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Comparison of the effect between two doses of vaginal misoprostol in the termination of first-trimester pregnancy: a double-blinded randomized trial

Abstract

Background and aim: a higher dose of misoprostol may increase its efficacy on the termination of pregnancy, we compared the impact of 400 μg every 6 hours daily with 800μg daily of vaginal misoprostol for termination of early pregnancy.

Methods and materials: in this randomized clinical trial 90 pregnant women with gestational age less than 96 days were randomized to receive vaginal misoprostol either the 400μg every 6 hours (group A) or 800μg once a day (group B) for three days, then, success of abortion and complication of these methods were compared with each others.

Results: Of 90 recruited women, successful medical abortions occurred in 44 patients, 27 (60%) women in group A and 17 (37%) women in group B. The difference of success was significant (P=0.043). The severity of vaginal bleeding was significantly lower in group A(p=0.004), but diarrhea and fever were more common in group A. No other serious complications such as massive hemorrhage were found in both groups.

Conclusion: lower but multiple doses of vaginal misoprostol (400 mcg every 6hrs) was more effective than 800mcg daily in the medical termination of first-trimester pregnancy.

Keywords: pregnancy trimester, first - misoprostol – abortion

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Introduction

The management of pregnancy termination by induced abortion is a prevalent obstetrics and gynecologic operation, however, it is invasive and in some cases risky procedure.[1,2] Therefore, some specialists have presented medical abortion as an alternative for surgical abortion especially in mothers with early gestational age less than 7 weeks.[3] Mifepristone was the first agent used for medical termination of pregnancy[4] and some years later methotrexate was approved for medical abortion.[5] Prostaglandin agents are the most common drugs, to achieve the medical termination in women in the first and second trimester of pregnancy.[4] Misoprostol is a synthetic analog of prostaglandin E1 that firstly was approved by the Food and Drug Administration (FDA) for peptic ulcer[4] and later it has been administered in patients with unwilling pregnancy to induce abortion.[5,6] Bugalho et al.[7] administered vaginal misoprostol for medical abortion and demonstrated that it was effective agent to terminate the pregnancy and the successful rate was about 80%,[7] furthermore, these results repeated in some other trials used misoprostol and revealed it is high efficient agent with low serious side effects in women under medical abortion.[8–12] To increase the efficacy of misoprostol, it has been used in combination with other agents such as methotrexate and mifepristone for the termination of pregnancy in the first trimester and reported a highly efficacy ranged from 83-97%.[13,14] On the other hand, recent experiences proved that women are more satisfied with medical abortion using misoprostol. In this regard, a study by Zikopoulos revealed that 91.3% of the women are satisfied with medical termination and they were very keen to choose it again and recommended it to other women.[15] Some other practices confirmed more efficacies with higher doses of misoprostol.[16–20] Therefore, in this randomized double-blinded clinical trial we compared the efficacy of two doses of vaginal misoprostol for elective termination of pregnancies in women with gestational age less than 96 days.

Materials and methods

The study was prospectively conducted at Imam Hussein University Hospital between 2013 and 2014. The research has been approved by the ethic committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (registration number sbmu.rec.1393.553). Our plan is comparison of the effect between two doses of vaginal misoprostol in the termination of first-trimester pregnancy. The criteria for enrollment were singleton pregnancy, indication for pregnancy termination due to either fetal or maternal causes or gestational age ≤96 days (e.g, missed abortion, blighted ovum, and maternal medical problem). The exclusion criteria were any sign or symptom of threatened or spontaneous abortion before therapy such as bleeding, any degree of dilatation in cervix or uterine regular contractions before drug administration, evidence of septic abortion, serum hemoglobin level <10 g/dl, coagulopathy disorders, cardiovascular or cerebrovascular diseases, uterine leiomyoma and allergy to the misoprostol. The study procedure was explained to the patients and informed written consent was obtained. A demographic questioner was filled then pelvic examination and the gestational age was calculated and 90 women with gestational age less than 96 days were recruited and randomized into two groups. To randomization we used sequential numbers, in this case the first number was given to the first patient and received misoprostol 400μg every 6 hours up to three days (group A, n=45) sequentially the next number was given to next patient and received misoprostol 800μg daily plus three doses of placebo every 6 hours for three days (group B, n=45). Both groups and study staff (site investigators and trial coordinating center staff)

were masked to treatment allocation. During the treatment period (3 days) any side effects such as diarrhea, fever (tempreture≥38), chills, nausea and vomiting and vaginal discharge were recorded in a chart in both groups, moreover, two groups visited regularly and the level of hemoglobin and amount of vaginal bleeding such as spotting, less than menses, equal to menses and more than menses were measured. Successful abortion was defined as complete passage of the pregnancy with no need for curettage, complete passage of tissue and transvaginal ultrasound was done for them and confirmed by ultrasonography. If the presence of remnants of gestational sac in ultrasound was less than 20 mm, it was complete abortion (within 72 hours after the initiation of misoprostol). Failure was defined as a need for surgical dilatation and curettage (D&C) due to the presence of remnants of gestational sac in ultrasound (more than 20 mm), abnormal bleeding or prolonged vaginal bleeding because of incomplete abortion or no response to treatments after 72 hours. For each unsuccessful abortion, two separate gynecologists independently evaluated the conditions and confirmed the failure to decide on the surgical intervention. If needed, D&C was done by manual vacuum aspiration after taking written informed consent.

