Efficacy of vaginal misoprostol and vaginal washing with 3% acetic acid for first trimester pregnancy termination: A randomized single blind clinical trial

Aida Najafian [1] Minoo Rajaei [1] Saghar Beheshti [1]

Deprtment of Obstetrics and Gynecology [1], Infertility and Reproductive Health Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

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Original Article

Abstract

Introduction: This study was conducted to evaluate the efficacy of 800μg vaginal misoprostol after wetting alkaline PH vagina with 3% acetic acid in comparison with 800μg vaginal misoprostol alone in the alkaline PH vagina in terminating first trimester pregnancies.

Methods: In this clinical trial, a total of 100 healthy women between 20 and 40 years old requesting legal termination of pregnancy before 12 weeks gestation (98 missed cases 50 in group A and 48 in group B and 2 fetus with great anomaly in group B) were randomly assigned to either of the treatment groups to receive 800μg vaginal misoprostol after wetting vagina with three pieces of cotton soaked in 3ml of 3% acetic acid or 800μg vaginal misoprostol alone for induction abortion. Pregnant women with active vaginal bleeding, rupture of membrane, coagulopathy, corticosteroid consumption, previous cesarean section and any contraindication of misoprostol using were excluded. Duration of extraction or expulsion of the pregnancy product, complications, and treatment failure were collected. Data was analyzed using SPSS 19 by descriptive statistics and statistical tests comprising independent t-test and chi-square.

Results: Totally 14 patients had complete abortion (7 subjects in each group) and 86 had incomplete abortion (43 patients in each group). The success rate was not significantly different between both groups. The overall median induction-abortion interval was 19±14 hour.

Conclusion: Vaginal misoprostol in alkaline PH vagina wetted with 3% acetic acid was not significantly more effective than vaginal misoprostol alone in alkaline PH vagina in first trimester pregnancies.

Correspondence:
Saghar Beheshti, MD.
Department of Obstetrics and Gynecology, Hormozgan University of Medical Sciences.
Bandar Abbas, Iran
Tel:+98 9123901740
Email:
saghar.beheshti@gmail.com

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Introduction:

Annually more than 46 millions pregnancies are terminated throughout the world (1). In some countries, abortion is allowed and known as a practical intervention (2). Surgical methods and non medical interventions have been applied for terminating pregnancy (3). Some of these techniques are less painful and safer than others (4).

In recent decades, some medical treatments have been developed for pregnancy termination.

Medical termination can be used early in pregnancy. Misoprostol is a synthetic analogue of prostaglandin E1 that inhibits progesterone synthesis and leads to myometrial contraction (1,5).

Evidence shows vaginal misoprostol is more effective than oral administration for terminating pregnancy. However, an important subject is that, misoprostol can't be completely dissolved in the vagina (6). Some investigators reported that absorption of vaginal misoprostol depends on the PH of the vagina (7,8). Also, some other studies demonstrated that vaginal misoprostol can be more effective if dissolved in an acidic medium (9). The aim of this study was to assess the efficacy of vaginal misoprostol in vagina wetted by 3% acetic acid compared with misoprostol alone, in terminating first trimester pregnancies.

Methods:

This prospective single blind randomized, controlled trial was conducted between 21 March 2011 and 20 March 2012 in Shariati Hospital of Hormozgan University of medical sciences.

100 healthy pregnant woman seeking termination of first trimester pregnancy were progressively enrolled in the study.

All subjects gave informed consent to participation in the study. The study was confirmed in ethic committee of Hormozgan University of medical Sciences.

After sonographic diagnosis of fetal structural abnormality or intra uterine fetal death and detection of chromosomal abnormality, all patient, who were counseled by the perinatologist, genetic counselor and who were allowed by law with a letter of satisfaction from court of justice to permit abortion of fetus with great structural or chromosomal anomalies were offered termination of pregnancy.

