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

**Azra Batool, *Shazia Shakeel, Nilofer Mustafa**

Military Hospital Rawalpindi, *Combined Military Hospital Gilgit

## ABSTRACT

***Objective:*** To compare the efficacy and side effect profiles of two different dosage protocols of intra-vaginal misoprostol.

***Study Design:*** Randomized control trial.

***Setting:*** Department of Gynaecology and Obstetrics, Combined Military Hospital, Lahore.

***Duration of Study:*** From March 2004 to May 2005.

***Material and Methods:*** Total of 128 women, aged 19 – 39 years, planned for 2nd trimester pregnancy termination, was randomly assigned to two groups of 64 women each. Group – I women received vaginal misoprostol 200µg four hourly for a maximum of 6 doses in 24 h. Women in group – II received vaginal misoprostol 200µg six hourly for a maximum of four doses in 24 hours. If abortion did not occur in 24 h, the same regimens were repeated. Without successful 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 h was significantly shorter than in group – II (18 h) ($p < 0.01$). The incidence 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 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 effects were diarrhea followed by nausea and vomiting in both the groups.

***Conclusion:*** Protocol of 200µg misoprostol administered four 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:** Second trimester medical abortion, side effects, misoprostol, efficacy

## INTRODUCTION

Medical termination of second trimester pregnancy is routinely performed by administration of vaginal prostaglandins or their analogues [1], and has largely replaced less effective and more invasive surgical methods of abortion induction e.g. with cervical foley catheter, F2∞ administration via foley catheter followed by oxytocin infusion and / or amniotomy. Misoprostol, a synthetic analogue of prostaglandin E1 is also the

**Correspondence**: Brig Azra Batool, Advisor in Gynaecology, Military Hospital, Rawalpindi.

preferred single method for pregnancy termination in primigravida with Bishop Score ≤ 4, who earlier required cervical pre treatment with prostin E2 pessaries before surgical induction of labour [2]. It is also cost effective in our setup being, easily available and being thermostable, it can be stored at room temperature. The aim of our randomized trail was to compare the efficacy and side effects of 200µg misoprostol administration intravaginally every four hours as compared to longer dosage interval of 6 hours to determine which regimen may be followed which should have fewer side effects and still be effective in inducing complete abortion in 24 – 48 h.

## PATIENTS AND METHODS

Generally 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, PPROM [3] 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 mothers were excluded from the study [4].

Informed written consent for legal termination of pregnancy was obtained from all the couples and pelvic USG examination was performed to confirm gestation and exclude multiple pregnancies. The group assignments were put into sealed envelops, and opened in gynae OPD and then women were admitted to hospital [5].

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 misoprostol 200µg (1 tab of cytotec, Searle) in posterior vaginal fornix every four h, upto a maximum of six 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 were collected on signs and symptoms including blood pressure, pulse, and temperature; recorded before treatment over 24 hours and after misoprostol administration. Side effects were recorded hourly for 12 hours, then three hourly for further 12 hours.

Main outcome measures of the trial were to measure length of induction – abortion interval in both regimens, and efficacy to achieve complete abortion in 24 – 48 hours after initial administration of misoprostol. Side effects were classified as pregnancy related symptoms (nausea, vomiting, breast tenderness, fatigue, dizziness, headaches), drug related side effects (diarrhea, fever, rash, blood pressure changes) and side effects related to the abortion process itself (lower abdominal pain, amount of bleeding p/v). Aim was to detect a difference of at least 10% between regimens. Percentages of women with each side effect were calculated and Chi square test was applied to explore differences in side effects between the two groups. 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 woman 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 physician discretion.

The induction – abortion interval was defined as the interval between the time of administration of first dose of misoprostol till

expulsion of fetus and placenta. Complete abortion was defined as the expulsion of both without operative intervention. The primary outcome indicator was abortion rate within 24 hours.

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, 22 women (34.3%) and 17 in group – II (26.5%) 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 (60.9%) in group – II. The difference was not statistically significant (Chi square test). Within 48 hours after second course of misoprostol administration by the same protocols, the overall successful complete abortion rate in group – I was statistically higher than in group – II ($P < 0.02$). There were four and six women (7.8%) in group – I and II respectively, who did not abort completely within 48 h and needed surgical evacuation of RPOC's.

