Sublingual versus Vaginal Misoprostol for Preoperative Cervical Priming in First Trimester Missed Abortion

Bahaa Abdel Kader Fateen[1], Noha Homed Rabei[1] and Waleed Mohamed Mostafa[2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University
[2]M.B.B.Ch. Resident of Obstetrics and Gynecology, Zagazig Central Hospital
noha.rabei@yahoo.com

Abstract: Introduction: missed abortion has been defined as retention of the products of conception after death of the embryo or the fetus. Surgical evacuation using vacuum aspiration has been currently the standard management however it associated with major and minor morbidities. Cervical priming has been shown to result in a shorter operative time, less blood loss and easier mechanical dilation. Misoprostol, a prostaglandin E_1 analogue has been used for this purpose in the form of tables 200µg each. Aim of the Work: was to compare the effect of sublingual versus vaginal administration of misoprostol for preoperative cervical priming before surgical termination of pregnancy in first trimester missed abortion. Patients and methods: 120 patients were recruited for this study. Group I (60 cases) cervical priming with 2 tablets of vaginal misoprostol and sublingual placebo. Group II: (60 cases) cervical priming with 2 tablets of sublingual misoprostol and vaginal placebo. Results: There was no significant difference between both groups as regards the baseline cervical dilation and the ease of cervical dilation. There was no significant difference between both groups as regards the main operative time and operative blood loss. There was no significant difference between both groups as regards side effects as nausea, vomiting and diarrhea. Conclusion: The use of sublingual misoprostol to induce cervical priming in first trimester abortion was efficient and as effective as vaginal misoprostol with more convenience to the patient and avoided the need of the doctor to insert it.

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1.Introduction

Missed abortion is defined as retention of the products of conception after death of the embryo or the fetus. It is characterized by regression of earlier signs and symptoms of pregnancy, the uterus is small for dates, the cervix is closed and ultrasonic examination shows either a collapsed gestational sac or fails to detect the fetal heart or movement[(1)].

Surgical evacuation using vacuum aspiration is currently the standard management for termination of pregnancies in the first trimester in many parts of the world. It is considered to be safe and effective with a success rate of > 95%[(2)]. However, it is associated with major morbidity in <1% of women and minor morbidity in 10%[(3)]. A study of 170,000 first trimester abortions reported that <0.1% of the women had serious complications requiring hospitalization[(4)].

Cervical priming has been shown to result in a shorter operative time, less blood loss and easier mechanical dilatation[(5)], and thus may reduce the incidence of complications associated with surgical management of abortion including cervical injury, uterine perforation, hemorrhage and incomplete abortion[(5)].

Various methods have been used for pre-operative cervical priming in surgical management of abortion including laminaria tent, mifepristone and prostaglanding analogues. Laminaria tent has to be inserted for 12 hours and mifepristone has to be taken for 36-48 hours to have adequate cervical priming effect; therefore they are less convenient for day patients[(6,7)]. Misoprostol is a prostaglandin E_1 analogue, originally approved by the Food and Drug Administration (PDA) for the prevention of gastric ulcers during long-term use of non-steroidal anti-inflammatory drugs. It has been suggested as an alternative approach to managing early pregnancy failure[(8)]. Many authors believe that prostaglandin analogues are the cervical priming agents of choice [(6,7)].

The aim of this study is to compare the effect of sublingual versus vaginal administration of misoprostol for pre-operative cervical priming before surgical termination of pregnancy in first trimesteric missed abortions.

2. Patients and Methods

This study was performed at Ain Shams University Hospital and Zagazig Central Hospital. 120 patients were recruited from the obstetrics and gynecology outpatient clinic.

The patients in both groups were selected and matched according to the following criteria:

1- Age ranging between 20-28 years.
2- Primigravidae with missed abortion, defined as retention of the products of conception after death of the embryo.
3- Gestational age between 6-12 weeks.
4- Body mass index: (body weight in Kg/Height in m^2) between 22-28Kg/m^2.

A written informed consent was obtained from all participants and the study was approved by the hospital ethical committee of Ain Shams Maternity Hospital.

The Exclusion criteria included:

- Incomplete abortion.
- Vesicular mole.
- Patients with history of previous cervical surgery.
- Patients with allergy or contraindications to prostaglandin.
- Infection (Septic abortion).
- Any uterine anomaly.
- Chronically ill patients, like heart disease, chronic liver or kidney disease, severe asthma and hypertension[9].

