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Rectal Misoprostol in Women Undergoing Myomectomy for Intraoperative Blood Loss Reduction: A double-blinded randomized placebo-controlled study

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ABSTRACT

Objectives: To compare amount of intraoperative blood loss between patients using preoperative rectal misoprostol versus placebo group.

Materials and Methods: A randomized double-blinded placebo-controlled trial, 46 women with uterine leiomyoma indicated for myomectomy, both abdominal and laparoscopic approach were randomly assigned and received rectal misoprostol (400 µg) or placebo at 30 minutes before operation, then estimation of blood loss was recorded as primary outcome. Changes in hemoglobin, hematocrit, rate of transfusion and adverse events were also recorded.

Results: Median and interquartile range of intraoperative blood loss in misoprostol group was 350 (613) ml and 500 (663) ml in placebo group. Mann-Whitney U test showed no statistical significance (p = 0.136). Univariate analyses showed significant factors of intraoperative blood loss were intramural type, type of operation and larger size of mass. But after multivariate analyses, the only significant factor affecting more blood loss was intramural type of leiomyoma (odds ratio 23, 95% confidence interval 1.96-271.9, p = 0.013). Changes of hemoglobin, hematocrit, transfusion rate and other complications were not significant.

Conclusion: There was no significant benefit in blood loss reduction after using preoperative rectal misoprostol in the study.

Keywords: Leiomyoma, myomectomy, misoprostol, blood loss, hemoglobin.

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การเหน็บยาไมโซพรอสตอลทางทวารหนักก่อนผ่าตัดเนื้องอกมดลูก เพื่อลดการเสียเลือดจากการผ่าตัด: การศึกษาเปรียบเทียบกับยาหลอก

พฤฒพร มณีรัตน์, สิริกาญจน์ ทองใหม่

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบการเสียเลือดระหว่างผ่าตัดเนื้องอกมดลูกระหว่างกลุ่มที่ได้ยา ไมโซพรอสตอล กับยาหลอก*
วิธีดำเนินการทำวิจัย: *การศึกษาทดลองแบบสุ่มโดยมีกลุ่มควบคุมในสตรีไทยที่เป็นโรคเนื้องอกกล้ามเนื้อมดลูกชนิดไม่ใช่มะเร็ง และจะเข้ารับการผ่าตัดแบบนัดที่โรงพยาบาลราชวิถีระหว่างวันที่ 1 ตุลาคม พ.ศ. 2559 จนถึง 31 สิงหาคม พ.ศ. 2560 ทั้งหมด 46 ราย จากนั้นแบ่งเป็น 2 กลุ่มได้แก่ กลุ่มที่ได้รับยา ไมโซพรอสตอล 400 ไมโครกรัม และกลุ่มที่ได้รับยาหลอก โดยจะเหน็บยาทางทวารหนักก่อนผ่าตัด 30 นาที แล้วเปรียบเทียบการเสียเลือดระหว่างผ่าตัดใน 2 กลุ่ม*
ผลการวิจัย: *มัธยฐานของการเสียเลือดระหว่างผ่าตัดในกลุ่มที่ได้ยาไมโซพรอสตอลเท่ากับ 350 มิลลิลิตร เปรียบเทียบกับยาหลอกที่ 500 มิลลิลิตร (p = 0.136) แต่จากการวิเคราะห์ในกลุ่มย่อยพบว่าการใช้ยาอาจได้ประโยชน์ในการผ่าตัดเนื้องอกมดลูกผ่านกล้อง ผู้ป่วยที่มีก้อนเนื้องอกที่พื้นที่น้อยกว่า 30 ตารางเซนติเมตร และผู้ป่วยที่มีก้อนเนื้องอกที่ปริมาตรน้อยกว่า 40 มิลลิลิตร แต่จากการวิเคราะห์แบบโลจิสติกพบว่าปัจจัยที่มีผลกับการเสียเลือดมากได้แก่ เนื้องอกมดลูกชนิด Intramural (p = 0.013) ภาวะแทรกซ้อน และการได้รับเลือดไม่แตกต่างกันระหว่างสองกลุ่ม*
สรุป: *การเหน็บยาไมโซพรอสตอลทางทวารหนักก่อนผ่าตัด 30 นาทีไม่ช่วยลดการเสียเลือดจากการผ่าตัดเนื้องอกมดลูกอย่างมีนัยสำคัญ*

คำสำคัญ: *เนื้องอกกล้ามเนื้อมดลูก, การผ่าตัดเนื้องอกมดลูก, การเสียเลือดระหว่างผ่าตัด, ไมโซพรอสตอล ฮีโมโกลบิน*

Introduction

Leiomyoma of uterus is the most common benign gynecologic tumor of all ages. In Rajavithi hospital, more than 200 patients are newly diagnosed in each year. Clinical manifestations are varied based on size and location of tumor, such as pelvic pain, heavy menstrual bleeding, urinary frequency and inability to pregnant successfully.

