Pre-operative sublingual misoprostol and intra-operative blood loss during total abdominal hysterectomy: a randomized single-blinded controlled clinical trial

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Abstract

Objective: To determine the efficacy of sublingual misoprostol on intra-operative blood loss during Total Abdominal Hysterectomy (TAH), need for blood transfusion, hemoglobin drop, operation length, and hospital stay.

Methods: In this single-blinded randomized clinical trial, 60 patients who were candidates for TAH due to uterine fibroid or abnormal uterine bleeding were included. They were randomly divided to receive either misoprostol 400 mcg (30 cases) or vitamin B6 (30 cases) once sublingually 1 hour before TAH. All the procedures were performed by a single surgeon. The volume of blood loss, hemoglobin change, the need for blood transfusion, operation and hospital stay duration were recorded.

Results: The two groups were comparable regarding Body Mass Index (BMI) and age, gravidity, and parity. Mean (±SD) blood loss volume was lower in misoprostol group (370.13± 158.84) compared to control group (466± 204.7); P= 0.046. Hemoglobin level 24 hours after TAH had higher mean value in the misoprostol group (11.72) than in the control group (10.54 g/dL); P= 0.003. Mean hospital stay duration was shorter in the misoprostol group (3.25± 1.32 days) vs. control group (3.43± 0.5 days), P= 0.003. No significant difference was observed regarding need for blood transfusion during the operation between misoprostol (1/30 patients) vs. control group (4/30 patients). No fever was identified in either group after operation.

Conclusion: Sublingual misoprostol (400 mcg) administered 1 hour before TAH was effective in reducing blood loss volume, hemoglobin drop, and hospitalization duration.

Key words: Total abdominal hysterectomy; hemorrhage; misoprostol

Introduction

Uterine myomas are the most prevalent gynecologic benign tumors in women of reproductive age (1). Large symptomatic myomas which do not respond to medical therapies in women who have completed childbearing are considered for total abdominal hysterectomy. In fact, uterine fibroids are the most common indication for hysterectomies. Either in some regions of the world, hysterectomy is considered as the definitive treatment for large uterine fibroids (2). Another common condition for which hysterectomy is the definitive management is abnormal uterine bleeding (AUB) when medical managements fail to improve the condition.

TAH can be associated with several complications including major hemorrhage, thromboembolism, bladder injury, etc. Severe hemorrhage of more than 400 mL which may require blood transfusion is the most common complication of TAH, along with infectious complications (3). This complication is estimated to occur in about 2% of the procedures (4).

Several medical and surgical methods have been used. Shrinkage of the fibroids using hormonal manipulation by gonadotropin-releasing hormone (GnRH) analogues for 3 months before surgery has been shown to decrease the volume of fibroids and reduce their vascularity (5). Vasopressin is another option demonstrated in trials to be an effective method for this purpose (6). However, side effects of these therapies along with high costs may render these therapies unavailable or not appropriate for most patients.

One of the medical therapies that has gained attention for pre-hysterectomy use is prostaglandin E1 synthetic analogue, misoprostol. It has significant uterotonic properties. The older studies focusing on this agent have been conducted during labor and cesarean section (7-11) with promising outcomes. This practice has extended to hysterectomy and some limited trials have been done accordingly. One study assessed rectal misoprostol combined with oxytocin before laparoscopy-assisted vaginal hysterectomy (12) and showed that combination of these two uterotonic agents was efficacious in decreasing blood loss as well as procedure time. But another study did not demonstrate such effect (13). Two studies have investigated pre-operative sublingual misoprostol for blood loss during TAH (2, 14). One of these trials (2) which recruited 132 women undergoing TAH and administered 400 mcg misoprostol 30 minutes before TAH, concluded that the group for which misoprostol was used had lower blood loss (356 mL) compared to placebo group (435 mL). The authors concluded that misoprostol was an effective intervention for reducing blood loss during TAH. However, the other trial (14) studying 32 women with the same dose of misoprostol and the same administration route did not support the beneficial effect of misoprostol.

