Reduction of Vaginal Bleeding Following Surgical Evacuation for First Trimester Abortion with Oral Misoprostol: A Randomized Placebo-Controlled Study

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ABSTRACT

AIM: The aim of this study was to evaluate the role of oral misoprostol following surgical evacuation of first trimester abortion in reducing the amount and duration of vaginal bleeding and also to evaluate patient tolerability to this drug.

PATIENTS AND METHODS: This randomized placebo-controlled study was conducted on 120 patients with gestational ages of 6–12 weeks at the Obstetrics and Gynecology Department, Tanta University, Egypt, from July 2015 to May 2016. All patients underwent surgical evacuation for abortion regardless of its type (missed, inevitable, or incomplete abortion). Patients who were hypersensitive to misoprostol, had septic abortion, had ectopic pregnancy, or had molar pregnancy were excluded. Patients were allocated randomly into two groups equally: group I who will receive oral misoprostol 200 µg following surgical evacuation for two days and group II who will receive placebo and serve as a control group.

RESULTS: There was no significant difference between the two groups with respect to hemoglobin ($P = 0.426$) and hematocrit ($P = 0.547$) before surgical evacuation. There was a significant difference between the two groups with respect to hemoglobin ($P = 0.001$) and hematocrit ($P = 0.002$) after 15 days following evacuation. There was a statistically significant difference between the two groups with respect to days of vaginal bleeding or spotting ($P = 0.001$). There was also a statistically significant difference between the two groups with respect to days of *mild* bleeding ($P = 0.001$), *moderate* bleeding ($P = 0.005$), and *severe* bleeding ($P = 0.023$). In the misoprostol group (GI), there was no case of retained product (0.0%), whereas in the placebo control group (GII), there were five cases (8.33%) of retained product who needed repeated curettage. A statistically significant difference was observed between the two groups with respect to presence of retained product ($P = 0.020$).

CONCLUSION: Reduction of both the amount and duration of vaginal bleeding after the surgical evacuation of first trimester abortion was observed in the oral misoprostol group and was associated with high success rate and low incidence of side effects.

KEYWORDS: abortion, misoprostol, first trimester, vaginal bleeding

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Introduction

Abortion is defined in the British law as termination of pregnancy before 24 weeks of gestation with no evidence of life. In the United States, abortion refers to pregnancies terminating up to 20 weeks of gestational age or delivery of a fetus that weighs less than 500 g.[1]

Misoprostol is a synthetic prostaglandin E1 that induces cervical effacement and uterine contractions at all gestational ages, thus facilitating uterine evacuation and pregnancy termination. It is used for early abortion, to treat missed miscarriage, and to induce labor. Misoprostol is a water-soluble substance incorporated into a tablet with inactive ingredients such as hydrogenated castor oil, hypromellose, microcrystalline cellulose, and sodium starch glycolate.[2,3]

Misoprostol is widely available and registered in more than 80 countries to treat and prevent gastric ulcers. Many providers throughout the world have discovered that misoprostol is also a potent and valuable drug for managing and treating a wide range of obstetric conditions, including postpartum hemorrhage, intrauterine fetal death, labor induction, first and second trimester abortion, and incomplete and missed abortion. Two properties make misoprostol useful for these procedures, namely, the first, misoprostol causes contractions of the smooth muscles lining the uterus, and the second, misoprostol softens the cervix, allowing greater dilatation for intrauterine procedures as well as facilitating expulsions from the uterus.[4,5]

Despite its tremendous promise for many of these obstetric indications, there are no standard or labeled regimens for any of these conditions. Instead, providers have relied on the medical literature and colleagues in the field, as well as their own experience, for information on effective regimens. Consequently, in many cases, providers have developed their own regimens. This *trial and error* method of drug development, especially in the absence of large randomized

clinical trials, leaves many providers guessing at the best and safest regimens.[6]

However, in 2013, the WHO announced the addition of misoprostol to its Model List of Essential Medicines based on its proven safety and efficacy for the treatment of incomplete abortion and miscarriage.[7] The recommendation was made by an expert committee that evaluated available evidence, including numerous randomized comparative clinical trials and several guidelines developed by professional associations for this indication.[7]

Patients and Methods

This double-blinded, placebo-controlled study was performed on 120 patients at Obstetrics and Gynecology Department, Tanta University, Egypt, from July 1, 2015, to May 31, 2016. The research was approved by the Research Ethics Committee of Tanta University. Patients were selected according to inclusion and exclusion criteria.

