International Journal of Clinical Trials
Farzipour S et al. Int J Clin Trials. 2022 May;9(2):60-65
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20221104

Original Research Article

Comparing the effects of vaginal misoprostol and isosorbide mononitrate on cervical ripening in abortions under 20 weeks: a randomized controlled trial

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Received: 31 January 2022
Revised: 07 April 2022
Accepted: 08 April 2022

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ABSTRACT

Background: In the first trimester of pregnancy, 15 to 20 percent of pregnancies result in miscarriage. Misoprostol is a widely medication that used for induction of labor in the second trimester; therapies, early termination of pregnancy and also used in duration of term delivery. The objective of this study was to comparing the effects of vaginal misoprostol and isosorbide menonitrate on cervical ripening in abortion under 20 weeks.
Methods: In this prospective randomized clinical trial, 120 pregnant women with miscarriage were enrolled in the study and randomly divided into 3 groups: vaginal misoprostol, isosorbide mononitrate and control group. The effect of all drugs on cervical dilatation and ripening, time needed for abortion, and also their side effects were evaluated.
Results: The mean of VAS in misoprostol group with 6.2±2.3 was significantly more than isosorbide mononitrate group with 3.4±1.5 and control group with 3.2±2.4. The rate of abortion in misoprostol group was significantly lower than other two groups. The change in dilation rate more than 3 cm in misoprostol group with 50% was significantly more than other two groups with 35% and 20%. Nausea, diarrhea, fever and bleeding rate were higher in the misoprostol group than other two groups. Headache in the isosorbide mononitrate group was significantly higher than the other groups.
Conclusions: The results showed that we can use isosorbide mononitrate as a suitable alternative with better safety to vaginal misoprostol in cervical repining in abortions under 20 week.

Keywords: Misoprostol, Isosorbide mononitrate, Abortion, Cervical ripening

INTRODUCTION

In the first trimester of pregnancy, 15 to 20% of pregnancies lead to miscarriage. According to the definition of the National Health Center, miscarriage refers to the termination of a pregnancy under 20 weeks or the birth of a fetus under 500 grams and covers about 15% of pregnancies.[1] Induced abortion is the termination of a pregnancy by medical or surgical means before the fetus is able to survive, for fetal or maternal reasons. Since 1930, the standard treatment for first-trimester abortion has been dilatation and curettage, which can be associated with complications such as uterine perforation, bleeding, cervical laceration, and infection and, in order to reduce these side effects, cervical preparation methods are used in both mechanical and pharmacological methods, such as misoprostol and nitric oxide releasing drugs.[2-6] Numerous studies have been performed to evaluate the effect of these drugs on the termination of pregnancy and compare them with pharmacological methods, considering the extent side effects of each. Misoprostol is widely used to induce labor in the second trimester, cervical softening before

curettage, hysteroscopy, therapeutic abortions, endometrial biopsy, early termination of pregnancy, treatment of incomplete or missed abortion, treatment of postpartum hemorrhage, and induction of term labor is used.[2] The results of various studies have shown that prostaglandins are associated with adverse maternal and fetal consequences due to uterine contractions and therefore are not yet considered as a safe and secure method. It is better to use agents for induction and preparation of the cervix that prepares the cervix with minimal adverse effects on the mother and fetus.[7-9]

Recently, nitric oxide-releasing drugs, which are an endothelium-dependent relaxant and an important biological mediator in the human body, have been considered. Nitric oxide is a free radical gas that relaxes the smooth muscles of the arteries, stomach and myometrium. In obstetrics, nitric oxide releasing agents have been used to treat preterm labor, acute uterine relaxants for easy fetal delivery, manual placental abruption, and to improve fetal blood flow. Another proven role of these agents is the physiological nature of cervical preparation in the advanced stages of pregnancy.[10] In studies, the vaginal application of nitric oxide releasing agents has been effective in the process of cervical preparation before induction of labor. Nitric oxide softens the cervix both directly and by stimulating prostaglandins and cyclooxygenases and releasing cytokines, as well as rearranging cervical collagen.[10] As a result, these agents prepare the cervix for delivery without causing complications such as fetal distress.[4]

Previous studies have shown that compared to prostaglandins, nitric oxide products are more likely to inhibit uterine activity and increase uterine blood flow.[11-14] And the only potential risk of these agents is dilatation of the uterine arteries, followed by hypotension, which can lead to fetal hypoxia if severe.[9] However, there are still many questions about how to prescribe it that have not been well answered and therefore the need for further researches in this area seems necessary. The condition of the cervix is very important for the induction of labor, and in many conditions that require induction of labor before the onset of labor, the condition of the cervix is unfavorable.

