The Egyptian Journal of Hospital Medicine (October 2017) Vol.69(1), Page 1692-1697

Effect of Sublingual Misoprostol on Intraoperative Blood Loss During Abdominal Hysterectomy: Randomized Controlled Trial

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ABSTRACT

Objective: To investigate whether the use of preoperative misoprostol can reduce blood loss during total abdominal hysterectomy (TAH).

Methods: In a randomized single-blind placebo-controlled trial at Ain Shams university maternity hospital, between May 2016 and June 2017, women (n = 118) undergoing TAH with or without bilateral salpingo-oophorectomy for symptomatic myomas were randomly allocated to receive either 400 μg of misoprostol or placebo 30 minutes before surgery.

The primary outcome measure was postoperative drop in hemoglobin.

The secondary outcomes were intraoperative blood loss, need for blood transfusion, and incidence of adverse effects. **Results**: The 2 groups were similar with regard to demographic and clinical characteristics. There was a significant reduction of blood loss during TAH after sublingual administration of misoprostol compared with placebo before surgery (355.1 mL vs 531.4 mL; $P < 0.001$). The mean postoperative hemoglobin concentration was higher (11.1g/dL vs 10.7 g/dL; $P < 0.015$) and the postoperative drop in hemoglobin was smaller (1.2 g/dL vs 1.8 g/dL; $P < 0.001$) in the misoprostol group than in the placebo group.

No significant adverse effects occurred in either group.

Conclusion: The results showed that a single dose of misoprostol administered before abdominal hysterectomy resulted in a significant reduction of blood loss with minimal adverse effects.

Keywords: Blood loss, Misoprostol, Total abdominal hysterectomy.

INTRODUCTION

Hysterectomy is the surgical removal of the uterus. It is the most frequently performed major gynaecological surgical procedure, with millions of procedures performed annually throughout the world [(1)].

Hysterectomy can be performed for benign and malignant indications. Approximately 90% of hysterectomies are performed for benign conditions, such as fibroids causing abnormal uterine bleeding; other indications include endometriosis/adenomyosis, dysmenorrhoea, dyspareunia and prolapsed [(2)].

Hemorrhage requiring blood transfusion is one of the most frequently cited complications of total abdominal hysterectomy, occurring in 2%–12% of cases [(3)].

Various methods had been adopted by researchers to lessen blood loss during TAH. Preoperative administration of gonadotropin-releasing hormone (GnRH) analogs have been found to be effective in reducing the size and vascularity of large myomas; however, significant adverse effects like hot flushes and osteoporosis have been reported after its use [(4)].

Although injection of vasopressin in the lower uterine segment was found to be beneficial in reducing blood loss during abdominal hysterectomy, serious complications such as hypotension, myocardial infarction, and cuff cellulitis have been reported after use of this drug [(5)]. Misoprostol, a synthetic analogue of prostaglandin E1, has been extensively evaluated as an uterotonic agent in obstetrics mainly for prevention and management of postpartum hemorrhage and reduction of bleeding during cesarean delivery [(6)].

The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue. The peak concentration is achieved about 30 minutes after sublingual administration, a sublingual dose achieves a higher peak concentration than that of oral and vaginal administration. This is due to rapid absorption through the sublingual mucosa as well as the avoidance of the first-pass metabolism via the liver [(7)]. Among non-pregnant women, misoprostol has been used for cervical priming before trans-cervical procedures [(8)], and for reducing blood loss in myomectomy [(9)] **and** laparoscopy-assisted vaginal hysterectomy with promising results [(10)].

Received: 9 / 7/2017
Accepted:18 /7 /2017
DOI : 10.12816/0040119

Strong myometrial contractions induced by misoprostol indirectly cause relative a vascularity in the myoma and may also contribute to a reduction in bleeding. In addition, a decrease in uterine artery blood flow in myoma has been observed by Doppler velocimetry after misoprostol administration [(11)].

