Effect of Different Dosages of Intravaginal Misoprostol for Second Trimester Pregnancy Termination

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ABSTRACT

Miscarriage is a common complication of early pregnancy; however; curettage and dilation are considered standard methods taking care of early pregnancy failure. Misoprostol has been used as an alternative agent for termination of early pregnancy. Therefore, this study was aimed to compare the efficacy and side effects of two different intravaginal misoprostol trials for the second trimester pregnancy termination of missed miscarriage between 14 and 23 weeks.

A clinical trial was carried out in Basrah Maternity & Children Hospital during the period from October 2011 to November 2012. A total of 100 women experienced missed miscarriages at 14-23 weeks of gestation were admitted for medical termination of pregnancy. Patients were divided into the following two groups:

Group 1: 50 patients received 400 µg of intravaginal misoprostol/8 hours. Group 2: 50 patients received 800 µg of intravaginal misoprostol/8 hours. The patients were followed up for 24 hours. The primary outcome measure was induction-miscarriage interval; the secondary outcomes were the rate of successful miscarriage and complete miscarriage; the incidence of side effects was compared in both groups.

The rates of successful termination of pregnancy in both groups 1 and 2 were 86% and 90%, respectively. The success rates of the drug in group 1 were 0%, 12%, 36%, 34%, 10%, and 4% after first, second, third, fourth, fifth, and sixth doses, respectively; whereas, the success rates in group 2 were 24%, 34%, 24%, 12%, 4%, and 0% after first, second, third, fourth, fifth, and sixth doses, respectively. The mean numbers of doses required to achieve response were 3.66 and 2.44 in groups 1 and 2, respectively. The mean induction to miscarriage interval was significantly shorter for group 2 than for group 1 (15.46 ± 9.21 hours and 22.96 ± 9.44 hours, respectively) (P<0.00001). Drug dosages showed more side effects in group 2 patients than in group 1 patients with no significant differences. Miscarriages were reported more in group 2 patients (82%) than in group 1 patients (48%) (P<0.001) within 24 hours.

Both trials were effective for terminating the second trimester pregnancy of missed miscarriage. However, 800 mg intravaginal mistoprostol trial resulted in shorter induction-miscarriage interval. The non-significant higher incidence of side effects was reported in group 2 trial than in group 1 trial.

Keywords: Gynecology, Miscarriage, Misoprostol, Route of administration.

INTRODUCTION

A Miscarriage is the most common complication of pregnancy. Approximately 50% of all conception (1,2) and 15% of all recognized pregnancy (1) result in miscarriage. The World Health Organization defined miscarriage as "expulsion or extraction from the womb of an embryo or fetus weighting less than 500 g or having reached a gestational age of less than 24 weeks (1).

The termination of pregnancy can be achieved by surgical means or by pharmacological agents or in combination as an adjuvant to the surgical method. The medical methods become the first choice for the

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second trimester termination of pregnancy (3), which include the usage of oxytocin (4), mifepristone (5), methotroxate 5, or prostaglandins (6). Misoprostol is a synthetic prostaglandin analogue that has been marketed in the United Kingdom since 1988 as a gastric protective agent for preventing and treating peptic ulcer associated with the use of non-steroidal anti-inflammatory drugs (4). It also becomes an important drug in obstetrics and gynecologic practice because it has uterogenic and cervical ripening effects (7). Its uses must be restricted to clinical trials (8). The systemic bioavailability of vaginal-administered misoprostol is three times higher than that of the oral route (4).

The aim of this study was to compare the efficacy and side effects of two different misoprostol trials given intravaginally for the medical termination of second-term pregnancy.

MATERIALS AND METHODS

Prospective clinical trials were performed between October 2011 and November 2012 at the Department of Gynecology and Obstetrics, Basrah Hospital of Maternity and Children. The study involved 100 women with singleton pregnancy having the gestational age between 14 and 23 weeks. These patients were admitted to the Hospital as a case of missed miscarriage for medical termination of pregnancy. All patients agreed to participate in the study. The work was approved ethically by the College of Medicine, University of Basrah, Iraq. The demographic characteristics were assessed including age, body weight, gravity, parity, history of previous abortion, previous medical disorder, and gestational age (determined by last menstrual period and/or ultrasound examination). Vital signs were examined, and digital vaginal inspection was performed for any dilatation of the cervix.