So, special attention has been paid to the preparation of the cervix before the induction of labor.[15-17] Therefore, due to the importance of the subject, the aim of this study was to compare vaginal misoprostol and isosorbide mononitrate in cervical ripening at abortion of less than 20 weeks.

METHODS

Study design and participants

The single-blind randomized controlled clinical trial study was registered in Iran clinical trial center with the code number IRCT20190901044658N1. The study conducted on 120 pregnant women with less than 20 weeks gestation who were candidates for medical abortion. Based on statistical calculations at 95% confidence level, 80% test power, and 5% prevalence of abortion, the sample size was estimated at 120 patients. All women were randomly divided into three groups of 40 patients: Vaginal Misoprostol, isosorbide mononitrate and control group.

Inclusion and exclusion criteria

The study included patients who had pregnancy under 20 weeks and a candidate for medical abortion due to proven fetal death which was confirmed by ultrasonography or severe anomalies that the fetus could not survive. In this study, missed abortion patients were studied. The study excluded patients who had history of cesarean section more than two times, adrenal diseases, steroid-related cancers, asthma, and history of thromboembolism, glaucoma, and history of ML and drug sensitivity.

Measurements and data collection

The drug was prescribed by a freshman resident without knowing the type of prescribed drug. First, a detailed history was taken then a complete physical examination done and, CBC, LFT, and kidney function tests were obtained from all three groups. Patients were first explained about the treatment methods and their benefits and side effects and informed consent was obtained from them. The first group received vaginal misoprostol (200 µg every 6 hours, for patients <13 weeks gestational age and 200 µg for patients 14 to 20 weeks gestational age every 6 to 12 hours), and the second group received 40 mg of isosorbide mononitrate (after examination, repeat the drug every 6 to 12 hours if needed) in the posterior vagina fornix and the third group, as a control group, was given 12 hours to soften the cervix or excrete spontaneously. Patients were being examined regularly Every 6 hours and if the fetus did not be aborted, the drugs were repeated after 6 to 12 hours.

Patients who suffered severe vaginal bleeding during hospitalization were treated with emergency curettage. Patients with tissue excretion underwent transvaginal sonography and were considered as complete abortions and discharged if they did not have a report of pregnancy residues. Vital signs were checked every hour. Patients underwent curettage if they had a report of pregnancy residues or no tissue excretion. The required information including the dosage of required medications, the duration of hospitalization, the need for curettage (in case of placenta residue and pregnancy residue based on ultrasound at the day after fetus excretion), the need for analgesics, side effects of medications (nausea, vomiting, diarrhea, fever, hypotension) and the time interval between the beginning of treatment and fetus excretion based on the clock were evaluated in all three groups. A questionnaire including Visual analogue score (VAS), gestational age based on sonography or date of last menstruation, history of allergy and cause of termination of pregnancy, bleeding

rate, fever, nausea, diarrhea was completed for each patient.

Ethical approval

This research conducted by the license of medical ethics committee of Ardabil University of Medical Sciences.

Statistical analysis

Data were analyzed by SPSS 24 software. For qualitative data and quantitative data, t-test and Kai square test were used respectively. The significance level in all tests was 0.05.

RESULTS

In this study, 120 patients were enrolled in the study. The mean age of patients in the group receiving misoprostol was 29±6.8 years and in the Isosorbide group was 26±6 years and in the control group was 22.5±6.8 years and these three groups had a significant difference in terms of mean age (p=0.044). There was no significant difference among groups in terms of gestational age based on LMP and sonography (Table 1). Among nulliparous patients, 5 patients in the misoprostol group (83.3%), 9 patients in the isosorbide group (60%) and 2 patients in the control group (20%) had cervical dilatation above 1 cm. The results of post-Hoc statistical analysis showed that the difference between the misoprostol group and isosorbide group was not significant, but the difference between the two groups and the control group was significant. Among the multiparous in the misoprostol group (85.3%), 29 patients, 18 patients in the isosorbide group (72%) and 10 patients in the control group (33.3%) had cervical dilatation above 1 cm. The difference in dilatation between misoprostol and isosorbide groups was not significant. But the difference between these two groups and the control group was significant (Table 2).