The inclusion criteria were abortion (missed, inevitable, and incomplete), gestational age range between 6 and 12 weeks, and surgical vaginal evacuation. Exclusion criteria were patient's hypersensitivity to misoprostol, septic abortion, ectopic pregnancy, and vesicular mole. Patients gave their written, informed consent to participate in the research.

Patients were randomly allocated into two groups by the closed envelope method for equal randomization. Dispensers of envelopes would take another one. Allocation was made by block randomization methods where every block of envelopes contains a balanced number of treatment groups. Blinding was double where neither the clinician nor the patients know the group and drug present inside the envelope. Each envelope had a code number denoting the group and the drug inside the envelope made by the hospital pharmacy. After complete gathering of the study populations, the codes were explained by the hospital pharmacy.

Methods. Enrolled women were randomly allocated into two equal groups (60 patients for each). Both groups underwent complete history taking, including general, abdominal, and Per Vaginal (PV) examination. Each patient was asked to empty her bladder and was placed in the lithotomy position. The vagina, vulva, pubis, perineum, and inner aspects of the thighs were cleaned with chlorhexidine solution. Bimanual pelvic examination was done and the findings were noted. A Cusco's speculum was introduced to retract the vaginal walls, thereby exposing the cervix.

All patients were investigated for complete blood count (CBC) to determine hemoglobin (HB) level at admission, and an ultrasound examination was performed to determine the type of abortion and exclude ectopic pregnancy or vesicular mole. Surgical evacuation and curettage was done under general anesthesia for all patients enrolled in the study regardless of the type of abortion. All patients received the same antibiotic at the time of the operation and were maintained by oral type till 14 days according to local hospital policy.

Patients were allocated into 2 groups: Group I (60 patients; the misoprostol group) received 200 μg of oral misoprostol (Cytotec®; Pfizer Pharmaceuticals) taken after recovery from anesthesia and then every 6 hours for 48 hours after evacuation and kept admitted till the period of treatment ended. Group II (60 patients; the placebo control group) received placebo (sugar tablets) and the standard treatment as described above, without misoprostol.

All patients were followed up for the first six hours postoperatively for vital signs, any complications, and presence of severe vaginal bleeding.

Patients attended the follow-up visit 15 days after the evacuation procedure where all patient data were reviewed by the surgeon, including patient age, address, parity, gestational age of abortion, type of abortion, date of operation, and HB before procedure. The amount and duration of vaginal bleeding for each patient were evaluated by subjective estimation of the number of sanitary towels (pads) changed per day, fever, and HB and hematocrit (HCT) values.

The primary outcome measure was duration of spotting and/or vaginal bleeding in days following evacuation. Secondary outcomes were the percentage of patients suffering from severe post-evacuation bleeding within 15 days following the procedure, decrease in HB and HCT 15 days after the procedure, and tolerability of patients to misoprostol.

Severity of vaginal bleeding was estimated according to pictorial blood loss assessment charts (PBACs) that were first introduced by Higham et al.[8] as a visual representation of blood loss, which had a numerical score. The chart consists of a series of diagrams representing lightly, moderately, and heavily soiled tampons or towels. Higham et al.[8] reported that when the PBAC was used as a diagnostic clinical tool, a score of 100 or more diagnosed menorrhagia with a sensitivity and specificity of more than 80%. This research complied with the principles of the Declaration of Helsinki.

Statistical analysis. Data were checked and analyzed using Epi Info version 6 and SPSS for Microsoft Windows version 16. Mean and standard deviation tests were used. The threshold of significance was fixed at 5% level (*P*-value). The results were considered significant when the probability of error was less than 5% ($P < 0.05$).

Results

A total of 120 patients were enrolled and randomly allocated into two groups in this study, with the demographic data shown in Table 1.

The mean age was 31.17 ± 6.38 (years) and 28.62 ± 7.27 (years) in group I (oral misoprostol group) and group II (placebo control group), respectively. There was no significant difference between the two groups ($P = 0.996$).

The mean of gravidity was 3.57 ± 1.75 and 3.32 ± 1.89 for group I (oral misoprostol group) and group II (placebo control group), respectively. There was no significant difference between the two groups ($P = 0.542$).

Table 1. The age, gravidity, parity, gestational age, BMI, and types of abortions among studied groups.