Study inclusion criteria were: otherwise healthy women aged between 20 and 40 years old; a singleton, dead or alive fetus before 12 week's gestation with a complex fetal anomaly and/or abnormal fetal karyotype; with no cervical dilatation and effacement; and hemoglobin $\geq$ 10mg/dlit and vaginal PH $\geq$ 6.

The exclusion criteria were a known scarred uterus from either a previous cesarean delivery or myomectomy whereby the endometrial cavity was entered; those with active bleeding, allergy to prostaglandins, in case of ruptured membranes, vaginitis, corticosteroid consumption, detectable dilatation or effacement (bishop score $>$ 3), known anemia (Hb $<$ 10 mg/dlit) and disease including asthma, cardiovascular disease or adrenal insufficiency, active liver disease, uncontrolled convulsion, and coagulopathy or consumption of anticoagulant drugs.

The women were randomly allocated to receive intravaginal 800μg misoprostol in alkaline-PH vagina alone in group A (control group) or after wetting alkaline-PH vagina (PH $\geq$ 6) with three pieces of cotton soaked in 3 ml of 3% acetic acid in group B (case group).

A few minutes after using cotton soaked in acetic acid and before using vaginal misoprostol, PH of vagina was rechecked by PH meter tape to be sure of changing vaginal PH to acidic PH (PH $<$ 6).

Misoprostol was placed in the posterior vaginal fornix by the researcher at 12 h intervals for a maximum of three doses in 48 h, and curettage was done if abortion did not occurred within a maximum period of 48 h.

Patients were divided into two groups using a randomly method so the first patient who attended to our hospital for induction abortion of first trimester pregnancy and had vaginal PH $\geq$ 6 (alkaline-PH) was A (control group) and second patient who attended and had inclusion criteria was B (case group) and this method continued alternately for the third patient (A) and forth patient (B) till the end of sampling.

The researcher was blinded to the wetting or not wetting vagina with 3% acetic acid while placing misoprostol in the posterior fornix of vagina, except for the patients who could not be blinded because of vaginal burning after using acetic acid and a doctor who wetted vagina with 3% acetic acid of case group and then rechecked vaginal PH, therefore was aware of the treatment allocation, and this doctor ultimately did not assess treatment outcome, which was evaluated by the researcher.

Patients who were willing to participate in the study were informed that they would follow a pharmacological procedure to terminate pregnancy .subjects were also informed about the benefits,

adverse effects and possible risks. They were told that in the case of failure to abort completely after maximum period of 48h, surgical method for abortion would be performed.

Before the start of therapy, vaginal PH was evaluated by PH meter tape and patients with vaginal PH<6 were excluded from study, and a blood sample was taken to determine hemoglobin, blood group and Rh factor.

Side effects of misoprostol such as nausea, vomiting, diarrhea, fever were recorded, during treatment. No analgesic or antiemetic was used. After abortion all patients received 20 IU of oxytocin in 1000 ml of physiological serum at an infusion rate of 125 ml/h.

We determined that the products of gestation (fetus and placenta) had been successfully removed by transvaginal ultrasound to establish that the abortion was complete. Any retained products of the placenta (not delivered spontaneously 1 h after delivery of fetus) were curetted clean with sharp uterine curette.

The main outcome measures were: induction–abortion interval (time from placement of the first dose of vaginal misoprostol until the time of expulsion of the fetus); number of successful abortions (defined as delivery within 48 h after 3 dose of vaginal misoprostol with 12 h interval), the total dose of misoprostol administered for each patient as microgram, the number of incomplete abortions, the number of side effects of misoprostol including nausea, vomiting and fever.

The base sample size calculation was captured from previous articles about promoting efficacy of vaginal misoprostol in induction abortion published in 2002 American college of obstetricians and gynecologists journal (Vol 99. no 6 June) or 2010 European society of contraception and reproductive health journal.

The SPSS statistical package was used for statistical analysis.

Quantitative data between two groups was compared by independent t-test and differences between qualitative data were determined by chi-square test. A $P<0.05$ was considered statistically significant.

