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Low Dose Vaginal Misoprostol Versus Prostaglandin E2 Suppository for Early Uterine Evacuation: A Randomized Clinical Trial

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Abstract: Misoprostol is a cheap product of prostaglandin E1 which has gained interest in pregnancy termination. The aim of this study was to compare the effect of vaginal misoprostol and prostaglandin E2 suppository in pregnancy termination before 20 weeks of gestational age. In this clinical trial, 111 participants under 20 weeks of gestational age who needed pregnancy termination were enrolled. They were divided into two groups misoprostol and prostaglandine E2 treatment. Fifty four people received vaginal misoprostol as 25 μg per 4 h up to 3 days and 57 participants received prostaglandine E2 vaginal suppositories. Data were analyzed using SPSS software. Mean age of participants was 27.5 years and its standard deviation was 6.1 years. Mean gestational age was 13.1 weeks based on sonographic measurement and it was 14.5 weeks by LMP estimation. Mean induction to evacuation time was 3.1 days and in misoprostol group was 2.4±0.88 days. Half of the patients in control group and 70% of them in misoprostol group succeeded pregnancy termination in 48 h. Vaginal misoprostol compared to prostaglandine E2 vaginal suppository has higher efficacy in shorter time.

Key words: Misoprostol, prostaglandine E2, pregnancy termination, uteral evacuation

INTRODUCTION

Induced abortion is considered as a necessity in obstetrics and gynecology and developing more suitable methods to induce earlier termination of pregnancy has always been a challenge to researchers in this field. It has been reported that risk of legal abortion increases exponentially with gestational age and that, although, death from legal abortion is very rare, 87% of the deaths that are occur could be prevented if women terminating their pregnancies after 8 weeks of gestation had been able to access abortion services during the first 8 weeks of pregnancy instead (Bartlett *et al*., 2004).

Due to their inherent properties prostaglandins have always been thought of possible indication in induces abortion. Prostaglandins are synthesized from Arachidonic Acid (AA) first by cyclooxygenase (Cox) -1 or -2, which convert AA into PGH2. This precursor PG is further processed by isoform-specific cytosolic or microsomal prostaglandin synthases (c/mPGES) to become PGE2 or one of several other effector prostaglandins. They are mediators and have a variety of strong physiological effects, such as regulating the contraction and relaxation of smooth muscle tissue. An increasing proportion of early abortions are induced with the medications mifepristone and misoprostol rather than surgery. Risk of abortion increases with gestational age and varies with type of procedure (Bartlett *et al*., 2004).

The need for pregnancy termination in first or second trimester is a common referral reason while using oxytocin and prostaglandin E2 have not proven to be quick enough and completely satisfactory. This may lead to desperation of patients and higher economic burden on them. Some reference books in obstetrics have recommended to use misoprostol as an alternative to surgical procedures. Although, this may need complementary evacuation or curettage but the low complication rate with misoprostol makes it a preferable method (Brando *et al*., 2002; Graziosi *et al*., 2004, 2005). There are some reviews about efficacy of misoprostol in second and third trimesters. One review article on 16 papers has concluded about the insufficiency of information regarding induction of labor

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using misoprostol. A very recent review included 38 randomized controlled studies showing that vaginal misoprostol was as effective as other agents in inducing labor and achieving vaginal birth within 24 h, with a reduction in the occurrence of maternal side effects (Dodd and Crowther, 2010). Regarding the safety of the misoprostol after caesarean section it has been suggested to be safe among those with one previous section however, evidence is limited in this regard (Berghella *et al*., 2009). Misoprostol versus prostaglandine E2 has been the focus of research but very little is known about the compared efficacy of misoprostol under 20 weeks of gestational age especially at lower doses. The aim of this study was to compare the efficacy of low dose vaginal misoprostol and prostaglandin E2 suppository in pregnancy termination before 20 weeks of gestational age.

MATERIALS AND METHODS

In this randomized clinical trial study a total of 111 pregnant women under 20 weeks of gestational age who needed pregnancy termination were enrolled. The patients were those referred to Alzahra University Hospital in 2008.

The participants were randomly assigned to receive either vaginal misoprostol tablets or prostaglandine E2. So, 54 women received 25 μg vaginal tablet quarters for every 4 h up to maximum 3 days. The tablets were applied by physician in posterior fornix of cervix. The control groups were 57 eligible women who received dynoproston suppositories every 4 h. In both groups either couretage or syntocinone were used to terminate the pregnancy.

