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Original Article

The combination route versus sublingual and vaginal misoprostol for the termination of 13 to 24 week pregnancies: A randomized clinical trial

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ABSTRACT

Objective: The goal of this study was to compare the effectiveness of misoprostol via sublingual and vaginal administration versus the combination route in the termination of 13 to 24 week pregnancies.
Materials and Methods: One hundred and ninety-five patients, divided into three groups, were enrolled in this study. In the vaginal group, two 200-μg misoprostol tablets were inserted into the posterior fornix every 4 hours for 48 hours. In the sublingual group, patients took two 200-μg misoprostol tablets every 4 hours for up to 48 hours. In the combination group, two 200-μg misoprostol tablets were inserted within the posterior fornix followed by the administration of 400 μg misoprostol sublingually every 4 hours for a period of 48 hours. Efficacy was defined as a successful termination without the need for any interventions.
Results: The success rate, after 24–48 hours, was not significantly different among the three groups. It was significantly higher within the first 12 hours of misoprostol administration within the sublingual group ($p = 0.031$). Nonetheless, the overall failure rate was not significantly different between three groups. The mean duration of abortion was shortest among the sublingual group (655 ± 46 minutes), $p = 0.005$, and the number of misoprostol tablets administered was lower when compared to the other groups (5.9 ± 0.3), $p = 0.001$. The duration of abortion and the number of misoprostol tablets used significantly varied in the cases in which the patient had a history of a previous normal vaginal delivery (NVD; $p = 0.007$). The average number of tablets administered was the lowest in the sublingual group. The prevalence of fever among the NVD cases were significantly higher in the combination group ($p = 0.008$). Overall, of all the methods, patients preferred the sublingual route ($p = 0.001$).
Conclusion: Sublingual misoprostol has a higher efficacy when compared to the vaginal and combination methods.

Introduction

Second-trimester abortions, which can be carried out either medically or surgically, approximately constitute up to 10–15% of all induced abortions and is responsible for 50% of abortion-related maternal deaths [1]. With the development of prenatal diagnostic techniques, the need for the termination of mid-trimester pregnancies as a result of fatal fetal anomalies has consequently increased. Pregnancy termination techniques include dilation and curettage; administration of systemic drugs such as oxytocin infusions, misoprostol, combinations of misoprostol and mifepristone, and carboprost; and/or local administration of hypertonic saline or urea within the amniotic fluid [2]. If performed by a sufficiently skilled medical operator, surgical termination of pregnancies after 15 weeks via dilation and evacuation is a safe and effective method resulting in fewer adverse events, including less pain, than medical terminations [3]. Regrettably, due to the lack of surgical facilities or specialized personnel, some centers may not be

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well suited for these means. As a result, medical terminations of pregnancies are potentially safer. In addition, medical termination provides a good source of tissue samples, especially in cases which the indication of termination is a consequence of genetic malformations. For centers lacking in proper surgical facilities and skilled operators, medical termination by prescribing mifepristone and subsequently prostaglandin analogs has been recommended by the World Health Organization (WHO) and the Royal College of Obstetricians and Gynecologists (RCOG) [4,5]. The therapeutic regimen of mifepristone with misoprostol is effective. However, because of its unavailability and high costs of mifepristone, the use of misoprostol has become more popular [6].

Misoprostol is an E1 prostaglandin analog approved for the prevention and cure of nonsteroidal anti-inflammatory drug (NSAID)-related gastric ulcers [7]. However, in midwifery, misoprostol is used to soften the cervix and to induce uterine contractions. Hence, it is used for medical abortions in cases of fetal anomalies, premature rupture of membranes, fetal death, for the ripening of the cervix before curettage, and even for the induction of labor [1].

Misoprostol does not need to be refrigerated and is stable at room temperature. It is easy to use, has few tolerable side effects, and is economically more cost effective when compared to other prostaglandins. Therefore, in many countries, misoprostol is a standard treatment for the termination of second-trimester pregnancies [1]. Despite many studies, no consensus has been reached on the most effective dose, timing interval, and method of misoprostol administration. Thus, it seems necessary to conduct further studies in order to obtain a protocol of higher efficacy with the fewest amount of side effects that are tolerable by patients.