Myomectomy is a favorable choice of treatment because symptoms will be relieved effectively. But the main challenging problem is the intraoperative bleeding that contributes to blood transfusion and unintended hysterectomy. Studies regarding morbidity of myomectomy showed transfusion rate in myomectomy were about 9-20%[1, 2]. Vasoconstrictors and uterotonic drugs were applied to decrease blood loss during myomectomy, such as intravenous oxytocin[3], intramyometrial bupivacaine and adrenaline[4], tranexamic acid[5, 6] and prostaglandin analogues[7].

Misoprostol, a synthetic prostaglandin E1 analogue, promotes myometrial contraction after binding at EP3 and EP4 receptor that increase amount of intracellular calcium. Pharmacokinetic properties of misoprostol were studied and showed different onset of action and serum level depending on route of administration. Rectal misoprostol achieves maximal level at less than 30 minutes with narrowest serum level variation[8] resulting in the safest route. Thus, this study aimed to investigate the effective of misoprostol in blood loss reduction, transfusion rate and other postoperative complications comparing with placebo.

Materials and Methods

The study was a double-blind clinical trial with balanced allocation into two parallel groups and registered in Clinicaltrial.gov with registration number: NCT02908295. No protocol amendment was made after the trial commenced. Ethical committee of Rajavithi Hospital approved the study with registration number: 59147.

Women provisional diagnosed as uterine leiomyoma that myomectomy was scheduled, either abdominal or laparoscopic approach, during October 2016 to August 2017 in Rajavithi Hospital were enrolled in the study. Exclusion criteria included (1) medical diseases which increase bleeding tendency (2) history of antiplatelet and anticoagulant exposure less than seven days (3) exposure of prostaglandin analogue and/or non-steroidal anti-inflammatory drugs (NSAIDs) less than seven days (4) medical diseases which may become worsen after prostaglandin exposure, such as uncontrolled hypertension, asthma, glaucoma and heart diseases (5) preoperative platelet count less than 100,000 /cm3 or abnormal coagulation tests (6) allergy to misoprostol or other prostaglandin analogues (7) abnormal pathologic diagnosis unless leiomyoma and (8) mass in abnormal location, such as broad ligament or cervical leiomyoma.

The sample size was calculated by using a formula for continuous data[9].

$$N = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \left[\frac{\sigma^2_{int} + \sigma^2_{con}}{n_{con}/n_{int}}\right]}{(\mu_{int} - \mu_{con})^2}$$

Mean blood loss of misoprostol group and placebo were 230.60 and 322.39 ml, respectively. Standard deviations of blood loss of 55.72 and 88.13 ml respectively[10] were used in calculation. A sample size of 14 women per group was required to determine difference of this amount of blood loss (power = 0.9 and α = 0.05). But no adjunctive procedures were restricted in the study and expected loss rate of 10%, 20 participants per group were enrolled.

The randomization was performed by simple computer-generated random number table (Microsoft Excel) with ratio 1:1 divided into 2 parallel groups. The sequence of randomization was kept in sealed opaque envelope sequentially and sent to operating room. Thus, participants and operators were blinded to treatment assignment.

Flow diagram was showed in Fig. 1. 48 women were recruited then counselling about intervention and written informed consent were completed. 2 patients refused to join the study due to private cases. All 46 participants were interviewed, physically examined

and taken blood test for complete blood count (CBC) and coagulation test to exclude disorders contraindicated in the protocol. Then, they were randomized to the study group received 400 mg misoprostol (Cytotec™, 200 mg; Pfizer, USA) rectally at 30 minutes before operation and placebo group received 200 mg of vitamin B6, Pyridoxine hydrochloride (Besix®, 100 mg; Charoon Bhesaj, Thailand) rectally at the same time.

