

Comparison Between Sublingual and Vaginal Administration of Misoprostol in Management of Missed Abortion

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Abstract

Aim The aim of the present study is to compare between sublingual administration of misoprostol and vaginal administration in the management of missed abortion.

Materials and Methods The study was conducted in El-Shatby Maternity Hospital on 160 patients diagnosed as

missed abortion by ultrasonographic examination. Cases were divided into two groups according to the methods of misoprostol administration, whether sublingual or vaginal. Patients of the two groups were observed for the times of uterine colic starting, cervical dilation, and conceptus expulsion, along with recording of any side effects.

Result During the follow-up of our cases we found that sublingual route is more effective than vaginal route in the management of missed abortion. The difference between the two groups in percentage of conceptus expulsion was statistically significant. The most common side effects were nausea which was present in 55 % of cases in group I (sublingual) and in 40 % of cases in group II (vaginal) then severe pain in 25 % of cases in group I (sublingual) and in 20 % of cases in group II (vaginal) and hyperpyrexia in 15 % of cases in group I (sublingual) and in 5 % of cases in group II (vaginal).

Conclusion Sublingual administration of misoprostol is more effective than its vaginal administration in missed

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abortion management. Side effect of misoprostol as nausea, vomiting, fever is more common with sublingual administration in comparison with its vaginal administration.

Keywords Abortion · Misoprostol · Sublingual · Vaginal

Introduction

Missed abortion is defined as death of conceptus without expulsion of its contents with closed cervix before fetal viability age which differs in different countries. In Egypt, the age of viability is at 28 weeks of gestation, in the UK at 24 weeks, and in the USA at 20 weeks [1]. Early pregnancy loss includes spontaneous abortion which may be complete, in which all the products of conception has been expelled; and incomplete in which some products remain, blighted ovum in which no embryo has developed, and missed abortion [2]. Abortion occurs in approximately 10–20 % of all pregnancies. The risk of spontaneous abortion increases with old maternal age, high gravidity, and increased paternal age [3].

Management of missed abortion includes the following:

1. Surgical evacuation by using sharp curettage, vacuum aspiration.
2. Medical evacuation by using prostaglandin, oxytocin, and ergometrine.
3. Expectant management (waiting for spontaneous uterine contraction and cervical dilatation) [4].

Missed abortion is usually associated with bulky pregnancy products and its adherence to the uterine wall and closed cervix; that is why, surgical management may be complicated by incomplete evacuation, uterine perforation, and cervical trauma, while medical evacuation is safer, but the risk factors for medical therapy include bleeding, infection, possible incomplete abortion, and possible failure of the medication to work [5–7].

Medical management of abortion as regards effectiveness, side effects, route of administration, and drugs used should be evaluated, to be considered as a safe method of management.

Misoprostol is a synthetic prostaglandin E1 (PGE1) analog that is used for gastritis and gastric ulcers' treatment, to induce labor, and as an abortifacient. Misoprostol is an ester, and rapidly and completely deesterifies to pharmacologically active carboxylic acid in the stomach after oral administration [8]. Absorption of misoprostolic acid is rapid in reaching peak plasma concentration within 15–30 min and has a plasma half-life of 13–40 min. It can be used thorough oral, sublingual, buccal (between the cheeks and the gums), vaginal, and rectal routes. It can be

used for induction of labor, cervical ripening for surgical procedure as uterine curettage, pregnancy termination, and management of postpartum hemorrhage [9]. Many other studies had discussed the efficacies of two routes of misoprostol administration (sublingual and vaginal) for the treatment of missed abortion. Tanha et al. and Shah et al. have compared both routes for the management of missed abortion, but high doses as 400 µg of misoprostol have been used, while in this study, we reduced the dose to decrease the side effects [10].

Aim

The aim of the present study is to compare between the sublingual administration of misoprostol and the vaginal administration in the management of missed abortion.