	GROUPS		TEST OF SIGNIFICANCE	*P*-VALUE
	GROUP I (ORAL MISOPROSTOL) (No = 60)	GROUP II (PLACEBO CONTROL) (No = 60)		
Age (years) Mean ± SD	31.17 ± 6.38	28.62 ± 7.27	(t) = 2.777	0.996
Gravidity Mean ± SD	3.57 ± 1.75	3.32 ± 1.89	(t) = 0.374	0.542
Parity Mean ± SD	2.02 ± 1.54	1.72 ± 1.60	(t) = 0.728	0.396
Gestational age (weeks)	9.20 ± 2.33	8.54 ± 3.12	(t) = 1.313	0.192
BMI (kg/m^2)	23.09 ± 6.77	22.69 ± 7.80	(t) = 0.300	0.765
Type of abortion				
Missed	33 (55.0%)	31 (51.67%)	X^2 = 0.714	0.799
Inevitable	15 (25.0%)	19 (31.66%)		
Incomplete	12 (20.0%)	10 (16.67%)		

Abbreviation: BMI, body mass index.

The mean of parity was 2.02 ± 1.54 and 1.72 ± 1.60 for group I (oral misoprostol group) and group II (placebo control group), respectively. There was no significant difference between the two groups ($P = 0.396$).

The mean of gestational age at the time of abortion was 9.20 ± 2.33 (weeks) and 8.54 ± 3.12 (weeks) for group I (oral misoprostol group) and group II (placebo control group), respectively. There was no significant difference between the two groups ($P = 0.192$).

The mean of body mass index was 23.09 ± 6.77 (kg/m^2) and 22.69 ± 7.80 (kg/m^2) for group I (oral misoprostol group) and group II (placebo control group), respectively. There was no significant difference between the two groups ($P = 0.765$).

With respect to the types of abortions among the studied groups, it was found that more than half of the patients had missed abortion (55.0% and 51.17% in group I and group II, respectively), followed by inevitable abortion (25.0% and 31.66% in group I and group II, respectively), and finally incomplete abortion (20.0% and 16.67% in group I and group II, respectively). There was no significant difference between both groups with respect to distribution and types of abortions ($P = 0.799$).

Before surgical evacuation, the mean HB levels were 11.31 ± 0.942 (g/dL) and 11.14 ± 0.958 (g/dL) in group I (oral misoprostol group) and group II (placebo control group), respectively. There was no significant difference between the two groups ($P = 0.426$). Ten days after surgical evacuation, the mean HB levels were 10.73 ± 1.03 (g/dL) and 8.9 ± 1.43 (g/dL) in group I (oral misoprostol group) and group II (placebo control group), respectively. There was a significant difference between the two groups ($P = 0.001$; Table 2).

Before surgical evacuation, the mean HCT levels were 34.63 ± 2.87and 34.19 ± 3.56 in group I (oral misoprostol group) and group II (control group), respectively. There was no significant difference between the two groups ($P = 0.547$). Ten days after surgical evacuation, the mean HCT levels were 32.70 ± 3.56 and 30.09 ± 3.92 for group I (oral misoprostol group) and group II (placebo control group), respectively. There was a significant difference between the two groups ($P = 0.002$) as in Table 2.

Table 3 displays the days of vaginal bleeding due to abortion among the studied patients. It was found that the mean number of bleeding days was significantly less in group I (oral misoprostol group) than in group II (placebo control group) [6.17 ± 2.83 (days) and 11.77 ± 3.62 (days)], respectively. There was a statistically significant difference between the two groups with respect to days of vaginal bleeding or spotting ($P = 0.001$).

Table 4 shows that there was a significant difference between the studied groups regarding severity of bleeding: 75%

Table 2. The HB and HCT levels before and 10 days after surgical evacuation among studied groups.

	GROUPS		T TEST	*P*-VALUE
	G I (ORAL MISOPRISTOL) (No = 60)	G II (PLACEBO CONTROL) (No = 60)		
HB before surgical evacuation Mean ± SD	11.31 ± 0.942	11.14 ± 0.958	0.642	0.426
HCT before surgical evacuation Mean ± SD	34.63 ± 2.87	34.19 ± 3.56	0.366	0.547
HB 10 days after surgical evacuation Mean ± SD	10.73 ± 1.03	8.9 ± 1.43	25.730	0.001*
HCT 10 days after surgical evacuation Mean ± SD	32.70 ± 3.56	30.09 ± 3.92	3.120	0.002*

Note: *Significant.