PATIENTS AND METHODS

In a single-blind, randomized, placebo-controlled trial conducted at the Institute of Ain Shams University Maternity Hospital, Cairo, Egypt, women undergoing TAH with or without bilateral salpingooophorectomy (BSO) between May 2016 and June 2017, were enrolled. Written informed consent was obtained from each eligible participant.

The study was approved by the institutional ethics committee.

During the study period, women with symptomatic myomas were initially counseled about the available treatment options and those who opted for TAH with or without BSO were screened for eligibility. Women with heart disease, severe hypertension, hematologic disorders, glaucoma, bronchial asthma, liver disease, or pelvic endometriosis and adnexal mass, and those who had undergone previous myomectomy were excluded from the study. Women who received GnRH analogs and who were allergic to prostaglandins were also excluded.

A total of 118 women were included in the study. They were randomly allocated in two groups:

Group A: Patients undergoing total abdominal hysterectomy and will be receiving 400 μg of Misoprostol 30 minutes before operation (59 patients).

Group B: Patients undergoing total abdominal hysterectomy and will be receiving Placebo 30 minutes before operation (59 patients).

A few hours before the expected time of surgery, enrolled women were randomized to the study or control group via a computer generated random number sequence. Those randomized to the study group received a pre-prepared sealed opaque packet containing 400 μg of misoprostol (Misotac, SIGMA Pharmaceutical Industries, Cairo, Egypt;2 tablets of 200 μg), whereas those allocated to the control group received a similar packet containing 2 placebo tablets.

The placebo tablets were similar to the misoprostol tablets in size, shape, and color,

Baseline demographic data comprising age, parity, body mass index (calculated as weight in kilograms divided by the square of height in meters), and size of uterus were recorded. Preoperative hemoglobin levels were measured.

A gravimetric method was used to measure blood loss. The total volume of blood loss (M) during operation was measured by adding the volume of contents of the suction container (a) to the difference in weight (where 1.06 g is equivalent to 1 mL) between the dry (b) and wet (c) mops used during operation: $M = a + (c - b)$ [(8)].

The total duration of surgery from skin incision to skin closure was noted. Postoperative hemoglobin levels were measured 24 hours after the operation. An automated cyanmethemoglobin method was used for hemoglobin measurement. Records were kept regarding blood transfusions and complications during the postoperative period.

Patients were discharged on postoperative day 5 if permissible and asked to attend an outpatient department for follow-up 6 weeks after the operation or earlier if required.

The primary outcome measure was the drop in hemoglobin level 24 hours after the operation. Secondary outcome measures were the drop intraoperative blood loss, requirement for blood transfusion, duration of hospital stay, and incidence of complications.

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

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013.

Descriptive statistics were done for quantitative data as minimum & maximum of the range as well as mean±SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with normally distributed data. In qualitative data, inferential analyses for independent variables were done using Chi square

test for differences between proportions and Fisher's Exact test for variables with small expected numbers. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

RESULTS

The study was reported in accordance with the CONSORT scheme

(Fig. 1).

During the study period, 123 women with symptomatic myoma who opted for TAH with or without BSO were screened for eligibility. Four women were excluded as they didn't met inclusion criteria. One woman declined to participate.

As a result, 118 women were recruited and randomly allocated to the study and control groups before surgery.

Both groups were similar in terms of baseline variables as age, BMI, preoperative hemoglobin concentrations, size and weight of uterus, incidence of previous operative scars, and duration of surgery (Table 1).

The mean operative blood loss was significantly less in the misoprostol

group than in the placebo group 355.1±160.2 mL vs 531.4±216.5 mL; P <0.001) (Table 2).

The mean postoperative hemoglobin concentration was higher in the misoprostol group than in the placebo group (11.1±1.2 g/dL vs 10.7±0.9 g/dL; P < **0.015**); similarly, women in the misoprostol group had a smaller drop in hemoglobin levels after surgery compared with women in the placebo group (1.2±0.9 g/dL vs 1.9 ± 1.8±0.8 g/dL; P <0.001) (Table 3).

No significant difference was observed in the requirement for blood transfusions or duration of hospital stay between the 2 groups. The incidence of adverse effects was similar between the 2 groups (Table 4).

