Outcome and Adverse effects of Sublingual Misoprostol Compared to Local Misoprostol with Foleys Catheter Cervical Insertion in Missed Abortion Management

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Abstract

Background: Vaginal, oral, and sublingual doses of misoprostol are effective in abortion. A comparison of different doses and methods of misoprostol administration had done, preferred methods would shorten the duration between induction and delivery, and minimize adverse effects.

Aim: To compare the Outcome and Adverse effects of sublingual misoprostol, local misoprostol alone or in combination with intra cervical Foley's catheter in the clinical management for the missed abortions.

Patients and Methods: This prospective randomized controlled trial was conducted at Obstetrics Maternity (Emergency) Hospital, Faculty of Medicine, Zagazig University, 172 pregnant women were enrolled, Group A (Sublingual group) that subdivided into two subgroups: I (A) included 43 patients to whom misoprostol tablet was given sublingually every 4 hours up to 6 doses per day, I (B) included 43 patients to whom misoprostol tablet was given sublingually every 4 hours up to 6 doses per day plus Foley's catheter (18fr) insertion through cervix as far as the internal OS with inflation of its balloon with 30-50ml normal saline, Group B (Local "vaginal" group):= that subdivided into two subgroups; II (A) included 43 patients to whom misoprostol tablet was given vaginally every 4 hours up to 6 doses per day, II (B) included 43 patients to whom misoprostol tablet was given vaginally every 4 hours up to 6 doses per day plus Foley's catheter (18Fr) insertion through cervix as far as the internal Os with inflation of its balloon with 30-50ml normal saline, The protocol was followed for 48 hours after which further management was done.

Results: Our study revealed that sublingual misoprostol + cervical Foley's catheter insertion is associated with higher success rate and least induction to abortion interval; length of hospitalization, number/total of doses of misoprostol needed for termination of pregnancy and need for hysterotomy, sublingual misoprostol with/without cervical Foley's catheter insertion was associated with higher rate of adverse effects as nausea, vomiting and diarrhea.

Conclusion: From our study we can conclude that sublingual misoprostol + cervical Foley's catheter insertion is the best option for management of pregnant women with missed abortion, sublingual misoprostol with/without cervical Foley's catheter insertion was associated with higher rate of adverse effects as nausea, vomiting and diarrhea

Keywords: Outcome, Adverse effects, Sublingual Misoprostol, Local Misoprostol, Missed Abortion

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Introduction

Missed abortion is defined as a gestational sac containing dead embryo or fetus before 24 weeks of gestation without clinical symptoms of expulsion. Miscarriage is the most common complication of early pregnancy.The condition may present as an anembryonic gestation(empty or blighted ovum)or as fetal demise prior to24 weeks gestation.**(1)**

The incidence of missed abortion is estimated to be between 8% and 20% of all clinically confirmed intrauterine pregnancy failure. Missed abortion are more common in older women and in women with certain medical conditions, such as diabetes or thyroid disease, or in women who have had a previous miscarriage.**(2)**

The most common complication of prolonged retained fetus or product of conception are: (a)infection; (b)heavy bleeding and major coagulation disorders(it is rare if the fetus is retained for 4 weeks or more);(c)Emotional and psychological troubles for the mother.**(3)**

A combination approach of using Foley catheter with misoprostol has been proposed, suggesting that both ripening agents act synergistically rather than independently. misoprostol has been reported as more effective in improving the scores of cervical length and consistency, and transcervical Foley catheter as better at improving the cervical os dilatation score at preinduction cervical ripening; thus, the two methods improve different parameters of cervix**. (4).**

Various studies that explored the advantages of combining misoprostol with use of Foley catheter have been used vaginal misoprostol. Low-dose oral misoprostol is considered as effective and easier to administer than vaginal misoprostol. We propose that the combination of oral misoprostol and Foley catheter would be a better alternative. **(5).**

The combination of Foley catheter with low-dose misoprostol reduced the time needed by the women to reach full dilatation, and subsequently to expel uterine content **(5).**

This study aimed to compare the Outcome and Adverse effects of sublingual misoprostol, local misoprostol alone or in combination with intra cervical Foley's catheter in the clinical management for the missed abortions

Patients and Methods

This study was prospective randomized controlled trial conducted on patients with missed abortions who attended to Obstetrics maternity (emergency) Hospital, Faculty of Medicine , Zagazig University .in which termination of pregnancy was attempted in 172 women with missed miscarriage up to 24 week gestations.

