นิพนธ์ต้นฉบับ . Original Article

การใช้ยาไมโซพรอสตอล (Misoprostol) เหน็บทางรูทวารก่อนผ่าตัดเพื่อลดการเสียเลือดระหว่างเปิดช่องท้องผ่าตัดมดลูก: การศึกษาแบบสุ่มที่มีกลุ่มควบคุม

มนสิชา พงษ์สมัครไทย*, วรสุดา บุญสิทธิ์
กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลขอนแก่น

Preoperative Rectal Misoprostol in Reducing Blood Loss during a Total Abdominal Hysterectomy: A Randomized Double-Blinded Controlled Trial Study

Manasicha Pongsamakthai, Worasuda Boonsith,
Department of Obstetrics and Gynecology, Khon Kaen Hospital 40000, Thailand

Received: 23 April 2022 / Revised: 28 June 2022 / Accepted: 8 July 2022

บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบผลของการใช้ยาไมโซพรอสตอล (Misoprostol) เหน็บทางรูทวารก่อนผ่าตัดในการลดการเสียเลือดระหว่างผ่าตัดมดลูกโดยการเปิดช่องท้องในผู้ป่วยที่มีความผิดปกติของมดลูกที่ไม่ใช่มะเร็งกับการใช้ยาหลอก

วิธีการศึกษา: การศึกษานี้เป็นการศึกษาแบบสุ่มเปรียบเทียบการใช้ยาไมโซพรอสตอลขนาด 400 ไมโครกรัมเหน็บทางรูทวารก่อนผ่าตัดกับยาหลอกในผู้ป่วยที่มีอายุมากกว่า 18 ปีที่ได้รับการวินิจฉัยความผิดปกติของกล้ามเนื้อหรือโพรงมดลูกที่ไม่ใช่มะเร็งและได้รับการรักษาโดยการผ่าตัดมดลูกออก ในช่วงเดือนพฤศจิกายน พ.ศ. 2562 ถึงมิถุนายน พ.ศ. 2564 โดยได้แบ่งผู้ป่วยที่เข้าร่วมการศึกษาทั้งหมด 120 รายออกเป็น 2 กลุ่ม หลังจากที่ผู้ป่วยถูกถอนออกจากงานวิจัย มีผู้ป่วยจำนวน 58 ราย ถูกจัดอยู่ในกลุ่มไมโซพรอสตอลและ 57 รายอยู่ในกลุ่มยาหลอก การศึกษาได้ทำการบันทึกปริมาณการเสียเลือดระหว่างผ่าตัด การให้เลือด ระยะเวลาผ่าตัด ระยะเวลานอนโรงพยาบาลและผลข้างเคียงที่เกิดขึ้นจากการใช้ยา

ผลการศึกษา: กลุ่มใช้ยาไมโซพรอสตอลมีค่ามัธยฐานการเสียเลือดระหว่างผ่าตัด 162.0 (50.5-308.0) มิลลิลิตร และ 160.0 (50.0-309.0) มิลลิลิตรในกลุ่มที่ใช้ยาหลอก โดยไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ (p = 0.910) และมีการให้เลือด ระยะเวลาผ่าตัด ระยะเวลานอนโรงพยาบาลและผลข้างเคียงที่น้อยกว่าในกลุ่มใช้ยาไมโซพรอสตอลเมื่อเทียบกับกลุ่มที่ใช้ยาหลอกโดยไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ

สรุป: การใช้ยาไมโซพรอสตอลเหน็บทางรูทวารก่อนผ่าตัดไม่สามารถลดการเสียเลือดระหว่างผ่าตัดมดลูกโดยการเปิดช่องท้องในผู้ป่วยที่มีความผิดปกติของมดลูกที่ไม่ใช่มะเร็งได้

คำสำคัญ: ยาไมโซพรอสตอลเหน็บทางรูทวาร, การเสียเลือดระหว่างผ่าตัด, โรคความผิดปกติของมดลูกที่ไม่ใช่มะเร็ง

Abstract

Background and Objective: To compare the blood loss during a total abdominal hysterectomy of the benign uterine disease with preoperative rectal misoprostol administration and a placebo.

Material and Methods: One hundred–twenty patients over 18 years of age, who diagnosed of the benign uterine disease and underwent a total abdominal hysterectomy with or without adnexal surgery, were included from November 2019 to June 2021. The participants were randomized and allocated to undergo either the preoperative administration of the 400 micrograms rectal misoprostol (58 patients) or the placebo (57 patients). This randomized controlled trial recorded the intra-operative blood loss, blood transfusion requirement, operative time, hospital stay, and incidence of all side effects.