Some studies lean toward the use of vaginal misoprostol in second-trimester pregnancy terminations, possibly because of the positive and direct effects of misoprostol s on the ripening of the cervix [8]. However recent studies have demonstrated that the sublingual route of misoprostol administration is as effective as the vaginal route [9,10].

Therefore, the hypothesis of this study was that we could yield better results using the combination method (a vaginal route was used in the first dose for ripening of the cervix, followed by the sublingual route for additional doses), both in terms of patient compliance and better therapeutic results, such as increasing the success rate and shortening the duration of fetal expulsion. The goal of this study was to compare the efficacy and outcomes of misoprostol administration in terminating 13- to 24-week pregnancies via the sublingual and vaginal route versus the combination route (the first dose was administered vaginally, and the rest were administered sublingually).

Materials and methods

This study was an interventional, randomized, nonblinded clinical trial with no placebo, performed on 195 patients visiting the Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran from the period 2011 to 2012. The cases included pregnant women who were in their second trimester (13–24 weeks) and were advised to terminate their pregnancies due to fetal (chromosomal abnormalities, preterm premature rupture of membranes (PPROM) and intrauterine fetal death) or maternal indications. The exclusion criteria included pregnant women who were sensitive to misoprostol, pregnant women at high risk for uterine ruptures (a history of a hysterotomy or repeated cesarean sections, history of a classic or T-shaped uterine incision, history of extensive surgery on the fundus of the uterus, multiparous women with a history of more than five births, and pregnant women with intrauterine devices), pregnant women with specific medical conditions such as anemia, coagulation disorders or a history of anticoagulant drug use, active hepatic diseases, coronary arterial diseases, glaucoma, uncontrolled convulsive disorders, adrenal diseases, or disorders that require glucocorticoid treatment (such as bronchial asthma).

To calculate the sample size we used the results of a multicenter study that had been conducted in 2009 simultaneously in several countries. Based on the results of this study, the rate of successful abortions after 48 hours of receiving vaginal misoprostol was 96%. The 15% difference between the success rate of the sublingual and combination groups was clinically significant. Consequently, the calculated sample size was 195, which was divided equally into three groups; with a confidence interval of 95% and power of 80%.

All the patients signed a form of consent before entering the study. This study was approved by the ethical committee of Tehran University of Medical Sciences. A computer-generated randomization sequence was used to assign patients to the vaginal, sublingual, or combination groups by randomly permuted blocks of six cases per box.

In the vaginal group two 200-μg tablets of misoprostol (Cytotec, Pharmacia Limited, Ramsgate Road, Sandwich, Kent, UK) were inserted into the posterior fornix simultaneously by the investigator every 4 hours for a maximum of 48 hours. In the sublingual group the patient was instructed to take two 200-μg tablets every 4 hours for 48 hours. In the combination group, initially, two 200-μg tablets of misoprostol were inserted into the posterior fornix simultaneously and then the patient was subsequently instructed to take 400 μg of sublingual misoprostol every 4 hours for a 48-hour period. Before the next dose was administered, the rate of contractions was controlled and if there were more than three contractions of adequate force with a duration of > 10 minutes, the next dose was postponed for up to 1 hour. The maximum number of doses of misoprostol given to the patients in all three methods were approximately five doses within 24 hours. In cases whereby abortion did not take place within the first 24 hours, the same drug regimen was prescribed for another 24 hours. The patient's temperature, blood pressure, and pulse rate were regularly checked and the side effects, if any, were registered in the patient's file by the on-call resident. If fever was detected, acetaminophen was given. If the patient experienced any nausea or vomiting, promethazine was prescribed; if analgesics were required for abdominal cramps, pethidine was administered. Following the abortion, the expelled products of the pregnancy were examined and if an incomplete abortion was suspected or if the patient experienced any severe bleeding, curettage was performed. After the abortion, if the patients had a retained portion of the placenta, 50 units of oxytocin were administered into a 1000-cc Ringer solution over a period of half an hour. If the placenta was not expelled after 2 hours, the patient would undergo curettage. In all the patients whose pregnancies were terminated medically, transvaginal ultrasonography was performed the day following the abortion. If any remnant of pregnancy was observed or if the endometrial thickness was > 15 mm, the patient would undergo curettage. Patients who did not have an abortion after 2 days of treatment with misoprostol were excluded from the study. These patients' treatment went on for a further 24 hours and after a 24-hour period of rest, if the fetus was not expelled, another method of termination was used. Efficacy was defined as a successful termination with no need for interventions.