Materials and Methods

Following approval by Alexandria Medical School Institutional Ethics Committee, the study was conducted on 240 cases randomly allocated with missed abortion selected from the inpatient clinic of El-Shatby Maternity University Hospital. 160 cases continued the study for 24 h, and a written consent has been obtained from all patients.

All the cases are subjected to full history taking [age, gravity, parity, last menstrual period (LMP), and present complaint (e.g., amenorrhea, regression of symptoms of pregnancy, pain, bleeding)], complete general examination, obstetric examination, and transvaginal ultrasound examination to confirm the diagnosis, according to the following criteria:

- Gestational sac with mean sac diameter of >25 mm, without fetal pole (blighted ovum).
- The presence of fetal pole >7 mm, with no cardiac pulsations.
- Gestational sac mean diameter <18 mm, with no interval growth being observed on rescanning 10 days later.
- The absence of embryo with heartbeat at least 2 weeks after an ultrasound scan that showed a gestational sac without a yolk sac.
- The absence of embryo with heartbeat at least 11 days after an ultrasound scan that showed a gestational sac with a yolk sac [11].

Cases included in the study were divided into two groups on a randomized basis:

Group I (sublingual group); 100 µg of misoprostol (1/2 tablet) was administrated to group 1 cases sublingually and were repeated every 4 h for four doses.

Group II (vaginal group); 100 µg of misoprostol (1/2 tablet) was administered to group 2 vaginally in the posterior fornix, and this was repeated every 4 h for four doses [12, 13].

From intake of the first dose till 24 h after the last dose, follow-up was done and closely observed for gastrointestinal side effects such as nausea, diarrhea, stomach cramps, uterine colics, cervical dilation, passage of part of conceptus, and amount of vaginal bleeding. Transvaginal ultrasound was repeated after 24 h after the last dose and after expulsion of parts of conception to assure complete evacuation of the uterine cavity. The absence of remnant of conception or endometrial interface thickness less than 15 mm is mandatory to diagnose complete abortion [14].

Surgical evacuation was done to all other cases that showed no uterine colic, internal os dilatation, and complete evacuation with endometrial interface less than 15 mm within 24 h from the beginning of the first dose.

Statistical Analysis

After data were collected, it was revised, coded, and fed to statistical software SPSS version 16. The given graphs were constructed using Microsoft excel software. All statistical analyses were done using two-tailed tests with an alpha error of 0.05. *P* value less than or equal to 0.05 was considered to be significant. The following statistical tests were used. Descriptive statistics included the mean with standard deviation (SD) for normal distributed data, while percent to describe the categorical data shape of distribution was tested using histogram to identify outliers of independent samples. *t* test was used to compare means of the two groups for the study parameters. The Fisher's exact test was used for independent nominal data. A *P* value of <0.05 was considered significant.

Justification of Sample Size

80 patients per group were needed, with a significant difference in effectiveness rates between the two groups being equal to 30 %, a precision rate of 10 %, and powers of 80 % and 95 % in confidence interval levels.

Reference for Sample Justification

Tanha et al. [15].

The data of the study revealed the following result.

Result

During follow-up of our cases, we found that sublingual protocol is more effective than vaginal protocol in missed abortion management. The numbers of cases showing uterine colic were 75 in group 1 (sublingual group) versus 66 in group 2 (vaginal group), cases with cervical dilatation in group 1 were 67 versus 52 in group 2, the numbers of cases with complete evacuation were 56 in group 1 versus 41 in group 2. Cases managed by surgical evacuation were 24 in group 1 versus 39 in group 2. The mean (\pm SD) time interval between the first dose and the start of uterine colics in group I (sublingual group) was 7.1 ± 2.3 h, and that in group II (vaginal) was 5.3 ± 1.9 h. The mean (\pm SD) time interval between the first dose and cervical dilatation in group I (sublingual group) was 9.7 ± 2.9 h, and that in group II (vaginal group) was 7.9 ± 2.9 h (Fig. 1). The mean (\pm SD) time interval between the first dose and conceptus expulsion in group I (sublingual group) was 12.6 ± 3.1 h, and in group II (vaginal group), it was 9.0 ± 1.6 h (Table 1; Fig. 1). The differences between the two groups in percentage of conceptus expulsion were statistically significant (Table 2;