The gestational age was determined from the first day of the last menstrual period, and confirmed by ultrasonography

Before beginning the management an informed written consent was taken from each patient and the nature of the drug, route of administration, health benefits, side effects and the possibility of uterine rupture were clearly explained to each patient.

This study was approved from Zagazig University Institutional Review Board (IRB) number 10636.

Inclusion criteria:

The patients with the following criteria were included in the study :

1. Single pregnancy.
2. Ultrasound diagnosis of missed abortion upto 24wks.
3. Previous two or less uterine scar.
4. Normally situated placenta (fundal placenta).
5. Age (18years) and above.

Exclusion criteria:

1. History or evidence of diseases that represent a contraindication to the use of misoprostol (glaucoma, sickle cell anemia, bronchial asthma)or known allergy to prostaglandins .
2. History or evidence of medical disease (hypertension, cardiac disease , blood disorders , coagulative disorders , liver disease).

3. Previous uterine scar of three or more caesarean section.
4. Uterine scars either perforation ,rupture uterus or myomectomy scar.
5. Abnormal placentation.(Low lying placenta)
6. Extra uterine pregnancy or molar pregnancy.
7. Multiple pregnancy.

Patients included in this study were divided randomly into 2groups:

Group(I): Sublingual group :

That subdivided into two subgroups:

I(A) included 43 patients : misoprostol tablet was given sublingually every 4 hours up to 6 doses per day, if there was no response the regime repeated in the next day .It consider failure if no response after 48 hours .

I(B) included 43 patients : misoprostol tablet was given sublingually every 4 hours up to 6 doses per day plus folye's cathter(18fr) insertion through cervix as far as the internal os with inflation of its balloon with 30-50ml normal saline. It consider failure if no response after 48 hours .

The protocol was followed for 48 hours after which further management was done.

Group(II):Local(vaginal) group :

That subdivided into two subgroups:

II(A) included 43 patients : misoprostol tablet was given vaginally every 4 hours up to 6 doses per day if there was no response the regime repeated in the next day. It consider failure if no response after 48 hours .

II(B) included 43 patients : misoprostol tablet was given vaginally every 4 hours up to 6 doses per day plus Foley's catheter (18Fr) insertion through cervix as far as the internal Os with inflation of its balloon with 30-50ml normal saline. It consider failure if no response after 48 hours .

_ The misoprostol tablet was placed in the posterior fornix of the vagina, the tablet was moistened with few drops of normal saline or water as lubricant at time of insertion .

Under complete aseptic measures, patient in lithotomy position and empty bladder, Foley's catheter (18Fr) was introduced through cervix as far as the internal Os with inflation of its balloon with 30-50ml normal saline. Safe guarding of the Catheter with owed traction on it then was secured by adhesive tape to the medial side of the thigh. Collecting plastic bag filled with 200cc normal saline was connected the catheter to sure the traction. The catheter was reserved for 48hours if expulsion did not happen , it was considered as failure of that method.

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The protocol was followed for 48 hours after which further management was done.

Randomization:

Patients were randomly allocated into 4 groups , papers were numbered according to sample size placed in a draw box, odd numbers were allocated to sublingual misoprostol cases(with catheter and without catheter) ,even numbers were allocated to vaginal misoprostol cases(with catheter and without cathter) .when the patient arrived was asked to draw a paper randomly from the box, and we determine the system applied to the patient according to the number chosen. .(single blinded technique)

Misoprostol was adjusted according to gestational age according to FIGO :

1-Gestational age from 0-13 weeks gestations : 800 mg.
2-Gestational age from 13-16 weeks gestations: 600 mg .
3-Gestational age from 16-24 weeks gestations: 400 mg .

The following procedures were done to every patient on admission:

1) Patient counseling:

- The nature of the drug , route of administration ,health benefits, side effects and possibilities of uterine rupture were clearly explained to each patient.
- An informed consent was taken from each patient before starting the study.

2) Careful and detailed history was taken from the patient which included:
   A- Personal history: name, age, special habits, occupation, marital status and address.
   B- Menstrual history included: First day of last menstrual period(LMP), Regularity, rhythm of the menstrual cycles.
   C- Obstetric history included: Parity, Gravidity , Possible causes of recurrent fetal loss or recurrent intrauterine fetal death, Mode of previous deliveries or abortions.
   D- Past history included: History of diabetes mellitus, Hypertensive disorder, Cardiac problems, Renal troubles, Chest troubles , Bleeding tendency, Blood diseases.
   E- Surgical history including : Previous uterine scars.