Results:

One hundred women were enrolled for this study, 50 women in group A and 50 women in group B. All of the patients completed the study. The distribution of patient's age, gestational age was similar in both groups.

The characteristics of the abortion process and its relationship to misoprostol with or without wetting vagina with 3% acetic acid are shown in table 2, as shown abortion outcome among both groups was not significantly different.

The overall median (range) induction-abortion interval was 20 ± 13.3h in case group (group B) and 19.5 ± 14.1 in control group (group A). So the median induction-abortion interval revealed no significant difference between both group. The mean dose of misoprostol which was used among case subjects was $1640\pm738.4\mu$g and among control group was $1640\pm765.2\mu$g. This difference was not statistically significant ($P>0.05$).

Table 1. Patient's baseline charachteristics

		Mean	Standard	P-value
Age (years)	**Case**	28.66	7.5	>0.05
	Control	28.12	6.4	
Gestation (weeks)	**Case**	7.3	1.4	>0.05
	Control	7.2	1.4	

Table 2. Outcome of abortion among case and control groups

Abortion		Acid acetic washing		Total
		Yes	No	
Complete	Number	7	7	14
		50%	50%	100%
	P-value	>0.05		
Incomplete	Number	43	43	86
		50%	50%	100%
	P-value	>0.05		

Conclusion:

To the best of our knowledge, this is one the clinical trials evaluating the factor of vaginal PH in efficacy of vaginal misoprostol for induction-abortion. This randomized prospective controlled single-blind study showed that there were no significant differences for efficacy and complication between using vaginal misoprostol in alkaline PH vagina or in alkaline PH vagina which was wetted with 3% acetic acid before placing misoprostol in vagina.

Misoprostol has been widely used for induction of first trimester abortion, which is a potentially hazardous procedure. Recent studies focus mainly on the optimization of misoprostol efficacy by comparing various dosages, dosing intervals, rout of administration and media in which misoprostol dissolve better. The dosages of misoprostol used ranged from 100 to 800μg with the dosing intervals ranging from 3 to 12h. The efficacy of the misoprostol regime improved when a higher dose (400-800μg) was given (Nagaie et al., 2003). Thus the regime of 800 μg misoprostol was used in this study.

Successful termination was generally considered to be the expulsion of the fetus and placenta after 3 dose of misoprostol within 48 h. In our study the overall success rate was 100% with 20 h (5-35) median induction-abortion interval.

Misoprostol tablets are not prepared for vaginal use and local factors in vaginal Usage may play an important role in its efficacy. Since it is desirable to achieve a constant plasma profile, it is important to change the media of vaginal misoprostol to ensure more complete dissolving of the vaginal misoprostol tablets in order to achieve optimal efficacy.

Misoprostol tablets are known to liquefy better in acidic medium (Karim et al., 1989; American Hospital formulary service drug information, 1998).

The impact of moistening misoprostol tablets administered intravaginally has been assessed by several studies. It was found that moistened misoprostol tablets were more effective for medical termination of early pregnancy than dry tablets.

Others investigated whether misoprostol dissolved in acetic acid was more effective than misoprostol dissolved in water or saline solution. In a similar study the authors concluded that the use of acetic-acid to dissolve vaginal misoprostol had not improved the efficacy in achieving successful cervical dilatation for pre-abortion cervical priming. Vaginal PH affect the pharmacokinetics of vaginally administered misoprostol (Gunalp et al 2000).

In our present study we did not dissolved misoprostol tablets; instead we changed the PH of alkaline-PH vagina (PH$\geq$6) to acidic PH, and we didn't find any difference between effect of misoprostol tablets in acidic and alkaline-PH vagina.

It was observed in our study that the overall incidences of side effects were nausea 0%, vomiting 0%, diarrhea 0%, and fever 2%. Recent studies show the longer the dose interval, the less the side effects. (Carbonell et al., 2004) and (Wong et al., 2000).

The limitation of our study were small sample size and the different method of wetting alkaline-PH vagina with soaked pieces of cotton in 3ml of 3% acetic acid instead of dissolving misoprostol tablets in acidic solution before usage, like many other previous studies.