Results: The median (IQR) intra-operative blood loss was 162.0 (50.5-308.0) ml for the misoprostol group and 160.0 (50.0-309.0) ml for the placebo group was not statistically significant difference (p = 0.910). The misoprostol group demonstrated lower blood transfusion requirements, operative times, hospital stay, and incidence of side effects than those of the placebo group; but there were no statistically significant differences.

Conclusion: Pre-operative rectal misoprostol administration cannot reduce operative blood loss during a total abdominal hysterectomy.

Keywords: rectal misoprostol; operative blood loss; total abdominal hysterectomy.

*Corresponding author: Manasicha Pongsamakthai, E-mail: mod_30md@hotmail.com

Introduction

Hysterectomy is a common procedure in benign gynecologic surgery. There are various surgical approach for hysterectomy including vaginal, transabdominal and laparoscopic hysterectomy. Total abdominal hysterectomy (TAH) is the most common approach, accounting 60% of all hysterectomy. The complications of hysterectomy; intraoperative blood loss, nerve injury, ureteric injury, vaginal cuff dehiscence or wound infection are reported. Blood loss is the most common complication[1], especially TAH was reported more blood loss than laparoscopic hysterectomy[2]. Range of blood loss in TAH was 238-660 ml[3] which required a blood transfusion in 2-12 % of all cases[4].

Pharmacological agents, including intra-myometrial vasopressin, intravenous oxytocin, intra-myometrial sodium 2-mercaptoethanesulfonate, and intra-myometrial bupivacaine plus epinephrine, may be used to reduce intraoperative blood loss[5]. Various methods have been adopted by researchers to lessen blood loss during TAH; such as injection of Gonadotropin-releasing hormone (GnRH) agonist, uterine artery ligation, and preoperatively administration of uterotonic agents, such as misoprostol, oxytocin[6].

Misoprostol is a synthetic prostaglandin E1 analog. Prostaglandin decreases uterine arterial blood flow due to the direct vasoconstriction in the uterine arteries and increased myometrial contractions that lead to indirect avascularity in the uterine; which may also contribute to a reduction in bleeding[7]. Misoprostol is economical and remains stable in ambient room temperatures[8]. It can be administered orally, rectally, or sublingually. In the rectal route, misoprostol reaches its peak concentration in plasma at approximately 40-65 minutes after administration, and it remains in the patient's circulation longer than that of the oral route[9]. Shivering and hyperpyrexia were reported as side effects of misoprostol administration in both the oral and sublingual routes, whereas rectal route had lower incidences than others[10].

Several previous studies have reported various clinical outcomes of rectal misoprostol for reducing intraoperative blood loss in hysterectomy and myomectomy procedures, however, there is no consensus of its effects[11–13]. The purpose of this study was to evaluate the outcome of preoperatively rectal misoprostol administration in reducing intraoperative blood loss during total abdominal hysterectomy in cases of benign uterine disease.

Methods

A double-blinded randomized controlled trial was conducted from November 2019 to June 2021 at Khon Kaen hospital, Khon Kaen, Thailand; with ethical approval (KEF62020). The study subjects included 18 years of age and older women, who underwent a total abdominal hysterectomy with or without adnexal surgery for benign uterine disease. Any participants demonstrating any contraindication for misoprostol use; including mitral stenosis, glaucoma, sickle cell anemia, low diastolic blood pressure, or having an allergic reaction to misoprostol were excluded from the study. Severe asthma, history of coagulopathy, previous pelvic surgery, pre-operative mifepristone, GnRH treatment, and mental impairment were also exclusion criteria. The withdrawal criteria consisted with an incomplete data record, the operative procedure was changed, or the intraoperative diagnosis was carcinoma and postponed surgery more than 4 hours after misoprostol administration.

Patients with benign uterine disease planning to undergo TAH and/or adnexal surgery at Khon Kaen hospital were randomized by computer, through a block of four into two groups; the study and control groups. The randomized list was kept in sealed opaque, sequentially numbered envelopes, and all study personnel and participants were blinded to the treatment assignments for the duration of the study. After giving informed consent, the participants were randomly allocated to one of the two parallel groups. The participants received either 400 micrograms of misoprostol (2 tablets of 200-microgram Cytotec®) or the placebo tablets (identical size, color, and shape with misoprostol) rectally, one hour before the operation. The medications were administrated by the well-instructed and blinded nurses in the gynecologic ward. The participants, investigators, and surgeons were also blinded.