3) General examination included: Measurements of blood pressure, pulse and temperature**,** Presence of pallor or jaundice**,** Presence of petichae or ecchymosis of the skin to exclude presence of coagulation defects or blood disease**,** Cardiac and chest examination, Height and weight**.**

4) Abdominal examination to detect:

- Fundal level.
- Presence of scars of previous operations .

5) Vaginal examination:

- Cervical assessment including cervical dilatation, consistency, effacement and position.

6) The following investigations were done:

- Laboratory tests**:** Complete blood picture, Blood group and Rh , coagulation profile , Fasting Blood sugar, Urine examination, Viral screen, Cross matching of one unit of blood .
- Ultrasound was done for confirming the diagnosis of missed miscarriage , gestational age , estimated fetal birth weight , exclude placenta previa and multiple pregnancy .

The following was conducted to each patient after admission:

All patients were followed in the ward every four hours with observation of pulse rate, blood pressure, temperature and occurrence of side effects before next dose if would be given. uterine contraction was assessed by abdominal examination, and cervical status was assessed by vaginal examination.

No additional misoprostol dose was repeated if abortion is immenant (patient had at least(70%) cervical effacement with 2cm opening). The induction considered to be started when the patient received the first dose of misoprostol, and abortion defined as the time when the fetus was expelled (incomplete abortion) although in some cases placenta delivered at the same time (complete abortion)(**6).**

After abortion ultrasonographic examination was done to confirm that the products of gestation (fetus and placenta) had been successfully removed to establish that the abortion was complete . The success was defined as achieving expulsion of products of conception **.**

The misoprostol used in this study was a prostaglandin E_1 methyl analogue (misotac produced by Sigma Company) in tablets of 200 micrograms.

The following was given when necessary:

Pain relief

A. Paracetamol 500 mg, (1-2 tablets orally every 4-6 hours as needed).
B. Pethidine injection 50 mg I.M as needed.

When contractions became regular we follow up the following:

1- Nothing by mouth.
2- Intravenous dextrose 5% 500ml/8hours, normal saline solution at 500 ml/12 hour with plasil if the patient had vomitted.
3- Vital signs every hour.
4- Senior notification if the patient had:

- Excessive bleeding (> 100ml/hour).

- No abortion or expulsion of fetus in 48 hours.

Results included the following:

- Induction of abortion interval .
- The total doses received.
- Side effects or complications as chest pain, hyperthermia, hypotension, occurrence of post abortion pyrexia or sepsis.
- Failures as failing to evacuate uterus completely confirmed by U/S.

Failure of medical termination was considered if abortion has not been established within 48 hours of the first dose of misoproL

Statistical analysis

Collected data was processed using SPSS version 20. Quantitative data were expressed as mean ± SD while qualitative data were expressed as numbers and percentages. Student T-Test was used to assess the statistical significance of the difference between the two study group means. Chi-square test was used to examine the relationship between the qualitive variables. Fisher's exact test was used to examine the relationship between two qualitive variables when the expected count is less than 6 in more than 20% of cells

Results

Table (1): Maternal characteristic

	Group(I) (n=86)	**Group(II) (n=86)**	**t-test**	**P-value**
Maternal age (years) (mean±SD)	**26.50 ± 3.45**	**27.49 ± 3.72**	**1.7**	**0.07**
Parity(mean±SD)	**2.37±1.06**	**2.11±1.18**	**1.5**	**0.13**
Body mass index (kg/m^2) (mean±SD)	**28.02 ± 4.45**	**29.28 ± 4.77**	**1.79**	**0.075**

No Significant differences between the studied groups as regard maternal characteristic.

Table (2): Distribution of the studied groups according to gestational age at time of termination (weeks):

Gestational age (weeks)	**Group I (n=86)**				**GroupII (n=86)**				**P -value**
	GroupI(A) (n=43)		**Group I(B) (n=43)**		**GroupII(A) (n=43)**		**GroupII(B) (n=43)**		
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
From 0-13	25	58.1%	25	58.1%	23	53.4%	22	51.1%	0.88
From 13-16	12	27.8%	14	32.5%	14	32.5%	16	37.2%	0.86
From 16-24	6	13.9%	4	9.3%	6	13.9%	5	11.6%	0.75
Total	43	100%	43	100%	43	100%	43	100%	

No Significant differences between the studied groups as regard distribution of the cases according to gestational age at time of termination.

