ORIGINAL ARTICLE

Comparison of the efficacy of sublingual, oral, and vaginal administration of misoprostol in the medical treatment of missed abortion during first trimester of pregnancy: A randomized clinical trial study

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Background: This study was aimed at comparing the efficacy of different routes of misoprostol administration, including sublingual, oral, and vaginal, on the induction of medical abortion in the first trimester of pregnancy. **Materials and Methods:** This open-label, randomized clinical trial study was performed on 172 individuals in three parallel groups of vaginal, sublingual, and oral administration of misoprostol. The participants were randomized using permuted blocks of six. A dose of 600 μg of misoprostol every 6 h (maximum of 4 doses) was administrated to each group. Higham chart and demographic questionnaires were completed by the investigator. Data were analyzed using Stata software version 12. **Results:** The mean age of the participants was 29.81 ± 6.7 years, and the mean gestational age was 8.45 ± 2.32 weeks. We found a significant difference regarding the abortion success rate and the time interval between the administration of the drug among three groups (P = 0.036 and < 0.001 in turn). There was no statistically significant difference between the three groups in terms of severity and duration of vaginal bleeding until day 7 after induction (P = 0.091 and 0.143, respectively). Furthermore, we found statistically significant differences in some drugs, which induced side effects namely vomiting and headache, between the three groups (P = 0.032 and 0.028 in turn). **Conclusion:** The findings suggest that vaginal administration of misoprostol is more successful than the sublingual and oral route for complete abortion; vaginal administration of misoprostol is an appropriate alternative to curettage.

Key words: Abortion, first, misoprostol, missed, pregnancy trimester

How to cite this article: Souizi B, Akrami R, Borzoee F, Sahebkar M. Comparison of the efficacy of sublingual, oral, and vaginal administration of misoprostol in the medical treatment of missed abortion during first trimester of pregnancy: A randomized clinical trial study. J Res Med Sci 2020;25:72.

INTRODUCTION

A missed abortion (MA) is an intrauterine death of the embryo or fetus with retained products of conception.[1] The best criterion for every treatment including induced abortion is to be effective, safe, low cost, accessible, and acceptable to the patient.[2,3] Misoprostol is a synthetic analog of prostaglandin E1, available in three forms of oral, vaginal, and sublingual, which stimulates uterine smooth muscle contraction and cervical ripening.[4,5]

Previous studies have investigated the effects of various routes of misoprostol administration and reported some advantages and disadvantages for each administration route.[6,7] Some studies have reported higher effectiveness of vaginal administration over the oral route,[8] while a study by Mohammadi *et al*. has stated that there is no

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_393_19

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Submitted: 31-Jul-2019; **Revised:** 27-Nov-2019; **Accepted:** 27-Mar-2020; **Published:** 27-Jul-2020

significant difference between the success rate of the vaginal and oral route.[9] A study by Singh *et al*.[10] showed that the success rate of treatment in both vaginal and sublingual routes is not significantly different, but the side effects of the drug such as diarrhea and fatigue are reported higher in sublingual administration.

The main limitation of previous studies was the investigation of misoprostol effect during early pregnancy, before 9 weeks of gestational age.[11] Various reports with conflicting findings on the success rate and incidence of complications were observed across studies, and these results suggest the need for further research to address this issue. Increasing the use of medical treatments, particularly misoprostol, instead of invasive and complicated surgical procedures, in addition to a need to enhance the health-care professionals' knowledge on this drug, as well as the limitation of previous studies regarding comparisons of only two administration routes, clarifies the necessity of the current study aiming at comparing the impact of three different routes of administration of misoprostol (sublingual, oral, and vaginal) on the induction of medical abortion in first trimester of gestation.

MATERIALS AND METHODS

This open-label, randomized clinical trial study with parallel groups was conducted to compare the efficacy of vaginal, oral, and sublingual administration of misoprostol in MA s in the first trimester of pregnancy between 2014 and 2016.

