Original Research Article

Effect of preoperative single dose misoprostol on intraoperative blood loss during abdominal hysterectomy: a randomized controlled trial

Running title: Preoperative misoprostol on blood loss during TAH

Abstract:

Background: 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**.** Hysterectomy can be performed for benign and malignant indications. Misoprostol, a synthetic analogue of prostaglandin E1, has been extensively evaluated as an uterotonic agent in obstetrics mainly for prevention and management of postpartum haemorrhage and reduction of bleeding during caesarean delivery**.** The purpose of this research is to evaluate the impact and efficacy of pre-operative sublingual misoprostol given in women having hysterectomy in terms of blood loss.

Results: This randomized single blind controlled trial was carried on 70 women undergoing total abdominal hysterectomy. They were randomly allocated in two equal groups: misoprostol group: patients received two tablets of Misoprostol 400 μg (one tablet=200 μg) 30 minutes before operation and a control group (placebo group): patients received two tablets of Placebo 30 minutes before operation.

Haemoglobin and Haematocrit reductions were significantly lower among misoprostol group than among placebo group. Blood loss was significantly lower among misoprostol group than

among placebo group. The most common indication for hysterectomy were fibroid, dysfunction uterine bleeding and, adenomyosis. Fibroid was the most significance for the effect of misoprostol in decrease blood loss, haemoglobin and haematocrit during abdominal hysterectomy more than adenomyosis and dysfunction uterine bleeding.

Conclusions: A single preoperative dose of 400 μg of misoprostol administered 30 minutes before abdominal hysterectomy resulted in a significant reduction of blood loss.

Keywords: Misoprostol, Intraoperative Blood Loss, Abdominal Hysterectomy

Background

Misoprostol, a prostaglandin E1 analogue, has been widely studied as a uterotonic drug in obstetrics, primarily for the prevention and treatment of postpartum haemorrhage and the decrease of bleeding after caesarean birth [1, 2]. Misoprostol has been utilised for cervical priming before transcervical operations in non-pregnant women [3], for decreasing blood loss in myomectomy [4, 5] and laparoscopy-assisted vaginal hysterectomy with fruitful findings.

The most frequent surgical treatment for uterus big symptomatic leiomyoma remains abdominal hysterectomy (AH). One of the most commonly reported consequences of this operation is haemorrhage, which necessitates blood transfusion in 2%–12% of patients [6].

Low-dose mifepristone has also been used successfully for the same reason [7, 8]. Limited studies have evaluated the effects of preoperative misoprostol on AH related blood loss [9]. Misoprostol may induce direct vasoconstriction in uterine arteries, which is most likely beneficial in decreasing blood loss during AH. Strong myometrial contractions caused by misoprostol produce relative avascularity in the myoma and could further lead to a decrease in bleeding, especially in women who need concurrent myomectomy for cervical and wide ligament myoma. Furthermore, Doppler velocimetry revealed a reduction in uterine artery blood flow in myoma patients following misoprostol treatment [10].

Misoprostol, which is often incorporated in curing and preventing postpartum haemorrhage in obstetrics, has been shown to reduce intraoperative blood loss in abdominal hysterectomy. The purpose of this research is to evaluate the efficacy of pre-operative sublingual misoprostol given in women having hysterectomy in terms of blood loss.

Methods

This randomized controlled single blind trial was carried out at Obstetrics and Gynaecology Department, Tanta University Hospital, Egypt. This study was accredited by the Ethics Committee of the Department of Obstetrics and Gynaecology, the Faculty of Medicine, Tanta

University (Approval code: 33071/04/19). Informed written consent were collected from the entire group of participants prior to participation, and also post the explanation of research purpose and procedures.

The inclusion criteria were: (age ranging between 35-55 years-BMI (20-30) kg/m^2-Patients with abnormal uterine bleeding suffering from one or more of the following: fibroid, endometriosis, adenomyosis, dysfunctional uterine bleeding and pelvic inflammatory disease).

While the criteria of exclusion were: (Women suffering cardiovascular diseases, severe hypertension, hematologic illnesses, glaucoma, bronchial asthma, liver disease- women with adnexal mass- women who went for myomectomy before- females provided with GnRH analogs- females that received anticoagulant drugs- women allergic to prostaglandins- past history of Malignancy & extensive adhesions.