In view of the aforementioned findings, it seems that more studies are required for better elucidation of this topic. Hence, we intended to assess the efficacy of sublingual misoprostol as a single dose administered before TAH on intra-operative blood loss.

Materials and Methods

This was a randomized single-blinded controlled clinical trial. The study population consisted of women with large uterine fibroids who were candidates for TAH with or without salpingo-oophorecyomy (16 cases with uterine myoma and 14 cases with AUB in the misoprostol group; 11 patients with uterine myoma and 19 with AUB in the control group). Exclusion criteria were previous history of endometriosis, diabetes mellitus, obesity (BMI > 30 kg/m2), history of myomectomy, psychiatric disorders, taking GnRH agonists before operation, invasive endometrial or cervical cancers or ovarian malignancies. Also, any contraindication for misoprostol use including mitral stenosis, cardiac diseases, glaucoma, sickle cell anemia, severe hypertension, diastolic blood pressure of more than 100 mmHg, severe asthma, or severe allergic reactions to prostaglandins were excluded.

The day before TAH, demographic characteristics including age, weight, height, gravidity, and parity were recorded. In addition, blood pressure, body temperature, pulse rate at rest, and hemoglobin level were recorded. The vital sign measurements were made again before anesthesia induction and any abnormalities were documented.

A total of 60 patients were included. Using a random number table, the subjects were randomized into one of the study groups. One group received two tablets of misoprostol 200 mcg (Cytotec®, Pfizer, NY, US) sublingually one hour before TAH. The control group received two vitamin B6 tablets sublingually.

The operations were done under general anesthesia by a board-certified gynecologist. The variables recorded were blood transfusion during and after TAH (considering the hemodynamic situation of the patient), operation duration (measured from skin incision to skin closure), number of sterile gauzes used during the procedure, the volume of suction container, hemoglobin level 24 hours after TAH, temperature after the operation, and hospital stay duration. To measure the blood loss volume, the gravimetric method was used (15). In this method, the blood loss volume (m) is calculated as adding the volume of suction container (a) and weight difference of dry (b) and moist (c) gauzes: m= a + (c-b)

Statistical analyses

Descriptive indices including frequency, percentage, mean and its standard deviation were used to express data. The normal distribution of the continuous variables was determined using the Kolmogorov-Smirnov test and histogram. In order to compare quantitative variables with normal distribution, the Student t test was used. The comparison of continuous variables with non-normal distribution was made using the Mann-Whitney U test. To compare nominal variables, the Chi-square test of the Fischer's exact test was used. The significance level was set at 0.05. All analyses were performed using SPSS software (ver. 20.0, IBM).

Ethics

The study protocol and objectives were explained to the patients. Written consent was obtained prior to enrollment. The Ethics Committee of our medical university approved the study protocol. This study was registered in the website of Iranian Clinical Trial No. IRCT201610224025N8.

Results

Baseline variables

Mean (±SD) age of the sample was 47.9 (±5.23) years (range, 37 to 66). Mean (±SD) BMI (body mass index) value was 27.59 (3.82) kg/m2 (range, 22.3 to 37.3). The two groups were comparable regarding age, weight, height, BMI, gravidity, and parity (Table 1). Mean (±SD) pre-operative hemoglobin values in misoprostol and control group were respectively 11.86 (±2.26) and 11.80 (±1.81) g/dL, P= 0.9.

Table 1: Comparison of demographic variables between sublingual misoprostol and control (vitamin B6) groups

	Misoprostol (N= 30)	Control (N= 30)	P value
Age, year	47.6 (±6.29)	48.21 (±3.94)	0.48[a]
Weight, kg	70.17 (±10.76)	69.93 (±16.92)	0.56[b]
Height, cm	159.37 (±4.48)	159.32 (±5.94)	0.99[b]
BMI, kg/m²	28.06 (±4.29)	27.11 (±3.28)	0.34[a]
Gravidity	4.03 (±1.97)	4.38 (±2.04)	0.51[a]
Parity	3.87 (±2.14)	4.11 (±2.01)	0.61[a]