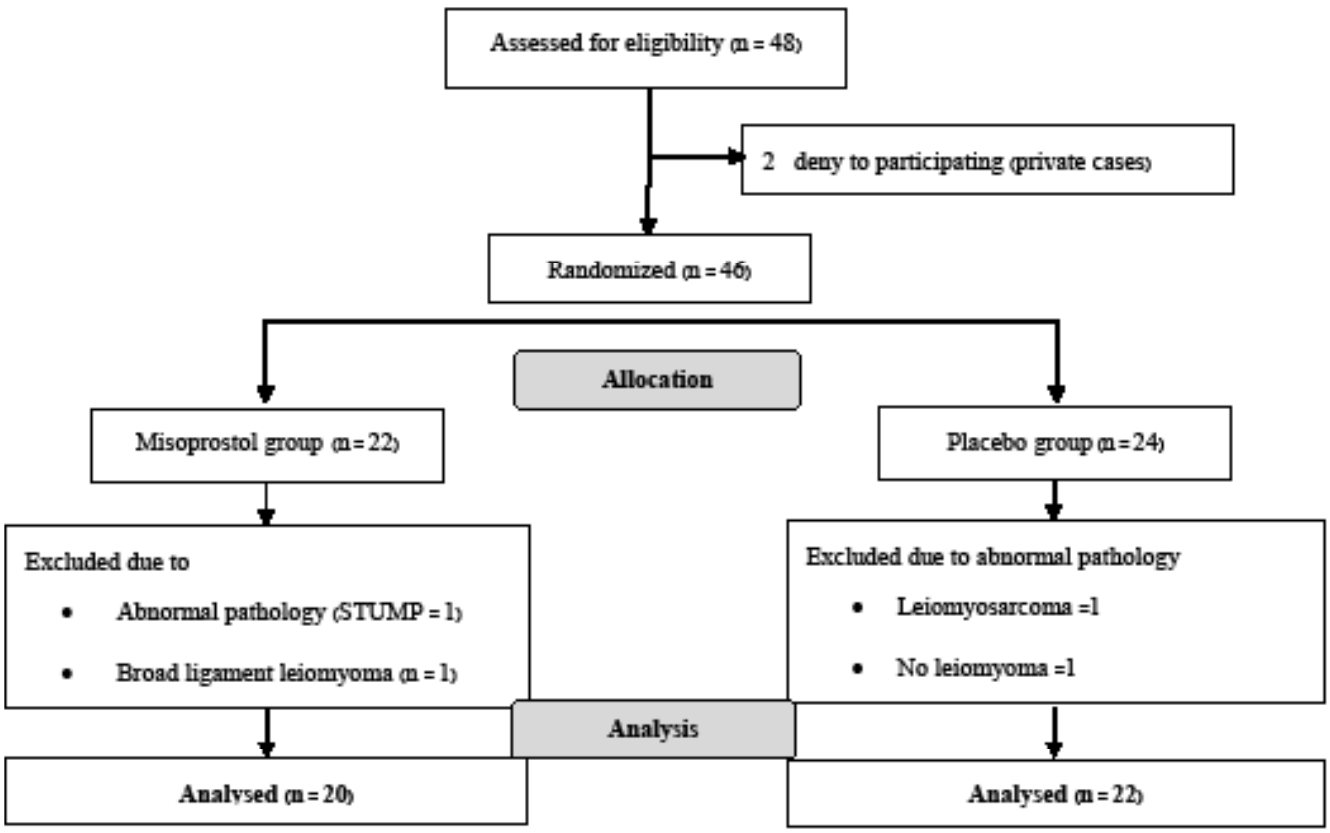

Fig. 1. Flow diagram of study allocation

During preoperative period, participants in both groups were omitted to use NSAIDs, prostaglandin and other drugs that contribute to bleeding tendency. In those undergoing laparoscopic myomectomy, the authors substituted preoperative misoprostol for cervical priming by hygroscopic cervical dilator (Dilapan-S®, 4mm x 55 mm; HPSRx, Virginia) to avoid exposure to prostaglandin.

On the date of surgery, a sealed envelope labelled by numeric code consisting of drug and data recorder was sent to operative theatre. The drug was inserted rectally at 30 minutes before operation by a trained doctor assigned to accompany the surgery. Few drops of normal saline were used to dissolve tablets before insertion. Intraoperative blood loss was recorded by measuring amount of blood on the surgical gauzes and swabs[11] compared with visual analog scale[12]. Another was recorded from blood in suction container after subtracted water using for irrigation and washing. Blood transfusion was considered if blood loss was more than 1,500 ml and/or the intraoperative hemoglobin was less than 8 g/dl. Duration of operation, intraoperative findings, adjuvant procedures, intraoperative complications

and blood transfusion were recorded.