Patients were allocated randomly into two groups: Study group: (misoprostol G): Patients undergoing total AH and received two sublingual Misoprostol tablets 400 μg (one tablet=200 μg)30 minutes before operation (35 patients). Control group: (placebo G): Patients undergoing total AH and received two sublingual Placebo tablets 30 minutes before operation (35 patients).

The outcome criteria which were evaluated and compared in both groups are: main consequence was intraoperative bleeding while 2ry outcome measures were postoperative haemoglobin reduction, required blood transfusion, and occurrence of opposing factors. Side effects of misoprostol including abdominal pain, nausea, vomiting and diarrhoea were recorded 30 minutes after administration of the drug.

Statistical analysis

The obtained data were documented, tabulated, and analysed using IBM SPSS statistics software version 22.0, IBM Corp., Chicago, USA, 2013. Descriptive statistics were computed

for quantitative data as the lowest and maximum of the range, as well as the mean SD (standard deviation) for quantitative normally distributed data, and for qualitative data as a number and a percentage. In the instance of two independent groups with normally distributed data, inferential studies for quantitative variables were performed using the independent t-test. Inferential studies for independent variables in qualitative data were performed using Chi square and Fisher's exact test for variables with small anticipated numbers. The threshold of significance was set at P value 0.050, which indicates that the data is significant; otherwise, it is not.

Results:

Regarding demographic characteristics, no significant variation was found between the studied groups. Table (1)

Table 1: Demographic features of studied groups:

		Misoprostol n=35	**Placebo n=35**	**T. test**	**P. value**
Age (years)	**Range**	35 – 55	35 – 55	0.172	0.864
	Mean ± SD	46.11 ± 6.27	46.37 ± 6.22		
BMI (kg/m^2)	**Range**	25 – 30	25 – 30	0.275	0.784
	Mean ± SD	27.94 ± 1.78	27.83 ± 1.69		
Parity	**Range**	1 – 5	1 – 5	0.103	0.918
	Mean ± SD	3.26 ± 1.20	3.29 ± 1.13		
Gravidity	**Range**	2 – 5	2 – 5	0.063	.802
	Mean ± SD	3.49 ± 0.95	3.43 ± 0.95		

BMI: body mass index

Regarding preoperative haemoglobin and haematocrit, the study discovered no significant variation among the studied groups. While postoperative haemoglobin and haematocrit were significantly elevated among the misoprostol group rather than the placebo group.

Haemoglobin reduction and Haematocrit reduction were significantly dropped among misoprostol group rather than the placebo group. Table (2)

Table 2: Pre and post-operative haemoglobin and haematocrit among the studied groups

			Misoprostol n=35	Placebo n=35	T. test	P. value
Hb	Pre	Range	10.7 – 14.7	10.7 – 14.2	0.064	0.949
		Mean ± SD	12.08 ± 1.15	12.06 ± 1.09		
	Post	Range	8.2 – 14.1	8.2 – 12.6	2.225	0.029*
		Mean ± SD	11.17 ± 1.45	10.44 ± 1.28		
	T. test		3.102	5.701		
	P. value		0.003*	0.001*		
HCT	Pre	Range	31.3 – 44.3	32 – 45	0.176	0.861
		Mean ± SD	37.89 ± 3.86	38.05 ± 3.76		
	Post	Range	28.1 – 43.4	27.5 – 40	2.971	0.004*
		Mean ± SD	36.64 ± 4.20	33.84 ± 3.65		
	T. test		1.302	4.749		
	P. value		0.199	0.001*		

Hb: haemoglobin, Hct: haematocrit

Regarding Blood loss(ml), it was significantly decreased among misoprostol group in contrast to placebo group. While operation time(minute) was insignificantly lower among misoprostol group than among placebo group and blood transfusion(unit) was non-significantly reduced frequent for misoprostol group. Table (3)

Table 3: Blood loss, operation time and blood transfusion among the studied groups

		Misoprostol n=35	Placebo n=35	T. test	P. value
Blood loss (ml)	Range	200 – 1000	300 – 1050	3.953	0.001*
	Mean ± SD	450 ± 206.16	635.71 ± 186.43		
Operation time(minutes)	Range	90 – 123	90 – 130	1.774	0.080
	Mean ± SD	104.51 ± 10.49	109.43 ± 12.59		
Blood Transfusion	Yes	3 (8.6%)	6 (17.1%)	FET: 1.167	0.477
	No	32 (91.4%)	29 (82.9%)		