Participants

All women referred to Shahidan Mobini Hospital in Sabzevar, Iran, diagnosed with MA s in the first trimester of pregnancy from August 2014 to August 2016, were recruited based on the following inclusion criteria: gestational age < 12 weeks with ultrasound-confirmed MA, confirmation of the need for termination of the pregnancy by a gynecologist, absence or slight vaginal bleeding, and axillary temperature < 37.5°C. Exclusion criteria included emergency status of the patient and urgent need for termination of pregnancy by surgical evacuation; anemia (hemoglobin < 9 g/dL); coagulation disorders or history of current anticoagulant therapy; history of hepatic, renal, and cardiovascular diseases; and history of prostaglandin allergy, smoking, inflammatory bowel disease, intrauterine device implantation, adnexal mass suspicious for ectopic pregnancy, uterine abnormalities, and lactation.

Clinical assessment

After admission and blood sampling for hemoglobin level, pelvic ultrasonography was performed for the assessment of pregnancy status and the need for the termination of pregnancy. The demographic information questionnaire was completed by the investigator. A maximum of four doses of 600-μg misoprostol were administered every 6 h until uterine evacuation or vaginal bleeding began. Patients were monitored in the hospital for at least 24 h until they were stable. The time interval between administration of the 600-μg dose of drug (induction) with initiation of vaginal bleeding and evacuation was checked and recorded (treatment outcomes form). Pethidine was used to relieve pain. In the first 24 h after starting treatment with misoprostol, the complication questionnaire was filled. The process was stopped in the case of severe bleeding, and patients were treated with surgical curettage. The patients were discharged from the hospital 1 day after the uterine evacuation and confirmation by ultrasonography. A follow-up visit was performed at 7 days after the procedure, to evaluate their clinical status, as well as hemoglobin and hematocrit tests and ultrasonography to ensure complete evacuation of uterus. The patients were trained to refer to the hospital in case of severe vaginal bleeding, abdominal cramps, and temperature >38°C during 1 week after discharge.

Outcomes

The primary endpoint of this study was the abortion success rate which is defined as the complete uterine evacuation without the need for further surgical curettage (products of the conception of 10 mm or less was acceptable after the first 24 h of treatment). The secondary endpoints of this study were as follows: (i) determination of the mean induction–abortion interval in hours (range); (ii) evaluation of the severity and volume of blood loss recorded by patients using Higham chart daily from the onset of treatment to 7 days later. The Higham chart is based on the number of sanitary pads consumed along with the amount of blood absorbed onto per cc. The Higham chart is considered one of the most useful, valid, and reliable measures for vaginal bleeding;[12] and (iii) assessment of the complications of the drugs namely nausea, vomiting, diarrhea, dizziness, fatigue, low abdominal pain, headache, chills, and fever evaluated within the first 24 h of treatment.

Sample size determination

According to the study by Lee *et al*.,[13] considering the abortion success rate of 0.65, 0.85, and 0.95 for vaginal, oral, and sublingual types of treatment, respectively, the sample size was estimated to be 195 participants, with approximately 65 participants in each group considering the following parameters; type 1 error (two sided) of 0.05, power of 90%, effect size of 0.27, as well as 10% dropout rate.

Randomization and allocation concealment

Eligible patients were randomly divided into three groups of vaginal, sublingual, and oral misoprostol. Permuted

block randomization was performed with random block sizes of six using allocation software provided by the statistic consultant. The 212 sequentially numbered opaque sealed envelopes that contained a group assignment for the participants were shuffled and distributed among the participants. The investigator opened each envelope and chose the administration method. It was impossible to blind the patients because they were informed about their treatment and administration route of the drug.

Ethical consideration

This study was approved by the regional ethics committee of the Sabzevar University of Medical Sciences with the code number of IR.MEDSAB.REC.1393.20 and also was registered at the Iranian Registry of Clinical Trials (IRCT2014101015905N2). Written informed consent was obtained from each participant before randomization and also no name and identification were defined in the questionnaires.

