A COMPARISON OF TWO PROTOCOLS OF INTRAVAGINAL MISOPROSTOL FOR SECOND TRIMESTRER MEDICAL TERMINATION OF PREGNANCY

Shahida Akhtar, Yasmin Fatima

Abstract

Objective: To compare the efficacy and side effect profiles of two different dosage protocols of intra-vaginal misoprostol.
Study Design: Randomized control trial.
Place and Duration of Study: Department of Gynaecology and Obstetrics, Combined Military Hospital, Rawalpindi, from May 2006 to December 2006.
Material and Methods: A total of 128 womens, aged 18-40 years, planned for 2nd trimester pregnancy termination, were randomly assigned to two groups of 64 each. Group – I women received vaginal misoprostol 400ug three hourly for a maximum of 8 doses in 24 hours. Women in group-II received vaginal misoprostol 400ug six hourly for a maximum of four doses in 24 hours. If abortion did not occur in 24 hours, the same regimens were repeated. Without succesful abortion in 48 hours, misoprostol administration was abandoned in favour of surgical induction.
Results: The median induction to abortion interval in group – I (14.4 hours) was shorter than in group – II (18.2) ($p< 0.001$). The frequency of fever was more common in group – I ($p = 0.01$). The pregnancy related symptoms decreased in both groups after misoprostol and decrease in breast tenderness was most marked two to three hours after administration. Misoprostol induced fever was seen at least five hours after administration in up to 37.5% women, this peak being slightly higher and occurring earlier in group – I than in group – II. Lower abdominal pain peaked after three to four hours in group – I and after five to six hours in group – II, with no significant difference in pain intensity or analgesic requirements. Other common side effect were diarrhea followed by nausea and vomiting in both the groups.
Conclusion: Protocol of 400ug misoprostol administered 6 hourly / 24 hours is more effective in reducing induction – abortion interval and inducing successful abortion within 48 hours without any major increase in side effects.

Keywords : Drug trail, Second trimester medical abortion, Misoprostol.

Article

INTRODUCTION

Termination of pregnancy has been practiced worldwide. Overall termination rates are similar in developing and developed world but illegal terminations are concentrated in developing countries. Common indications for termination of pregnancy include substantial risk of a child being born with serious congenital anomalies, intrauterine fetal demise and presence of medical disorders that pose a threat to the health or life of a mother1.

In Pakistan termination has been allowed legally for certain maternal and fetal indications, Annual abortion rate in Pakistan is 29 per 1000 women. An estimated 890,000 illegal terminations are performed anually.

Correspondence: Major Yasmin Fatima, Graded Gynaecologist, CMH DI Khan
Received: 7 Dec 2009; **Accepted:** 12 Aug 2010

Second trimester of pregnancy ranges between 13-26 weeks. Second trimester pregnancy termination is associated with three to five times higher maternal mortality and morbidity risks than termination during first trimester2. Both medical and surgical methods are used for termination of

pregnancy. Surgical termination carries its own risks to maternal life with advancing gestational age. It bears risks of pelvic infections, cevical injury, intrauterine adhessions, excessive bleeding and risks associated with anaesthesia. Incomplete evacuation occurs in 2-3 % of curettage procedures3. Medical termination has been largely accepted as an effective and safe management and also offers economic benfits from reduction in number of operations. Various preparations have been largely used with different results4. Medical termination of second trimester pregnancy is routinely performed by administration of vaginal prostaglandins or their analogues5, and has largely replaced less effective and more invasive surgical methods of abortion induction e.g. with cervical foley's catheter, F2 alpha administration via foley's catheter followed by oxytocin infusion and / or amniotomy. Misoprostol, a synthetic analogue of prostaglandin E1 is also the preferred single method for pregnancy termination in primigravida with Bishop Score < 4, who earlier required cervial pre treatment with prostin E2 pessaries before surgical induction of labour. It is also cost effective in our setup, being easily available and being thermostable, can be stored at room temperature. The aim of our study was to compare the efficacy and side effects of 400ug misoprostol administration intravaginally every three hours as compared to longer dosage interval of 6 hours to determine which regimen has fewer side effects and is effective in inducing complete abortion in 24-48 hours.

PATIENTS AND METHODS

These randamoized controlled trials (RCT's) were carried out at department of Gynaecology and Obstetrics,Combined Military Hospital (CMH) Rawalpindi from May 2006 to December 2006.

One hundered and twenty eight (n=128) healthy women with medical indications for termination of second trimester pregnancy between 14 – 24 weeks e.g. anencephaly, missed abortion, congenital anomalies chromosomal abnormalities, severe PET, severe oligohydramnios, immune / non-immune fetal hydrops, hydrocephaly, PPROM3 were recruited to the trial and randomly assigned into two groups. Women on regular prescription drugs e.g. those with cardiac disease, chronic essential hypertension or bleeding disorders, multiple pregnancy, previous two caesarean sections and nursing mother were exculded from the study.

