Comparison of oral and vaginal misoprostol for cervical ripening before evacuation of first trimester missed miscarriage

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ABSTRACT

الأهداف: تقييم ومقارنة فعالية عقار الميزوبروستول عن طريق الفم والمهبل لإنضاج عنق الرحم قبل إنهاء الحمل بوساطة جرف الرحم الآلي في الأشهر الثلاث الأولى من الحمل المنسي.

الطريقة: أجريت دراسة مقارنة عشوائية بمستشفى بغداد التعليمي – بغداد – العراق، خلال عام 2006م. شملت الدراسة 120 سيدة من ذوات الحمل المنسي في الأشهر الثلاث الأولى. تم تقسيمهن إلى 4 مجموعات، شملت كل مجموعة 30 سيدة. في مجموعتي دراسة أعطيت إحداهن العقار عن طريق المهبل، والأخرى عن طريق الفم بمقدار (400mcg). أما في مجموعتي التحكم أُعطين العلاج بنفس الطريقة. تم إجراء جرف الرحم الآلي لجميع السيدات بعد 3 ساعات من اخذ العقار. جمعت المعلومات حول توسع عنق الرحم بعد اخذ العقار، المدة المطلوبة لتوسيع عنق الرحم جراحيا بعد إعطاء العقار، كمية النزف الرحمي، وظهور المضاعفات.

النتائج: لوحظ توسع أكثر في عنق الرحم (PMCD) في مجموعة الميزوبرستول; (7.77±1.22mm) للميزوبرستول المهبلي، (7.07±1.36mm) للعقار المتناول عن طريق الفم، مقابل (2.43±0.5mm) لمجموعة التحكم. كما إن التوسع اكبر في مجموعة العلاج المهبلي مقارنة بمجموعة العلاج الفموي (p=0.04). كانت المدة اللازمة لتوسيع عنق الرحم بعد العلاج اقصر في مجموعتي الدراسة مقارنتاً بمجموعة التحكم. لم يكن هناك فرق يذكر في كمية النزف الرحمي لدى مجموعتي الدراسة (p=0.62) (p=0.74)، والمضاعفات المعوية كانت اقل لدى مجموعة العلاج المهبلي مقارنة بمجموعة العلاج الفموي (p=0.014).

خاتمة: إن عقار الميزوبروستول (سواء عن طريق الفم أو المهبل) ذو فعالية لإنضاج عنق الرحم عند إعطائه قبل 3 ساعات من عملية جرف الرحم الآلي في الأشهر الثلاثة الأولى من الحمل المنسي.

Objectives: To assess the effectiveness of misoprostol in cervical ripening before evacuation of conception in the first trimester missed miscarriages, and to compare between oral and vaginal routes of administration.

Methods: A randomized controlled study was carried out in Baghdad Teaching Hospital, Baghdad, Iraq in 2006. One hundred and twenty women with first trimester missed miscarriages were divided into 2 study groups, randomized for oral and vaginal (400 mcg) misoprostol priming of cervix, and 2 control groups randomized for oral and vaginal placebo, before undergoing surgical evacuation of conception after 3 hours. Measured outcomes were: post medication cervical dilatation, time needed to dilate the cervix surgically, blood loss, and development of the side effects of misoprostol.

Results: Post medication cervical dilatation was higher in the misoprostol group (7.07 ± 1.36 mm for oral misoprostol, 7.77±1.22 mm for vaginal misoprostol), versus the control groups (2.43 ± 0.5 mm). Post medication cervical dilatation was significantly higher in the vaginal misoprostol group, compared to the oral group(p=0.04). The time required to dilate the cervix in the misoprostol group was shorter, compared with placebo. There were no significant differences in the amount of blood loss between oral (p=0.74), and vaginal misoprostol groups (p=0.62), and gastrointestinal side effects were significantly more in the oral misoprostol group (p=0.014).

Conclusion: Misoprostol is an effective cervical priming agent when administered either orally or vaginally before evacuation of conception in the termination of the first trimester missed miscarriage.