There were two and ten women in group – I and II each, who required additional intervention (9.3%) for achieving abortion. The median induction – abortion interval was significantly shorter in group – I (14.4 h) than in group – II (18 h) ($P < 0.01$). 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 patient. The estimated blood loss during abortion was comparable in both groups (table-1).

The incidence of side effects with misoprostol in both groups (table-2). The incidence of fever was statistically higher ($P=0.003$) in group – I. the fever resolved within 24 h after the last dose of misoprostol and did not result in an increased use of antibiotics.

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. Both groups had no differences with regard to blood pressure changes after misoprostol compared to admission levels. The incidence of lower abdominal pain and cramping related to the abortion process peaked earlier and was more sustained and regular in group – I but parity was significantly associated with a decrease in frequency and perhaps perception of lower abdominal pain at all recording points. The most common treatment given for side effects was pain relief medication mainly within three to four hours after misoprostol administration.

## DISCUSSION

In this study, we compared the efficacy and side effect profiles of intra-vaginal misoprostol 200 µg administered in two different protocols regarding dosage intervals. There is no doubt that misoprostol is a safe, effective, inexpensive drug for induction of medical abortion in both first and second trimesters. The complete abortion rate is > 95% [1,3] and according to another report 24 hours abortion rate with 200 µg misoprostol 12 hourly in second trimester was 89% [4].

Our study shows comparable results for both protocols regarding overall 24 hours and 48 hours abortion rates. However, in direct comparison between these two protocols, our results showed that protocol of vaginal

misoprostol 200 µg every four hours was more effective than six hours interval protocol; not only was the overall induction – abortion interval shortened in group – I but also the abortion success rate within 48 hours was higher in the group with misoprostol administration at four hours intervals. The median dosages of misoprostol required in group – I and II were 1200 µg and 800 µg respectively [5]. The incidence of gastrointestinal side effects in our study was 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 effects [6]. While gastrointestinal side effects were mild after vaginal administration, occurrence of fever was noticeable in group – I, with decreased frequency in group – II ($P < 0.003$). Other studies show about 50% incidence of fever [7]. Similar findings 37.5% and 12.5% in groups – I and II respectively are reported in our study. Differing frequency of occurrence may be due to difference of dose frequency (four hours vs. six hours) of misoprostol administration.

In both groups, an increase in systolic blood pressure more than 10 mmHg and diastolic more than five mmHg occurred in less than 1/5th of women and a similar decrease occurred in about 1/4th of women about two to three hours after misoprostol administration; as prostaglandin has both vasodilator and vasoconstrictor actions [8]. The pain and cervical dilatation during abortion process may have contributed to the rise and fall in blood pressure respectively. In previous studies, no significant changes in blood pressure and pulse rate have been noted due to direct drug effect of misoprostol [9] and none were recorded in our study also.

## CONCLUSION

This study shows that the protocol of 200 µg misoprostol administration at four hours intervals over 24 hours is a safe and effective regimen for second trimester abortion induction. Dosage of misoprostol intra-vaginally upto 1600 µg over 48 hours is well tolerated with few systemic drug related side effects which are self limiting and not dose related.

**Table-1: Efficacy of medical abortion in the two protocols of misoprostol administration.**

| | Group-I (n=64) | Group-II (n=64) | P-value |
|---|---|---|---|
| Induction – abortion interval | 14.4 h | 18 h | < 0.01 |
| Complete abortion (24 h) | 48 (75%) | 39 (60.9%) | < 0.05 |
| Complete abortion (48 h) | 58 (90.6%) | 48 (75%) | < 0.02 |
| Incomplete abortion | 4 (6.2%) | 6 (9.3 %) | < 0.05 |
| Mean blood loss | 100 ml SD 98.1 | 140 ml SD 163.1 | – |

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

| Side Effects | Group-I (n=64) | Group-II (n=64) |
|---|---|---|
| Nausea | 5 (7.8%) | 7 (10.9%) |
| Vomiting | 4 (6.2%) | 4 (6.2%) |
| Diarrhea | 6 (9.3%) | 4 (6.2%) |
| Headache | 1 (1.5%) | 1 (1.5%) |
| Rash | 2 (3.1%) | 1 (1.5%) |
| Fever ( >38° C) | 24 (37.5%) | 8 (12.5%) |
| Breast tenderness | 1 (1.4%) | 2 (2.7%) |
| Genital infection | 0 | 0 |
| Abdominal cramping and pain lower abdomen | 64 (100%) | 63 (98.8%) |

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