After the operation, CBC was repeated within 24 hours. Pain and other adverse effect of misoprostol uses, such as diarrhea, abdominal cramp, flushing and fever (more than 38°C in body temperature) were recorded by research nurses and doctors attending in each case. Abdominal cramping was categorized into mild, moderate and severe using visual analog scale and amount of opioid requests was recorded as an objective data that represents pain. One patient had a broad ligament leiomyoma, so she was excluded. After pathologic diagnoses were reported, another 3 participants with abnormal pathology were excluded; one for uterine smooth muscle tumors of uncertain malignant potential (STUMP), one for leiomyosarcoma and another one without leiomyoma in pathologic tissue.

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM© Corp., Armonk, NY, USA) with intention-to-treat analysis. Data were presented as frequencies with percentage in categorical variables and statistical significance was determined by Pearson's chi square and Fischer's exact test. Means ± standard deviation (SD) or median with interquartile ranges (IQR) are used to demonstrate continuous variables based on distribution of data. Student's t-test and Mann-Whitney U-test were used in analyses. The distribution of blood loss was right skewed and normalized by logarithmic transformation. Univariate and multivariate linear regression analysis were used to estimate factors influencing the primary outcome. Finally, meta-analysis was used to summarize pool effects with other studies.

The primary outcome was estimated intraoperative blood loss (EBL). Secondary outcome measures were postoperative hemoglobin difference, blood transfusion rate, duration of surgery, complication of surgery and postoperative adverse events.

Results

48 patients were recruited. After exclusion of 6 patients, 42 participants were in final analysis. Table 1 shows patient demographic data, characteristics of leiomyoma and operative factors. There were no significant differences in both groups.

The primary outcome was presented in Table 2, the median (IQR) of EBL in misoprostol and placebo were 350 (613) and 500 (663) ml, respectively. Nonetheless, no significant difference was found in both groups (p = 0.136). Grouped by operation type, EBL in misoprostol group was significant lower in patients undergoing laparoscopic myomectomy with median EBL difference 200 ml, 150 versus 350 ml (p = 0.022). Due to positively skewed distribution of EBL showed in Fig. 2, it was logarithmic transformed, termed Log EBL, then student t-test was used and resulted in the same way as in Mann-Whitney U-test. Changes in hemoglobin/hematocrit, intraoperative transfusion rate, duration of surgery, hysterectomy conversion rate and adjuvant procedures used during surgery were not different in both groups. There had one patient in placebo group converted to hysterectomy due to huge leiomyoma, 16-cm in largest diameter, with severe pelvic adhesion after her previous abdominal myomectomy for 2 times.

Univariate analysis of significant factors contributed to EBL at cut point of more than 250 mL was used then demonstrated in Table 3. Intramural type, larger diameter, area and volume and type of operation were significant factors of more than 250 ml of blood loss.

Figure 3 shows subgroup analyses, mioprostol uses in laparoscopic myomectomy could reduce EBL more than 250 ml with OR 0.03 (95%CI 0.002 – 0.68, p = 0.025), but not in abdominal myomectomy group (p = 0.535). Furthermore, largest mass with area less than 30 cm2 or volume less than 40 cm3 had significant benefit in reduction of EBL more than 250 ml from misoprostol uses, OR 0.12 (95%CI 0.02 – 0.97, p = 0.037).

But after performing binary logistic regression, the only significant variable was intramural type leiomyoma (Table 4).

Postoperative adverse events were showed in Table 5. Nausea and vomiting were most common. No significant difference of frequencies between two groups (p = 0.925).

Table 1. Demographic and clinical characteristics of enrolled women.