In conclusion, in this study, it was shown that, regardless of the method used, the regime of

vaginal misoprostol 800μg every 12h for a maximum of three doses in 48 h was not effective method for first trimester abortion, so shorter interval seems to be more effective. In addition, changing PH of alkaline vagina with 3% acetic acid to acidic PH was not effective in intravaginal misoprostol efficacy.

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مقایسه اثر میزوپروستول واژینال به تنهایی و میزوپروستول بعد از شستشوی واژن با اسید استیک ۳ درصد برای سقط‌های سه ماهه اول بارداری: یک مطالعه بالینی یک سو کور تصادفی

آیدا نجفیان [۱] مینو رجایی [۱] ساغر بهشتی [۱]

[۱] گروه زنان و زایمان، مرکز تحقیقات باروری و ناباروری، دانشگاه علوم پزشکی هرمزگان، بندرعباس، ایران.

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چکیده

مقدمه: *این مطالعه جهت ارزیابی تأثیر ۸۰۰ میکروگرم میزوپروستول واژینال بعد از اسیدی کردن واژن قلیایی در مقایسه با ۸۰۰ میکروگرم میزوپروستول واژینال در واژن قلیایی بدون اسیدی کردن واژن در ختم بارداری سه ماهه اول انجام شد.*

روش کار: *در این مطالعه کارآزمایی بالینی، ۱۰۰ زن باردار سالم ۲۰ تا ۴۰ ساله کاندید سقط قانونی سه ماهه اول قبل ۱۲ هفته بارداری (۹۸ مورد بارداری سقط فراموش شده {۵۰ مورد در گروه A و ۴۸ مورد در گروه B} و ۲ مورد جنین مبتلا به ناهنجاری مادرزادی {در گروه B}) به طور تصادفی در دو گروه درمان (مورد) که ۸۰۰ میکروگرم میزوپروستول واژینال بعد از مرطوب کردن واژن با سه تکه پنبه خیس خورده در ۳سی سی اسید استیک ۳ درصد دریافت نمودند یا گروه شاهد که فقط ۸۰۰ میکروگرم میزوپروستول واژینال به تنهایی جهت القاء سقط دریافت نمودند، قرار گرفتند. بارداراني که خونریزی فعال واژینال، پارگی کیسه آب، اختلال انعقادی، مصرف کورتن، سزارین قبلی و یا هر کنتراندیکاسیون مصرف میزوپروستول داشتند، از مطالعه حذف شدند. مدت زمان خروج محصولات بارداری، عوارض و شکست درمان جمع‌آوری شد. داده‌ها توسط نرم‌افزار SPSS 19 و با شاخص های آماری توصیفی و همچنین تست‌های آماری کای دو و آزمون T مستقل مورد تجزیه و تحلیل قرار گرفت.*

نتایج: *کلاً ۱۴ بیمار سقط کامل داشتند (۷مورد در هر گروه) و ۸۶ مورد سقط ناکامل داشتند (۴۳ بیمار در هر گروه) میزان موفقیت بین دو گروه تفاوت چندانی نداشت. مدت زمان متوسط سقط ۱۴±۱۹ ساعت بود.*

نتیجه‌گیری: *میزوپروستول واژینال در واژن با PH قلیایی که با اسید استیک ۳ درصد مرطوب شده بود، چندان مؤثرتر از میزوپروستول به تنهایی در واژن با PH قلیایی در سقط سه ماهه اول نبود.*

کلیدواژه‌ها: *سه ماهه اول بارداری، میزوپروستول، اسید استیک*

نویسنده مسئول:
دکتر ساغر بهشتی
گروه زنان و زایمان دانشگاه علوم پزشکی هرمزگان
بندرعباس – ایران
تلفن: ۹۱۲۳۹۰۱۷۴۰ ۹۸+
پست الکترونیکی:
saghar.beheshti@gmail.com

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