No major complication or morbidity occurred in either group.

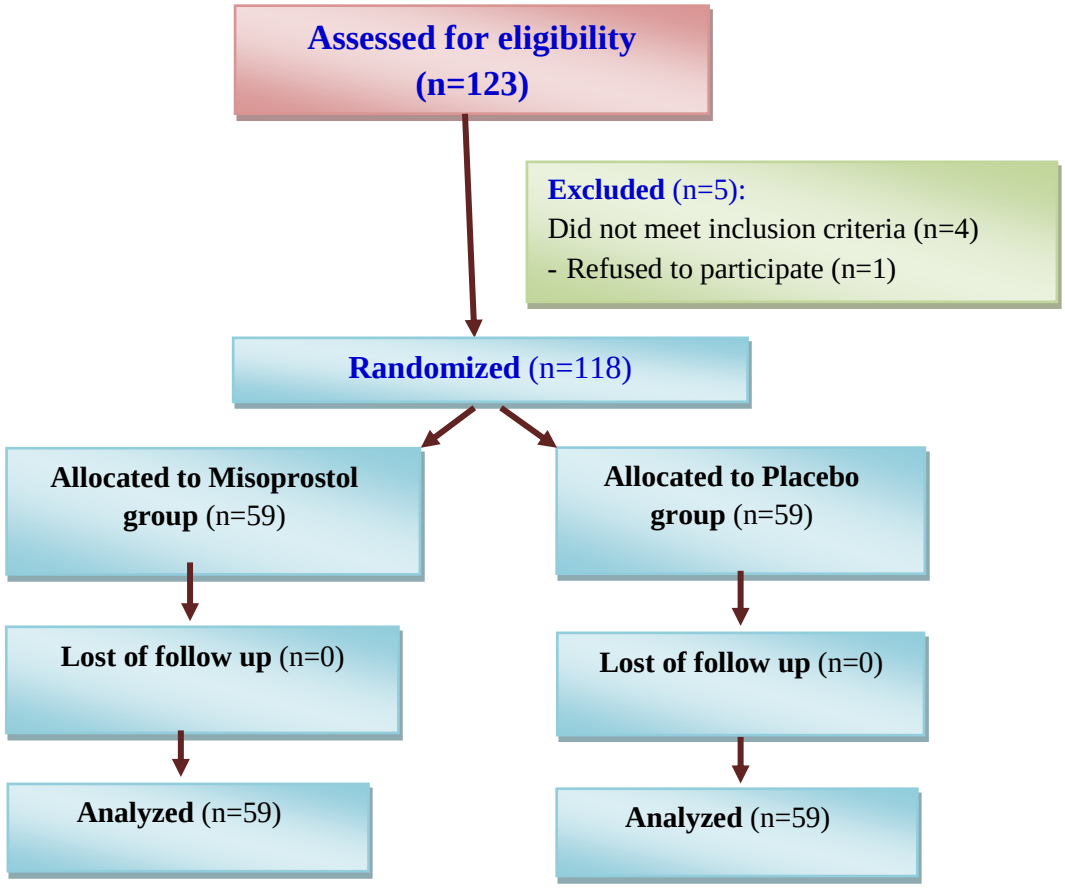

Figure (1): Consort, Patient flow chart.

Table (1): Demographic characteristics among the studied groups.

Items	Measure	Misoprostol (N=59)	Placebo (N=59)	P-value
Age (years)	**Mean±SD**	45.5±2.0	45.2±2.1	^0.419
	Range	41.0–50.0	40.0–50.0	
BMI (kg/m^2)	**Mean±SD**	27.5±1.0	27.6±1.0	^0.495
	Range	25.1–29.8	25.4–29.6	
Parity	**Mean±SD**	3.0±0.9	3.0±0.8	^0.914
	Range	1.0–5.0	1.0–5.0	

^Independent t-test, #Chi square test

Table (2): Blood loss (mL) among the studied groups.