Regarding side effects among the studied groups, Nausea & vomiting were significantly more frequent among misoprostol group than placebo group while diarrhea, headache, fever and shivering were non-significantly prevalent with misoprostol group in contrast to the placebo group. Table (4)

Table 4: Side effects among the studied groups

Side effects			Misoprostol	Placebo	FET	P-value
Nausea& vomiting	Yes	N	6	1	3.968	0.046*
		%	17.1%	2.9%		
	No	N	29	34		
		%	82.9%	97.1%		
Diarrhoea	Yes	N	1	0	1.401	1.0
		%	2.9%	.0%		
	No	N	34	35		
		%	97.1%	100.0%		
Headache	Yes	N	3	1	1.061	0.303
		%	8.6%	2.9%		
	No	N	32	34		
		%	91.4%	97.1%		
Fever	Yes	N	2	0	2.831	0.493
		%	5.7%	.0%		
	No	N	33	35		
		%	94.3%	100.0%		
Shivering	Yes	N	1	0	1.401	1.0
		%	2.9%	.0%		
	No	N	34	35		
		%	97.1%	100.0%		

Regarding indication of hysterectomy, fibroid (42.9%) was the commonest indication in our study then dysfunctional uterine bleeding then endometriosis, pelvic inflammatory disease and adenomyosis. Table (5)

Table 5: Distribution of groups according to indication of hysterectomy:

	Misoprostol (n=35)		Placebo (n=35)		X2	P-value
	N	%	N	%		
Fibroid	15	42.9	15	42.9	0.0	1.0
Endometriosis	4	11.4	4	11.4	0.0	1.0
Adenomyosis	3	8.6	3	8.6	0.0	1.0
Dysfunctional uterine bleeding	10	28.6	10	28.6	0.0	1.0
Pelvic inflammatory disease	3	8.6	3	8.6	0.0	1.0

Regarding effect of misoprostol and placebo on fibroid groups, Fibroid was the most significance for the effect of misoprostol in decrease haemoglobin, haematocrit and blood loss during AH more than other indications. Misoprostol group more significance in decrease haemoglobin, haematocrit and blood loss than placebo group. Table (6)

Regarding effect on dysfunctional uterine bleeding (DUB) groups, there was decrease in haemoglobin, haematocrit and blood loss among misoprostol group than placebo group. Table (6)

Table 6: Effect of misoprostol and placebo on fibroid and DUB groups:

Fibroid		**Misoprostol (n=15)**	**Placebo (n=15)**	**T. test**	**P. value**
Hb	**Range**	9.5 – 14.1	8.2 – 12.5		
	Mean ± SD	11.57 ± 1.56	10.46 ± 1.27	2.128	0.042*
Hct	**Range**	30.7 – 43.4	28.5 – 40		
	Mean ± SD	38.01 ± 3.56	34.84 ± 3.74	2.380	0.024*
Blood loss	**Range**	200 – 400	480 – 980		
	Mean ± SD	313.33 ± 63.99	707.33 ± 136.56	10.118	0.001*
DUB		**Misoprostol (n=10)**	**Placebo (n=10)**		
Hb	**Range**	8.2 – 12.8	8.2 – 10.7		
	Mean ± SD	10.42 ± 1.65	9.51 ± 0.74	1.594	0.128
Hct	**Range**	28.1 – 41	27.5 – 36.5		
	Mean ± SD	34.11 ± 4.96	31.34 ± 3.12	1.495	0.152
Blood Loss	**Range**	400 – 1000	400 – 1050		
	Mean ± SD	650.00 ± 267.71	692.00 ± 11.07	0.390	0.701

DUB: Dysfunctional uterine bleeding, Hb: haemoglobin, Hct: haematocrit

Discussion

Total abdominal hysterectomy (TAH) is the most often used final therapy for symptomatic uterine myoma in parous women, especially in low-resource countries where expensive treatment modalities such as GnRH analogues, uterine artery embolization, and endometrial ablation aren't generally accessible [(11)].