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Missed miscarriage refers to a clinical situation in which intrauterine pregnancy is present, but is no longer developing normally, and this can be manifested as empty gestational sac, or fetal demise prior to 20 weeks gestation. It may be preceded by signs of threatened abortion, regression of signs and symptoms of pregnancy, cessation of uterine growth, and falling levels of human chorionic gonadotrophins (HCG).[1] The unmet need for safe pregnancy termination in many countries makes it desirable to find effective, non-expensive methods for uterine evacuation with low complication rates. Mechanical dilatation of the cervix followed by curettage is the most commonly used method for termination of first trimester pregnancy. It remains the treatment of choice if bleeding is excessive, and vital signs are unstable, or when an infected tissue is present in the uterine cavity. Studies suggest that >10% of women who miscarry fall into these categories.[2] Forced mechanical dilatation of the cervix may result in cervical laceration, uterine perforation, hemorrhage, and infection, increased incidence of spontaneous abortion, and cervical incompetence in subsequent pregnancies. The reported incidence of serious morbidity using surgical techniques for induced abortion is 2.1%,[3] with a mortality of 0.5/100,000.[4] To decrease the rate of these complications, many agents have been investigated for their effectiveness in cervical priming action. The most commonly used medical agents used are the prostaglandins: with, or without the antiprogesterone agent (mefipristone). Gemeprost has been shown to be effective for cervical priming. However, this drug is expensive, unstable, and requires refrigeration for storage.[5,6] Misoprostol, a synthetic prostaglandin E1 (PGE) analogue used for the prevention and treatment of peptic ulcer disease has been studied for medical abortion,[7] induction of labor at term,[8] and for cervical priming prior to surgical abortion.[5] It has the advantage of easy availability, ease of administration, lower cost, stability at room temperature, and fewer side effects,[9] and is suitable for settings of limited resources. This study aims to investigate the effectiveness and side effects of misoprostol, as a cervical priming agent prior to evacuation of conceptional products in the first trimester missed miscarriage, in order to have a ripe, dilated cervix, and to avoid complications resulting from forced cervical dilatation.

Methods. This prospective, randomized, controlled blind study was carried out in the Department of Obstetrics and Gynecology in Baghdad Teaching Hospital, Baghdad, Iraq between March 2006 and January 2007. One hundred and thirty-five pregnant ladies with missed miscarriages in the first trimester were recruited in this study. Only 120 of them were included in this study. Eight of those 135 women had basal cervical dilatation more than 4 mm, and 7 of them had a history of asthma, which is one of the contraindications for misoprostol so they were excluded. Exclusion criteria were: systemic diseases contraindicating misoprostol use, history of operations that may affect the competence of cervical canal-like conization, and basal cervical dilatation >4 mm. All patients in this study were admitted to the Department of Obstetrics and Gynecology. Detailed history, general, and gynecological examinations were carried out. The demographic characteristics of each patient were assessed including age, body weight, gravidity, parity, history of previous miscarriages, and gestational age that was determined by the last menstrual period, and by transvaginal ultrasound (**Table 1**). The criteria for diagnosis of missed miscarriage were: regression of the signs and symptoms of pregnancy, low HCG for gestational age, intra-uterine gestational sac >20 mm in diameter with no embryo, or with 6 mm embryo with no fetal heart activity on transvaginal ultrasound scan. A number of investigations were conducted for each patient including complete blood picture, renal function tests, liver function tests, blood group, Rhesus factor, and plasma fibrinogen. All patients had pelvic examination, and evaluation of basal cervical dilatation using Hegar's dilators in descending order, starting with Hegar number 5 without using a tenaculum, and those with cervical dilatation of >4 mm were excluded from the study. The patients were informed of the study, and informed consent was obtained from each patient. Treatment allocation concealment was achieved, and the patients were allocated either to placebo or misoprostol groups, as well as, the route of administration (oral or vaginal groups), by drawing a piece of paper with the allocation from 2 envelopes, one for the placebo or misoprostol, and the second for the route of administration. Patients were randomized into 4 groups (2 study groups, and 2 control groups) as follows: group one (n=30), received 400 mcg vaginal misoprostol (2 tablets), group 2 (n=30), received 400 mcg oral misoprostol (2 tablets), and control group one (n=30), received 2 vaginal placebo tablets, and control group 2 (n=30), received 2 oral placebo tablets. All patients fasted over night, and were admitted in the morning of the surgical procedure. They were given their tablets according to their recruitment as study, or control groups as stated above.

A pad was placed after the application of medication, and the difference in its weight before, and 3 hours after the medication was calculated. An increase of one gram in the pad's weight was considered to be equivalent to one ml of blood (namely, specific gravity one gm=ml), which was considered as pre-operative blood loss.