Data analysis

All continuous and categorical variables were expressed as mean ± standard deviation, SD or median, interquartile range and frequency (%) respectively. After checking the normality of variables using Shapiro–Wilk test, Chi-square test was used to compare the severity and duration of bleeding among groups. Fisher's exact test was applied to compare the abortion success rate and side effects between the three groups. The Kruskal–Wallis test was used to compare the mean induction–abortion interval among groups as well as Dunn's test was launched to adjust for multiple significance testing in the Kruskal–Wallis tests. In addition, Bonferroni *post hoc* test was performed for adjusting multiple significance testing in the Fisher's exact test. All the analyses were performed using STATA (version 12, Stata Corp, College Station, Texas, USA), and also the sample size calculation was conducted using Pass software (Hintze, J. 2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com). Statistical significance was set at $P < 0.05$.

RESULTS

In total, after assessing for eligibility, 212 participants were randomized and of whom, 172 participants were analyzed [Figure 1]. The mean age of the participants was 29.81 ± 6.7 years, and the mean gestational age was 8.45 ± 2.32 weeks. The majority of participants, 72.73% ($n = 58$), were experiencing the third pregnancy. All the demographic characteristics are presented in Table 1.

As shown in Table 2, based on Fisher's exact test, there was a statistically significant difference regarding abortion success rate among the three groups ($P = 0.036$). However, the Bonferroni *post hoc* test did not reflect any significant differences between the three groups ($P > 0.05$). The results of the Kruskal–Wallis test revealed statistically significant differences regarding median induction–abortion interval in hours among groups ($P < 0.001$). Moreover, Dunn's test showed statistically significant differences between the three groups as shown in Table 3 ($P < 0.001$).

As shown in Table 4, the severity of vaginal bleeding was found to be highest in the sublingual group followed by the vaginal and oral groups. There was no statistically significant difference between the three groups in terms of

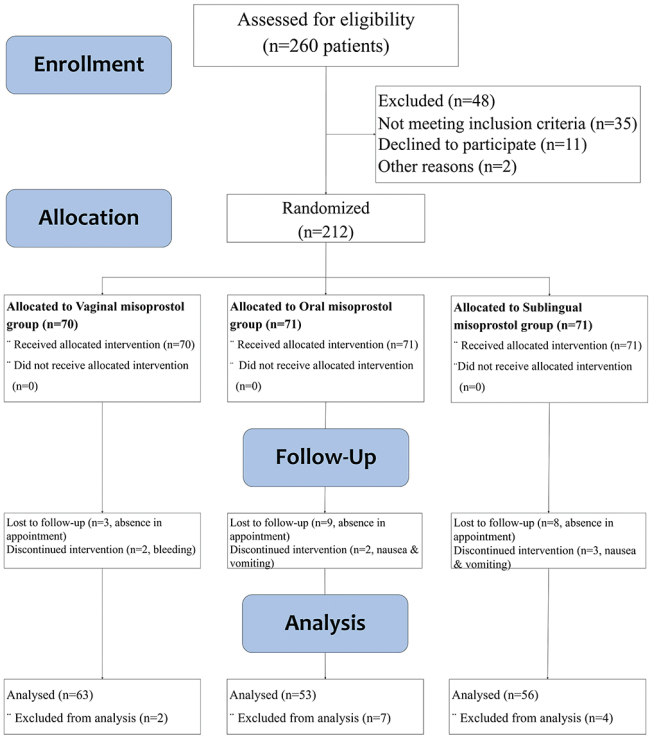

Figure 1: CONSORT diagram of the study

Table 1: Baseline demographic and clinical characteristics among groups; *n* (%) and mean±standard deviation

Parameters	Groups			*P*
	Vaginal (*n*=63)	Oral (*n*=53)	Sublingual (*n*=56)	
Age (years)	29.2±6.0	29.9±6.4	30.3±5.7	0.121*
Gestational age (weeks)	8.4±2.2	8.3±2.3	8.5±2.3	0.971*
Primary hemoglobin (g/dL)	12.1±1.1	14.4±14.7	12.2±1.2	0.301*
Previous delivery (yes)	45 (71.4)	34 (64.1)	36 (64.22)	0.211**
Previous abortions (yes)	17 (26.9)	18 (33.9)	14 (25)	0.331**

*ANOVA test, **Chi-square test

severity and duration of vaginal bleeding until day 7 after induction ($P = 0.091$ and 0.143, respectively).