The patients were allocated randomly into two groups:

- Group I (60 Cases): Cervical priming with 2 tablets of vaginal misoprostol (each tablet containing 200µg) and sublingual placebo.
- Group II (60 cases): Cervical priming with 2 tablets of sublingual misoprostol (each tablet containing 200µg) and vaginal placebo.
- It was a double blinded randomized study.

All women had been given drug A in the form of 2 tablets sublingually (one tablet contained 200 µg of Misoprostol or placebo) and drug B vaginally by the same regimen 2 tablets had been inserted into the posterior fornix of the vagina. One of the two drugs A or B was placebo and the other was misoprostol and this had been known only by supervisors. After administration of the drug, the patients were admitted to hospital, then after 4 hours the patient was taken to the operative theatre for uterine evacuation to ensure that the cavity was empty by D&C operation and the following outcome criteria were evaluated.

The outcome criteria which were evaluated and compared in both groups are:

1. Base line cervical dilation in millimeter (mm) which was assessed by the researcher only at the time of evacuation using Hegar dilators in descending order starting with size 12.
2. Cervical dilation was assessed as either easy or difficult by the researcher only during the operation according to the ease of introducing the Hegar dilators.
3. Operative time in minutes (min) was calculated from the start of cervical dilation.
4. Operative blood loss was calculated.
5. Side effects were reported as presence or absence of any of the following:

- Nausea.
- Vomiting.
- Diarrhea.
- Abdominal pain.
- Pre-operative vaginal bleeding.

Side effects of misoprostol including abdominal pain, nausea, vomiting, diarrhea and vaginal bleeding were recorded 2 hours after administration of the drug, immediately preoperative (4 hours after administration of the drug) and also postoperative.

The evacuation was done 4 hours after the administration of the misoprostol and was done by the same surgeon.

All the procedures were done under general anesthesia. Intraoperatively, cervical dilation before performing evacuation was assessed using Hegar dilators. The largest Hegar dilator passing through the internal os without resistance was regarded as the dilation achieved by the misoprostol alone.

The amount of blood loss intra-operatively was measured with a graduated cylinder as the volume of total uterine aspirate, after sieving away the products of conception. The appropriate amount of liquor for that period of gestation (Amniotic Fluid at 6 weeks about 15-20 ml. & at 10 weeks about 30 ml. and at 12 weeks about 50 ml.), was subtracted from this amount to achieve the amount of actual blood loss[9].

The duration of surgery was measured from the start of dilation to the end of curettage and any complications encountered during the procedure were recorded.

3. Results

There was no significant difference as regards maternal age, gestational age and BMI between the two groups as shown in tables (1, 2, 3).

There was no significant difference between both group as regards the side effects. Preoperative vaginal bleeding and abdominal pain were the commonest side effects in both groups: abdominal pain occurred in 70% and 80% of patients in group I and group II respectively, as shown in table (4).

Vaginal bleeding occurred in 28.3% and 40% of patients in group I and II respectively, as shown in table (4).

Nausea was less commonly encountered (13.3 % and 15% in group I and II, respectively), as shown in table (4).

Vomiting was encountered in three cases (5%) in each of the two study groups, while diarrhea occurred in only two cases (3.3%) of the sublingual group, as shown in table (4).

There was no significant difference as regards the baseline cervical dilation (8.35 ± 1.54 mm in group I and 8.80 ± 1.98 mm in group II), as shown in table (5).

As regards the ease of cervical dilatation there was no significant difference between the two groups (83.3% and 78.3% in group I and group II respectively were easily dilated), as shown in table (6).

There was no significant difference as regards the mean operative time (7.40 ±1.21 min. in group I and 7.07 ± 1.60 min. in group II), as shown in table (7).

As regards the amount of operative blood loss there was no significant difference between both groups (60.00 ± 20.75 ml in group I and 62.83 ± 19.84 ml in group II), as shown in table (8).

Table (1): Comparison between the two studied groups regarding maternal age.

	Group I "vaginal route"		**Group II "Sublingual route"**		**T**	***P***
	N	**%**	**N**	**%**		
Age group (years)						
< 25	24	40.00	21	35.00		
≥25	36	60.00	39	65.00		
Range	22-28		22-28		-0.36	0.72
Mean	25.05		25.18		*P*> 0.05 NS	
Median	25.00		25.00			
±S.D.	2.02		1.99			

NS: Non significant (*P*>0.05)

There was no significant difference between both groups as regards maternal age.

Table (2): Comparison between the two studied groups regarding gestational age.