The patients waited for 3 hours, no pre-medication was given, but they were told that analgesics and anti-emetics were available if required. Their blood pressure, pulse rate, and body temperature were measured just before the surgical procedure. The side effects related to misoprostol in terms of nausea and vomiting, abdominal pain, headache, and elevation of body temperature were recorded. All patients underwent evacuation of conceptional products, 3 hours after the administration of tablets. The post-medication cervical dilatation was measured by passing Hegar's dilator in descending order starting with Hegar number 10. The size of the largest dilator that could pass through the cervical os without resistance was recorded as post medication cervical dilatation achieved. No further dilatation was performed when the cervix was dilated to 7 mm or greater, and evacuation of conception was carried out. If the cervical dilatation was less than 7 mm, the cervix was dilated up to 7 mm for evacuation. The change in cervical dilatation was calculated by subtracting basal cervical dilatation from post medication cervical dilatation achieved. The duration of the procedure was calculated as the time required for dilatation, where additional dilatation was necessary. Intra-operative blood loss was taken as the volume of blood measured after sieving away the products of conception from the uterine products. Patients were observed for 2 hours after the operation. Amoxicillin 500 mg, and metronidazole 500 mg taken orally were prescribed for 24 hours after the procedure. Each patient was instructed to report any abdominal pain or discomfort, vaginal discharge, fever, general malaise, and passage of any tissue mass vaginally. If any of these symptoms occur they were asked to return to the hospital immediately.

Main outcomes. Change in the cervical dilatation: the difference of 2 mm or greater, between the pre-medication and post-medication cervical dilatation was considered as significant. Duration of procedure: which is the time required for cervical dilatation up to 7 mm or more. Amount of blood loss pre-operatively and intra-operatively: development of side effects.

Statistical analysis. Statistical analysis was computerized using the Statistical Program for Social Sciences (SPSS version 12). The t-test of significance was used to compare numerical values, and the Chi square test was used to compare percentages. A *p*-value less than, or equal to 0.05 were considered as statistically significant.

Results. The 4 groups were similar in terms of demographic variables (**Table 1**). None of the patients aborted during the interval between drug administration and the evacuation procedure. The basal cervical dilatation was almost similar between the 4 groups, yet there was a significant change in the post-medication cervical dilatation in the misoprostol group, compared to the placebo group (p=0.00) (**Table 2**). However, when the oral and vaginal misoprostol groups were compared

Table 1 - Demographic variables between the study and control groups.

Variables	Studied groups (%)				Total	*P*-value
	Oral placebo	Oral misoprostol	Vaginal placebo	Vaginal misoprostol		
Age group (years)						0.421*
15-25	22 (73.3)	19 (63.3)	13 (43.3)	17 (56.7)	71 (59.2)	
26-35	7 (23.3)	9 (30.0)	14 (46.7)	11 (36.7)	41 (34.2)	
>35	1 (3.3)	2 (6.7)	3 (10.0)	2 (6.7)	8 (6.7)	
Gravida						0.982*
1-2	18 (60.0)	17 (56.7)	17 (56.7)	16 (53.3)	68 (56.7)	
3-4	10 (33.3)	9 (30.0)	9 (30.0)	10 (33.3)	38 (31.7)	
5-6	2 (6.7)	4 (13.3)	4 (13.3)	4 (13.3)	14 (11.7)	
Parity						0.485*
0-1	24 (80.0)	18 (60.0)	22 (73.3)	19 (63.3)	83 (69.2)	
2-3	4 (13.3)	9 (30.0)	7 (23.3)	10 (33.3)	30 (25)	
4-5	2 (6.7)	3 (10.0)	1 (3.3)	1 (3.3)	7 (5.8)	
Previous abortion						0.866*
0	19 (63.3)	21 (70.0)	20 (66.7)	19 (63.3)	79 (65.8)	
1	8 (26.7)	8 (26.7)	6 (20.0)	7 (23.3)	29 (24.2)	
2	3 (10.0)	1 (3.3)	4 (13.3)	4 (13.3)	12 (10)	
Age, years (mean ± SD)	23.37 ± 6.7	24.17 ± 7.21	26.6 ± 6.78	24.7 ± 6.82		0.314*
Gestational age, weeks (mean ±SD)	8.48 ± 1.96	8.23 ± 1.92	8.21 ± 2.14	8.85 ± 2.03		0.186*
Body weight, kg (mean ± SD)	61.43 ± 8.59	60.57 ± 6.42	62.6 ± 7.37	64.7 ± 8.14		0.59*