Data are presented as mean (±SD); [a] Student t test; b Mann-Whitney U test

Peri-operative variables

The mean (±SD) body temperature just before anesthesia induction was significantly higher in the misoprostol group (37.44± 0.55ºC) than in the control group (35.9 ±6.78ºC); P= 0.01. Table 2 presents comparison of the measured variables during TAH between the two groups. Observed suction container volume and blood loss volume were significantly lower in the misoprostol group compared to control group. Regarding need for blood transfusion, one patient in the misoprostol group and four patients in the control group required transfusion (P= 0.16). TAH duration was marginally shorter in the misoprostol group (99.39± 17.79 min) compared to the control group (109.5± 21.74 min): P= 0.058.

Table 2: Comparison of the variables related to blood loss volume during total abdominal hysterectomy between sublingual misoprostol and control groups

	Misoprostol (N= 30)	Control (N= 30)	P value
Suction container volume, mL	27.10 (±17.79)	89 (±29.51)	< 0.001[a]
Weight difference between wet and dry gauzes	343.33 (±139.39)	420.6 (±256.48)	0.153[b]
Blood loss volume, mL	370.13 (±158.84)	466.40 (±204.7)	0.046[b]

Data are presented as mean (SD); [a] Mann-Whitney U test; b Student's t test

Post-operative variables

None of the patients in either group developed fever after the operation. Table 3 shows hemoglobin level 24 hours after the operation, change in hemoglobin, and hospital stay. Hemoglobin drop was significantly more prominent in the control group. Also, hospitalization duration was shorter in the misoprostol group.

Table 3: Comparison of hemoglobin change after total abdominal hysterectomy and hospitalization duration between sublingual misoprostol and control groups

	Misoprostol (N= 30)	Control (N= 30)	P value
Hemoglobin 24 hours after TAH, g/dL	11.72 (±1.06)	10.54 (±1.81)	0.003
Hemoglobin change, g/dL	0.59 (±0.57)	1.33 (±0.73)	< 0.001
Hospital stay, day	3.25 (±1.32)	3.43 (±0.5)	0.003

Discussion

Hysterectomy is considered the most common gynecologic procedure performed (3). Hemorrhage is one of the main complications of hysterectomy and some factors affect this complication. Perhaps, the most important factor is the route of hysterectomy. Blood loss in abdominal hysterectomy is more severe than vaginal or laparoscopic method (16). In addition, other factors that can affect the volume of blood loss are technical considerations, obesity, medications (aspirin), anatomy, etc(3). As hemorrhage increases the risk of blood transfusion and post-operative morbidities, prevention of significant blood loss is one of the main priorities in TAH.

Efforts have been done in order to determine the efficacy of various pre-operative methods in preventing significant blood loss. One of these methods is use of uterotonic medications such as misoprostol. As stated earlier the early studies which used misoprostol in this field relate to post-partum hemorrhage control (either alone or in combination with oxytocin) with mixed results (7, 9-11). More studies favor the usefulness of misoprostol for post-partum hemorrhage control. Based on these observations, experts started to study misoprostol in gynecologic procedures such as abdominal myomectomy (1, 12, 17) owing to its uterotonic effects as well as increasing uterine artery resistance (2). The results of these studies were promising as reflected in a systematic review on 283 patients in 2015 and noted that mean difference of blood loss between misoprostol and placebo groups was -148.55 mL per operation (95 % CI, -233.10 to -64), $p < 0.001$ (18). Based on the current findings, misoprostol was an effective method in decreasing blood loss and hospital stay duration. Although the need for blood transfusion was not statistically significant, more patients in the control group required blood transfusion and only one patient in the misoprostol group required such intervention.