Before being discharged, each patient had a questionnaire that was filled out by the researchers, listing the number of misoprostol doses administered, the side effects of misoprostol, and the patient's level of satisfaction. The collected data were then analyzed using the SPSS version 18 software (SPSS Inc., Chicago, IL, USA). χ^2 and analysis of variance tests were used for the analysis, and $p < 0.05$ was considered significant.

Table 1
The demographic characteristics of patients receiving misoprostol through the sublingual, vaginal, and combination routes of administration.

Variable	Combination	Sublingual	Vaginal	*p*
Maternal age (y)	27.65 ± 5.1	29.82 ± 7.31	28.89 ± 4.7	NS
Pregnancy age	17.75 ± 3.2	17.26 ± 3.5	17.26 ± 3.1	NS
BMI	26.06 ± 3.2	26.08 ± 3.4	26.35 ± 4.3	NS
Nulliparous	42 (64.6)	36 (55.4)	32 (49.2)	NS
Previous history of at least 1 NVD/multiparous	15/23 (65.2)	22/29 (75.9)	19/33 (57.6)	NS
Previous history of a Cs/Multiparous	9/23 (39.1)	11/29 (37.9)	15/33 (45.5)	NS

Data are presented as *n*/*N* (%) or mean ± standard deviation.
BMI = body mass index; NS = not significant; NVD = normal vaginal delivery.

Table 2
Indications for pregnancy termination.

	Combination	Sublingual	Vaginal	*p*
Intrauterine fetal death	27.30	43.20	29.50	NS
Preterm premature rupture of membranes	28.60	52.40	19.00	NS
Oligohydramnios	33.30	—	66.70	NS
Structural anomaly	36.80	27.40	35.80	
Aneuploidy	33.30	33.30	33.30	NS
Others	33.30	33.30	33.30	NS

Data are presented as %.
NS = not significant.

Results

Of the 195 cases, the patients were enrolled in three groups of 65. The mean age of the patients was 28.7 ± 5.8 years and the mean gestational age was 17.4 ± 3.1 weeks. One hundred and ten patients (56.4%) were nulliparous. Of the 85 multiparous patients, 56 (65.9%) had at least one previous vaginal delivery and 35 of the patients had the indications of a previous uterine scar. This information is outlined in more detail in Table 1.

Age, body mass index, pregnancy age, parity, history of a normal vaginal delivery (NVD), or cesarean section did not vary significantly among the three groups (Table 1). The indications for a pregnancy termination are outlined in Table 2.

The overall success rate was 52.8% after 12 hours, 89.2% after 24 hours, and 96.9% after 48 hours. The main results are shown in Table 3. The success rate within the first 12 hours was significantly higher when compared to the other two groups ($p = 0.031$). The overall rate of failure was six of 195 cases (3.1%). The difference between the failure rates was not significant among the three groups. The overall curettage rate was 35.4% (67 of 195 cases). There was no statistically significant difference ($p = 0.188$) found among the three groups.

There was a significant difference in the mean duration between the three groups, with the shortest duration belonging to the sublingual group having a mean value of 655 ± 46 minutes ($p = 0.005$). The number of misoprostol tablets used among the three groups was significantly different. As a result, the lowest number of misoprostol tablets administered belonged to the sublingual group, having an average number of 5.9 ± 0.3 tablets ($p = 0.001$).