Statistical analyses

The data were analyzed using Statistical Package for Social Studies version 22.0 (SPSS Inc, Chicago, Ill). Categorical data are presented as numbers (%), and continuous data as mean±SD. We used the Chai_2 or to compare categorical variables and the Student's t test to compare continuous variables. P<0.05 was considered significant.

Results

90 pregnant women mean age 28.75±5.95 and mean gestational age 11.25±1.85 weeks were evaluated (Table 1). The number of patients with successful abortion in group A was significantly more than B (27 patients in group A versus 17 patients in group B, P=0.043). The failure of the misoprostol treat was significantly lower in group A. The women who did not respond to misoprostol in both groups were divided in three categories (all ended with D&C): first with ongoing pregnancy, second with incomplete abortion, third with persistent bleeding after misoprostol. These categories were, also compared in both groups. The failure of the misoprostol treat in the ongoing pregnancy was significantly lower in group A. (2 patients in group A versus 5 patients in group B, P=0.004). The number of incomplete uterine passage of gestational tissue with remain product of conception which was another indication of D&C was non-significantly more in group B (12 versus 14, P=0.76). Persistent bleeding occurred in 4 patients in group A and 9 in group B, (P=0.001), D&C was performed in this patients (Table 2). Anaphylaxis after administration of the first dose of misoprostol was not observed in both groups. The frequency of fever and diarrhea in group A was significantly higher than group B (P=0.009). No, severe complications including transfusion, emergent surgery for hemorrhage, or sepsis occurred in both groups (Table 3). Regarding bleeding, the spotting was nonsignificantly more in group A than B, but bleeding less, equal and more than mense was significantly more in group B than A (Table 3).

Table 1 The patients' characteristics

Group	Group A (n=45) misoprostol 1600 miq/day)	Group AB(n=45) misoprostol 800 miq/daily	P
Age(year)	28.42±5.132	29.22±6.675	0.887
Gestational age(week)	8.78±1.664	10.27±2.016	0.001
BMI	24.46±2.74	25.00±3.14	0.319
Total drugs dose (μg)	1208.89±515.144	1506.76±614.432	0.001
Volume of remaining sac in vaginal sonography	18.56±12.0632	26.40±19.088	0.003
Pain score during treatment(VAS)	5.222±2.678	4.467±2.582	0.074
Missed abortion	42.2%(19)	46.7%(21)	0.067
Blighted abortion	33.3%(15)	35.6%(16	0.043
Maternal abortion	8.9%(4)	8.9%(4)	0.124
Induced Abortion	15.6%(7)	8.9%(4)	0.095
Transvaginal sonography(volume of residual remnants of fetus) gr	18.56±12.0632	26.40±19.088	0.003
Curettage (%)	40%(18)	64.4. %(29)	0.002
Closed cervix (%)	91.1%(41)	77.8%(35)	0.375

Table 2 The frequency of successful abortion rate

Groups	Group A (n=45) misoprostol 1600 miq/day)	Group AB(n=45) misoprostol 800 miq/daily	P
complete abortion	27(60.0%)	17(37.8%)	0.043
No respond to misoprostol (D&C)	2(4.4%)	5(11.1%)	0.004
Incomplete uterine passage (D&C)	12(26.7%)	14(31.1%)	0.765
persistent bleeding (D&C)	4(8.9%)	9(20.0)	0.001

Table 3 The frequency of side effects of medical abortion in two groups

		Group A (n=45) misoprostol 1600 miq/day)	Group AB(n=45) misoprostol 800 miq/daily	P
Bleeding	spotting	20(44.4%)	17(37.8%)	0.087
	Less than mense	7(15.6%)	10(22.1%)	0.004
	Equal to mense	3(6.7%)	4(8.9%)	0.034
	More than mense	5(1.1%)	11(2.2%)	0.044
fever		10(22.2%)	3(6.7%)	0.001
diarrhea		2(4.4%)	1(2.2%)	0.905
Vaginal discharge		33(73.3%)	35(77.8%)	0.345
Pain(VAS)		5.55±2.67	4.46±2.58	0.074
No side effect		73.3%(33)	77.8%(35)	0.345

