

Efficacy of Intravaginal Misoprostol in Different Media for First and Second Trimester Termination of Pregnancy

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ABSTRACT:

BACKGROUND:

Medical abortion becomes the 1st choice for early 1st and 2nd trimester termination of pregnancy in many countries although dilatation and evacuation is commonly used in USA ,Medical abortion has been more patchy in its introduction in England and Walse and there continuous to be significant variation in its provision across health authorities .Medical method are often favored because they appear more physiological ,like a miscarriage and avoid the need for uterine instrumentation and also share the advantages of low rate of complication and failure.

OBJECTIVE:

To evaluate the effect of different media (acetic acid , normal saline or dry)on the efficacy of intravaginal misoprostol used for induction of first and second trimester abortion.

PATIENTS AND METHOD:

During the 12 months of the study period, 90 pregnant women seeking termination of early pregnancy loss up to 24 weeks, as an indication for induction of abortion, their mean age were 27.7 ± 5.5 years, and mean weight 72.3 ± 3.9 kg. The first 30 pregnant patients received intravaginal 400 μ g misoprostol moistened with 2 ml of 5% acetic acid for 4hours interval up to 5 doses for 24 hours ,if the participant failed to achieve abortion the same regimen repeat for the next 24 hours, including 8 primiparous and 22 multiparous. Next 30 patients received intravaginal 400 μ g misoprostol moistened in 2ml of normal saline for 4 hours interval up to 5 doses for 24 hours ,if abortion failed then the trial repeated once again , including 15 primiparous and 15 multiparous. The last 30 patients received dry intravaginal 400 μ g misoprostol , 4hours intervals up to 5 doses for 24 hours. if abortion failed the same regimen repeat for the next 24 hours, including 10 primiparous and 20 multiparous.

RESULT:

All patients aborted within 48 hour. Significantly shorter induction –abortion interval for the moistened misoprostol tablet in acetic acid (mean 8.3 ± 2.2 hours), P value (0.000) ,than induction-abortion interval for moistened misoprostol tablet in normal saline (mean 19.5 ± 7.7 hours) , and dry misoprostol tablet (mean 23.1 ± 8.8 hours) .

The number of doses required to achieve response for moistened misoprostol in acetic acid was significantly less(mean 1.5 ± 0.5), P value (0.000),than that required for moistened misoprostol in normal saline(mean 3.1 ± 0.8),and for the dry misoprostol tablet (mean 3.7 ± 0.8). The side effects being of no statistical significant.

CONCLUSION:

Acidic medium enhance the effect of misoprostol administered for induction of abortion. Moistening intra vaginal misoprostol may affect the pharmacokinetics of the drug to achieve a constant plasma profile.

KEY WORDS: abortion, misopristol, vaginal ph

INTRODUCTION:

Research on medical abortion was initiated in the year 1972 . it was welcomed as a non – invasive option for early abortions as it avoids the risk of anesthesia and surgical trauma to the cervix ,

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uterus and other organs⁽¹⁾.

Misoprostol is a prostaglandin E1 analogue licensed for the prevention and the treatment of gastroduodenal ulcers. it has been extensively studied In reproductive health and it is widely recommended for the treatment of missed and incomplete miscarriages , the induction of

abortion, and cervical preparation before uterine instrumentation.⁽²⁾ The route of administration may be chosen according to the clinical situation and preference of the patient these routes are: oral, intravaginal, rectal, sublingual and buccal.⁽³⁾ Misoprostol tablet was manufactured and developed for oral administration. Vaginal absorption of misoprostol has been shown to be inconsistent, with large individual variation. It is not uncommon to identify particulate remnant of the tablet in the vagina at the time of repeated dosing, indicating that dissolution and absorption are variable and incomplete⁽⁴⁾; it is clear that vaginal route is a very effective way of misoprostol administration with minimal systemic side effects and they hypothesized that absorption of vaginally administered misoprostol may vary according to the medium in which it is placed. In this regard, researches are going on to improve the absorption of vaginal misoprostol by moistening the tablets with acetic acid, water or saline solution⁽⁵⁾.