There was a significant difference among the groups in terms of side effects including nausea, diarrhea, headache and fever, complete abortion and the need for curettage, which nausea, diarrhea and fever were more in the misoprostol group. Headache in the isosorbide group was significantly higher than the other groups. There was no significant difference between the 3 groups in terms of hypotension. Complete abortion was the most common in the misoprostol group and the need for curettage was the lowest in the misoprostol group. Dilation below 3 cm in the vaginal misoprostol group with 50% was significantly higher than the other two groups. The difference among the groups was significant in terms of dilatation (Table 3). The time interval between induction and abortion was longer in the control group than the other groups.

The shortest time interval was related to the isosorbide receiving group. The difference among the groups was not significant in terms of the time interval between induction and abortion. In terms of complete abortion and the need for curettage, the difference among groups was significant, so that complete abortion in the misoprostol group was the most and the need for curettage was the lowest in this group (Table 5). There was moderate bleeding in 19 patients (47.5%) in the misoprostol group, 13 patients (32.5%) in the isosorbide mononitrate group and 11 patients (27.5%) in the control group. The amount of bleeding in the study groups was statistically significant (p=0.001) and bleeding more than menus period in the misoprostol group was significantly more than the other two groups (Figure 1). The pain had statistically significant difference among the three drug groups. The amount of pain in the misoprostol group was significantly higher than the other two groups (Table 4).

Table 1: Mean of gestational age of mothers in three groups by LMP and ultrasound results.

Groups index	Misoprostol	Isosorbide mononitrate	Control	P value
The first day of the last menstrual period	10.1±3.8	10.6±3.3	11±4.5	0.59
Ultrasound	9.6±3.5	10.3±3.4	10.9±4.3	0.32

Table 2: Compare dilatation cervix in multiparous and nulliparous.

Groups index	Misoprostol		Isosorbide mononitrate		Control		P value
	N	%	N	%	N	%	
Nulliparous	5	83.3	9	60	2	20	0.001
Multiparous	29	85.3	18	72	10	33.3	0.001

Table 3: Compare dilatation rate in all groups.

Groups index	Misoprostol		Isosorbide mononitrate		Control		P value
	N	%	N	%	N	%	
Without change	5	12.5	13	32.5	27	67.5	
0.5-2 cm	15	37.5	13	32.5	5	12.5	0.001
≥3 cm	20	50	14	35	8	20	

Table 4: Time between induction and abortion and VAS in three groups.

Groups	Misoprostol	Isosorbide mononitrate	Control	P value
Time duration (hour)	8.4±2.6	7.1±3.9	10	0.29
VAS	6.2±2.3	3.4±1.5	3.2±2.4	0.001

Table 5: Frequency of abortion and needing for abortion in three groups.

Groups	Misoprostol		Isosorbide mononitrate		Control		P value
	N	%	N	%	N	%	
Abortion	17	42.5	11	27.5	3	7.5	0.002
Need for abortion	23	57.5	29	72.5	37	92.5	0.004