	Group I "vaginal route"		**Group II "Sublingual route"**		**T**	***P***
	N	**%**	**N**	**%**		
Age group (years)						
6-8	18	30.00	15	25.00		
9-10	18	30.00	30	50.00		
> 10	24	40.00	15	25.00		
Range	6-12		6-12		0.54	0.59
Mean	9.53		9.35		*P*> 0.05 NS	
Median	10.00		9.50			
±S.D.	1.96		1.77			

NS: Non significant (P>0.05)

There was no significant difference between both groups as regards gestational age.

Table (3): Comparison between the two studied groups regarding BMI.

	Group I "vaginal route"		Group II "Sublingual route"		T	*P*
	N	%	N	%		
Age group (years)						
22-24	6	10	6	10	0.61	0.54
25-26	15	25	21	35	*P*>0.05	
>26	39	65	33	55	NS	

NS: Non significant (*P*>0.05)

There was no significant difference between both groups as regards BMI.

Table (4): Comparison between the two studied groups regarding the side effects.

	Group I "Vaginal Route" "n=60"		**Group II "Sublingual route" "n=60"**		***P* (*P*>0.05)**
	%	**(No.)**	**%**	**(No.)**	
Nausea	13.3	(8)	15.00	(9)	0.79 (NS)
Vomiting	5.00	(3)	5.00	(3)	1.00 (NS)
Diarrhea	00.00	(0)	3.3	(2)	0.15 (NS)
Pre-operative Vaginal bleeding	28.3	(17)	40.00	(24)	0.18 (NS)
Abdominal pain	70.00	(42)	80.00	(48)	0.21 (NS)

NS: non significant (*P* > 0.05).

There was no significant difference between both groups as regards side effects.

Table (5): Comparison between the two studied groups regarding the baseline cervical dilation (mm)

Baseline Cervical dilation (mm)	Group I "Vaginal route" "n=60"	Group II "Sublingual route" "n=60"	t	P
Range	6-11	6-12		
Mean	8.35	8.8	-1.39	0.17
Median	8.00	8.00	P>0.05	
±S.D.	-1.54	1.98	(NS)	

NS= Non Significant (*P*>0.05).

There was no significant difference between both groups as regards cervical dilation.

Table (6): Comparison between the two studied groups regarding the ease of cervical dilation.

Ease of cervical dilatation	Group I "Vaginal Route" "n=60"		Group II "Sublingual route" "n=60"		t	P
	%	(No.)	%	(No.)		
Easy	83.3	(50)	78.3	(47)	0.69	0.49
Difficult	16.7	(10)	21.7	(13)	*P*>0.05 (NS)	

NS: Non Significant (*P* > 0.05).

There was no significant difference between both groups as regards ease of cervical dilation.

Table (7): Comparison between the two studied groups regarding the operative time (min).

Operative time (min.)	Group I "Vaginal Route" "n=60"	Group II "Sublingual route" "n=60"	t	P
Range	5-9	4-10		
Mean	7.4	7.07	1.29	0.20
Median	7.5	7.00	*P*>0.05	
±S.D.	1.21	1.60	(NS)	

NS: Non Significant (*P* > 0.05).

There was no significant difference between both groups as regards the operative time.

Table (8): Comparison between the two studied groups regarding the operative blood loss (ml).

Operative blood loss (ml)	Group I "Vaginal Route" "n=60"	Group II "Sublingual route" "n=60"	t	P
Range	30-100	40-110		
Mean	60.00	62.83	-0.77	0.45
Median	60.00	60.00	*P*>0.05	
±S.D.	20.75	19.84	(NS)	

NS: Non Signifiant (*P* > 0.05).

There was no significant difference between both groups as regards the operative blood loss

4. Discussion

The sublingual route could facilitate self administration at home before clinic admission and could add to convenience; this could help to achieve optimal priming intervals before surgical abortion. It may also reduce the workload for health care services[10].

Sublingual misoprostol is convenient to use; avoids vaginal administration and avoids the ingestion of water before aesthesia[5].

The sublingual route uses the most vascular area of the buccal cavity and avoids the first-pass effect through the liver, which is associated with oral administration. It has been reported that the sublingual administration of misoprostol resulted in higher serum peak concentration and higher area under the curve compared with oral and vaginal administration, which indicates greater systemic bioavailability[11].