	Misoprostol group (n = 20)	Placebo group (n = 22)	p value
Age (yr), mean ± SD	35.9 ± 5.30	36.3 ± 5.18	0.774
Body mass index (kg/m^2), mean ± SD	22.3 ± 3.89	22.9 ± 2.95	0.556
Preoperative hemoglobin (g/dl), mean ± SD	11.6 ± 1.31	11.8 ± 1.31	0.595
Preoperative hematocrit (%), mean ± SD	36.2 ± 3.72	36.9 ± 3.35	0.691
Previous abdominal surgery, n (%)			0.418
• Cesarean delivery	0 (0)	1 (4.5)	
• Ovarian surgery	1 (5)	0 (0)	
• Appendectomy	0 (0)	1 (4.5)	
• Others	0 (0)	1 (4.5)	
Operation, n (%)			0.582
• Abdominal myomectomy	14 (70)	15 (68.2)	
• Low midline	6 (42.9)	6 (40)	
• Pfannenstiel	8 (57.1)	9 (60)	
• Laparoscopic myomectomy	6 (30)	7 (31.8)	
Surgeon, n (%)			0.574
• Gynecologic oncologists	15 (75)	17 (77.3)	
• General gynecologists	5 (25)	5 (22.7)	
Hormonal uses in 3 months, n (%)			
• No	12 (41)	17 (77.3)	
• COCs	1 (5)	1 (4.5)	
• DMPA	5 (25)	3 (13.6)	
• GnRH agonist	2 (10)	1 (4.5)	
Type of leiomyoma, n (%)			0.435
• Intramural	15 (75)	17 (77.3)	
• Subserous	5 (25)	5 (22.3)	
Largest mass diameter (cm), mean ± SD	7.7 ± 2.36	8.3 ± 2.28	0.408
Median number of leiomyoma	2 (3)	3 (3)	0.303
Number of resected leiomyoma, n (%)			0.424
• 1	8 (40)	5 (22.7)	
• 2 - 3	7 (35)	8 (36.4)	
• 4 – 5	1 (5)	5 (22.7)	
• 5 – 10	2 (10)	3 (13.6)	
• > 10	2 (10)	1 (4.5)	

Table 2. Primary and secondary outcomes.

	Misoprostol group (n = 20)	Placebo group (n = 22)	p value
EBL (ml), median (IQR)‡	350 (613)	500 (663)	0.136
• Abdominal myomectomy	500 (713)	500 (1000)	0.505
• Laparoscopic myomectomy	150 (163)	350 (450)	0.022
Changes in hemoglobin (g/dl), mean ± SD	- 0.4 ± 0.84	- 0.8 ± 1.23	0.305
Changes in hematocrit (%), mean ± SD	- 1.9 ± 3.29	- 2.72 ± 3.93	0.445
Intraoperative transfusion rate, n (%)	3 (15)	5 (22.7)	0.406
Duration of surgery (minutes)			
• Abdominal myomectomy	132.9 ± 38.77	139.0 ± 50.01	0.714
• Laparoscopic myomectomy	210 ± 40.67	167.1 ± 100.41	0.342
Hysterectomy conversion rate, n (%)	0 (0)	1 (4.5)	0.524
Adjuvant treatment used, n (%)			
• Tranexamic acid	9 (45)	10 (45.5)	0.610
• Tourniquet	1 (5)	0 (0)	
• Bupivacaine and epinephrine	2 (10)	2 (9.1)	0.563

EBL: estimated blood loss; SD: standard deviation

‡ Mann-Whitney U test

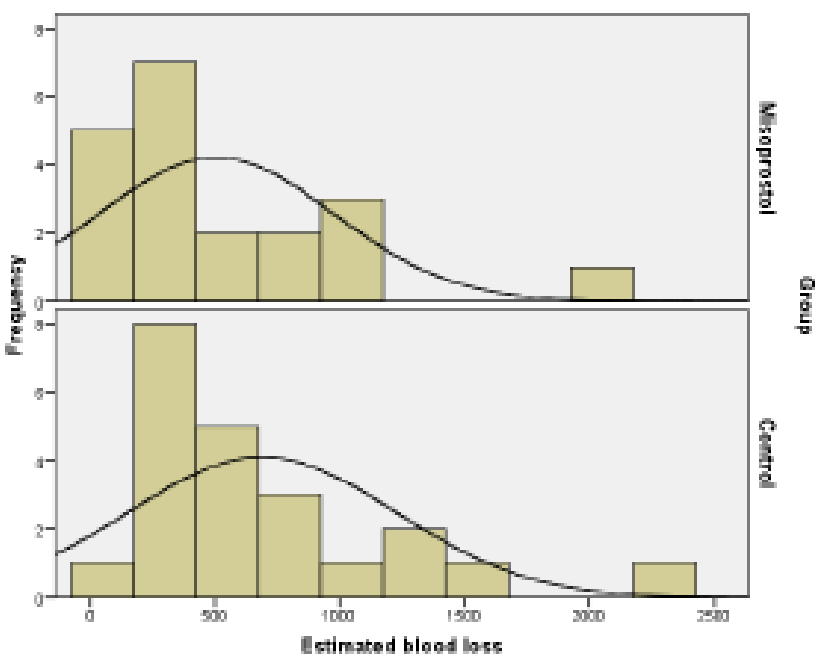

Fig. 2. Histogram of EBL distribution in two groups.