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Discussion

We compared the success rate and complications of medical abortion with two misoprostol doses (400μg /6houres and 800μg daily) for three days in women with gestational age lower than 96 days and revealed successful abortion in the half of the women (44 of 90), this rate in group under 400μg /6 hours (1600µg daily) was significantly more than group treated with 800μg daily (27 versus 17, P=0.001), Furthermore, the severity of vaginal bleeding was significantly lower in group A(p=0.004). In agreement with these findings, a study in Mashhad in 2008 by Ayati et al.[17] on 100 women was performed to evaluate the effect of misoprostol role in the termination of pregnancy in the first trimester. They administered 800μg vaginal misoprostol for initiation and 800μg after 24 hours if the abortion was not successful. They reported a significant difference between abortion rate after administration of first (800μg) and second dose (1600μg) of misoprostol (55% vs 83%). However, the successful rate was more than our practice (83% vs 49%) and failure rate was 17% (needed curettage) (17). A similar study in methodology to our work by Zikopoulos, evaluated the role of the vaginal misoprostol (800μg daily) in 160 women with <42 and <56 days of gestational age and repeated every 24 hours for three days. They revealed the abortion rate about 96% and 86%, respectively, moreover the study indicated that the complete termination was significantly different after the 1st and 2nd dose (71.3 vs 92.5% in group A, 51.3 vs 80% in group B). Harmoniously, 47 of 90 patients in our trial needed curettage in the group treated with misoprostol 800μg daily that was remarkably higher than Zikopoulos practice with only two patients, needing curettage (15). Another study by Grapsas et al.[18] reported higher complete abortion rate than our practice. The authors administered single vaginal misoprostol (800μg/day) to the 113 women in the first trimester (up to 12 weeks of gestational age) and revealed 74% complete abortion on the first day(37% in our study in group treated with 800μg daily), the authors confirmed that the gestational age was not correlated with the abortion rate.[18] In line with these studies, a review by Faúndes et al.[19] in 2007 reported 85-90% complete abortion in patients with a gestational age of 12 weeks under misoprostol 800μg first dose and additional doses at 6,12 and 24 hours later. Moreover, this review indicated more acceptances among the patients with oral and sublingual routes and more efficacies with the vaginal route of administration.[19] These results were supported by further studies including a study by Singh et al.[20] with 800μg of vaginal misoprostol and 3 doses with three hours' interval and a success rate about 96%. In keeping with our findings, this study emphasized that the rate of complete termination in patients under repeated dose was more than a single dose.[20] In 2005 a trial by Sifakis et al.[21] administered a high dose of vaginal misoprostol (400-3600μg) in three days, 400μg for initiation and 400μg every 4 hours and reported 68.5% complete abortion in first day (2400μg/day) and more than 90% successful rate after 3600μg maximum dose.[21] The reasons for such discrepancy between our results and these studies regarding the successful abortion rate may be due to the route of misoprostol administration, the studies indicated a wide range of the complete abortion rate from 25% in oral administration to 97% for vaginal route in some studies,[22] in this case a study by Kutlu et al.[23] combined the routes of administration, they initiated with misoprostol vaginal and continued with oral administration (1200μtotal dose) and achieved 95% of complete abortion.[23] In addition to the route of the administration, the misoprostol dose, the definition of success rate, exclusion, and inclusion criteria, and different of the methodology are another possible factors. For instance, the patients' selection and exclusion criteria in our study were basically different from Zikopoulos et al.[15] study, because Zikopoulos excluded women with prior elective abortion and parity more than three, but we only excluded patients with prior infected abortion.[15] Only one study by Shuaib et al.[24] in 2013 administered a similar dose of misoprostol (1600μg/day) to our study and showed lower successful rate than our experience. The study compared the success rate and complications of medical abortion by 400μg misoprostol for induction and 200μg every 4 hours with the surgical abortion and showed 21% success rate after 12 hours (1000μg) and 57% success rate after 24 hours (1600μg) of treatment[24] that was lower than our results in group treated with 1600μg daily with 60% success rate.

We did not find any study comparing different doses of vaginal misoprostol regimens in the first trimester of pregnancy, however, a randomized controlled trial by Pongsatha et al.[25] compared the vaginal misoprostol loading and non-loading dose regimens and revealed that a loading dose of misoprostol was significantly related to higher rates of adverse effects and comparable success rate, they concluded that loading dose of misoprostol is not more effective than non-loading dose to induce abortion in second trimester,[25] that was in contrast to all studies ,evaluating the misoprostol effect, on the first trimester of pregnancy.

The main limitations of our study were the relatively small sample size and short duration of follow-up. Further investigations are recommended with longer follow- up and larger series to validate the findings reported here

Conclusion: lower but multiple doses of vaginal misoprostol (400μg / 6 hours) were more effective with lower serious bleeding than higher single dose (800μg daily) in the medical termination of pregnancy in the first trimester.

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Conflicts of interest

Authors declare there is no conflict of interest in publishing the article.

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