The primary outcome is the intraoperative blood loss, measured by calculating blood volume in suction bottles and the difference of weights between dry and wet (used) swabs and gauzes before and after the operation. A single gram of weight

difference is equivalent to 1 ml of blood loss, measured by standard scales, which excluded 50 milliliters of povidone-iodine antiseptic solution, used for painting vaginal stump intraoperatively. Vital signs, including blood pressure, pulse rate, and temperature at the time of admission and during the 24-hour period after administration of the medication, were recorded. TAHs with or without adnexal surgery were performed with the usual procedure by the randomly assigned gynecological staff and residents. The operative time from skin incision to closure also was recorded. The side effects of the medication were evaluated six hours postoperatively, which included fever, shivering, nausea, vomiting, diarrhea, and headache. Both intraoperative and postoperative blood transfusions were recorded. Diagnoses were confirmed after the operation by reviewing the tissue pathological report from a pathologist. The length of each hospital stay was also recorded.

The sample size was calculated based on the mean volume of intraoperative blood loss. The pooled standard deviation of blood loss was 154.7 ml[12] with 0.05 of alpha and 90 % of the power. Fifty-seven participants per group were required for this study. Considering 5% drop out rate, 120 participants were finally recruited for this study. The differences in continuous variables were analyzed via the Student's t-test or non-parametric test depending on the data distribution characteristics, reported as mean and standard deviation or median and interquartile range (IQR). The categorical variables were analyzed with Chi-square or Fisher's exact test and reported as percentages. The intention to treat principle was applied in cases of loss.

Results

One hundred-twenty patients, having been diagnosed with a benign gynecologic disease, underwent a TAH, and were enrolled in this study. After withdrawal of some participants, 58 participants in misoprostol group and 57 participants in placebo group were analyzed. The flow of the participants throughout the study is illustrated in Figure 1. The baseline characteristics of the participants, including mean age, Body Mass Index, present of underlying disease, mean uterine weight, pathological diagnosis, and level of surgeon, were not statistically significant. (Table 1).

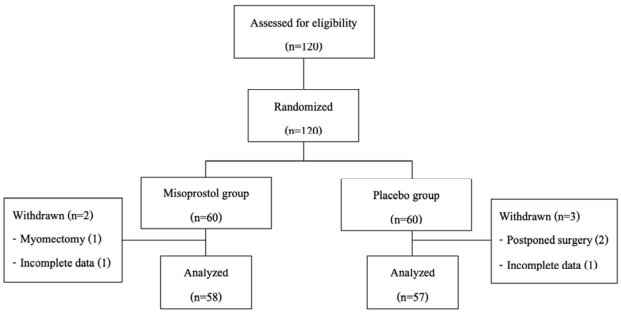

Figure 1 Study flow of the study.

Table 1 Demographics and characteristic data.

Characteristic	Misoprostol (n=58)	Placebo (n=57)	p-value
Age (years) mean ± SD	45.3 ± 4.4	46.0 ± 5.4	0.111
Body Mass Index (BMI) (kg/m^2) mean ± SD	24.3 ± 3.8	25.4 ± 4.4	0.194
Underlying disease (n, %)	9 (15.5)	6 (10.5)	0.070
Uterine weight (grams) median (IQR)	531.0 (350.3-711.0)	692.0 (382.5–927.0)	0.86
Diagnosis			0.113
Uterine	43 (74.1)	47 (82.4)	
leiomyoma (n, %)	11 (19.0)	8 (14.0)	
Adenomyosis (n, %)	4 (6.9)	1 (1.8)	
Adenomyosis with uterine leiomyoma (n, %)	0	1 (1.8)	
Endometrial hyperplasia (n, %)			
Surgeon			0.377
Staff (n, %)	40 (69.0)	44 (77.2)	
Resident (n, %)	18 (31.0)	13 (22.8)	

The median and interquartile range (IQR) intraoperative blood loss, the primary outcome, was more in the misoprostol group (162.0 (50.5-308.0) ml) compared to that of the placebo group (160.0 (50.0-309.0) ml); however, the difference was not statistically significant (p = 0.910). Two patients (3.4 %) in the misoprostol group and six patients (10.5 %) in the placebo group required blood transfusions, with no statistically significant differences (p = 0.066). The mean operative time for the operations was 101.3 ± 35.7 minutes in the misoprostol group and 106.3 ± 44.7 minutes in the placebo group, however, a statistically significant difference was not present (mean difference = 5.0 ± 8.2, 95 % CI; -11.4, 21.3, p = 0.153). The mean duration of each hospital stay was 3.4 ± 0.8 and 3.6 ± 0.9 days in the misoprostol and placebo groups, respectively, without statistically significant differences (mean difference = 0.2 ± 0.2, 95 % CI; -1.7, 0.5, p = 0.107). The incidence of side effects was lower in the misoprostol group than in the placebo group, without any statistically significant difference. The primary and secondary outcomes are presented in Table 2.

