published between May 2003 and June 2019. The number of participants in each study ranged from 25 to 80, with a total of 385, of which 192 were in the misoprostol experimental group. Studies were conducted in Egypt (Rashed, 2014; Abdel-Hafeez *et al*., 2015 and Mohamed *et al*., 2019), Turkey (Celik *et al*., 2003), Thailand (Maneerat and Tongmai, 2019), Uganda (Moses, 2020) and Iran (Niroomand *et al*., 2015 and Vahdat *et al*., 2019)[10, 14-21].

The studies had similar inclusion and exclusion criteria. The studies varied in their misoprostol regimen in terms of dose, timing and route of administration. Six studies used 400 lg (Rashed, 2014; Abdel-Hafeez *et al*., 2015; Mohamed *et al*., 2019; Celik *et al*., 2003;Maneerat and Tongmai, 2019 and Moses, 2020) and two used 200lg (Niroomand *et al*., 2015 and Vahdat *et al*., 2019) of misoprostol. (10 , 16-20. 22)

The drug was administered vaginally 60–180 minutes preoperatively (Celik *et al*., 2003; Niroomand *et al*., 2015 and Moses, 2020) rectally 30–60 minutes preoperatively (Rashed, 2014, Abdel-Hafeez *et al*., 2015; Mohamed *et al*., 2019 and Maneerat and Tongmai, 2019) or sublingually 30 minutes preoperatively (Niroomand *et al*., 2015)[10, 15-19, 21].

Primary outcomes were estimated blood loss; drop in hemoglobin and blood transfusion. Data on blood loss was available from seven studies (Celik *et al*., 2003;Niroomand *et al*., 2015; Rashed, 2014, Abdel-Hafeez *et al*., 2015; Mohamed *et al*., 2019; Maneerat and Tongmai, 2019 and Moses, 2020). The pooled standardized mean difference (SMD) was 169.56ml (95%CI_200.70 to_138.41), $P< 0.00001$[10, 15-19, 21].

Three studies Niroomand *et al*., (2015); Abdel-Hafeez *et al*., (2015) and Mohamed *et al*., (2019) reported on change in hemoglobin with a statistically significant SMD of _0.48g/dl (95% CI _0.65 to _0.31), $P < 0.00001$[16, 20].

All eight studies reported on need for blood transfusion; however, (Maneerat and Tongmai, 2019) data were not included in the analysis as they do not separate their data for open and laparoscopic myomectomy for this outcome. Use of misoprostol resulted in a lower need for blood transfusion with an odds ratio of 0.29 (95% CI 0.16–0.52), $P < 0.00001$[18].

Secondary outcomes were operative time and duration of postoperative hospital stay. Data on operative time was available from all studies except (Rashed, 2014) and demonstrated a lower SMD operative time in the misoprostol group of _11.64 (95% CI_15.73 to_7.54) minutes, $P < 0.00001$.

Three studies provided data on postoperative hospital stay Celik *et al*., (2003), Abdel-Hafeez *et al*., (2015) and Mohamed *et al*., (2019)[10, 15-17].

The SMD in the misoprostol compared with the placebo group was _0.14 days (95% CI_0.31 to 0.04), *P* = 0.12.

All primary outcomes in the misoprostol group showed ongoing statistical significance, with all confidence intervals increasing with this conservative analysis. There was no change in the lack of statistical significance for the secondary outcomes (Wali *et al*., 2021)[14].

The strengths of current study were due to:

- Every effort was made to ascertain that all follow-up data were correct, and only complete information was included in data analysis.
- All clinical assessment, abdominal myomectomies and assessment of study outcomes were done by the same team.

The limitations of current study were due to:

- COVID 19 pandemic.
- Relatively small sample size regarding accuracy of study outcomes.
- Side effects of study medications.

## CONCLUSION

In women undergoing abdominal myomectomies, preoperative intravenous tranexamic acid and rectal misoprostol were very effective in reducing intraoperative blood loss, need for intra and postoperative blood transfusion, post-operative stay and operation and myomectomy time compared with placebo.

## RECOMMENDATIONS

In women undergoing abdominal myomectomies, preoperative intravenous tranexamic acid and rectal misoprostol could be routinely used to reduce intraoperative blood loss, need for intra and postoperative blood transfusion, post-operative stay and operation and myomectomy time.

More clinical trials with larger sample size and more data are needed for further evaluation of study outcomes.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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