The inclusion criteria were as: gestation under 20 weeks, fetal death diagnosed by sonography or other induced aborthion indications and informed consent of participation. The exclusion criteria were as: severe vaginal bleeding, contraindications in using study drugs and ectopic pregnancy.

Statistical analysis: Data were analyzed using STATA statistical software package. Stata Statistical Software: Release 8. College Station, TX: StataCorp LP). The main outcome of interest was the time to termination and the main statistical method applied was survival analysis. Weibul and Cox parametric regression models were used to estimate survival and hazard ratios. Weibul method was used to compare the efficacy of drugs. Log-log graphical evaluation was used for model evaluation. Statistical significance was set at 0.05 point for an equivalence hypothesis testing. Study was approved by committee of ethics in Tabriz University of Medical Sciences.

Age of the participants ranged from 17 to 42 years with a mean of 27.5±6.1 (±SD) years. Mean gestational age was 13.1 days. Mean gravity and mean pariety were 2.1 and 0.8, respectively. The 23.2% of participants had at least one abortion in their history. Twenty three percent had at least one previous live child birth.

RESULTS

Study participants had spotting or vaginal bleeding in 22.3 and 57% of them were symptom free. The reason for termination of pregnancy was fetal anomaly in 17%, fetal death or missed abortion in 17%, preterm rupture of membranes in 12.5% and other causes as remander.

Mean time to Termination of Gestation (TTG) was 3.1±2 days in group receiving prostagandine E2 and 2.4±0.88 days in misoprostol group (Fig. 1a, b).

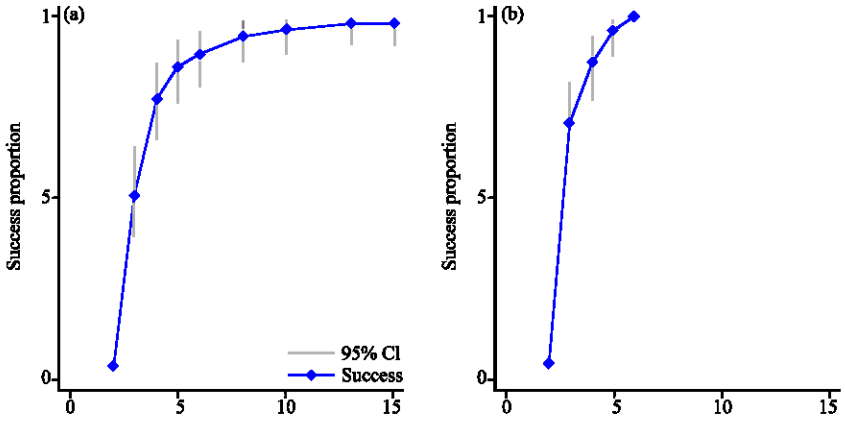

Fig. 1: Survival graphs for successful early pregnancy termination compared between (a) misoprostol and (b) prostaglandine E2

Table 1: Estimated success probability at daily intervals after receiving each of the treatment modalities

Time interval (days)		No. beginning	Expulsion	Missed	Cumulative expulsion probability	95% confidence interval	
Prostaglandin E2 group							
1	2	57	2	0	0.0351	0.0089	0.1331
2	3	55	27	0	0.5088	0.3875	0.6433
3	4	28	15	0	0.7719	0.6570	0.8702
4	5	13	5	0	0.8596	0.7572	0.9344
5	6	8	2	0	0.8947	0.7998	0.9572
7	8	6	3	0	0.9474	0.8681	0.9862
9	10	3	1	0	0.9649	0.8926	0.9935
12	13	2	1	0	0.9825	0.9180	0.9986
14	15	1	0	1	0.9825	0.9180	0.9986
Misoprostol group							
1	2	54	2	0	0.0370	0.0094	0.1401
2	3	52	36	0	0.7037	0.5800	0.8183
3	4	16	9	0	0.8704	0.7670	0.9430
4	5	7	5	0	0.9630	0.8871	0.9931
5	6	2	2	0	1.0000	0.0000	0.0000

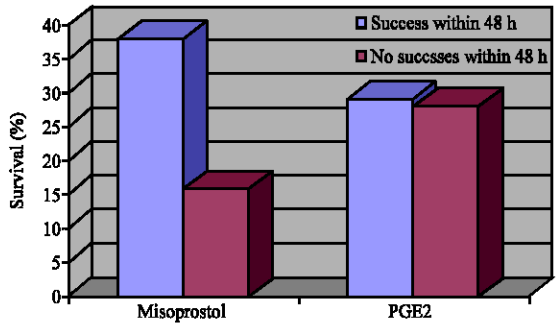

Fig. 2: Compared efficacy of misoprostol and PgE2 48 h after treatment

The means were not different statistically using independent t-test. Mean TTG without considering the study group was 2.8 days. Minimum TTG was 1 day and maximum TTG 12 days but in majority of cases the gestation was terminated in 2 days. Half of the patients receiving PgE2 terminated gestation compared to 70% in misoprostol group. The relative risk of termination for misoprostol compared to PgE2 was 1.6 (Fig. 2).