Table 2 Primary and secondary outcomes.

Outcomes	Misoprostol (n=58)	Placebo (n=57)	Mean difference ± SE	95%CI	p-value
Intra-operative blood loss (ml), median (IQR)	162.0 (50.5-308.0)	160.0 (50.0-309.0)	N/A	N/A	0.910
Blood transfusion (n, %)	2 (3.4)	6 (10.5)	N/A	N/A	0.066
Operative time (min), mean±SD	101.3 ± 35.7	106.3 ± 44.7	5.0 ± 8.2	-11.4, 21.3	0.153
Hospital stay (day), mean±SD	3.4 ± 0.8	3.6 ± 0.9	0.2 ± 0.2	-1.7, 0.5	0.107
Side Effect (n, %)			N/A	N/A	0.065
- Fever	0	5 (8.6)			
- Shivering	1 (1.7)	0			
- Nausea/vomitting	0	0			
- Diarrhea	1 (1.7)	0			
- Headache	1	1 (1.8)			

Discussion

The present study demonstrated that the pre-operative rectal misoprostol had no significant effect in reducing intraoperative blood loss, the primary outcome, nor did it provide any significant differences in the secondary outcomes; namely, blood transfusion requirement, operative time, duration of hospital stay, or side effects. The study herein was randomized and double-blinded controlled, with adequate sample size, and a thorough and accurate measurement of actual blood loss. The possible reason of the unreduced intraoperative blood loss was the result of low average intraoperative blood loss, comparing with the overall previous reports[3].

Our results were consistent with the previous literature of Maneerat and Tongmai[13], which conducted a double-blinded randomized study of 46 women who were rectally administered misoprostol before the myomectomy procedure. Their results showed no significant effect in reducing blood loss under measurements similarly conducted to those in the present study. Naib, et al[11] presented a randomized controlled trial of 100 cases, in which preoperative rectal misoprostol was administrated before various gynecological surgeries, including hysterectomies and

myomectomies. Unfortunately, they were unable to substantiate the benefit of reduced blood loss, suggesting that further study in this area is needed.

Tabatabai, et al[12] conducted a randomized double-blinded clinical trial of 80 participants, demonstrating the effects of a single rectal dose of misoprostol within abdominal hysterectomies. Their results showed a significant decrease in perioperative bleeding in women undergoing abdominal hysterectomy with symptomatic leiomyoma. Their results differed from the present study, most probably due to their blood loss measurements, which were a non-actual estimation of the amount of blood loss from 15 ml for each standard gauze and 50 ml for each long gauze. Abdel-Hafeez, et al[5] also conducted a randomized double-blinded controlled trial of rectal misoprostol in 50 women who underwent an abdominal myomectomy. Their study group presented significantly lower blood loss measured by the amount of blood accumulated in the suction container; and, more accurately, by the amount of blood present on the surgical gauze measured via the alkaline haematin technique.

Additional studies have been conducted regarding the outcome of misoprostol used in similar surgical procedures. Khan, et al[14] conducted a randomized controlled trial, which evaluated the efficacy of higher dosages of preoperative rectal (800 micrograms) misoprostol in reducing bleeding during the abdominal myomectomies of 50 patients. Their results showed that rectal misoprostol was effective in reducing intraoperative blood loss during the abdominal myomectomies. In laparoscopy-assisted vaginal hysterectomy procedures, Park, et al[15] studied rectal misoprostol in a retrospective case-control design in 117 participants. Their results also showed no significant difference in estimated blood loss.

Other routes of misoprostol have also been studied. Iavazzo, et al[7] conducted a systematic review and meta-analysis of the usage of vaginal and rectal misoprostol in the myomectomy procedures of 283 patients. Their results revealed significant differences in the mean difference of decreasing blood loss. Chai, et al[16] conducted a pilot study of single sublingual misoprostol (400 micrograms) to reduce blood loss in 64 women who underwent abdominal hysterectomies. Their results, however, were ineffective in reducing intraoperative blood loss, as well as blood transfusion requirements.

