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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.