Table 3. Univariate analysis on factors affecting EBL more than 250 mL.

Factors	EBL > 250 ml (n, %)	OR (95% CI)	p value
Group			
• Misoprostol	13 (65)	0.41 (0.10, 1.71)	0.188
• Placebo	18 (81.8)	1	
Age			
• ≥ 35 yr	14 (70)	0.69 (0.17, 2.73)	0.426
• < 35 yr	17 (77.3)	1	
BMI			
• ≥ 25 kg/m^2	6 (85.7)	2.40 (0.26, 22.56)	0.398
• < 25 kg/m^2	25 (71.4)	1	
Operation			
• Abdominal	24 (82.8)	4.11 (0.96, 17.63)	0.049
• Laparoscopic	7 (53.8)	1	
Types of leiomyoma			
• Intramural	28 (84.8)	11.2 (2.09, 60.16)	0.005
• Subserous	3 (33.3)	1	
Number of leiomyoma			
• ≥ 3 myomas	10 (71.4)	0.83 (0.20, 3.52)	0.541
• < 3 myomas	21 (75)	1	
Largest diameter			
• ≥ 8 cm	19 (90.5)	7.13 (1.31, 38.77)	0.016
• < 8 cm	12 (57.1)	1	
Largest area			
• ≥ 30 cm^2	21 (91.3)	9.45 (1.70, 52.10)	0.006
• < 30 cm^2	10 (52.6)	1	
Largest volume			
• ≥ 40 cm^3	21 (91.3)	9.45 (1.71, 52.10)	0.006
• < 40 cm^3	10 (52.6)	1	

EBL: estimated blood loss

Table 4. Predictive factors of EBL > 250 ml from binary logistic regression.

Factors	Total	EBL > 250 mL			
		Coefficient	n (%)	Adjusted OR (95% CI)	p value
Misoprostol	20	-0.71	13 (65)	0.49 (0.08, 2.99)	0.441
Intramural type	33	3.14	28 (84.8)	23.08 (1.96, 271.87)	0.013
Largest volume < 40 mL	19	-2.31	10 (52.6)	0.10 (0.008, 1.20)	0.070
Constant		0.79			