Routine investigations were conducted for each patient including complete blood picture, renal function test, liver function test, blood group and Rh, and serum fibrinogen level. Ultrasound was also conducted to confirm diagnosis and to exclude twin pregnancy.

The patients were then divided into two groups. Group 1 included 50 patients who received 400µg misoprostol intravaginally/8 hours. Group 2 included 50 patients who received 800µg misoprostol intravaginally/8 hours. The tablets were placed in the posterior fornix of the vagina, and the patients lay in the supine position for 30 minutes.

All patients were followed up in the ward every 3 hours for watching the frequency of uterine contraction and vital signs or any systemic symptoms. The side effects including nausea, vomiting, diarrhea, and fever were recorded.

After miscarriage, the fetus and placenta were examined to see whether the miscarriage was completed, and ultrasound scanning was also done for the same purpose. If a woman in either group failed to get aborted within 24 hours after the initiation of therapy, she was given a second course of misoprostol with the same trial. The patient was hospitalized for only 48 hours.

Statistical analysis

Data were collected and analyzed using the SPSS version 10. Differences between groups were examined using student t test, chi-sequare (X^2) test, or Fisher test. These tests were used to detect the relations between various variables. P value < 0.05 was considered as statistically significant.

RESULTS

It is obvious that both groups were comparable in demographic assessment (Table 1). So it is unlikely for these factors to distort the effect of the studied drug.

TABLE 1: Maternal demographic characteristics for two groups.

Characteristics	G1 n=50	G2 n=50	P value
Maternal age (years) (mean±SD)	26.08±4.72	26.06±4.98	0.98
Weight (kg) (mean±SD)	72.28±6.15	73.9±7.22	0.230
Maternal height (cm) (mean ±SD)	158±291	158±3.98	0.728
Gestational age (weeks) (mean ± SD)	18.84±2.82	18.66±3.05	0.76
Gravity (mean ± SD)	2.58±1.11	2.66±1.12	0.720
Parity (mean ± SD)	2.73±1.28	2.39±1.11	0.69
Parity (mean ± SD)	29(58%)	19(38%)	0.840
Primigravida n. and %	21(42%)	31(62%)	0.78
Number of previous abortion (mean±SD)	1.19±1.26	1.1±1.15	0.362

Table 2: Types of response in the two groups.

Types of response	G1		G2		P value
Complete success	Primigravida	N=26, 89.65%	Primigravida	N=17, 89.47%	0.50
	Multigravid	N=17, 80.95%	Multigravid	N=28, 90.32%	
	Total	N=43, 89%	Total	N=45, 90%	
Partial success	Primigravida	N=5, 17.14%	Primigravida	N=3, 14.28%	0.35
	Multigravid	N=0, 0%	Multigravid	N=0, 0%	
	Total	N=5, 10%	Total	N=3, 6%	
Failure of termination	Primigravida	N=2, 6.89%	Primigravida	N=0, 0%	0.50
	Multigravid	N=0, 0%	Multigravid	N=1, 3.22%	
	Total	N=2, 4%	Total	N=1, 2%	
Discontinuation of treatment	Primigravida	N=0, 0%	Primigravida	N=0, 0%	0.50
	Multigravid	N=0, 0%	Multigravid	N=1, 3.22%	
	Total	N=0, 0%	Total	N=1, 2%	

Table 3: Comparison of number and total dose of misoprostol in both groups.

Parameters		G1			G2			
Number of		Multi.	Primi.	Total	Multi.	Primi.	Total	
doses	Mean	3.24	3.97	3.66	2.13	2.95	2.44	0.00001
required	SD	0.94	1.09	1.08	1.09	1.27	1.21	
Total doses	Mean	1295.24	1586.21	1464	1600	2189.47	1824	
of drugs	SD	377.40	434.02	432.25	772.87	1061.39	929.02	0.015
in µg								

A complete uterine evacuation without intervention was achieved in 43 patients (86%) in group 1 and 45 patients (90%) in group 2 (Table 2). While pregnancy termination with surgical intervention occurred in five patients (10%) in group 1 and three patients (6%) in group 2, failure to abort after receiving two courses of drug was noticed among two (4%) patients in group 1 and one (2%) patient in group 2. The termination was done by oxytocin infusion. The discontinuation of treatment was observed in one (2%) patient in group 2 due to the development of allergic reaction (Table 2).