Table 1 shows that although, cumulative expulsion probability is similar for the 1st day after receiving treatment in both groups but during 2-3 day period this probability increases 20% more for mispoprostol group.

Based on results from weibul regression, misoprostol terminates the pregnancy earlier than PgE2 with a Hazard ratio equal to 2.1 (95% CI: 1.4-3.1). Without considering the effect of treatment type, gestational age was the main predictor of time to termination of pregnancy ($p<0.01$).

One-third of participants receiving misoprostol had spontaneous pregnancy termination compared to five% in PgE2 group. The relative risk for spontaneous pregnancy termination was 2.1 for Misoprostol versus PgE2.

DISCUSSION

This study uses vaginal misoprostol. Although, the efficacy is shown to be similar to sublingual misoprostol but the side effect profile puts a question mark on its routine usage in maternal care (Souza *et al*., 2008).

The main side effects of misoprostol are reported to be tachi-systol and hyperstimulation. Previous studies discuss higher incidence of specific side effects along with higher efficacy for misoprostole (Crane *et al*., 2006; Frohn *et al*., 2002; Jain and Mishell, 1994; Makhlouf *et al*., 2003). Uteral rupture has also been reported (Willmott *et al*., 2008). This seems to be one of the first reported cases of uteral rupture after induction with misoprostol in early pregnancy. Other cases are reported to happen at term pregnancy or have risk factors of rupture of uterus. No specific complication was observed using misoprostol in this study. However, a larger study with 720 second trimester abortions in women with previous cesarean section has also showed that complication rate is not different for women with a history of cesarean section compared to those without it. This rate can be even smaller when used in low doses and early through the pregnancy (Dickinson, 2005). In present study, even no non serious complication of the misoprostol was observed which can be due to the very low dose of drug used which was quite different from the previous studies.

Misoprostol was shown to be capable of terminating the pregnancy in shorter period of time. Long hospital stays may impose a psychological pressure on the patient affecting her health status. Economical factors must also be taken into account. Mean termination time in our study was 2.4 days compared to findings of Jansen *et al*. (2008) to be 18 h. They used a primary 200 μg mifipriston followed by 200 μg vaginal misoprostol given at 3 h intervals (Jansen *et al*., 2008). Median termination time at

second and third trimesters of pregnancy was 13 h in another study and 88% of the pregnancies were terminated in first 24 h (De Heus *et al*., 2004). Shorter time span in this study can be either due to higher dose or termination time at third trimester. Another study on misoprostol conducted in 13-30 weeks of gestational age showed a mean 12.7 h of effect time (Langer *et al*., 2004).

In a review article drug induced abortion mean termination time was stated to vary from 13.8 to 45 days (Tang and Ho, 2002).

Oral versus vaginal misoprostol is compared in a study on 214 pregnant women showing the oral form to be more efficate, quicker and cosstbenefit (Hassan, 2005).

Consistent with present findings another study comparing misoprostol and prostaglandin E2 has found quicker effect for misoprostol (Sifakis *et al*., 2007). Crane *et al*. (2006) have also consistent findings with others have observed quicker efficacy for misoprostol but they also found that misoprostol didn't decrease the rate of cesarean section and it causes tachsystols and hyperstimulation (Crane *et al*., 2006). Nanda *et al*. (2007) in their study comparing vaginal misoprostol and prostaglandin E2 found that 80% of misoprostol receivers compared to 62% in prostaglandin group terminated pregnancy in 24 h (Nanda *et al*., 2007).

The findings of the present study is found to be in line with previous research in quicker efficacy of misoprostol than prostaglandins, even though our study used a very low dose of misoprostol which may explain longer mean termination time. Regarding the acceptability of using misoprostol, studies have shown that people prefer it to procedural termination of pregnancy and accept the possible complications even knowing about higher efficacy of procedural methods (Graziosi *et al*., 2005, 2006).

CONCLUSION

Using misoprostol even in very low doses is as efficient and more quicker than prostaglandin E2.

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