The duration of termination between the three groups was the shortest among multiparous patients; however, when calculated, it was not considered statistically significant ($p = 0.065$).

Among the nulliparous women, when compared to the combined and vaginal groups (908.05 ± 388 and 927.77 ± 459 minutes, respectively), the induction to abortion time was shortest among the sublingual group (700.6 ± 432 minutes); nevertheless, this was not statistically significant ($p = 0.052$).

The duration of abortion significantly varied among the normal vaginal delivery cases ($p = 0.007$), with the least duration belonging to the sublingual method.

There was a significant difference found in the number of misoprostol tablets used in the NVD cases ($p = 0.002$). Nonetheless, the sublingual group used the least number of misoprostol tablets.

Table 3
Main results.

	Combination	Sublingual	Vaginal	*p*
Response to treatment (%)	100.00	100.00	94.70	0.371
Median abortion time (min)	717.2	553.64	963.33	0.007
Median abortion time in nulliparous cases (min)	840	660	780	0.052
Median abortion time in multiparous cases with a history of a NVD (min)	699	480	780	0.007
Median abortion time in multiparous cases with a history of a cesarean section (min)	540	660	600	0.84
Abortion (%)				
Within 12 h	33.8	60	38.5	0.031
Within 24 h	90.8	93.8	83.1	0.18
Within 48 h	95.4	98.5	96.9	0.59
The mean number of misoprostol tablets	6.53	5.36	8.56	0.003
Analgesia requirement (%)	45.20	42.20	44.40	0.454
Indication for curettage (%)	6.70	18.20	22.20	0.464
The mean endometrial thickness	13.067	15.591	15.167	0.637

NVD = normal vaginal delivery.

Table 4
Adverse effects of misoprostol.

		Combination	Sublingual	Vaginal	
Severity of bleeding	Less than the menstrual period	4 (6.50)	4 (6.30)	6 (9.50)	NS
	Equal to the menstrual period	12 (19.40)	20 (31.30)	12 (19.00)	NS
	More than the menstrual period	46 (74.20)	40 (62.50)	45 (71.40)	
Severity of pain	Low to medium	0 (0.00)	1 (1.60)	0 (0.00)	NS
	Severe but tolerable	32 (51.60)	34 (53.10)	32 (50.80)	
	Severe and intolerable	30 (48.40)	29 (45.30)	31 (49.20)	
Need for analgesic		28 (45.20)	27 (42.20)	28 (44.40)	NS
Fever		40 (64.50)	40 (62.50)	37 (58.70)	NS
Nausea		43 (69.40)	37 (57.80)	36 (57.10)	NS
Vomiting		31 (50.00)	25 (39.10)	19 (30.20)	NS
Diarrhea		41 (66.10)	36 (56.30)	42 (66.70)	NS

Data are presented as *n* (%).
NS = not significant.

However, the response to treatment and the need for curettage were not significantly changed in the NVD cases ($p > 0.05$). Among the patients with no a history of a previous NVD (pertaining to nulliparous women or women having a history of a cesarean section), the number of misoprostol tablets used, duration of abortion, response to treatment, and need for curettage did not vary significantly. In addition, the severity of bleeding, severity of pain, need for analgesics, nausea and vomiting, diarrhea, and fever did not vary significantly (Table 4). However, fever among the NVD cases was significantly higher in the combination groups, at 13 of 30 cases (43%; $p = 0.008$). Patient preference differed significantly among the three groups; all three groups preferred the sublingual route of misoprostol administration ($p = 0.001$).

Discussion

The medical termination of second-trimester pregnancies with mifepristone and misoprostol leads to shorter induction-to-abortion interval; nonetheless, mifepristone is expensive and not readily available in developing countries. Therefore, misoprostol can be used alone instead [1]. Some studies claim that the effect of vaginal misoprostol on the duration of abortion is equal to or more than that of sublingual misoprostol (especially in nulliparous patients). This claim, in part, can be attributed to the direct and local effects vaginal misoprostol has on the cervix. According to von Hertzen et al [11], this duration is significantly shorter in nulliparous women receiving the vaginal method.