PATIENTS AND METHODS:

A prospective study was conducted between the 1st of January 2010 to the 1st of February 2011 in Baghdad Teaching Hospital, comparing the efficacy of 400 µg misoprostol moistened either with acetic acid, normal saline or dry tablets and subsequently administered intra vaginally in (90) healthy women matched for age (20-40) years and within (65-80) kg, seeking termination for early pregnancy loss up to 24 weeks of gestation. The inclusion criteria include: Singleton pregnancy at (6-24) gestational weeks, Bishop score of <3, normal partial thromboplastin time (PTT) and plasma fibrinogen value, no vaginal infection, absence of fetal heart or alive fetus with severe congenital abnormality.

The exclusion criteria: The presence of blood – containing vaginal discharge, ruptured membrane, Under lying medical condition e.g. hypertension or diabetes mellitus, scarred uterus, Grand multiparity.

Study Groups: All the patients gave informed consent to participate in this study. Detailed history, Gestational age determined by LMP and ultrasound, Full medical and obstetrical examination had been carried out. Routine investigations were conducted for each patient including: Complete blood picture, blood group and Rh, plasma fibrinogen, random blood sugar, blood urea and serum creatinine, high vaginal swab. The patient lie in lithotomy position and under aseptic technique speculum examination

was performed and vaginal PH was assessed. 90 pregnant patients were grouped and matched as three groups according to the media used. All received 400 µg misoprostol tablets inserted in posterior vaginal wall at 4 hours interval for maximum 5 doses within 24 hours as indicated. The first 30 pregnant patients received misoprostol moistened in 2ml of 5% acetic acid, next 30 patients received misoprostol moistened in 2 ml normal saline and the last 30 patients received dry misoprostol table. Before giving the next dose uterine contraction and cervical status assessed by vaginal examination, if the patient developed regular uterine contractions and dilatation of cervix i.e. being in the active phase of labour, no further doses inserted. During the period of observation the patients were followed in the ward every 4 hours for the following: Vital signs, record for the time onset of regular uterine contraction, Side effects, Time of expulsion of conception.

The trial was considered successful if the participant aborted within the first 24 hours. After 8h following the fifth dose if the patient had not adequate uterine contraction, the same regimen had been repeated over the next 24 hours. After abortion an ultrasound examination had been performed to detect any retained product.

RESULT:

The results were based on the analysis of three groups of 90 pregnant women admitted to the obstetrical department seeking termination and evacuation of early pregnancy loss up to 24 weeks, 30 patients received moistened 400µg intravaginal misoprostol in 5% of acetic acid (33.3%), 30 patients received the same dose of misoprostol moistened in 2ml of normal saline (33.3), while the last 30 patients received dry misoprostol tablets, of same dose of 400µg intra vaginal.

Description of the study

the demographic characteristics of the three groups, (maternal age, weight, gestational age, parity and vaginal pH). Maternal age (mean 27.7±5.5) years. Maternal weight (mean 72.3±3.9) kg. The primiparous 33(36.7%) and multiparous 57 (63.3%). The pregnant women with vaginal pH>5 were 49 (54.4%), and pregnant women with vaginal pH<5 were 41 (45.6%). pregnant women within 1st trimester were 28 (31.1%) and women within 2nd trimester were 62(68.9%) table 1 show The mean induction –abortion interval was significantly shorter for the moistened tablet in acetic acid with mean

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time (8.3±2.2) hours, than for moistened tablet in normal saline (the mean 19.5±7.7 hours), or dry tablet (the mean 23.1±8.8 hours), with P value (0.000) which is statistically significant. It is also shown that all the patients were aborted within 48 hours.