The strengths of this present study were the study design, which was the randomized double-blinded controlled trial, and adequate sample size with acceptable withdrawal and drop-out rate. The limitation was the unrecorded duration of drug-administration to operation. The surgeons able to use this results for considering usage of preoperative misoprostol for prevention of blood loss. Fortuitously, misoprostol is an inexpensive, easy to use and store medication, without serious side effects, and its pharmacokinetic benefits aid in the reduction of gynecological procedures. We feel that further study is needed to substantiate our primary and secondary outcomes; as well as in other areas; such as primary hospital circumstances with a high risk of bleeding, including pelvic adhesion and previous pelvic surgery. Varied dosages, as well as different routes of misoprostol administration, also warrant investigation.

Conclusion

Pre-operative rectal misoprostol administration cannot reduce operative blood loss, blood transfusion requirement, operative time, duration of hospital stay and incidence of side effect in patient who undergone a total abdominal hysterectomy.

Potential conflicts of interest

The authors declare no conflicts of interest exist.

References

1. Hodges KR, Davis BR, Swaim LS. Prevention and management of hysterectomy complications. Clin Obstet Gynecol 2014;57(1):43–57.
2. Nieboer TE, Johnson N, Lethaby A, Tavender E, Curr E, Garry R, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2009;(3):CD003677.
3. Clarke-Pearson DL, Geller EJ. Complications of hysterectomy. Obstet Gynecol 2013;121(3): 654–73.
4. Harris WJ. Early complications of abdominal and vaginal hysterectomy. Obstet Gynecol Surv 1995;50(11):795–805.

5. Abdel-Hafeez M, Elnaggar A, Ali M, Ismail AM, Yacoub M. Rectal misoprostol for myomectomy: A randomized placebo-controlled study. Aust N Z J of Obstet Gynaecol 2015;55(4):363–8.
6. Chavez NF, Stewart EA. Medical treatment of uterine fibroids. Clin Obstet 2001;44(2):372–84.
7. Iavazzo C, Mamais I, Gkegkes ID. Use of misoprostol in myomectomy: a systematic review and meta-analysis. Arch Gynecol Obstet 2015; 292(6):1185–91.
8. Berard V, Fiala C, Cameron S, Bombas T, Parachini M, Gemzell-Danielsson K. Instability of misoprostol tablets stored outside the blister: A potential serious concern for clinical outcome in medical abortion. PLoS One 2014;9(12):e112401.
9. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: Pharmacokinetic profiles, effects on the uterus, and side-effects. Int J Gynecol Obstet 2007;99 (S2):S160–7.
10. Khan R-U, El-Refaey H, Sharma S, Sooranna D, Stafford M. Oral, rectal, and vaginal pharmacokinetics of misoprostol. Obstet Gynecol 2004;103(5 Pt 1):866–70.
11. Naib JM, Naveed P, Fatima S. Pre-operative use of misoprostol in major gynecological surgeries. J Med Sci (Peshawar) 2013;21:171–3.
12. Tabatabai A, Karimi-Zarchi M, Meibodi B, Vaghefi M, Yazdian P, Zeidabadi M, et al. Effects of a single rectal dose of Misoprostol prior to abdominal hysterectomy in women with symptomatic leiomyoma: a randomized double-blind clinical trial. Electron Physician 2015;7(6):1372–5.
13. Maneerat P, Tongmai S. Rectal misoprostol in women undergoing myomectomy for intraoperative blood loss reduction: A double-blinded randomized placebo-controlled study. Thai J Obstet Gynaecol 2019;88–99.
14. Khan QQ, Liaqat N, Shafqat T, Bawar S. Efficacy of preoperative misoprostol in reducing hemorrhage during abdominal myomectomy. J Ayub Med Coll Abbottabad 2020;32(2):198–203.
15. Park H, Yoon BS, Seong SJ, Kim JY, Shim JY, Park CT. Can misoprostol reduce blood loss in laparoscopy-assisted vaginal hysterectomy?. Aust N Z J Obstet Gynaecol 2011;51(3):248–51.
16. Chai J, Hon E, Li CF, Pun TC, Yeung SB, Ho PC. A pilot study of pre-operative misoprostol in reducing operative blood loss during hysterectomy. Eur Obstet Gynecol Reprod Biol 2011;158(1):72–5.

SMJ