Table (3): Clinical criteria of the studied groups

Character	Group(I) (n=86)		Group(II) (n=86)		*2	P-value
	N	%	N	%		
Number of previous LSCS						
1	56	65.1%	50	58.1%	0.86	0.34
2	30	34.9%	36	41.9%		
Previous cervical intervention						
Biopsy	2	2.3%	3	3.4%	0.0	1.0
Cautery	10	11.6%	8	7.2%	0.25	0.61
D&C	8	7.2%	10	11.6%	0.25	0.61

No Significant differences between the studied groups as regard clinical criteria

Table (4): Number of doses of misoprostol needed for termination of pregnancy in studied groups

Gestational age (weeks)	Group I (n=86) (Mean ±SD)		GroupII (n=86) (Mean ±SD)		P -value
	GroupI(A) (n=43)	Group I(B) (n=43)	GroupII(A) (n=43)	GroupII(B) (n=43)	
From 0-13	5.72±0.56	4.35±0.32	6.11±0.12	7.17±0.18	<0.001**
From 13-16	7.72±0.84	5.35±0.29	10.11±0.82	10.97±0.92	<0.001**
From 16-24	8.72±0.54	6.35±0.22	11.11±0.02	10.17±0.98	<0.001**

There were highly Significant differences between the studied groups as regard number of doses of misoprostol needed for termination of pregnancy that were lower in Group I(B) followed by Group I(A) then GroupII(B) and GroupII(A).

Table (4): Outcomes of induction of abortion in studied groups

Gestational age (weeks)	Group I (n=86)				GroupII (n=86)				P - value
	GroupI(A) (n=43)		Group I(B) (n=43)		GroupII(A) (n=43)		GroupII(B) (n=43)		
	N	%	N	%	N	%	N	%	
Complete expulsion	36	83.7%	37	86%	27	62.8%	24	55.8%	0.001**
Incomplete expulsion	5	11.6%	5	11.6%	11	25.6%	15	34.9%	0.001**
Hysterotomy	2	4.7%	1	2.3%	5	11.6%	4	9.4%	0.31
Total	43	100%	43	100%	43	100%	43	100%	

There was highly Significant differences between the studied groups as regard outcomes of induction of abortion that complete expulsion was higher in Group I(B) followed by Group I(A) then GroupII(B) and GroupII(A), hysterotomy was lower in Group I(B) followed by Group I(A) then GroupII(B) and GroupII(A), incomplete expulsion was lower in Group I(B) followed by Group I(A) then GroupII(B) and GroupII(A)

Table (5): Adverse effects in studied groups

Side effect	Group I (n=86)				Group II (n=86)				P –value
	Group I(A) (n=43)		Group I(B) (n=43)		GroupII(A) (n=43)		GroupII(B) (n=43)		
	N	%	N	%	N	%	N	%	
Fever	2	4.7%	1	2.3%	5	11.6%	4	9.4%	0.31
Nausea or vomiting	18	41.9%	18	41.9%	6	13.95%	5	11.6%	0.001*
Diarrhea	19	44.2%	19	44.2%	11	25.3%	8	18.6%	0.019*

There was Significant differences between the studied groups as regard vomiting and diarrhea which were significantly higher in Group I compered to Group II.

Table (6): Success rate in studied groups

	Group I (n=86)		GroupII (n=86)		P -value
	GroupI(A) (n=43)	Group I(B) (n=43)	GroupII(A) (n=43)	GroupII(B) (n=43)	
Success rate	83.7%	86%	62.8%	55.8%	<0.001**
Failure rate	16.3%	14%	37.2%	44.2%	<0.001**

There was highly Significant differences between the studied groups as regard success rate that were higher in Group I(B) followed by Group I(A) then Group II(B) and Group II(A).