In table 2: Regarding the number of giving doses of misoprostol required for termination, we found that the patient who received misoprostol moistened in acetic acid required significantly less numbers of doses (mean 1.5±0.5) and P value (0.000), than misoprostol tablets moistened in normal saline (mean 3.1±0.8), and those for dry tablets (mean 3.7±0.8). The majority of patients (100%) with moistened tablet in acetic acid aborted with the 1st (46.7%) and (53.3%) 2nd dose. While 53.3% of those moistened tablet in normal saline required a 3rd dose for abortion and 40% of those with dry tablets required a fourth dose of misoprostol to achieve abortion.

In table 3 we see the effect of vaginal PH, parity, gestational age and different media used. There is significant differences between vaginal PH and

the use of acetic acid and normal saline, it may be due to the reaction of the media with the environment of the vagina because the vaginal PH had no effect on dry tablet. Also there were no significant differences between parity, gestational age and type of media used.

Table 4: There were no significant differences between adverse effect (fever, diarrhea and vomiting), the need for D&C and types of media used whether acetic acid, normal saline or left dry. The P value for D&C (0.227), fever (0.117), diarrhea (0.429), and vomiting (0.307).

Statistical analysis Data were collected and analyzed using SPSS version 18 (Statistical Package for Social Sciences Version 18) used for data input and analysis. Continuous variables presented as mean ± Standard deviation (SD) and discrete variables presented as numbers and percentage. Chi square test for independence used to test the association between discrete variables. P value used for all tests was asymptomatic and two-sided. Findings with P value less than (0.05) were considered significant.

Table 1: Induction abortion time (hr)

Media	Mean±SD	95%CI	Minimum	Maximum	P
Acetic Acid	8.3±2.2	7.4-9.1	5	12	0.000
Normal Saline	19.5±7.7	16.6-22.3	10	48	0.000
Dry	23.1±8.8	19.8-26.4	9	40	0.000
Total			5	48	

SD; standard deviation, % percent, CI, confidence interval, P; P value

Table 2: Number of doses to induce abortion according to each media

Media	Mean±SD	95%CI	Minimum	Maximum	P
Acetic Acid	1.5±0.5	1.3-1.7	1	2	0.000
Normal Saline	3.1±0.8	2.8-3.4	2	5	
Dry	3.7±0.8	3.4-4.0	2	5	
Total			1	5	

SD; standard deviation, %; percent, CI; confidence interval, P; P value.

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Table 3: Different variables and media used.

	Acetic Acid		Normal Saline		Dry		Total	
	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
Overall	30	8.3±2.2	30	19.5±7.7	30	23.1±8.8	90	16.9±9.3
Vaginal pH								
pH > 5	14	8.9±1.9	18	20.6±5.6	17	27.7±8.6	49	19.7±9.7
pH < 5	16	7.8±2.4	12	17.8±10.2	13	17.0±4.4	41	13.7±7.7
		P=0.003		P=0.000		P=0.006		
Parity								
Multiparous	22	8.1±2.1	15	18.5±6.1	20	23.2±8.0	57	16.2±8.8
Primiparous	8	8.6±2.6	15	20.4±9.2	10	22.9±10.8	33	18.3±10.1
		P= 1		P=0.6		P=0.4		
Trimester								
First	9	7.8±1.9	10	23.8±10.5	9	15.8±3.2	28	16.1±9.3
Second	21	8.5±2.3	20	17.3±4.9	21	26.2±8.6	62	17.3±9.4
		p=0.7		P=0.7		P=0.2		

SD: standard deviation; P:P value

Table 4: Side effects and media used

	Acetic Acid		Normal Saline		Dry		Total		X ²	P
	N	%	N	%	N	%	N	%		
D&C	1	3.3	3	10.0	5	16.7	9	10.0	2.963	0.227
Fever	0	0.0	2	6.7	4	13.3	6	6.7	4.286	0.117
Diarrhea	1	3.3	1	3.3	3	10.0	5	5.6	1.694	0.429
Vomiting	1	3.3	2	6.7	1	3.3	4	4.6	4.043	0.307

DISCUSSION:

Karim et al., 1989⁽⁶⁾ where the first to report on successful use of PG in the management of intrauterine ,following this the use of PG for termination of missed abortion has been extensively researched in many trials where different types of PG , both natural and synthetic , are used and currently PG are the most widely used as a method for termination .