Fig. 1 Comparison between the two studied groups regarding the starts of uterine colics, cervical dilatation, and spontaneous expulsion

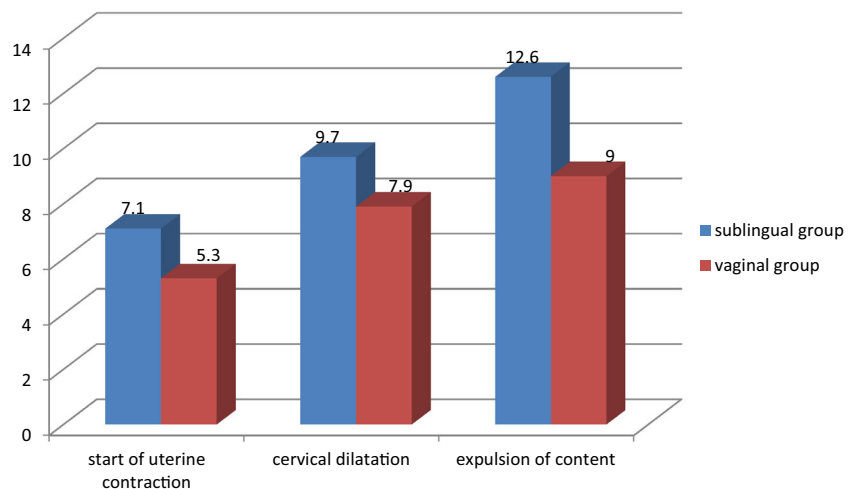


Table 1 Comparison between the two studied groups regarding the times lapsed till starting of uterine colics, cervical dilatation, and complete spontaneous expulsion

Parameter	Group		<i>t</i>	<i>P</i>
	Sublingual misoprostol (<i>n</i> = 80)	Vaginal misoprostol (<i>n</i> = 80)		
Start of uterine colic (h)			5.8	0.000*
Range	4.0–14.0	2.5–11.0		
Mean ± SD	7.1 ± 2.3	5.3 ± 1.9		
Median	6.8	5.0		
Cervical dilatation (h)			3.6	0.000*
Range	5.3–18.0	4.8–17.0		
Mean ± SD	9.7 ± 2.9	7.9 ± 2.9		
Median	9.0	7.0		
Spontaneous expulsion (h)			7.4	0.000*
Range	7.5–22.0	6.5–14.0		
Mean ± SD	12.6 ± 3.1	9.0 ± 1.6		
Median	12.0	9.0		

Vaginal misoprostol is significantly faster in inducing uterine contraction, cervical dilatation, and expulsion of uterine content than sublingual misoprostol

t Student's *t* test

* *P* < 0.05 (significant)

Table 2 Comparison between the two studied groups regarding clinical outcomes

Outcome	Group I		Group II	
	No.	%	No.	%
Successful	56	70.00	41	51.25
Unsuccessful	24	30.00	39	48.75
Fisher's exact test	0.0231			
Two-tailed <i>P</i> value				

P is significant at ≤ 0.05

Successful clinical outcome in this study was defined as complete evacuation of the uterine contents (product of conception) without surgical cervical dilatation or uterine evacuation, and documented by transvaginal ultrasound. 70 % of cases in group I (sublingual group) showed complete evacuation versus 51.25 % of cases in group II (vaginal group). The difference was statistically highly significant

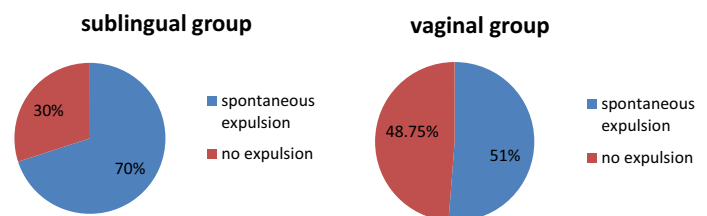
Fig. 2 Comparison between the two studied groups regarding clinical outcomes