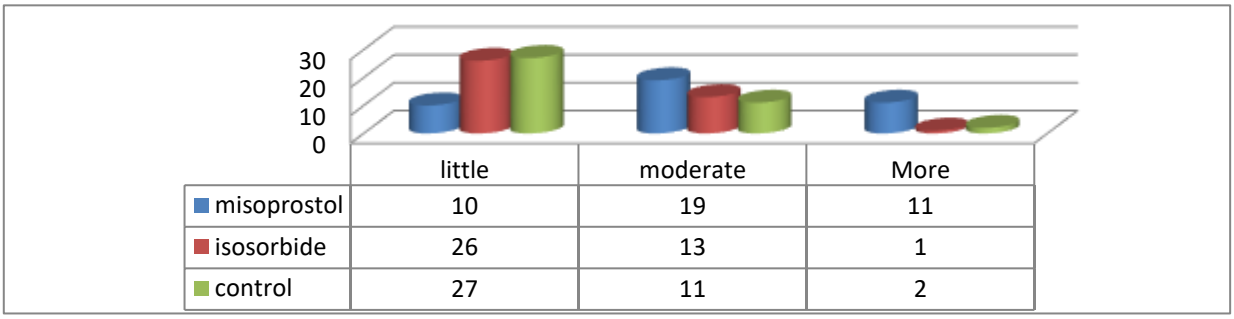

Figure 1: The rate of bleeding in three groups.

DISCUSSION

In this study, 120 patients were enrolled in the study. The mean age of patients in the misoprostol group was 29±6.8 years, in the isosorbide group was 26±6 years and in the control group was 22.5±6.8 years. In the study of Mokhah et al in order to evaluate the effect of ISMN both vaginally and orally to prepare cervix, they selected 99 nulliparous pregnant women with full-term or prolonged pregnancies. The mean age of patients was 23.2 years.[18] A study was performed by Dehghani Firoozabadi to determine the effect of isosorbide mononitrate and compare it with low-dose syntocinone in cervical preparation during labor. In this study, the mean age of patients was 24.6 and the results showed that the difference of age between our patients and other studies is not much different.[19] In a study by Lee et al, the success rate of vaginal Misoprostol alone in terminating pregnancy was studied a d mean age of patients was 27.9.[16] Chanrachakol et al in 2002 performed a study, which compared the two drugs isosorbide mononitrate and misoprostol, the mean age was 28.5.[17]

It seems that the mean age of patients in foreign studies is higher than the average of patients in our study, and this finding is most likely due to the low age of marriage and Pregnancy in Iran and Ardabil province.[17] In terms of cervical dilation, 5 nulliparous pregnant mothers, in the misoprostol group (83.3%), 9 in the isosorbide group (60%) and 2 in the control group (20%) had dilatation above 1 cm. The results of statistical analysis showed that misoprostol group was not significantly different from isosorbide group. However, both of these drugs significantly cause dilatation compared to the control group. In a study conducted by Mokhah et al to evaluate the effect of ISMN in both vaginal and oral forms, for cervical preparation. Intervention groups included a vaginal ISMN group (N=50, 40 mg) and an oral ISMN group (N=49, 20 mg). After 24 hours, Bishop score increased significantly in each of the vaginal ISMN and oral ISMN groups. Both groups were compared in terms of termination method and causes of cesarean section and no significant difference was observed between the two groups.[18] A study by Dehghani Firoozabadi to determine the effect of isosorbide mononitrate and compare it with low-dose syntocinone in cervical preparation during childbirth 100 nulliparous pregnant women, randomly divided into two groups receiving isosorbide mononitrate pill 40 mg mg (N=50) and low-dose syntocinone (N=50). The efficacy and safety of the both methods were compared in terms of cervical preparation and the time between the start of treatment and delivery in the two groups. The mean time of cervical preparation to induction of labor in the group of isosorbide mononitrate was 36.13±4.05 hours and in the low-dose syntocinone group was 36.28±3.88 hours. There was no significant difference between the two groups in terms of type of delivery (cesarean section and vaginal delivery).[19] According to the present study and other studies, it does not seem that the different methods of induction of abortion in cervical dilatation are very different, although they are significantly more effective than the control group. Patients who had abortions were evaluated in the study groups in terms of time interval between induction and abortion. The results of statistical analysis in our study showed that this time interval in the group receiving misoprostol is more than the other groups and the shortest time interval belongs to the group receiving isosorbide. Also in the study of

Yazdizadeh et al, the time interval of induction with oxytocin to the active phase of labor in the isosorbide mononitrate group was shorter than the other groups.[20]

The mean length of the active phase of labor did not differ between the two groups. Our study also found that the shortest time interval was for the group receiving isosorbide. But in a study by Rachakol et al who compared the two drugs isosorbide mononitrate and misoprostol, the time interval between induction and active phase was longer in the isosorbide mononitrate group than in misoprostol. It seems that the time relationship between induction and active phase is various in different studies and more studies and researches are needed to achieve this issue.