According to Table 5, based on Fisher's exact test, we found statistically significant differences in some drug-induced side effects namely vomiting and headache between the three groups ($P = 0.032$ and 0.028 in turn).

DISCUSSION

This study aimed at evaluating the effectiveness of misoprostol on MA induction through different routes of administration (vaginal, oral, and sublingual) in the first trimester of pregnancy.[7]

In the present study, in the first 24 h within treatment, in most of the cases, induction resulted in complete abortion without the need for surgical curettage. Comparing the treatment outcomes between the three groups showed that the success rate in abortion is the highest in vaginal rather than sublingual and oral groups. Some studies have shown that higher effectiveness of drugs administered was observed via vaginal route rather than oral one.[8,14] A study by Khairnar and Patil[15] stated that if the dose and the interval of drug administration in the sublingual and vaginal methods are correctly implemented, similar results on the efficacy of the drug for two routes are observed. The study by Imširija *et al*.[16] indicated that there is no valuable research showing the comparison of effectiveness between the vaginal and oral methods during weeks 9 and 12 of pregnancy; however, overall, more success rate has been reported for the vaginal method.

The present study found the lowest efficacy of misoprostol for the oral group that could be attributed to the higher instability and irregularity of uterine activity in the vaginal group versus the sublingual group. Contrary to our results, the study by Nautiyal *et al*.[7] indicated that sublingual administration has the greatest success in treatment over the vaginal and oral methods within the first 24 h of induction. Treatment failure was defined as residue values >10 mm at the end of the 1st week of induction. Although there was no statistically significant difference between the groups, the highest failure rate and the most need for surgical curettage were observed in the oral group, which is clinically important. In this regard, similar findings were reported by Nautiyal *et al*.[7]

The findings revealed that the peak of drug effect is observed by the second dose, for all the three routes (sublingual, vaginal, and oral), as well. Some researchers stated that[17,18] there is no further effect after the second dose of the drug. However, in the present study, about one-fourth of the participants in the oral group were needed to receive the third and fourth doses of the drug. A statistically significant difference in the number of doses was observed between the three groups.

In the present study, the lowest interval between the induction and onset of vaginal bleeding was recorded in the vaginal group (8 h on an average), which was followed by the sublingual group (10 h on an average). Oral group showed the highest interval of induction to bleeding. Inconsistent with our study, Nautiyal *et al*.[7] also reported this interval as < 12 h, in vaginal and sublingual routes.

The severity and duration of vaginal bleeding after administration of the drug were compared in the three groups. Although there was no statistically significant difference between the groups, the severity of bleeding was highest in the sublingual group and the highest duration was recorded for the vaginal group. This can be clinically important. Regarding changes in hemoglobin level, there was no significant difference between the three groups. The

Table 2: Comparisons of abortion success rate among the three groups

Group	*n*	*n* (%)	*P**	Bonferroni *post hoc* test		
				Vaginal	Oral	Sublingual
Vaginal	63	61 (96.8)	0.036	-	0.069	1.000
Oral	53	45 (84.9)		0.069	-	0.114
Sublingual	56	54 (96.4)		1.000	0.114	-

*Fisher's exact test

Table 3: Comparisons of induction-abortion interval in hours among the three groups

Group	*n*	Median (IQR)	*P**	Dunn's test		
				Vaginal	Oral	Sublingual
Vaginal	63	7.95 (1.66)	<0.001	-	<0.001	<0.001
Oral	53	12.12 (4.00)		<0.001	-	<0.001
Sublingual	56	9.79 (1.83)		<0.001	<0.001	-

*Kruskal-Wallis test. IQR=Interquartile range

Table 4: Comparison of the severity and duration of bleeding between the groups; *n* (%)

Groups	Severity			Bleeding period in days			
	Mild	Moderate	Severe	4	5	6	7
Vaginal (*n*=63)	19 (30.1)	31 (49.2)	13 (20.6)	1 (1.5)	12 (19.0)	16 (25.4)	34 (53.9)
Oral (*n*=53)	17 (32.0)	27 (50.9)	9 (16.9)	7 (13.2)	13 (24.5)	11 (20.7)	22 (41.5)
Sublingual (*n*=56)	7 (12.7)	31 (56.3)	17 (30.9)	4 (14.7)	9 (16.0)	19 (33.9)	24 (42.8)
*P**		0.091				0.143	