Fig. 2). As regards failures of start of uterine contraction, they were 6.25 % in sublingual group and 16.25 % in vaginal group; in relation to cervical dilatation failures, they were 17.5 % in sublingual group and 35 % in vaginal group, while failures of spontaneous expulsion were 30 % in sublingual and 48.75 % in vaginal group. The most

common side effects were nausea: 55 % of cases in group I (sublingual) and 40 % of cases in group II (vaginal); then severe pain 25 % of cases in group I (sublingual) and 20 % of cases in group II (vaginal); and hyperpyrexia 15 % of cases in group I (sublingual) and 5 % of cases in group II (vaginal).

Discussion

Surgical evacuation of missed abortion is not without hazard, as the contents of dead conceptus are adherent to uterine wall, in addition to closed cervix, and bulky contents. Complications like uterine perforation, intrauterine remnants, and sepsis are not uncommon. Although this procedure was introduced to reduce the risk of hemorrhage, it is reported to be associated with many complications including cervical trauma, perforation of the uterus, and endometritis. In addition, uterine synechia, reduced fertility, tubal damage, and pelvic pain have been reported as long-term complications [5]. Medical methods' of uterine evacuation are safer and accepted by the patients [7].

The present study has been designed to compare the safety and efficacy aspects of sublingual versus vaginal misoprostol for medical management of missed abortion. It is suggested that sublingual misoprostol is more effective than vaginal misoprostol and that it requires fewer dosages in both cervical dilatation and expulsion of the conceptus, but with some side effects.

Other studies used high doses of misoprostol like 400 µg, however, associated with side effects; that is why in the present study, low dose was used to decrease side effects.

Time intervals between the administration of misoprostol and the start of uterine colics, cervical dilation, and spontaneous expulsion of the conceptus have an important bearing on the acceptability of the drug. There were significant differences between group I (sublingual group) and group II (vaginal group) as regards time interval between the first dose and these three parameters. The mean (\pm SD) time interval between the first dose and the start of uterine colics in group I (sublingual group) was 7.1 ± 2.3 h, and that in group II (vaginal) was 5.3 ± 1.9 h. The mean (\pm SD) time interval between the first dose and start of cervical dilatation in group I (sublingual group) was 9.7 ± 2.9 h, and that in group II (vaginal group) was 7.9 ± 2.9 h. In relation to expulsion of contents, the mean (\pm SD) time interval between the first dose till expulsion was 12.6 ± 3.1 h in sublingual group and that in the vaginal group was 9.0 ± 1.6 h. From these results, we conclude that the vaginal route is more significantly rapid than the sublingual route in terms of its effects.

Shah et al. found that the mean times to expulsion were also similar in respect of both groups (13.07 ± 6.95 h for sublingual versus 13.29 ± 5.63 h for vaginal group) [10], while Tanha et al. found that the mean time to expulsion was shorter (9.68 h, $SD = 5.51$, 95% CI = 8.61 – 10.57) in the sublingual group than that in the vaginal group (16.64 h, $SD = 14.01$, 95% CI = 13.8 – 19.48), $P = 0.000$ [15]. The reason for the contradiction between the previous

two studies and this study, in relation to rapid action of vaginal route, is that those studies have used higher doses of misoprostol than the present study.