The interesting finding in our study was that, although the isosorbide mononitrate group had less dilatation, but the time interval between induction and abortion was less in this group, it might be concluded that in fact, the time interval between induction and abortion is not related to dilatation. There was a statistically significant difference in the amount of vaginal bleeding in the studied groups, so that bleeding more than menus period in the misoprostol group was significantly more than the other two groups. Unfortunately, we did not find a similar study that considered bleeding as a factor in the study, but what we found in the present study was that there was more bleeding than menus period in the misoprostol group. Perhaps the reason for this was the greater diameter of cervix in this group. There was a significant difference between the groups in terms of the prevalence of side effects of nausea, diarrhea, headache and fever, which nausea, diarrhea and fever were more in the misoprostol group.

Headache in the isosorbide group was significantly higher than the other groups. There was no significant difference between the 3 groups in terms of hypotension, but there was a significant difference between the groups in terms of abortion and the need for curettage, which complete abortion was the most common in the misoprostol group and the need for curettage was the lowest in the misoprostol group. In the study of Firouzabadi et al the most common side effect of the isosorbide mononitrate tablets, was mild headache (70%) and in the low dose syntocinone group, was tachysystole/hypertonia (4%).[19] In the study of Yazdizadeh et al to determine the effect of vaginal administration of isosorbide tablets, no maternal and fetal side effects were observed except headache in the intervention group, which was more than the placebo group.[20]

In the study of Habib et al on headache in isosorbide mononitrate group, it was more than the placebo group and it can be concluded that the headache complication is more common in isosorbide mononitrate than other groups.[21]

One of the limitations of our study was the limitation of the dose of isosorbide mononitrate for more than 24 hours due to the possibility of hypotension. Also, the small number of samples in this study led to some conclusions such as the distance between induction and abortion less in the isosorbide group (1.7 hours) compared to the mesoprostol group (4.8 hours) despite more dilatation in the mesoprostol group (85%) in compare isosorbide with (67%) which may be variable with more samples and also in this study we have used pregnancies with missed abortion that due to physiological causes of uterine contractions can be in this group as It occurs spontaneously, so perhaps the rate of more than 30% increase in cervical dilatation in the control group is due to this.

CONCLUSION

The mean rate of dilatation in the misoprostol and isosorbide mononitrate groups was significantly higher than the control group. No significant difference in cervical dilatation was observed in multipart and nulliparous pregnants in the three groups. In this study, it was concluded that the time interval of abortion was not significantly related to the degree of dilatation. One of the limitations of our study was the limitation of the use of isosorbide mononitrate for more than 24 hours due to the possibility of hypotension. Also, the small number of samples in this study led to some conclusions such as the lesser time interval between induction and abortion in the isosorbide group (7.1 hours) compared to the misoprostol group (8.4 hours) despite more dilatation in the Misoprostol group (85%) than isosorbide group (67%), which may be different with greater samples. And we've also used pregnancies with Missed abortion reports that can spontaneously develop in this group due to physiological causes of uterine contractions. Therefore, the rate of more than 30% in increasing cervical dilatation in the control group may be is because of this. This study introduces isosorbide mononitrate a suitable alternative to misoprostol. Further studies are suggested to reach definitive results. Isosorbide mononitrate can also be used in patients who have contraindications to misoprostol.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Cunningham FG, Hauth JC, Leveno KJ, Gilstrap L, Bloom SL, Wenstrom KD. Williams obstetrics. 24th ed. New York, NY: McGraw Hill; 2015: 41-42.
2. Gynuity Health Project. Map of Misoprostol Approval page, 2008. Available at: https://gynuity.org/downloads. Accessed on 21 January 2022.
3. Bollagragada S, Mackenzie F. A randomized placebo controlled trial of outpatient cervical ripening with isosorbidemononitrate prior to induction of labour. BMC Pregnancy Childbirth. 2006;6:25.