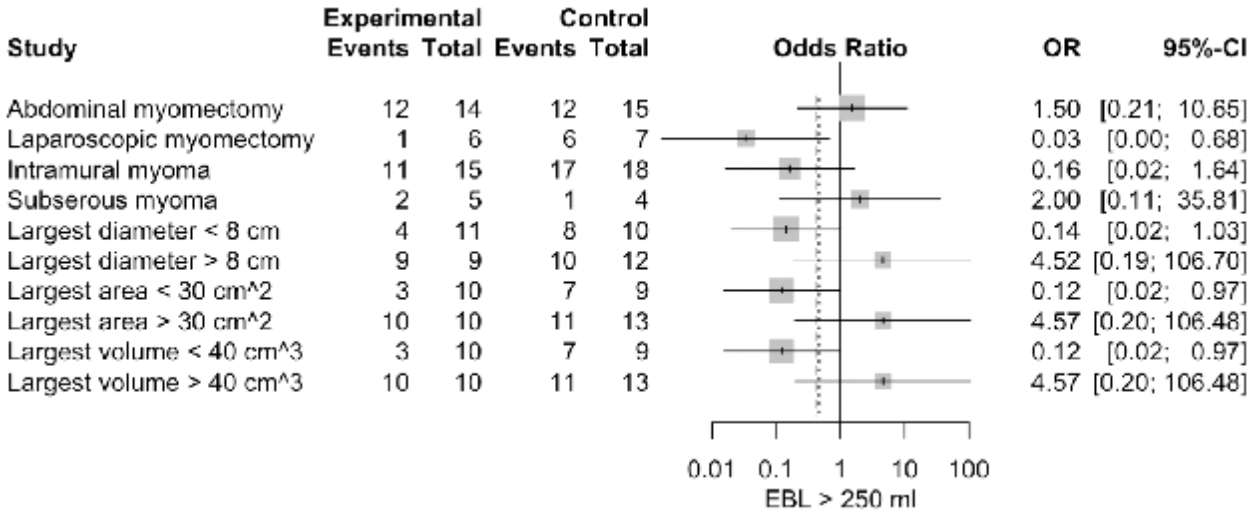

Fig. 3. Subgroup analysis on factors affecting EBL > 250 ml after using misoprostol.

Table 5. Postoperative adverse events.

	Misoprostol group (n = 20)	Control group (n = 22)	p value
Nausea and vomiting, n (%)†	5 (25)	6 (27.3)	0.574
Diarrhea, n (%)	0 (0)	0 (0)	
Fever, n (%)†	1 (5)	2 (9.1)	0.537
Abdominal pain, n (%)‡			0.422
• Mild	1 (5)	0 (0)	
• Moderate	15 (75)	15 (68.2)	
• Severe	4 (20)	7 (31.8)	
Vaginal bleeding, n (%)†	4 (20)	3 (13.6)	0.444
Total analgesic requests, mean ± SD‡‡	1.9 ± 0.67	2.1 ± 0.84	0.414
• Abdominal myomectomy	1.8 ± 0.84	2.1 ± 0.90	
• Laparoscopic myomectomy	2.06 ± 0.90	2.0 ± 0.71	

† Fischer's exact test, ‡ Pearson chi-square, ‡‡ t-test

Discussion

Several mechanisms of misoprostol were proposed. Releasing of prostaglandin induces myometrial contraction that constricts spiral vessels resulting in bleeding control. Besides, prostaglandin has vasoactive effect demonstrated by uterine Doppler study[13].

The study concluded that preoperative rectal 400 ug of misoprostol at 30 minutes prior to surgery had no significant benefit in decreasing amount of intraoperative blood loss. Because Rajavithi Hospital is the referral and training center that crowed of complicated cases, especially in abdominal myomectomy, with many different surgical team. Moreover, there were no restrictions of other procedures that could be confounders. Variation of blood loss in both groups were

noticed and lowering the power of study. Thus, more participants were needed. The result was inconsistent with Abdel H[14] and Celik[15]. They studied in women undergoing abdominal myomectomy then compared effectiveness of misoprostol versus placebo and the result showed that blood loss and operation time were significantly decreased in misoprostol group. Kalgoiannidis[16] included only laparoscopic myomectomy participants, the results were similar. Characteristics of masses in these three studies were comparable with the study (Table 6). Meta-analysis was performed to summarize pool effect (Fig. 4), and found significant benefit of misoprostol use in random effects model with mean difference of -182.41 mL (95% CI -274.71, -90.11).

Table 6. Comparison of previous studies on misoprostol in myomectomy.

Study, year	n	Inclusion criteria	Intervention (route/dose)	Operation	EBL (SD), mL
Celik, 2003	25	Mean diameter 15 cm Median number 5	Misoprostol (Vg, 400 ug)	Abdominal myomectomy	472 (77) vs 621 (121) p < 0.05
Abdel, 2015	50	Mean area 150 cm^2 ≤ 5 myomas	Misoprostol (RS, 400 ug)	Abdominal myomectomy	574 (195) vs 874 (172) p < 0.05
Niroomand, 2015	80	Mean diameter 8 cm	Misoprostol (Vg, 200 ug)	Abdominal myomectomy	458 (287) vs 696 (411) p < 0.05
Kalgoiannidis, 2011	6	Mean diameter 5 cm	Misoprostol (Vg, 400 ug)	Laparoscopic myomectomy	126 (41) vs 217 (74) p < 0.05
This study	42	Median diameter 8 cm Median number 2.5	Misoprostol (RS, 400 ug)	Abdominal, laparoscopic myomectomy	502 (475) vs 686 (535) p = 0.248