Informed written consent for legal termination of pregnanacy was obtained from all the couples and pelvic USG examination was performed to confirm gestation and to exclude multiple pregnancies. The group assignments were put into sealed envelops, and opened in gynae OPD and then women were admitted to hospital. The two groups were comparable with respect to maternal age, parity indication for pregnancy termination, gestational age and maternal height and weight. Women allocated to group–I were given misoporstol 400ug (1 tab of cytotec, Searle) in posterior vaginal fornix every three h, upto a maximum of eight doses over 24 hours. Women in group – II were given same drug dose intra-vaginally at intervals of six hours, up to maximum of four doses. Data on main outcome measures of the trial was collected to measure the duration of induction–abortion interval in both regimens, and efficacy to achieve complete abortion in 24-48 hours after initial administration of misoprostol.

Inj campax and tab paracetamol 500 mg for pain relief and fever were given. Post abortion, fetus and placenta were examined for completeness. Surgical evacuation for incomplete abortion was done under general anaesthesia. Amount of blood loss was assessed clinically by the attending physician. If a women in either group failed to abort 24 hours after misoprostol administration, a second course of misoprostol with same protocol was given. If successful abortion did not occur after 48 hours either regimen was abandoned or patient re-assessed for alternative management, according to the physician discretion.The standard deviation with average induction-interval time was 16.2 h.

The induction – abortion interval was defined as the interval between the time of administration of first dose of misoprostol till explusion of fetus and placenta. Complete abortion was defined as the expulsion of both without operative interventoin.

Student t test and Chi square were applied as tests of significance for quantitative and qualitative data, respectively.

RESULTS

A total of 128 women in this trial were randomly divided into two groups of 64 women each. In group – I, 20 women (40%) and 17 in group – II (34%) were primi gravida with no statistically significant

difference.
Regarding efficacy of the abortion process in comparison of the two protocols; 48 women (75%) in group – I aborted within 24 hours compared to 39 women (60.9%) in group – II (Table-1).

Table-1 Efficacy of medical abortion in the two protocols misoprostol adminsitration

	Group-1 (n=64)	Group- II n=64)	p-value
Induction– abortion interval	14.4h	18.0 h	< 0.01
Complete aborition (24 h)	48 (75%)	39 (68.9%)	< 0.05
Complete abortion (48h)	12(18.3%)	19 (30.3%)	< 0.02
Incomplete aborotion	4 (6.2%)	6(9.3%)	< 0.05

Within 48 hours after second course of misoprostol administration by the same protocols, the overall successful complete abortion rate in group – II was statistically higher than in group – I There were 4 (6.2%) and 6 women (9.3%) in group – I and II respectively, who did not abort completely within 48 h and needed surgical evacuation of RPOC's. The median induction – abortion interval was significantly shorter in group – I (14.4 hours) than in group –II (18 hours) Regarding analgesia requirements, 38 and 34 women in group I and II respectively, received inj campax; the difference was not statistically significant and second dose was not required in any pateint. The frequency of side effects with misoprostol in both groups (Table-2).

Table-2: Incidence of side effects in the two protocols of misoprostol administration.

Side Effects	Group-1 (n=64)	Group-II (n=64	p-value
Nausea	5 (7.8%)	7 (10.9 %)	0.001
Vomiting	4 (6.2%)	4 (4.6%)	0.00
Diarrhea	6(9.3%)	4(4.6%)	<0.005
Headche	1 (1.5%)	1 (1.5%)	0.01
Rash	2 (3.1%)	1(1.5)	>0.05
Fever (>38° C)	24(37.5%)	8(12.2%)	>0.005
Brest tenderness	1(1.4%)	2 (2.7%)	0.00
Genital infection	0	0	-
Abdmominal cramping and pain lower abdomen	64(100%)	62 (94%)	>.001.

Baseline (on admission) pregnancy related signs and symptoms were reported by 60% women and were markedly reduced within two to three hours of misoprostol administration, except for nausea and vomiting, reported by 9.3% and 6.2% of women from both groups collectively. The incidence of diarrhea occurred on average two hours after misoprostol administration in 7.8% of all women. The percentage of women with rash was very low (2.3%) in both groups at all times. The incidence of lower abdominal pain and cramping related to the abortion process peaked earlier and was more sustained and regualr in group – I . The most common treatment given for side effects was pain relief medication mainly within three to four hours after misoprostol administration.

DISCUSSION

Medical termination in the second trimester is the best method of choice to accomplish the pregnancy termination. Misoprostol is a known safe and efficious agent for pregnancy termination, produces the least number of complications, the least amount of stress for patient and is most effective6. In this study, we compared the efficacy and side effect profiles of intra-vaginal misoprostol 400 ug administered in two different protocols regarding dosage intervals. The complete abortion rate with 400 ug misoprostol 6 hourly in second trimester was 89%7. In our study we found that the use of Misoprostol by this route is a safe and effective method of termination of pregnancy. The basic method using Misoprostol vaginally is inexpensive and was effective in 52% of the women carrying out uterine evacuation within first 24 hours since the start of induction as compared to 86% in the group 2. It is to mentioned here that other prostaglandin preparations like PGE2 pessaries, vaginal inserts and intra-cervical gels are other comparable methods for inductions of labour in these situations but relatively costly and or not freely available . Since cost is major concern in developing countries, therefore finding an intermediate method that is more effective than the conservative method of oxytocin infusion and at the same time is less expensive than the latest and fancy PGE2 preparations was of utmost importance.