Measure	Misoprostol (N=59)	Placebo (N=59)	P-value
Mean±SD	355.1±160.2	531.4±216.5	^<**0.001***
Range	200.0–1000.0	200.0–1050.0	
Value of misprostol			
Blood loss difference	**Mean±SE**	**95% CI**	
Blood loss reduction	176.3±35.1	106.8–245.7	

Independent t-test, **CI**: Confidence interval, S: significant

Table (2) show that: **Blood loss** was significantly lower among misoprostol group than among placebo group.

Table (3): Hemoglobin (gm/dL) among the studied groups.

Variable	Measure	Misoprostol (N=59)	Placebo (N=59)	P-value
Pre Operative	**Mean±SD**	12.3±0.9	12.4±0.8	^0.489
	Range	10.7–14.7	10.8–14.2	
Post operative	**Mean±SD**	11.1±1.2	10.7±0.9	^**0.015***
	Range	8.2–14.1	8.2–12.6	
Reduction	**Mean±SD**	1.2±0.9	1.8±0.8	^<**0.001***
	Range	0.1–4.1	0.4–3.4	
Value of misprostol				
	Mean±SE	**95% CI**		
Reduction difference	0.6±0.2	0.3–0.9		

Independent t-test, CI: Confidence interval, NS: Non-significant, S: significant

Table (3) show that: No significant difference between the studied groups regarding preoperative hemoglobin. Postoperative hemoglobin was significantly higher among misoprostol group than among placebo group. Hemoglobin reduction was significantly lower among misoprostol group than among placebo group.

Table (4): Side effects among the studied groups

Conditions	Misoprostol (N=59)	Placebo (N=59)	#P	RR (95% CI)
Blood transfusion	3 (5.1%)	6 (10.2%)	0.490	0.65 (0.25–1.66)
Nausea& vomiting	6 (10.2%)	2 (3.4%)	0.272	1.56 (1.00–2.43)
Diarrhea	1 (1.7%)	0 (0.0%)	1.000	--
Headache	3 (5.1%)	1 (1.7%)	0.619	1.53 (0.84–2.77)
Fever	2 (3.4%)	1 (1.7%)	1.000	1.35 (0.59–3.06)
Shivering	1 (1.7%)	0 (0.0%)	1.000	--

#Fisher's Exact test, *Significant, RR: Relative risk, **CI:** Confidence interval

Blood transfusion was non-significantly less frequent among misoprostol group, while nausea & vomiting, diarrhea, headache fever and shivering were non-significantly more frequent among misoprostol group.

DISCUSSION

Total abdominal hysterectomy (TAH) is the widely practiced definitive management for symptomatic myoma of the uterus among parous women, particularly in low-resource countries, where costly modalities of treatment such as GnRH analogs, uterine artery embolization, and endometrial ablation are not universally available [12]. TAH is associated with considerable operative blood loss, resulting in the need for transfusions and related hazards in 2%–12% of cases, reducing this blood loss might not only lessen the requirement for transfusion but also prevent postoperative anemia and the need for hematinic drugs [13]. Effective myometrial contractions along with increased uterine artery resistance induced by misoprostol may help to reduce blood supply to the diseased uterus and thus may be an effective alternative to preoperative GnRH or intraoperative vasopressin in reducing blood loss during TAH [14].

The aim of the current study was to investigate whether preoperative administration of sublingual misoprostol is beneficial in reducing intraoperative blood loss among women undergoing total abdominal hysterectomy (TAH).

A total of 118 women were included in the study. They were randomly allocated in two groups:

Group A: Patients undergoing total abdominal hysterectomy and will be receiving 400 μg of Misoprostol 30 minutes before operation (59 patients).

Group B: Patients undergoing total abdominal hysterectomy and will be receiving Placebo 30 minutes before operation (59 patients).

In the current study, there was no significant difference between the studied groups regarding demographic characteristics (mean age 45.5 vs 45.2) (mean BMI 27.5 vs 27.6) (mean parity 3).

In the current study, there was a significant reduction of blood loss during TAH after sublingual administration of 400 μg of misoprostol 30 minutes before surgery compared with placebo (355.1 mL vs 531.4 mL; $P < 0.001$).