Tang et al [8] performed another study in 2004 in which the sublingual and vaginal routes were investigated by the administration of 400 μg of misoprostol every 3 hours. The results of this study showed that the success rate within 48 hours and the duration of the induction-to-abortion interval did not vary significantly between the two methods. However, the success rate within the first 24 hours of the vaginal route was higher than the sublingual method, which may be attributed to the local effects of misoprostol in the ripening of the cervix [8].

In 2004 Hamoda et al [12] stated, in regard to the dilating of the cervix, the effect of sublingual misoprostol was similar to its vaginal counterpart. According to their research, there was no significant statistical difference between the two groups, which refers to the dilating of the cervix for fetal abortion, the duration between cervical dilatation, and the expulsion of the products of pregnancy or the rate of blood loss [12]. Moreover, in 2013 Tanha et al [10] found no difference in the outcome of vaginal and sublingual misoprostol administration.

Yet another study by Dickinson et al [9] demonstrated that the combination method (oral and vaginal) was somewhat similar to the vaginal route of misoprostol administration [9].

Our original hypothesis was that vaginal administration of the initial dose would lead to better dilation of the cervix, and by continuing with the sublingual method—which is easier—would be more effective when compared to the aforementioned methods, i.e., sublingual and vaginal. According to our study, the mean duration of abortion and the total dose of misoprostol used in the sublingual method were significantly lower than that of the other two methods. Perhaps the reason behind this observation lies in the pharmacodynamics of misoprostol [13].

Parallel to our study, Cabrera et al's [13] meta-analysis on the comparison of the efficacy of sublingual versus vaginal misoprostol in 2011 showed that the mean duration of abortion in the sublingual method was significantly shorter than the vaginal method. Elhassan et al's [14] findings in Sudan also confirmed our results by reporting similar outcomes as the study by Cabrera et al [13].

Tang et al [15] studied the pharmacodynamics of vaginal and sublingual misoprostol in 2002 and found that the maximum plasma level and efficacy of sublingual misoprostol was greater than its vaginal counterpart. According to this study, sublingual misoprostol reaches its peak serum concentration and bioavailability in a shorter period of time, which is 30 minutes, whereas it takes 75 minutes in the case of vaginal misoprostol. In the sublingual route, misoprostol enters the bloodstream without passing the liver. A quicker rise to the peak plasma level creates the best bioavailability for the cells. Likewise, the greatest area under the curve has also been reported for the sublingual administration of misoprostol as well, which is within the first 6 hours. Thus, according to this pharmacokinetic study, upon administering sublingual misoprostol, the peak plasma concentration is reached within a shorter period of time and its bioavailability is higher when compared to the vaginal route [15].

Vaginal misoprostol may remain in the vagina for hours after its administration and its absorption may, in some cases, be incomplete and variable. The reasons may be a consequence of the physical differences among women, the pH of vaginal secretions, and the differences in the amount of bleeding from the uterus. It is important to keep in mind that vaginal bleeding may lead to poorer absorption of the drug. A recent study investigating the pharmacokinetics of repeated doses of vaginal and sublingual misoprostol (400 μg every 3 hours for 5 days) showed that the peak plasma concentration and bioavailability of misoprostol acid (an active metabolite of misoprostol) were greater in the sublingual method [16]. According to the article, the reason for this phenomenon is that vaginal bleeding, which begins with the fetal abortion process, may coincide with the absorption of misoprostol [16].

In 2009 Tang et al [16] compared the sublingual and vaginal routes of administration in those who did not have vaginal bleeding. No significant differences were observed. Many efforts

have been made to improve the vaginal absorption of the drug, but the bioavailability of the vaginal type is still a topic of debate [13].

In our study the number of misoprostol tablets used and the duration of abortion were significantly less in the sublingual group of multiparous women having a previous history of a NVD. This is an important finding because these associations were not significant in cases without a history of a vaginal delivery. The reason is probably due to the cervix being more prepared in women who have had a previous NVD.