In our study: we found significant shorter induction – abortion interval in acidic media (mean 8.3±2.2)hours, (p<0.05) ,than that moistened in normal saline(mean 19.5±7.7) hours or dry tablets (mean 23±8.8)hours, Which agree with the result of (B.Yilmaaz et al.,2005) who use intravaginal misoprostol 800µg moistened either with saline or with acetic acid at 6 hr interval⁽⁷⁾ and also agree with (Ngai et al.,2003) when (400µg-800µg) intravaginal misoprostol given for shorter interval (2-3)hours⁽⁸⁾. The misoprostol tablets did not prepare for vaginal use, and local factors in vagina use may play an important role in its efficacy ,since it is desirable to achieve a constant plasma profile , it

is important to develop a preparation or medium that would ensure more complete dissolution of the moistened misoprostol tablet vaginally in order to achieve optimal efficacy⁽⁷⁾. Misoprostol tablet are known to liquefy better in acidic medium (Karim et al., 1989)⁽⁶⁾, as we found in our study using misoprostol tablet moistened in acetic media give better result than misoprostol tablet moistened in normal saline or left dry. (Feldman et al., 2003) reported that the use of an acetic acid of value in cervical priming⁽⁹⁾. Other studies found that moistened misoprostol tablet in water were more efficient for medical termination than dry tablet (Wiebe et al., 2001)⁽¹⁰⁾, like others reported that the using of misoprostol moistened with saline solution resulted in a higher success (Mishell et al., 1998)⁽¹¹⁾, also this agree with our study as misoprostol tablet moistened with saline has shorter induction – abortion interval than dry tablet. Kelekci et al., 2004 reveled that the use of intravaginal moistened with acetic acid were more effective in pre-abortion than misoprostol moistened with

normal saline⁽¹²⁾. In contrast, (Creinin et al., 1999)⁽¹³⁾ and (Gilles et al., 2004),⁽¹⁴⁾ concluded that tablet moistened before vaginal administration did not significantly improve efficacy of misoprostol in first trimester pregnancy failure. In addition, (Singh et al., 1999) investigated misoprostol tablet dissolved in acetic acid was more effective than misoprostol dissolved in water, had not improved the efficacy in achieving successful dilatation for pre-labor cervical priming⁽¹⁵⁾. Since induction of labor is a challenge of time, factors affecting the therapeutic interval should be verified, from that point of view vaginal pH has been investigated in (Levernas et al., 2004)⁽¹⁶⁾ and (Ramsy et al., 2003)⁽¹⁷⁾ and a thesis conducted in Iraq by (Sarmad S. and Azhar A. 2010) that may account for variability observed clinically with the vaginally administered prostaglandin for cervical ripening /labor induction^(16,17). They found a significant effect of vaginal PH on prostaglandins but in our study no such relation. Our study showed no significant differences between type of media used and the adverse effect. The overall incidence of side effects (vomiting 4%, diarrhea 10%, and fever 6.7%) were less than other study like B.Yilmaz et al, 2005⁽⁷⁾ whose side effects reported were (vomiting 20%, diarrhea 21.5%, and fever 27.6%) and this may be due to higher dose he had been used.

CONCLUSION:

This study demonstrates that misoprostol moistening in acidic medium was significantly more effective and has short induction-abortion interval, than misoprostol moistened in normal saline and dry tablet.

Moistened misoprostol ensure complete dissolution of the tablet in order to achieve a constant plasma profile.

Lower doses are associated with fewer side effects and these are minimum and self limiting.

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