In the current study there was no significant difference between the two groups as regards the base line cervical dilation which was (8.35 ±1.54 mm in the vaginal group and 8.8 ± 1.98 mm in the sublingual group) (*P* = 0.17). Similarly, ***Tang et al.*** found that the base line cervical dilation was 7.7±0.73 mm and 7.6±1.3 mm in the vaginal and sublingual groups respectively with no significant difference[5]. ***Carbonell et al.*** found that the baseline

cervical dilation achieved was 6.8 ± 0.8 mm and 6.7 ± 0.9 mm for the sublingual and vaginal groups respectively, with no significant difference[12]. ***Saxena et al.*** found that sublingual misoprostol significantly increased the baseline cervical dilation compared to vaginal group without increasing the side effects (P>0.001)[9].

In the current study there was no significant difference between the two groups as regards the operative time which was 7.4±1.21 min. in the vaginal group and 7.07±1.6 min. in the sublingual group (P = 0.20). In the study conducted by ***Carbonell et al.,*** the mean surgical time was 7.4±2.5 min. and 7± 2.8 min. for the vaginal and sublingual groups respectively with no significant difference[12]. ***Saxena et al.*** found that sublingual misoprostol significantly reduced the operative time compared to vaginal misoprostol (P<0.001)[9]. This may be attributed to the difference in the criteria of the patients as ***Saxena et al.*** did not include the parity as a criteria of patient selection[9].

In the current study there was no significant difference between the two groups as regards the amount of operative blood loss which was 60±20.75 ml in the vaginal group and 62.83±19.84 ml in the sublingual group (P=0.45). ***Tang et al.*** found that the amount of operative blood loss was 48.3±12.3 ml and 52.1±20.2 ml in the vaginal and sublingual groups respectively with no significant difference[5]. Also, ***Hamoda et al.*** found no significant difference between the two groups as regards the amount of operative blood loss (P>0.05)[11].

Abdominal pain and pre-operative vaginal bleeding were the commonest side effects. Sublingual misoprostol did no significantly increase pre-operative vaginal bleeding compared to vaginal misoprostol (28.3% and 40% of cases in the vaginal and sublingual groups respectively (P=0.18).

Also, abdominal pain occurred in 70% and 80% of cases in the vaginal and sublingual groups respectively with no significant difference between the two groups (P=0.21). In the study conducted by ***Tang et al.,*** abdominal pain and vaginal bleeding were the commonest side effects, vaginal bleeding occurred in 22.5% and 37.5% of cases in the vaginal and sublingual groups respectively, while abdominal pain occurred in 77.5% and 85% of cases in the vaginal and sublingual groups respectively with no significant difference in pre-operative abdominal pain and vaginal bleeding between two groups (P>0.50)[5]. Similarly, ***Saxena et al.*** found that, the pre-operative side effects were comparable in both groups, but the mean pain score of the vaginal group was higher compared to the sublingual group, as it was 3.2 ± 1.6 in the vaginal group and 2.7 ± 1.1 in the sublingual group with no statistical significance[9].

Nausea occurred in 13.3% of cases in the vaginal group and 15% of cases in the sublingual group with no significant difference. In the study conducted by ***Tang et al.,*** nausea occurred in 35% and 20% of cases in the vaginal and sublingual respectively with no significant difference[5]. In the study conducted by ***Hamoda et al.,*** women in the sublingual group had more nausea compared with the women in the vaginal group and there was a significant difference between the two groups (P=0.008)[11].

In the current study, vomiting occurred in 5% of cases in both group and there was no significant difference. ***Tang et al.*** found that, vomiting occurred in 7.5% and 2.5% of cases in the vaginal and sublingual groups respectively with no significant difference[5]. While in the study conducted by ***Hamoda et al.,*** vomiting was more common in the sublingual group compared to vaginal group with a significant difference[11].

In the current study, diarrhea occurred in two cases (3.3%) only in the sublingual group and no diarrhea occurred in any of the vaginal group with no significant difference. In the study conducted by ***Tang et al.,*** diarrhea occurred in one case (2.5%) in each group with no significant difference[5]. While in the study conducted by ***Hamoda et al.,*** diarrhea was more common in the sublingual group compared to in the vaginal group with a significant difference[11].

Hamoda et al. reported that, in the sublingual group 65% of women were satisfied with the route of misoprostol administration compared with 78% in the vaginal group (P=0.l 1) and most of the staff members (84%) said that, they would recommend the sublingual administration of misoprostol (P=0.0001)[11].

Conclusion

The use of sublingual misoprostol is effective for cervical priming as vaginal misoprostol without significantly increasing the side effects. Sublingual misoprostol avoids the need of the doctor to insert vaginal misoprostol tablets. Sublingual misoprostol can be conveniently self-administered at home thereby decreasing hospital stay and cost. It also has a good patient acceptability rate.

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