As regards effectiveness of sublingual route in relation to vaginal route of misoprostol, in sublingual group, 70 % of cases had a complete expulsion versus 51.25 % in vaginal group, and the difference between both groups in relation to expulsion rates is significant. Sublingual route is more effective in successful evacuation than the vaginal route, but the main point of weakness here is delayed action. Another study showed a similar result to that of Tanha FD et al. who showed that the effectiveness was higher in the sublingual group and the difference statistically significant (sublingual 84.5 %, vaginal 46.4 %, $P = 0.000$, $RR = 0.54$, 95% CI = 0.442 – 0.681) [15] and the study by Shah et al. found that there was no significant difference in the complete evacuation rates between the sublingual misoprostol and the vaginal misoprostol groups (52 vs. 48 %, $P = 0.571$) [10]. The explanation for this difference was that the last study had a fewer numbers of cases and it had extended the gestational age of cases up to 20 weeks. In relation to complication, the sublingual group showed more complications as diarrhea was present in 70 % of cases in sublingual group versus 35 % in vaginal group, fever in 20 % of sublingual versus 10 % in vaginal, severe abdominal cramps in 70 % in sublingual versus 40 % in vaginal. From these results, we can conclude that sublingual misoprostol for the medical management of missed abortion is more effective than the vaginal route. However, it showed more adverse effects and delayed action than those of vaginal route.

Compliance with Ethical Standards

Conflict of interest None.

Ethical approval It meets ethical guidelines as the manuscript has been approved by ethics committee of Alexandria medical school, and a written consent has been taken from all patients about participation in research.

References

1. Alberma E, Grudzinskas G, Chardt G. Spontaneous abortion: diagnosis and treatment. London: Springer; 1992. p. 9–20.
2. Grimes DA, Stuart G. Abortion jabberwocky: the need for better terminology. *Contraception*. 2010;81(2):93–6.
3. Schorge JO, Schaffer JI, Halvorson LM, et al. First-trimester abortion. In: Schorge JO, Schaffer JI, editors. *Williams Gynecology*. New York: McGraw-Hill; 2008.
4. Geyman JP, Oliver LM, Sullivan SD. Expectant, medical, or surgical treatment of spontaneous abortion in first trimester of pregnancy? A pooled quantitative literature evaluation. *J Am Board Fam Pract*. 1999;12(1):55–64.
5. Chung TK, Cheung LP, Sahota DS, et al. Spontaneous abortion: short-term complications following either conservative or surgical management. *Aust N Z J Obstet Gynaecol*. 1998;38(1):61–4.

6. Scroggins KM, Smucker WD, Krishen AE. Spontaneous pregnancy loss: evaluation, management, and follow-up counseling. *Prim Care*. 2000;27(1):153–67.
7. Kripke C. Expectant management vs. surgical treatment for miscarriage. *Am Fam Physician*. 2006;74(7):1125–6.
8. Davies NM, Longstreth J, Jamali F. Misoprostol therapeutics revisited. *Pharmacotherapy*. 2001;21(1):60–73.
9. Denison FC, Calder AA, Kelly RW. The action of prostaglandin E2 on the human cervix: stimulation of interleukin 8 and inhibition of secretory leukocyte protease inhibitor. *Am J Obstet Gynecol*. 1999;180(3 Pt 1):614–20.
10. Shah N, Azam SI, Khan NH. Sublingual versus vaginal misoprostol in the management of missed miscarriage. *J Pak Med Assoc*. 2010;60(2):113–6.
11. Doubilet PM, Benson CB, Bourne T, et al. Diagnostic criteria for nonviable pregnancy early in the first trimester. *N Engl J Med*. 2013;369(15):1443–51.
12. Weeks AD, Fiala C, Safar P. Misoprostol and the debate over off-label drug use. *BJOG Int J Obstet Gynaecol*. 2005;112:269–72.
13. El-Sayed MM, Mohammed SA, Jones MH. Expectant management of first-trimester miscarriage. *J Obstet Gynaecol*. 2009;29(8):681–5.
14. Chia KV, Ogbo VI. Medical termination of missed abortion. *J Obstet Gynaecol*. 2002;22(2):184–6.
15. Tanha FD, Feizi M, Shariat M. Sublingual versus vaginal misoprostol for the management of missed abortion. *J Obstet Gynaecol Res*. 2010;36(3):525–32.