Discussion

Termination of pregnancy is a common obstetric procedure, with the advance of gestational age beyond 20 weeks it becomes progressively more risky **(7).**

Termination of pregnancy in the late second trimester in women with previous multiple cesarean sections may be complicated with rupture of the uterus and severe hemorrhage **(8).**

Foley's catheter is an effective, safe, and cheap method for termination of pregnancy **(9).**

During this study, 172 pregnant women were enrolled, after consenting each of them and divided into two groups; **Group A (Sublingual group)** that subdivided into two subgroups**: I (A) included 43 patients** to whom misoprostol tablet was given sublingually every 4 hours up to 6 doses per day, if there was no response the regime repeated in the next day it consider failure if no response after 48 hours, **I (B) included 43 patients to whom** misoprostol tablet was given sublingually every 4 hours up to 6 doses per day plus Foley's catheter

(18fr) insertion through cervix as far as the internal os with inflation of its balloon with 30-50ml normal saline it consider failure if no response after 48 hours. The protocol was followed for 48 hours after which further management was done. **Group B (Local "vaginal" group):=** that subdivided into two subgroups**; II (A) included 43 patients** to whom misoprostol tablet was given vaginally every 4 hours up to 6 doses per day if there was no response the regime repeated in the next day it consider failure if no response after 48 hours. **II (B) included 43 patients to whom** misoprostol tablet was given vaginally every 4 hours up to 6 doses per day plus Foley's catheter (18Fr) insertion through cervix as far as the internal Os with inflation of its balloon with 30-50ml normal saline it consider failure if no response after 48 hours. The misoprostol tablet was placed in the posterior fornix of the vagina; the tablet was moistened with few drops of normal saline or water as lubricant at time of insertion. The protocol was followed for 48 hours after which further management was done.

Most of studies that disagreed with our results were due to several causes as different study methodology, outcomes, sample size and different medical conditions and gestational age of studied cases at time of enrollment

No differences were noted between study groups as regard maternal age, parity, body mass index and gestational age at time of termination.

Saleh et al (10) agreed with us and reported that the demographic criteria of both groups revealed no significant difference (P-value>0.05).

Barakat et al (11) also agreed with us and stated that the patients' characteristics and baseline data for the three groups including the age, weight, gravidity, parity, duration of pregnancy, number of previous scar(s) showed no significant difference ($p > 0.05$).

On the other hand, sublingual misoprostol with/without cervical Foley's catheter insertion was associated with higher rate of adverse effects as nausea, vomiting and diarrhea, however no differences were noted between study groups regarding incidence of fever, hemorrhage, intrauterine infection and rupture uterus. Also, sublingual misoprostol without cervical Foley's catheter insertion was associated with better women's compliance and preference.

Saleh et al. (10) disagreed with us and reported that No significant difference as regard occurrence of adverse effects between both groups except the incidence of fever (17.1%) in G I and (5.7%) in G II with P value 0.01 that might be due to different study methods.

Fathalla et al. (12) reported that the most common complication recorded was retained placental parts, 39 patients (26,5%) followed by surgical evacuation. Uterine perforation occurred accidentally in 3 cases during evacuation followed by laparotomy and repair of perforation without hysterectomy. Infection recorded in 3 cases (1.7%). Sever haemorhage occurred in 4 cases where they needed hysterotomy.

Barakat et al. (11) agreed with us and reported that the occurrence of diarrhea being lowest in GII (no cases), highest in GI (5 cases) in compare to 1 case only recorded in GIII (P0.024). The occurrence of post induction nausea and vomiting, fever was higher among misoprostol group.

As regard total dose (μg) of misoprostol used in this study, there was significant difference between both groups which is less in GII (645.35±322) than GI (1100.72± 23.54) with P-value 0.001. Also about interval from admission to start induction to abortion and discharge {total hospitalization (days)} was significant longer in GI (4.11±1.02) than in GII (2.371±1.98) with P-value 0.004. That agreed with study of **Barakat et al. (11).**

The strength points of this study are that it was prospective randomized controlled trial design and having no patients who were lost during the study period.

It was the first study in Zagazig University Hospitals to compare the safety and efficacy of different regimens for termination of missed abortion either by using sublingual misoprostol or vaginal misoprostol alone, versus sublingual or vaginal misoprostol with cervical Foley's catheter insertion.

Every effort was made to ascertain that all data were documented, and only complete information was included in data analysis.

All clinical assessment, deliveries and assessment of study outcomes were done by the same team.
The limitations of the study are worthy of mention, this study was a hospital-based study, hence there was a limited number of cases with relatively smaller sample size relative to study outcomes, not being a multicentric study and this represents a significant risk of publication bias and did not represent a particular community.

Conclusion

From our study we can conclude that sublingual misoprostol + cervical Foley's catheter insertion is the best option for management of pregnant women with missed abortion, sublingual misoprostol with/without cervical Foley's catheter insertion was associated with higher rate of adverse effects as nausea, vomiting and diarrhea

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