Table 3. The days of vaginal bleeding or spotting among studied groups.

DAYS OF VAGINAL BLEEDING OR SPOTTING	GROUPS	
	G I (No = 60)	G II (No = 60)
Range	5–10	5–15
Mean ± SD	6.17 ± 2.83	11.77 ± 3.62
T test	17.012	
P value	0.001*	

Note: *Significant.

of patients in group I (oral misoprostol group) suffered mild bleeding, whereas 22.5% of them suffered moderate bleeding and 2.5% suffered severe bleeding, compared to more than one-third of group II (control group; 35%) who suffered mild bleeding, more than one half (52.5%) suffered moderate bleeding, and 12.5% suffered severe bleeding.

There was a statistically significant difference between the two groups with respect to days of *mild* bleeding ($P = 0.001$), *moderate* bleeding ($P = 0.005$), and *severe* bleeding ($P = 0.023$).

In the misoprostol group (GI), there were no cases of retained products (0.0%), whereas in the placebo control group (GII), there were five (8.33%) cases of retained product who needed repeated curettage. There was a statistically significant difference between the two groups with respect to presence of retained product ($P = 0.020$; Fig. 1).

With respect to tolerability of misoprostol, side effects were mild and of short duration and did not require any treatments. The reported side effects were as follows: one case of diarrhea (1.6%), one case of mild nausea (1.6%), and three cases (5%) of low-grade fever (<38°C) for less than 24 hours and resolved without treatment.

Discussion

Termination of first trimester abortion with oral misoprostol was associated with shorter time at onset and maximum tonus compared to the vaginal and sublingual routes.[9,10]

The enrolled patients had nearly similar demographic characteristics in each group of the study as well as the types of abortion, and there was no significant difference in both groups ($P > 0.05$) as shown in Table 1. The blood loss in both groups was also not significant, which was indicated by HB level before discharge as shown in Table 2. In the current study, misoprostol reduced the amount of vaginal bleeding after evacuation in all types of abortion presented in this study. Duration of vaginal bleeding was prolonged in the placebo group more than in the misoprostol group, and this finding was further documented by decrease in the HB and HCT levels 10 days after evacuation in both groups where the descent was more in the placebo group.

Table 4. Distribution of the severity of bleeding among studied groups.

SEVERITY OF VAGINAL BLEEDING	GROUPS				TOTAL		X^2	*P*-VALUE
	G I (No = 60)		G II (No = 60)					
	N	%	N	%	N	%		
Mild	45	75.0	21	35.0	66	55.0	24.37	0.001*
Moderate	13	21.67	31	51.67	44	36.67	7.680	0.005*
Severe	2	3.33	8	13.33	10	8.33	5.13	0.023*
Total	60	100.0	60	100.0	120	100.0		

Note: *Significant.

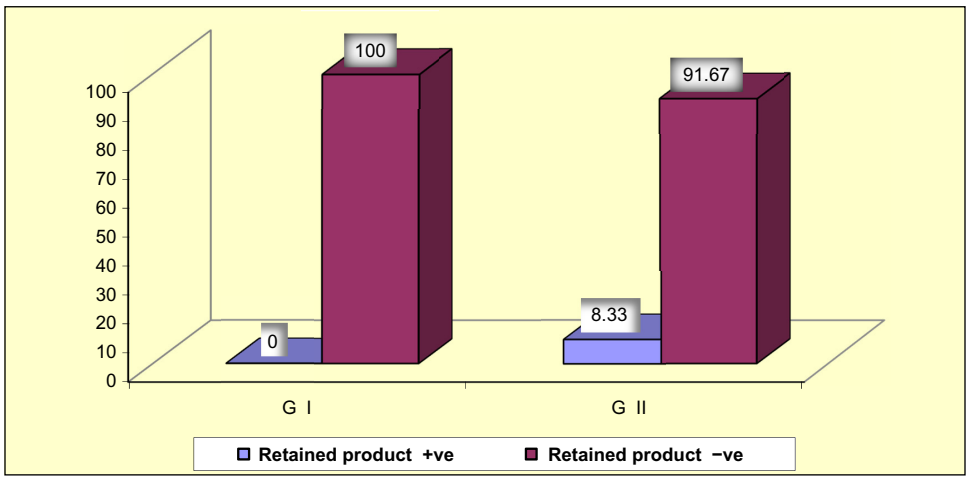

Figure 1. Retained products among studied groups.