*No significant difference in demographic characters between the study and control groups.

together, the vaginal misoprostol group showed significantly higher post-medication cervical dilatation (p=0.04). The need for further cervical dilatation up to 7 mm was more frequent in the oral and vaginal placebo groups (100%), compared with 20% (n=6) of women who received oral misoprostol, and 6.7% (n=2) of those who received vaginal misoprostol. And when both study groups were compared together, the vaginal misoprostol group showed significantly less need for cervical dilatation than the oral study group (chi square=8.571, p=0.003). The pre-operative blood loss was significantly higher in the misoprostol groups (p=0.0000), however, there was no significant difference in the pre-operative blood loss between oral and vaginal misoprostol groups (p=0.74), nor the intra-operative blood loss between both groups (p=0.629) (**Table 3**). The duration of the procedure was significantly shorter in the misoprostol groups (oral misoprostol 1.91 ± 1.0 minutes, vaginal misoprostol 1.7 ± 0.8 minutes), when compared with placebo groups (oral placebo 4.76 ± 1.6 minutes, vaginal placebo 5.13 ± 1.4 minutes) (p=0.00). There was no statistical significant difference between

Table 2 - Comparison of basal cervical dilatation and mean change in cervical dilatation between study and control groups.

Studied groups	N	Basal cervical dilatation	*P*-value	Post medication cervical dilatation	*P*-value	Mean change in cervical dilatation	*P*-value
Oral placebo	30	2.43 ± 0.5	1.0*	2.43 ± 0.5	0.00†	0.00 ± 0.00	
Oral misoprostol	30	2.43 ± 0.5		7.07 ± 1.36		4.7 ± 1.42	
Vaginal placebo	30	2.43 ± 0.5	0.61*	2.43 ± 0.5	0.00†	0.00 ± 0.00	
Vaginal misoprostol	30	2.5 ± 0.51		7.77 ± 1.22		5.23 ± 1.28	
Total	120						
Oral misoprostol versus vaginal misoprostol			0.61*		0.041†		0.032†

*non-significant, †significant.

Table 3 - Comparison of preoperative blood loss and intraoperative blood loss between study and control groups.

Studied groups	N	Preoperative loss ± SD (mls)	*P*-value	Intraoperative loss ± SD (mls)	*P*-value
Oral placebo	30	0.00 ± 0.00		54.67 ± 31.46	0.00†
Oral misoprostol	30	3.27 ± 2.78		22.67 ± 19.64	
Vaginal placebo	30	0.3 ± 0.95	0.00†	52 ± 27.56	0.00†
Vaginal misoprostol	30	3.1 ± 2.54		19.6 ± 16.39	
Total	120				
Oral misoprostol versus vaginal misoprostol			0.74*		0.629*

*non-significant, †significant.

Table 4 - Comparison of development of side effects of misoprostol between study and control groups.

Side effects	Oral placebo n (%)		Oral misoprostol		Vaginal placebo		Vaginal misoprostol		*P* value
Nausea	2	(6.7)	8	(26.7)	1	(3.3)	2	(6.7)	0.014†
Vomiting	0	(0)	4	(13.3)	0	(0)	0	(0)	0.006†
Headache	1	(3.3)	5	(16.7)	0	(1.0)	1	(3.3)	0.03†
Fever	1	(3.3)	4	(13.3)	1	(0)	1	(3.3)	0.251*
Abdominal pain	0	(0)	14	(46.7)	0	(0)	0	(0)	0.00†
Diarrhea	0	(0)	5	(16.7)	1	(3.3)	1	(3.3)	0.03†

*non-significant, †significant.

the oral and vaginal misoprostol groups (p=0.503) in terms of the duration of cervical dilatation. The side effects are summarized in **Table** 4. Side effects occurred significantly more in the misoprostol study groups. There was a statistically significant difference in the occurrence of abdominal pain, that required opiate analgesia in the oral misoprostol group (47%, n=14), and the vaginal misoprostol group (6.7%, n=2) (p=0.00). Gastrointestinal side effects were significantly more in the oral misoprostol group (p=0.014). None of the misoprostol study groups needed interruption of the procedure because of side effects, and the patients were discharged home uneventfully.