4. Ekerhovd E, Bullarbo M, Andersch B, Norström A. Vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening at term: a randomized controlled study. Am J Obstet Gynecol. 2003;189(6):1692-7.
5. Buhimschi I, Ali M, Jain V, Chwalisz K, Garfield RE. Differential regulation of nitric oxide in the rat uterus and cervix during pregnancy and labour. Hum Reprod. 1996;11(8):1755-66.
6. Tommiska MR. Nitric oxide in the human uterine cervix: endogenous ripening factor. Ann Med. 2008;40(1):45-5.
7. Wing DA. Labor induction with misoprostol. Am J Obstet Gynecol. 1999;181(2):339-45.
8. Herabutya Y, Prasertsawat P, Pokpirom J. A comparison of intravaginal misoprostol and intracervical prostaglandin E2 gel for ripening of unfavorable cervix and labor induction. J Obstet Gynaecol Res. 1997;23(4):369-74.
9. Nicoll AE, Mackenzie F, Greer IA, Norman JE. Vaginal application of the nitric oxide donor isosorbide mononitrate for preinduction cervical ripening: a randomized controlled trial to determine effects on maternal and fetal hemodynamics. Am J Obstet Gynecol. 2001;184(5):958-64.
10. Chwalisz K, Shao-Qing S, Garfield RE, Beier HM. Cervical ripening in guinea-pigs after a local application of nitric oxide. Hum Reprod. 1997;12(10):2093-101.
11. Buhimschi I, Ali M, Jain V, Chwalisz K, Garfield RE. Differential regulation of nitric oxide in the rat uterus and cervix during pregnancy and labour. Hum Reprod. 1996;11(8):1755-66.
12. Facchinetti F, Piccinini F, Volpe A. Chemical ripening of the cervix with intracervical application of sodium nitroprusside: a randomized controlled trial. Hum Reprod. 2000;15(10):2224-7.
13. Wölfler MM, Facchinetti F, Venturini P, Huber A, Helmer H, Husslein P, et al. Induction of labor at term using isosorbide mononitrate simultaneously with dinoprostone compared to dinoprostone treatment alone: a randomized, controlled trial. Am J Obstet Gynecol. 2006;195(6):1617-22.
14. Gelber S, Sciscione A. Mechanical methods of cervical ripening and labor induction. Clin Obstet Gynecol. 2006;49(3):642-57.
15. Zargar M, Nazari MA, Hormozy L, Mohammadi MH. Efficacy of transcervical foley catheter and laminaria on induction of labor in post-term pregnancy: a clinical study. Tehran Univ Med J (TUMJ) 2014;72(3):161-6.
16. Lee VC, Tang OS, Ng EH, Yeung WS, Ho PC. A pilot study on the use of letrozole with either misoprostol or mifepristone for termination of pregnancy up to 63 days. Contraception. 2011;83(1):62-7.
17. Chanrachakul B, Herabutya Y, Punyavachira P. Randomized trial of isosorbide mononitrate versus misoprostol for cervical ripening at term. Int J Gynaecol Obstet. 2002;78(2):139-45.
18. Moukhah S, Ahmadi F. Preinduction cervical ripening using oral and vaginal isosorbide dinitrate in patients with term pregnancy : A randomized clinical trial. Koomesh. 2016;17(4):863-70.
19. Dehghani FR, Sekhavat L, Ghafoorzadah M, Tabatabaii R, Farajkhoda T. A comparison between Efficacy of Vaginal Isosorbide Mononitrate and Low Dose Syntocinon on Cervical Ripening at Labor. Iranian J Obstetr Gynecol Infert. 2011;14(3):29-39.
20. Yazdizadeh H, Abedi P, Najar SH, Ahmadi AK. The Effect of Vaginal Administration Isosorbide Mononitrate on Cervical Ripening and Iduction of Labor In Postterm Pregnancy. Jundishapur Scientif Med J. 2012.
21. Habib SM, Emam SS, Saber AS. Outpatient cervical ripening with nitric oxide donor isosorbide mononitrate prior to induction of labor. Int J Gynaecol Obstet. 2008;101(1):57-61.

Cite this article as: Farzipour S, Amani F, Rezaei M. Comparing the effects of vaginal misoprostol and isosorbide mononitrate on cervical ripening in abortions under 20 weeks: a randomized controlled trial. Int J Clin Trials 2022;9(2):60-5.