A study by Javed and Maryam showed that sublingual misoprostol (Group 1) is as effective as

vaginal misoprostol (Group 2) but with more nausea and vomiting. Sucessful termintion was achieved in 96% patients in in group 1 and 94 % in group 2 but with lesser side effects, so it was shown that vaginal route is better option for pregnancy termination, as seen in our study with compareable results7.

Results of our study showed significant difference between the two dosage protocols. The protocol of vaginal misoprostol 400 ug every six hours was more effective than three hours interval protocol. The abortion success rate within 24 hours was higher in the group with misoprostol administration at six hours interval, though the complete abortion rate in 48 h was not much different in two groups, so it was calculated that in 400 ug 6 hourly the overall induction to abortion time is not much significant than in 400 ug 3 hourly protocol, but same results can be achieved in low dosage misoprostol protocol which is well tolerated with few systemic drug related side effects which are self limiting and not dose related.. The total dosage of misoprostol required in Group–I and II were 3200 ug and 1600 ug respectively8.

The frequency of gastrointestinal side effects in our study were low and not directly related to total dose of misoprostol used in either group. Our results show that pregnancy related symptoms decrease soon after misoprostol administration, even before the abortion process has started, with exception of nausea and vomiting, which are also misoprostol related side effects9,10. While gastrointestinal side effects were mild after vaginal administration, occurrence of fever was noticeable in group – I with decreased frequency in group – II. Other studies show about 40% incidence of fever11,12. Similar findings 37.5% and 12.5% in groups – I and II respectively and reported in our study. Differing frequency of occurrence may be due to difference of dose frequency (three hours vs. six hours) of misoprostol administration13,14.

CONSLUSION

This study shows that, the protocol of 400 ug misoprostol administration at six hours intervals over 24 hours is a safe and effective regimen for second trimester abortion induction. Dosage of misoprostol intravaginally upto 1600 ug over 24 hours is well tolerated with few systemic drug related side effects which are self limiting and not dose related. Thus, Misoprostol is an effective and safe drug, so it should be used with confidence for termination of pregnancy.

Reference

1.Ashok PW, Penny GC, Flett GMM. An effective regimen for early medical abortion: a report of 2000 consecutive case. Hum Reprod 1998; 13:2962-65.

2.EI-Refaey H, Templetoin A. Induction of abortion in the second trimester by a combination of misoprostol and mifepristone; a randomized comparison between two misoprostol regimens. Hum Repord 1995; 10:475-78.

3.Gupta A. Early non-surgical abortion-give women the choice. Hum Repord 1998; 13:2379-81.

4.Sedgh G, Hanshaw S, Singh S, Ahman E, Shah IH.Induced abortion: estimated rates and trends worldwide. Lancet 2007;370(9595):1295-7.

5.Sathar ZA, Susheela S, Fikree FF. Estimating the incidence of abortion in Pakistan. Studies in family planning,2007;38:11-12.

6.Jain JK, Mishell DR Jr. A comparison of inta-vaginal misoprostol with prostaglandin E2 for termination of second - trimester pregnancy N Engl J Med 1994; 175:173 – 77.

7.Javed L, Malik M, Jamal N, Umar A. Mid trimester termination of pregnancy-comparison of sublingual with vaginal misoprostol. Biomedica 2004;20(1):735-7.

8.Islam A, Abbasi AN, Sarwar I. Use of foley,s atheter and prostaglandin F-2 alpha in second trimester termination of pregnancy .J Ayub Med Coll Abotabad 2006; 18(3): 35-9.

9.Tang OS, Gao PP, Cheng. A randomized double blind placebo controlled study to assess the effect of oral contraceptive pillls on the outcome of medical abortion with mifpristone and misoprostol. Hum Repord 1999; 14:722-25.

10.Hussain N, Soomro S, Umam. Medical management of fetal demise using Misoprostol. JCPSP 2002;12:735-7.

11.Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficiency and patient satisfaction in medical or surgical treatment of miscarrage. Fertile Steril

2006;86(2):367-72.
12.WHO – UMC (WHO collaboratting centre for international drug monitoring). Available from http://www.who-umc.org, search on adverse reaction to misoprostol, performed in May 2004.
13.Naz S, Sultana N. Role of misoprostol for the therapeutic termination of pregnancy from 10-28 weeks of gestation.J Pak Med Assoc 2007;57(3);129-32.
14.Tang OS, HO PC. The Pharmacokinetics and different regimens of misoprostol in early first triemester medical abortion. Contraception 2006;7491):26-30.