Group 2 required significantly less number of doses than group 1 (2.44 ±1.21 and 3.66 ±1.08, respectively) (P<0.00001). Nulliparous women required more doses to achieve response than women with previous vaginal birth (Table 3).

The success rates of the drug in group 1 were 0%, 12%, 36%, 34%, 10%, and 4% after first, second, third, fourth, fifth, and sixth doses, respectively; whereas, the success rates in group 2 were 24%, 34%, 24%, 12%, 4%, and 0% after first, second, third, fourth, fifth, and sixth doses, respectively (Table 3).

It was observed that the successful termination of pregnancy was achieved after 1 dose of misoprostol in group 1 compared with 12 doses (24%) in group 2 (P<0.05). The maximum response was achieved in primigravida after the fourth dose (37%) in group 1 and after the second dose (42.1%) in group 2 (Table 4).

The mean induction-miscarriage interval was significantly shorter for group 2 patients than for group 1 patients (15.46+9.21 and 22.96 ±9.44 hours, respectively) (P<0.00001) (Table 5). Miscarriage occurred more in group 2 patients (82%) than in group 1 patients (48%) (P<0.001) (Table 5) in 24 hours. It was also observed that women in group 1 required more than 24 hours achieving successful termination of pregnancy (Table 5).

Patients in group 2 were aborted in less than 12 hours (52%) compared with patients in group 1 (12%) (P=0.001. Patients in group 2 (82%) were aborted in 24 hours compared with patients group 1 (48%) (P=0.001) (Table 6). It was also shown that women receiving group 1 regimen required more than 24 hours to achieve the successful termination of pregnancy (52%) compared with women receiving group 2 regimen (18%) (P=0,001) (Table 6).

Complications during trial including postabortal bleeding, blood transfusion, retained placenta, surgical intervention, allergic reaction, and uterine rupture were reported in Table 7.

An increase rate of side effects was observed in group 2 than in group 1, but these were statistically non-significant (P>0.05) (Table 8). The side effects included abdominal pain, fever, headache, chills, nausea, vomiting, and diarrhea.

Table 4: A comparison of cumulative response rate at the end of each dose interval between group 1 and group 2.

Number of doses	G1						G2						P value
	Primigravida N=29		Multigravida N=21		Total N=50		Primigravida N=29		Multigravida N=21		Total N=50		
	n.	%	n.	%	n.	%	n.	%	n.	%	n	%	
First	0	0	0	0	0	0	1	5.30	11	35.5	12	24	0.002
Second	1	3.40	5	23.8	6	12	8	29	9	42	17	34	0.008
Third	10	34.5	8	38	18	36	4	21.10	8	25.8	12	24	0.19
Fourth	11	37.9	6	28.6	17	34	4	21.10	2	6.5	6	12	0.008
Fifth	3	10.3	2	9.50	5	10	1	5.30	1	3.20	2	4	0.23
Sixth	2	6.9	0	0	2	4	0	0	0	0	0	0	0.15
Failure after sixth	2	6.9	0	0	2	4	1	5.30	0	0	1	2	0.55
Total	29	100%	21	100%	50	100%	19	100	31	100	5	100	

Table 5: Induction-abortion interval for primiparous and multiparous women in both groups.

		G1		G2	P value
Primiparous	Mean	25.69	Mean	19.110.03	
	SD	9.85	SD	11.35	
Multiparous	Mean	19.19	Mean	13.23	0.001
	SD	7.54	SD	6.91	
Total	Mean	22.69	Mean	15.46	0.00001
	SD	9.44	SD	9.21	

DISCUSSION

Although prostaglandin-based regimen could be associated with the high incidence of maternal side effects such as nausea, vomiting, fever, and diarrhea, medical miscarriage frequently performed by administrating prostaglandins has been approved to be a safe and effective alternative to the surgical method (9-12). This regimen is expensive and needs cold storage. Misoprostol as an alternative has a more selective action on the myometrium and causes fewer gastrointestinal side effects. Therefore, misoprostol has been used for this purpose, but the optimal dosage and the route of administration are yet to be defined.

The results of this study were encouraging suggesting that misoprostol alone was an effective agent for terminating pregnancy by using both the high and the low dosages. The success rates were 90% and 86% in both regimens, respectively.