Discussion. There was a statistically significant difference between the study groups and the control groups, in terms of pre-medication and post-medication cervical dilatation, shortening of evacuation procedure, and development of side effects. This result agrees with Cakir et al,[10] who found that post medication cervical dilatation was significantly higher in the misoprostol group, as compared with the placebo group. However, better cervical dilatation was achieved by the vaginal route than the oral route (p=0.041) in the study groups. This is in contrast to Cakir et al's[10] study, which found that vaginal and oral applications of misoprostol were equally effective in achieving cervical dilatation. The observed effect is likely to be due to improved pharmacokinetics associated with vaginal administration, as demonstrated by Zeiman et al[11] who compared the absorption kinetics of misoprostol between oral and vaginal administration. They found that systemic bioavailability of vaginally administered misoprostol is 3 times higher than that of orally administered misoprostol. With vaginal route peak plasma level are reached more slowly and slightly lower, but are sustained for up to 4 hours. These effects likely result from pre-systemic gastrointestinal tract (GIT), or hepatic metabolism that occurs with the oral, but not the vaginal route. Tang et al[12] demonstrated that tablet moisturisation through the non-oral route can increase the drug bioavailability, which may explain why the vaginal route is more effective that the oral one. The bioavailability had also been shown to be more, when misoprostol was used through other routes of administration, like the sublingual route.[13,14] Fong et al[15] compared 2 doses of vaginal misoprostol 400 mcg versus 200 mcg administered either at 3 or 4 hours interval, and found that 400 mcg vaginal administration will dilate the cervix to more than 8 mm in 96.7% of patients when it is given up to 3 hours or more, prior to suction curettage in the first trimester abortion, an effect similar to our study. Other studies investigated the effectiveness of misoprostol when used for pre-operative cervical dilatation.[16-20] Oral, as well as intra-vaginal administration was studied in different doses used 30 minutes-12 hours before the surgical procedure. They concluded that misoprostol is significantly more effective than placebo - an effect similar to the results of our study, and it is at least as effective as other PGs, such as gemeprost in terms loss of blood, duration of surgery, and cervical dilatation. They have also shown that an increased dosage and time interval before evacuation is associated with an increase in the side effects. Cakir et al[10], and Ashok et al[21] found that the pre-operative blood loss was significantly higher in the misoprostol group, and they found that in vaginal and oral misoprostol had similar operating time, and intra-operative blood loss.

In our study, we attained the aimed post medication cervical dilatation in about 93.3% in the vaginal route, and 80% in oral route without relatively significant increase in the mentioned side effects. We found that there was a statistical significant difference between the misoprostol group, and the placebo group regarding side effects, such as nausea, vomiting, abdominal pain, diarrhea, which were comparable with other studies.[10] However, there was statistical significant difference in the development of side effects between oral and vaginal misoprostol not found in other studies, that did not recover significant differences in the development of side effects, when both oral and vaginal routes were tested.[10]

Abdominal pain in the oral group was severe enough to require opiate analgesia in some patients. This may be due to the systemic side effects of misoprostol that stimulate smooth muscle contraction especially of the GIT.[22,23] Bebbington et al[24] found that there was an increase in febrile morbidity in the vaginal group (25% versus 6.7%), which was not the case in our study. We found that fever was observed only in half those percentages, and was not significant (p=0.056). Other side effects are infrequent and minimum in both groups, and resolved spontaneously without treatment, such as headache. So drug related side effects were more frequent in the misoprostol group compared with the placebo group, probably because of the 3 hour waiting time in the ward before surgical intervention.

None of the above significant differences in the action of misoprostol has the potential to cause profound clinical improvement, except the decrease in the number of patients requiring additional cervical dilatation, which may decrease the number of complications associated with surgical cervical dilatation, namely, uterine perforation that may complicate up to 2% of the first trimester surgical abortions.[25]

In conclusion, misoprostol (synthetic PGE 1 analogue) is a very effective cervical priming agent when administrated at 400 mcg per oral, or per vaginal route 3 hours before surgical termination of the first

trimester missed miscarriage. It facilitates the procedure by decreasing the need for further cervical dilatation, and by shortening its duration resulting in decreased complications associated with the dilatation of the cervix for evacuation of conceptional products. Side effects were found to be less with the vaginal route of misoprostol.

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