The present study is in agreement with the study of **Chang and colleagues 2005** who investigated the efficacy of misoprostol and oxytocin on reducing blood loss during laparoscopy-assisted vaginal hysterectomy in a placebo-controlled trial [10].They observed a significant reduction of blood loss (198.1 mL vs 396 mL; $P <0.0001$) among women receiving uterotonic drugs compared with placebo. The blood losses were lower in both the study group and the control group of Chang and colleagues 2005 than in the current study, possibly due to the use of oxytocin along with misoprostol and the laparoscopic approach of operation.

This result also agrees with **Celik and colleagues 2003** who administered misoprostol before abdominal myomectomy in a placebo-controlled study, reported blood losses of (472 mL and 621 mL) in the misoprostol and placebo groups, respectively ($P < 0.05$) [11].

Our results are also similar to that carried out by **Biswas and colleagues 2013** who recruited 132 women where misoprostol was administered in randomized controlled trial to study and control groups before total abdominal hysterectomy. They observed that the mean operative blood loss was significantly less in the misoprostol group than in the placebo group (356.9 ± 303.7 mL vs 435.2 ±277.8 mL; $P = 0.049$) [12].

The present result agrees with **Tabatabai and colleagues 2015** who used a 400 microgram rectal dose before total abdominal hysterectomy and demonstrated that single rectal dose of misoprostol significantly decreases peri-operative bleeding in comparison to a placebo [14].

Our results are also in consistent with **Chai and colleagues 2011** who designed a pilot study among 64 women undergoing TAH and failed to show any significant reduction of intraoperative blood loss during TAH when compared to placebo (570 mL vs 521 mL; $P = 0.904$); This may be due to non-exclusion of women with major adhesions and a smaller sample size [15].

In the current study, the mean postoperative hemoglobin concentration was higher (11.1g/dL vs 10.7 g/dL; $P < 0.015$) and the postoperative drop of hemoglobin was smaller (1.2 g/dL vs 1.8 g/dL; $P < 0.001$) in the misoprostol group in comparison to a placebo. This result agrees with **Chang and colleagues 2005** who observed a smaller drop in postoperative hemoglobin (1.5 g/dL vs 1.9 g/dL; $P = 0.02$) and hematocrit levels (4.8 % vs 5.8%; $P = 0.04$) among women receiving uterotonic drugs compared with placebo [10].

The result also agrees with **Celik and colleagues 2003** who observed postoperative hemoglobin levels of (9.7 g/dL and 8.9 g/dL) in the misoprostol and placebo groups respectively ($P < 0.05$) [11]. In addition, our result is similar to **Biswas and colleagues 2013** who demonstrated the mean

postoperative hemoglobin concentration was higher in the misoprostol group than in the placebo group (10.5 ± 1.2 g/dL vs 9.5 ± 1.3 g/dL) [12].

The result of this study is in consistent with **Tabatabai and colleagues 2015** who noted that Hb levels decrease significantly 8 hours following the operation, but this change was similar in both groups [14]. The route and timing of administration of misoprostol varies between reported studies. Vaginal and rectal administration 1 hour before surgery was used by **Celik and colleagues 2003** and **Chang and colleagues 2005** respectively.

Similar to the study of **Chai and colleagues 2011** and **Biswas and colleagues 2013** a sublingual route of misoprostol administration 30 minutes before surgery was used in the current study.

The sublingual route offers unique pharmacokinetic advantages in terms of rapid onset of action and greater bioavailability, leading to a longer duration of action compared with other administrative routes [16].

CONCLUSION

This study concludes a single preoperative dose of 400 μg of misoprostol administered 30 minutes before abdominal hysterectomy resulted in a significant reduction of blood loss and the subsequent need for blood transfusion and risk of morbidity related to anemia.

The foremost advantage of misoprostol would be its low cost compared with popular methods of reducing bleeding with GnRH analogs and vasopressin. Large trials comparing the efficacy of misoprostol with that of GnRH and vasopressin are required to verify the beneficial effects of this drug.

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