Although studies about misoprostol use in obstetrics and myomectomy are sufficient, limited studies about misoprostol use in TAH, as the most common gynecologic procedure, has been done. In a previous study (2), the authors studied sublingual misoprostol for TAH (administered half an hour before operation) performed in 132 women. Mean blood loss in the misoprostol group (356 mL) was significantly lower than in the control group (435 mL). This finding is compatible with what we observed herein. According to our findings, hemoglobin level assayed 24 hours after TAH was significantly higher in the misoprostol group. This is in agreement with the previous study (2) which reported mean hemoglobin level of 10.5 in the misoprostol group which was higher compared to the control group (9.5 g/dL). The authors did not find any significant difference regarding hospital stay. In contrast, we observed that patients in the misoprostol group had significantly shorter hospital stay.
Another study (14) investigated sublingual misoprostol in 32 TAH patients. They reported that blood loss in the misoprostol group was on average 570 mL and not much different from the placebo group which was 521 mL. Also, intra-operative and post-operative rates of blood transfusion were not different between the groups. In contrast to our findings, the authors of the mentioned study did not find any changes in hemoglobin level.

The misoprostol dosage (400 mcg) and route of administration (sublingual) is identical in our study and two pertinent previous studies (2, 14). Misoprostol dosage and administration route are important factors in studies. Different methods of administration include sublingual, rectal, or vaginal routes. Bioavailability of misoprostol is higher in sublingual method compared to other methods (19).

Conclusion

Sublingual misoprostol (400 mcg) administered 1 hour before TAH was effective in reducing blood loss volume, hemoglobin drop, and hospitalization duration.

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References

1. Abdel-Hafeez M, Elnaggar A, Ali M, Ismail AM, Yacoub M. Rectal misoprostol for myomectomy: A randomised placebo-controlled study. Aust N Z J Obstet Gynaecol 2015;55(4):363-8.
2. Biswas J, Chaudhuri P, Mandal A, Bandyopadhyay SN, Dasgupta S, Pal A. Effect of a single preoperative dose of sublingual misoprostol on intraoperative blood loss during total abdominal hysterectomy. Int J Gynaecol Obstet 2013;122(3):244-7.
3. Clarke-Pearson DL, Geller EJ. Complications of hysterectomy. Obstet Gynecol 2013;121(3):654-73.
4. Maresh MJ, Metcalfe MA, McPherson K, Overton C, Hall V, Hargreaves J, et al. The VALUE national hysterectomy study: description of the patients and their surgery. Bjog 2002;109(3):302-12.
5. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev 2000(2): Cd000547.
6. Okin CR, Guido RS, Meyn LA, Ramanathan S. Vasopressin during abdominal hysterectomy: a randomized controlled trial. Obstet Gynecol 2001;97(6):867-72.
7. Chaudhuri P, Majumdar A. Sublingual misoprostol as an adjunct to oxytocin during cesarean delivery in women at risk of postpartum hemorrhage. Int J Gynaecol Obstet 2015;128(1):48-52.
8. Chaudhuri P, Mandi S, Mazumdar A. Rectally administrated misoprostol as an alternative to intravenous oxytocin infusion for preventing post-partum hemorrhage after cesarean delivery. J Obstet Gynaecol Res 2014;40(9):2023-30.
9. El Sharkwy IA. Carbetocin versus sublingual misoprostol plus oxytocin infusion for prevention of postpartum hemorrhage at cesarean section in patients with risk factors:

a randomized, open trail study. Archives of gynecology and obstetrics. 2013 Dec 1;288(6):1231-6.
10. Tewatia R, Rani S, Srivastav U, Makhija B. Sublingual misoprostol versus intravenous oxytocin in prevention of post-partum hemorrhage. Arch Gynecol Obstet 2014;289(4):739-42.
11. Owonikoko KM, Arowojolu AO, Okunlola MA. Effect of sublingual misoprostol versus intravenous oxytocin on reducing blood loss at cesarean section in Nigeria: a randomized controlled trial. J Obstet Gynaecol Res 2011;37(7):715-21.
12. Chang FW, Yu MH, Ku CH, Chen CH, Wu GJ, Liu JY. Effect of uterotonics on intra-operative blood loss during laparoscopy-assisted vaginal hysterectomy: a randomised controlled trial. Bjog 2006;113(1):47-52.
13. 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.
14. 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 J Obstet Gynecol Reprod Biol 2011;158(1):72-5.
15. Johar RS, Smith RP. Assessing gravimetric estimation of intraoperative blood loss. J Gynecol Surg 1993;9(3):151-4.