In a retrospective analysis of second trimester pregnancies by Sak et al [17], the administration of 400 μg of intravaginal misoprostol established no correlation between the duration of abortion, the number of pregnancies, deliveries, age, hemoglobin levels, or platelet count. The induction-to-abortion interval was longer in hyperglycemic patients and in pregnant women of advanced gestational age [17].

The success rate within 48 hours was 96.9% (189 of 195 cases); 3.1% of the cases (6 of 195) were not successful. The success rates within the first 24 hours were 93.8% in the sublingual group, 90.8% in the combination group, and 83.1% in the vaginal group, which was not statistically significant. The success rates in the study by von Hertzen et al [11] were 85.9% in the vaginal group and 79.8% in the sublingual group, which did not vary significantly. Though the success rate in our study was higher, the study by von Hertzen et al [11] had been conducted on 600 patients. The 2004 study by Tang et al [8] showed that the success rate within 48 hours was 91% in the sublingual group and 95% in the vaginal group, which was not significantly different. However, the success rate within 24 hours in the vaginal group (85%) was significantly higher than the sublingual group (64%), with $p = 0.02$. This significant association was observed in the nulliparous group as well, with $p = 0.008$ [8].

A study by Bhattacharjee et al [18] did not report any significant difference among the sublingual and vaginal methods of termination of second trimester pregnancies between 13 weeks and 20 weeks. Nevertheless, in 2004, Hamoda et al [12] reported that the sublingual route of administration had a higher efficacy when compared to the vaginal route in the termination of mid-trimester pregnancies, but at the same time they reported more side effects.

Many researchers have shown misoprostol to be a safe and tolerable drug. Thus far, misoprostol has had no effects on the endocrine, biochemical, respiratory, immune, and/or cardiovascular systems. Gastrointestinal symptoms such as nausea and vomiting are self-limited, and they do not lead to serious side effects. The prevalence of fever was 60% in our study, and was observed in 30–35% of the cases in each group. In line with these findings, two studies also reported that in high fever ($\geq$ 40°C) developed in 32–57% of women receiving misoprostol [19,20]. Nevertheless, in our study, no significant difference was observed among the three groups.

Rupture of the uterus is rare during the first trimester of pregnancy [21] and one of its risk factors is the presence of a previous uterine scar [22]. Nonetheless, there were no cases of uterine rupture in our patients, even in those with a previous history of cesarean section. Dickinson [23] concluded that the administration of vaginal misoprostol in the second trimester for patients with a history of a prior cesarean section would not lead to an increase in side effects. There were, also, no cases of uterine rupture in this study either. Moreover, having a history of a cesarean section does not increase the duration of abortion [23]. The systematic review by Goyal [24] estimated the risk of a uterine rupture in misoprostol-induced abortions is 0.28% for women with a history of a prior cesarean section and 0.04% in women without a history of a previous cesarean delivery. This estimate is similar to the risk of a uterine rupture during a vaginal birth after a cesarean delivery [24].

In our study, the patients preferred using sublingual misoprostol. Many other studies have also supported this preference, in addition to reporting the patients' preference of oral over vaginal misoprostol [12,25]. This finding confirms the results of studies in which the patients preferred sublingual misoprostol over its vaginal counterpart [11,18].

According to our study, we concluded that the sublingual administration of misoprostol has a greater efficacy when compared to the vaginal and combination methods. In this method the duration of abortion is shorter, fewer misoprostol tablets are taken, and most importantly, it is preferred by the patients. Moreover, with this method, the success rate was higher and the clinical indications for surgical interventions were fewer. A further cohort study on the pharmacodynamics of misoprostol and a clinical trial are required to investigate the mechanisms and basis behind these phenomena. Therefore, we recommend the use of misoprostol (with an efficacy rate of 96%) as an alternative to surgical treatment for mid-trimester abortions, and suggest the sublingual route of administration over the vaginal or the combination route.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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