Vg: per vagina, RS: per rectal

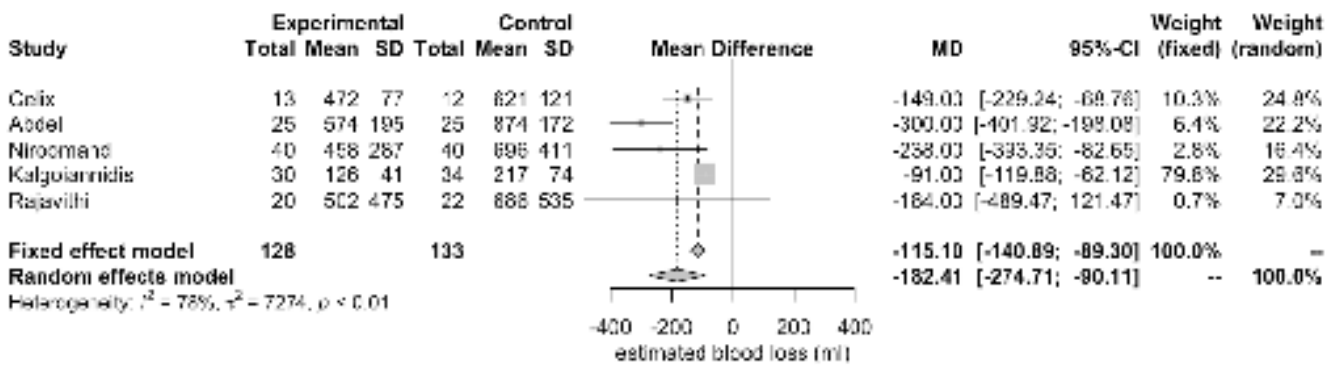

Fig. 4. Meta-analysis of studies focusing on misoprostol in reduction of EBL.

In laparoscopic subgroup, misoprostol uses could decrease intraoperative blood loss (p = 0.022). This could be explained by the fact that there have many interventions that can be performed rapidly to stop bleeding, such as suturing and clamping. These were confounders affecting variation of EBL in each

case. Also, difficulty in laparoscopic group was lower than in abdominal myomectomy, because patients with complicated diseases tended to choose abdominal myomectomy after counselling risk of uncontrolled bleeding leading to hysterectomy conversion.

Changes of hemoglobin and hematocrit showed no significant difference in both groups, differ from those in Celik that mean hemoglobin difference was 0.9 g/dl ($p < 0.05$) and Abdel summarized mean changes of hemoglobin and hematocrit as 0.4 g/dl and 1.3%, respectively ($p < 0.05$). Also, blood transfusion rate was not significantly increased in control group of Abdel, but difference in Celik was significant (4 versus 2 patients in total of 13 in each group). In this study showed 5 participants (22.7%) in control group whereas 3 (15%) in misoprostol group that received perioperative blood transfusion but no significant difference ($p = 0.406$)

Common adverse effects of misoprostol were abdominal cramp, fever with chill, vomiting and diarrhea. The authors recorded these events and found 5 participants in each group experienced mild nausea and vomiting that recovered with supportive treatment. Postoperative opioid uses might contribute to incidence of nausea and vomiting, however no significant difference of opioid uses between two groups.

Different administration time prior to surgery and route might affect the outcome, after the authors reviewed study protocol of previous studies and found that time of administration was at least 60 minutes before operation started. This difference was also a possible cause of the discrepant result that further evaluation is needed.

The study was a prospective study with placebo-controlled and clearly defined study protocol based on patient safety, but due to a brief period, the study recruited smaller group of participants than previous studies with limited of restriction criteria that lowering power of the study. However, despite the diversity of patients, randomization can divided participants properly (Table 1). Thus, confounding bias was decreased.

Another weak point was the means evaluating amount of blood loss that were based on counting, not the most accurate way but concomitant with postoperative hemoglobin, hematocrit and transfusion rate that determined clinical significance.

For clinical applications, overall data showed that use of misoprostol tended to be benefit in decreasing intraoperative blood loss with acceptable adverse effects, especially in laparoscopic myomectomy which mechanical hemostatic procedures were limited.

Conclusion

A 30-minute preoperative dose of rectal misoprostol had no significant benefits in reducing amount of intraoperative blood loss in myomectomy, but it could help in small leiomyoma (less than 30 cm^2 or 40 ml). In a small laparoscopic subgroup, misoprostol might be useful. Adverse events were mild and acceptable. Clear benefit on abdominal myomectomy, and different protocol of administration need further investigations with larger participants. Either abdominal or laparoscopic myomectomy should be selected.

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Potential conflicts of interest

The authors declare no conflict of interest.

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