*Kruskal-Wallis test

Table 5: Comparison of the side effects among the three groups; *n* (%)

Side effects	Groups			*P**
	Vaginal (*n*=63)	Oral (*n*=53)	Sublingual (*n*=56)	
Nausea	2 (3.2)	3 (5.8)	6 (10.9)	0.301
Vomiting	0 (0)	3 (5.6)	7 (12.5)	0.032
Diarrhea	2 (3.1)	4 (7.5)	3 (5.3)	0.891
Dizziness	2 (3.2)	4 (7.8)	4 (7.2)	0.501
Fatigue	1 (1.6)	4 (7.8)	4 (7.2)	0.231
Low abdomen pain	61 (96.8)	51 (96.2)	55 (98.2)	0.862
Headache	0 (0)	5 (9.8)	4 (7.2)	0.028
Chills	0 (0)	3 (5.8)	1 (1.8)	0.072
Fever	15 (31.2)	13 (27)	20 (41.6)	0.281

*Fisher's exact test

highest drop in hemoglobin level (<10 g/dl) was observed in the sublingual group.

In this study, low abdominal pain was found as the most common complication in nearly all participants, similar to the results of some other studies.[19,20] The results of this study showed a significant difference in the incidence of vomiting and headache among the three groups. The highest incidence of headache and vomiting was observed in the oral and sublingual groups, respectively. Fever named as a malignant hyperthermia in Senger *et al*. study,[21] which was also experienced by a large number of participants in our study significantly in sublingual route.

In this study, it seems that the vaginal route with the least complication rate was a safer route than others, although some studies have reported the same incidence of complications for vaginal and oral routes.[22,23] The difference in the incidence of drug complications, reported in different studies, is probably due to the difference in dosage, the interval between the doses, and the number of doses and the pharmacokinetics of the drug. Obviously, taking medications at lower intervals may lead to higher complications.

According to the findings of this study, misoprostol is more effective in uterine evacuation in MAs compared other drug administration route, during the first trimester of pregnancy. Misoprostol is cost-effective, accessible, and can be maintained at room temperature. The vaginal administration of misoprostol, regarding its pharmacokinetic properties, is the most successful method in terms of the treatment efficacy during the first 24 h of induction with the lowest incidence of complications compared with sublingual and oral methods.

Limitations and strengths

The main limitation of this study was the impossibility of blinding the research due to the patient's awareness of the treatment route. Conversely, the main strength of this study was a relatively large sample size so that it gives more reliable results with greater precision and power. Another noticeable point of this research is comparing three routes of misoprostol administration, which provides a variety of findings in different routes.