The completion rates of pregnancy termination with the misoprostol regimens tested were high, but if associated with a shorter dosing interval it appears to be associated with more frequent reports of side effects (13,14). In this study, the high dose was more effective than the low dose with several side effects that are not statistically significant. This result was in agreement with many recent studies (9,15,16). In a study performed in Hongkong Hospital, most patients had delivered within 24 hours using the high dose of misoprostol than using the low dose of misoprostol (15). It was demonstrated that the higher-dose regimen resulted in a significantly shorter median induction to abortion interval

Table 6: The difference in induction-abortion interval between the two groups.

Parameters		G1			G2			P value
		Primigravida n.=29	Multigravida n.=21	Total n.=50	Primigravida n.=19	Multigravida n.=31	Total n.=50	
Abortion <12 hours	n.	1	5	6	8	18	26	
	%	3.44	23.8	12	42.10	58.10	52	
Abrotion within 24 hours	n.	11	13	24	13	28	41	0.001
	%	37.93	61.90	48	68.40	90.30	82	
Abortion > 24 hours	n.	16	8	24	5	3	8	0.001
	%	55.17	30.09	48	26.30	9.70	16	

Table 7: Intrapartum complications in both groups.

Parameters		G1			G2			P value
		Primigravida n.=29	Multigravida n.=21	Total n.=50	Primigravida n.=19	Multigravida n.=31	Total n.=50	
Postabortal bleeding	n.	0	2	2	1	0	1	0.50
	%	0	9.52	4	5.30	0	2	
Blood trunsfusion	n.	0	2	2	1	0	1	0.50
	%	0	9.52	4	5.30	0	2	
Retained placenta >1 hour	n.	1	1	2	1	0	1	0.50
	%	3.44	4.76	4	5.30	0	2	
Retained part of product	n.	3	0	3	2	0	2	0.50
	%	10.34	0	6	10.50	0	4	
Surgical intervention	n.	4	1	5	3	0	3	0.35
	%	13.79	4.76	10	15.80	0	6	
Allergic reaction	n.	0	0	0	0	1	1	0.50
	%	0	0	0	0	3.20	2	
Rupture uterus	n.	0	0	0	0	0	0	1.00
	%	0	0	0	0	0	0	

Table 8: Frequency of each side effect in both groups.

Reported side effect	G1 Number	%	G2 Number	%	Total Number	%	P value
Gastrointestinal tract side effect							
Nausea	3	6	6	12	9	9	0.24
Vomiting	1	2	3	6	4	4	0.30
Diarrhea	1	2	2	4	3	3	0.50
Abdominal pain	3	6	7	14	10	10	0.15
Fever >38°C	4	8	9	18	13	13	0.04
Headache	1	2	3	6	4	4	0.30
Chills	1	2	1	2	2	2	0.50

(15.1 hours) and the greater percentage of patients delivered within 24 hours (76%) compared with the low-dose regimen (59%) (16). It was also observed that the premoistened misoprostol tablets inserted vaginally appeared more effective than dry tablets, although the difference was statistically insignificant (13).

Vaginal route is preferable, although the oral misoprostol is an effective way for terminating pregnancy in the second trimester. However, the vaginal route is associated with longer induction-miscarriage interval and more frequent side effects, especially gastrointestinal tract side effects, and more number of doses is needed to achieve the successful termination of pregnancy (16-18). This is possibly related to pharmacokinetic improvement associated with the vaginal route (19). The absorption is fast and the first uterine contraction may appear after 5-10 minutes; the half-life of misoprostol is 90 minutes (15). Plasma concentration of misoprostol peaks in 2 hours, which sustains for up to 4 hours. The efficacy of misoprostol is improved when higher doses are given at shorter intervals (11,15).

The systemic bioavailability of the vaginal route is three times higher than that of the oral route; the peak plasma levels of misoprostol are reached more slowly and the levels are slightly lower even though are sustained for up to 4 hours. This is likely the outcome of presystemic gastrointestinal or hepatic metabolism that occur in the oral route but not in the vaginal administration (18,20). The oral route is found to be less effective and with unacceptable higher incidence of complication such as uterine hyperstimulation as observed in a trial carried out to compare the oral versus vaginal misoprostol (14).

In conclusion, both regimens are effective for terminating second trimester pregnancy. The high dose of misoprostol

resulted in a shorter induction-abortion interval. In addition, no significant side effects of the drug were observed with high dose than with low dose.

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