Patients who reported persistent bleeding in the misoprostol group did not require repeat curettage.

In a similar study carried out at the Women Health Hospital, Assiut University, Egypt, by Shokry et al.[11], the efficacy of oral misoprostol was evaluated in reducing the percentage, duration, and amount of vaginal bleeding after surgical evacuation for first trimester abortion and compared with the group that received no misoprostol. The authors concluded that oral misoprostol was effective in reducing both duration and amount of postabortive bleeding with minimal side effects.

Aramide et al.[12] conducted a study on 84 patients who were classified into three groups: Group 1: oral misoprostol 400 μg, Group 2: intravenous ergometrine 0.5 mg, and Group 3: intravenous oxytocin 10 IU. They concluded that a single oral dose of misoprostol is better than parenteral administration of either oxytocin or ergometrine in reducing the amount and duration of vaginal bleeding after surgical evacuation of a first trimester abortion. Oral misoprostol was, however, associated with more gastrointestinal side effects.

In the present study, oral misoprostol was given in a high dose (800 μg daily for 48 hours), which was higher than the doses given in other studies.[13–15] Another study conducted by Allison et al.[16] supporting the dose of 800 μg in first trimester abortion reported that medical termination of missed or incomplete abortion was effective and successful in 80%–90% of patients. Allison et al.[16] used misoprostol 800 μg by the vaginal route showing high completion rates.

Significantly fewer patients in the misoprostol group reported prolonged bleeding of more than 15 days after evacuation and fewer patients reported severe bleeding after evacuation. None of the women who received misoprostol needed repeat curettage compared with five women in the control group. Aramide et al.[12] reported a significant reduction in the number of days of vaginal bleeding in the misoprostol group (2.00 ± 0.86 days) compared with 4.43 ± 0.92 and 4.64 ± 1.06 days in the ergometrine and oxytocin groups, respectively ($P < 0.05$).

Low-resource settings have emphasized on the requirement for further doses of misoprostol to ensure complete evacuation of first trimester abortions. The success of misoprostol was assessed by passage of tissues or old blood clots after a second misoprostol dose of 800 μg.[17,18]

In the present study, the decrease in HB and HCT levesl 15 days after surgical evacuation was less in the misoprostol group than in the control group, indicating less vaginal bleeding after surgical evacuation in the misoprostol group. Similar results were obtained by Ng et al.[19] who conducted a study on 154 patients with first trimester incomplete miscarriage and were randomized to receive misoprostol either as outpatient or inpatient. They found that duration of bleeding was 6.0 days in both groups ($P = 0.317$). Mean reduction in HB was lesser in the outpatient group (0.4 g/dL) as compared to that in the inpatient group (0.6 g/dL), which was statistically significant ($P = 0.048$).

In the current study, there were no cases of retained products of conception following surgical evacuation except for five cases in the placebo group, and these occurred because (1) placebo had no uterine contractility effect to expel these remnants like misoprostol where no cases had positive remnants in the misoprostol group and (2) most patients were receiving progesterone supplementations making firm attachment of products of conception to uterine wall.

In the current study, the adverse effects reported were transient and tolerable, which were in accordance with other studies, where 96% of women received 600 μg of oral misoprostol for pregnancy termination and documented mild tolerable adverse effects and 95% reported that the experience was satisfactory.[20]

One of the rapid-onset side effects is the cramping that usually starts within the first few hours but may begin within minutes after misoprostol administration. Another common side effect reported in misoprostol users was severe abdominal pain, especially when misoprostol was administered for pregnancy termination in the late first and early second trimesters.[20] Higher requirement for analgesia in women using misoprostol was reported by Hamoda et al.[21] Other studies concluded that misoprostol in first trimester abortion has no side effects.[22]

Conclusion

Reduction of both amount and duration of vaginal bleeding after the surgical evacuation of first trimester abortion was observed in the oral misoprostol group and was associated with high success rate and low incidence of side effects. We recommend the dose of 200 μg oral misoprostol immediately after evacuation and then every 6 hours for 48 hours to ensure maximal success and fewer side effects.

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Author Contributions

Conducted the scientific writing and revisions: HB. Conducted statistical analysis of data: HB. Operated in most of the cases of abortion: AS. Gathered data for this article: AS. Contributed to the writing and revision of the text: AS. Both authors reviewed the manuscript and approved it for publication.

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