Financial support and sponsorship

This study was conducted with the financial support of Sabzevar University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Fei H, Hou J, Wu Z, Zhang L, Zhao H, Dong X, *et al*. Plasma metabolomic profile and potential biomarkers for missed abortion. Biomed Chromatogr 2016;30:1942-52.
2. Gambir K, Kim C, Necastro KA, Ganatra B, Ngo TD. Self-administered versus provider-administered medical abortion. Cochrane Database Syst Rev 2020;3:CD013181.
3. Klingberg-Allvin M, Cleeve A, Atuhairwe S, Tumwesigye NM, Faxelid E, Byamugisha J, *et al*. Comparison of treatment of incomplete abortion with misoprostol by physicians and midwives at district level in Uganda: A randomised controlled equivalence trial. Lancet 2015;385:2392-8.
4. Bakker R, Pierce S, Myers D. The role of prostaglandins E1 and E2, dinoprostone, and misoprostol in cervical ripening and the induction of labor: A mechanistic approach. Arch Gynecol Obstet 2017;296:167-79.
5. Pierce S, Bakker R, Myers DA, Edwards RK. Clinical insights for cervical ripening and labor induction using prostaglandins. AJP Rep 2018;8:e307-e314.
6. Huang MC, Hsieh CH, Huang JP, Tsai HT, Lee MS. Comparison of sequential vaginal and sublingual misoprostol after a vaginal loading dose for second-trimester abortion. Taiwan J Obstet Gynecol 2017;56:312-4.
7. Nautiyal D, Mukherjee K, Perhar I, Banerjee N. Comparative study of misoprostol in first and second trimester abortions by oral, sublingual, and vaginal routes. J Obstet Gynaecol India 2015;65:246-50.
8. Lapuente-Ocamica O, Ugarte L, Lopez-Picado A, Sanchez-Refoyo F, Lasa IL, Echevarria O, *et al*. Efficacy and safety of administering oral misoprostol by titration compared to vaginal misoprostol and dinoprostone for cervical ripening and induction of labour: Study protocol for a randomised clinical trial. BMC Pregnancy Childbirth 2019;19:14.
9. Mohammadi E, Jayaprakash G, Shiva A, Motallebzadeh N. Comparison of effectiveness and patient satisfaction of vaginal versus oral misoprostol in treatment of missed miscarriage. Open Access Maced J Med Sci 2019;7:955-8.
10. Singh S, Gupta H, Shrivastava K, Rathi V, Gupta U. Evaluation of efficiency of Sublingual misoprostal and vaginal misoprostal administration for induction of labour. Indian J Obstet Gynecol Res 2018;5:143-7.
11. Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70 days gestation. Contraception 2015;92:197-9.
12. Magnay JL, O'Brien S, Gerlinger C, Seitz C. A systematic review of methods to measure menstrual blood loss. BMC Womens Health 2018;18:142.

13. Lee YY, Kim TJ, Kang H, Choi CH, Lee JW, Kim BG, *et al*. The use of misoprostol before hysteroscopic surgery in non-pregnant premenopausal women: A randomized comparison of sublingual, oral and vaginal administrations. Hum Reprod 2010;25:1942-8.
14. Marwah S, Gupta S, Batra NP, Bhasin V, Sarna V, Kaur N. A comparative study to evaluate the efficacy of vaginal vs oral prostaglandin e1 analogue (misoprostol) in management of first trimester missed abortion. J Clin Diagn Res 2016;10:QC14-8.
15. Khairnar MM, Patil AM. Study of the efficacy and success rate of single dose oral mifepristone and vaginal misoprostol v/s vaginal misoprostol alone for second trimester termination of pregnancy. MVP J Med Sci 2019;5:216-21.
16. Imširija N, Imširija L, Godinjak Z, Deković S, El Ardat MA. Contemporary treatment of pathological pregnancies in the first trimester. Med J 2015;21:34-7.
17. Mizrachi Y, Tamayev L, Shemer O, Kleiner I, Bar J, Sagiv R. Early versus delayed follow-up after misoprostol treatment for early pregnancy loss. Reprod Biomed Online 2019;39:155-60.
18. Seuc AH, Shah IH, Ali M, Diaz-Olavarrieta C, Temmerman M. How to assess success of treatment when using multiple doses: The case of misoprostol for medical abortion. Trials 2015;16:510.
19. Susan ZS, Chowdhury A, Halder S, Ahamed S, Afrin H, Hossain T, *et al*. Use of combination of mifepristone and misoprostol to terminate early pregnancy: experience at a tertiary care teaching hospital. J Sci Foundation. 2017;15 (1):9-13.
20. Krugh M, Maani CV. Misoprostol. StatPearls. Treasure Island (FL): StatPearls Publishing,StatPearls Publishing LLC.; 2020. PMID: 30969695.
21. Senger N, Agrawal N, Gupta S, Nath K, Gupta A. Malignant hyperthermia following intravaginal prostaglandin-misoprostol. J Evolution Med Dental Sci 2015;4:11570-3.
22. Ezechukwu PC, Ugwu EO, Obi SN, Chigbu CO. Oral versus vaginal misoprostol for induction of labor in Enugu, Nigeria: A randomized controlled trial. Arch Gynecol Obstet 2015;291:537-44.
23. Yenuberi H, Abraham A, Sebastian A, Benjamin SJ, Jeyaseelan V, Mathews JE. A randomised double-blind placebo-controlled trial comparing stepwise oral misoprostol with vaginal misoprostol for induction of labour. Trop Doct 2016;46:198-205.