TAH is associated with considerable operative blood loss, resulting in the need for transfusions TAH is linked with significant operational bleeding, leading to required for transfusion and related risks in 2%–12% of patients; decreasing this blood loss may not only reduce the need for transfusion but also avoid postoperative anaemia and required hematinic medications [(12)]. Effective myometrial contractions along with elevated uterine artery resistance developed by misoprostol can decrease blood supply to the diseased uterus, hence it could be a good alternative to preoperative GnRH or intraoperative vasopressin in dropping TAH related blood loss.

The current research agrees with the study of Chang and colleagues (2005) who studied the effectiveness of misoprostol and oxytocin in decreasing blood loss during laparoscopic-assisted vaginal hysterectomy [13]. When comparing uterotonic medicines to placebo, they found a substantial decrease in blood loss (198.1 mL vs 396 mL; P 0.0001). Blood losses were smaller in both the study and control groups of Chang and colleagues (2005) than in the present research, perhaps owing to the use of oxytocin in conjunction with misoprostol and the laparoscopic approach to surgery.

This result also agrees with Celik and colleagues (2003) who gave misoprostol in a placebo-controlled trial before abdominal myomectomy, and blood losses were (472 mL and 621 mL) in the misoprostol and placebo groups, respectively (P 0.05) [10].

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 lower in misoprostol group in comparison to placebo group (356.9 ± 303.7 mL vs 435.2 ±277.8 mL; P = 0.049). [11]

The present result agrees with Tabatabai and colleagues (2015) who used a 400-microgram rectal dose before TAH and demonstrated that a single rectal misoprostol dose significantly reduced 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 on 64 TAH women and didn't give any significant decrease in intraoperative blooding during TAH when compared to placebo (570 mL vs 521 mL; P = 0.904); This may be due to not excluding females with major adhesions and a fewer sample [15].

In the current study, the mean postoperative haemoglobin concentration was more (11.1g/dL vs 10.4 g/dL; P < 0.042) and the postoperative haemoglobin reduction was slighter (1.2 g/dL vs 1.8 g/dL; P < 0.001) among misoprostol group in contrast with placebo. This result agrees

with Chang and colleagues (2005) who observed a slighter drop in postoperative haemoglobin (1.5 g/dL vs 1.9 g/dL; P = 0.02) and haematocrit rates (4.8 % vs 5.8%; P = 0.04) for females taking uterotonic drugs in comparison to placebo [13].

The result also agrees with Celik and colleagues (2003) who observed postoperative haemoglobin rates of (9.7 g/dL and 8.9 g/dL) among misoprostol and placebo groups respectively (P < 0.05). [16] In addition, our result is similar to Biswas and colleagues (2013) who demonstrated the mean postoperative haemoglobin concentration was raised in misoprostol group rather than among the placebo participants (10.5 ± 1.2 g/dL vs 9.5 ± 1.3 g/dL) [11].

The result of this study is in consistent with Tabatabai and colleagues (2015) who learnt that Hb rates significantly drop during 8 hours post operation, yet this alteration was equivalent in both groups [14].

The method and time of misoprostol delivery differs across published research. Celik and colleagues utilised vaginal and rectal administration one hour before surgery (2003) and Chang and colleagues (2005) accordingly. In parallel with the study of Chai and colleagues (2011) and Biswas and colleagues (2013) In the present research, misoprostol was administered sublingually 30 minutes before surgery. When compared to other administration methods, the sublingual route provides distinct pharmacokinetic benefits in terms of quick start of action and increased bioavailability, resulting in an extended effect period [16].

Another research looked at how misoprostol affected bleeding after a hysterectomy. In contrast to the current study's findings, the preoperative dosage of misoprostol had no meaningful impact on decreasing intraoperative bleeding [5]. This may be owing to the smaller sample size in the previous research compared to the current study, which could have an impact on the statistical significance of the findings. Although the direct impact of sublingual misoprostol on postoperative bleeding hasn't been studied, the effect of this

medication on decreasing intraoperative bleeding has been studied in gynaecological surgical research. In this respect, a research conducted by Soleimani et al. showed that sublingual misoprostol was helpful in reducing intraoperative bleeding, with the decrease in haemoglobin and haematocrit levels in the misoprostol group being substantially lower than those in the placebo group. Furthermore, there was no statistically significant variance amongst both groups in terms of the requirement for a blood transfusion or the occurrence of medication-related side effects [17]. These findings are consistent with the findings of the present research, which looked at the impact of misoprostol on decreasing intraoperative bleeding. The referenced research, like ours, found that the decrease in bleeding did not reduce the requirement for a blood transfusion [17].

Misoprostol's beneficial impact in reducing bleeding after myomectomies was verified in another research. Furthermore, there was no difference between the groups in the requirement for a postoperative blood transfusion [14, 18].

In parallel with Lyari General Hospital, Dow University of Health Sciences Karachi 2007, the most frequent indications for hysterectomy in our research were fibroid, dysfunction uterine haemorrhage, and adenomyosis. Even in affluent nations, hysterectomy is still the most often utilised therapeutic technique. The most frequent pathology is leiomyoma, which is caused by menstrual irregularities. The most common cause of menstruation problems is adenomyosis.

Most diseases had a peak age category incidence of 35-55 years and a peak parity of 3-6. In 93 percent of cases, the indications were benign illnesses. In the United States, 91.7 percent of hysterectomies are performed for benign reasons [19, 20]. The primary reason for hysterectomy in this research was leiomyoma. A research from Karachi found the same thing [21]. Hormonal disruption causes symptomatic menstruation alterations throughout the perimenopausal years. In our research, leiomyoma was the most common reason for

hysterectomy. According to several research, it's the second most common reason for hysterectomy [22, 23].

On histology, leiomyoma was the most frequent pathology, and it was the primary pathology in several investigations. Its prevalence is 25.8 percent in Saudi Arabia's Abbah city, 78 percent in the United States, 48 percent in Nigeria, and 8 percent in Sweden [24-27]. Geographical and ethnic effects on the incidence of uterine leiomyoma are therefore evident. Its highest age category was 35-55 years, which was nearly identical to a Saudi Arabian research (48 percent) [25]. In 78 percent of cases, Aboyeji et al reported an age category of 30-44 years in their research from Ilorin, Nigeria [28]. The majority were multipara, despite previous research indicating a high incidence in the low parity category [25]. Since of their multiparity, they chose hysterectomy as the treatment of choice because it reduces the morbidity related to large vascular leiomyoma [29].

As observed in previous research, adenomyosis was a frequent uterine disease [25, 30]. Its prevalence (8.6 percent) was nearly identical to national statistics (21%). A similar number was discovered in a research conducted in Karachi (20.6 percent) and Swat (20.6 percent) (20.6 percent) [31, 32]. In an Indian research, it was found to be 26 percent, 24.9 percent in Italy, and 6 percent in the West Indies [22, 33]. The prevalence of adenomyosis increases with increasing parity, lending credence to the hypothesis of basal endometrial implantation deep inside the myometrium. Menstrual irregularities caused by adenomyosis are usually resistant to medical therapy and endometrial excision [34].

Although MRI is highly specific for accurate diagnosis of adenomyosis, it is expensive and not available in most hospitals; however, transvaginal ultrasound is a good option, with features such as impoverished description of endometrial myometrial junction and sub endometrial linear striations, heterogeneous myometrial texture, and globular uterus having the highest accuracy. As a result, in women who have menstruation problems and

adenomyosis on transvaginal ultrasound, hysterectomy must be given early to alleviate their pain [26, 34].

In our study Prevalence of dysfunction uterine bleeding (28.6%). When aberrant bleeding occurs that is unrelated to observable local disease, pharmacological drugs, intrauterine contraception, or systemic hemostasis problems, it's characterized as dysfunctional uterine bleeding; it presents as irregular timing, volume, and/or duration of flow [35].

In our study fibroid was the most significance for the effect of misoprostol in decrease blood loss, haemoglobin and haematocrit during AH more than adenomyosis and dysfunction uterine bleeding. The results of our study similar to Lady Reading Hospital Peshawar-Pakistan 2020 showed that a single preoperative dosage of rectal misoprostol, a widely accessible uterotonic, reduced intraoperative blood loss by 328 mls vs 484 mls with placebo. Our findings are similar to those of Naib J, who found that misoprostol reduced blood loss by 15–18% (370 mLs versus 310 mLs) [36]. Celik H reported a 149 ml decrease in blood loss, i.e., mean loss was 621 mls with placebo vs 472 mls with misoprostol. Another research by Ishrat et al and the Cochrane database show that misoprostol is helpful in decreasing bleeding after abdominal myomectomy [37, 38].

Conclusion

A single 400 μg misoprostol preoperative dose administered at 30 minutes prior to AH led to significant bleed loss drop.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is

absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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