

Comparison of Oral versus Vaginal Misoprostol for Mid-Trimester Pregnancy Termination

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ABSTRACT

Aim: To compare the clinical efficacy, side effect and acceptability of oral versus vaginal misoprostol for second trimester termination of pregnancy.

Study design: Quasi Experimental study.

Place and duration of study: The Department of Obstetrics and Gynaecology Unit-II, Post Graduate Medical Institute, Lahore General Hospital, from 27-03-2009 to 26-09-2009.

Methods: One hundred and ten pregnant women at second trimester of gestation who were candidates for therapeutic termination of pregnancy were recruited for the study. The subjects were assigned into two equal groups. Group A (n=55) had misoprostol orally, while the group B (n=55) received the drug by the vaginal route. Dosage regimen was similar in both groups that was 400µg 6 hours apart till expulsion of fetus or maximum of up to 4 doses. Both the groups were compared for efficacy, side effects and acceptability in terms of induction – expulsion interval and complete expulsion without the need for syntocinon to augment process of expulsion or need of post expulsion evacuation for retained products of conception. Grandmultipara, women, who had scarred uterus and history of hypersensitivity to prostaglandins were excluded. Chi-square test was applied for test of significance. P-value < 0.05 was considered significant.

Results: The mean induction-expulsion interval in the group A and B was 22.87±7.74 and 19.15±8.24 hours respectively p-value (0.016) which was statistically significant. Out of 55 patients included in each group, 21 (38%) in group A and 32 (58%) in group B had complete expulsion with 1 to 4 doses of misoprostol and remaining 34 (62%) in group A and 23 (42%) in group B either needed syntocinon to augment process of expulsion after four doses of misoprostol, post expulsion evacuation for retained product of conceptions or alternate method of termination of pregnancy after 24 hours period of rest after last dose of Misoprostol. Chi-square test was applied as test of significance and p-value was 0.036 which was statistically significant. There was no reported case of nausea, diarrhea, headache, dizziness, shivering, and hyperstimulation in both the groups.

Conclusions: The efficacy of vaginal misoprostol was better than oral misoprostol for second trimester termination of pregnancy.

Keywords: Misoprostol. oral route. vaginal route. pregnancy termination. mid-trimester.

INTRODUCTION

A woman may need to give birth prior to the spontaneous onset of labour in situations where the fetus has died in utero, or if born alive, would not survive or would have significant disability. This situation is psychologically stressful for the woman, her partner, family, and for the health professionals caring for her. When a baby dies before birth, the options for care are either to wait for labour to start spontaneously or to induce labour. Most of the women (over 90%) go into spontaneous labour within three weeks of their baby dying, but if labour does not begin, there is a risk of developing a disseminated intravascular coagulopathy (DIC). More over long interval between fetal death and birth limits the

amount of information that can be obtained from postmortem examination of baby about the cause of death.

Before the availability of misoprostol other prostaglandin such as prostaglandin E₂ and prostaglandin F₂ alpha (PGF₂α) were mostly used for second trimester terminations. These agents are efficacious but expensive, require refrigeration and needed higher doses which is associated with side effects such as nausea, vomiting, diarrhea and fever in high percentage of patients^{1,2}.

The abortifacient properties of misoprostol for second trimester termination have been reported in medical literature since 1993³. Misoprostol is a synthetic prostaglandin that is structurally related to prostaglandin E₁ (PGE₁). Misoprostol is licensed for use as an anti-ulcer medication in the treatment of gastric ulcer disease and does not have a product license for use in pregnancy anywhere in the world.

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Despite this, the use of misoprostol in obstetric and gynaecological practice has increased, being used widely in the management of first and second trimester abortion.

Potential advantages to the use of misoprostol over other prostaglandin preparations include its low cost, stability at room temperature and low cost. This has important implications for women in low-resource setting and in countries with high temperature. Many studies has proved it to be a drug with effective abortifacient properties and with less side effects^{4,5,6}.

Misoprostol is well absorbed by oral route, with peak plasma concentration achieved earlier and higher than vaginal administration, although the plasma concentration are detectable for longer period by vaginal route^{7,8}. Although several studies have been carried out comparing different routes and dosage of misoprostol administration for second trimester therapeutic termination of pregnancies but the optimal dosage and route of administration have not been delineated. There is need for further work to decide optimal dosage and preferred route of administration of drug for better results. The aim of present study was to compare the efficacy, side effects, acceptability and of misoprostol by oral and vaginal route in similar dose for mid trimester termination of pregnancy in terms of induction expulsion interval and complete expulsion.

MATERIAL AND METHOD

This study was carried out in the Department of Obstetrics and Gynaecology Unit-II, Post Graduate Medical Institute, Lahore General Hospital, from 27-03-2009 to 26-09-2009. The sampling technique was non probability convenient sampling technique. A total of 110 women in their mid-trimester pregnancy, who were candidates for therapeutic termination of pregnancy, were recruited in the study by non-probability convenient sampling technique. Those who were having uterine contractions, grandmultipara (parity five and above), scarred uterus or had hypersensitivity to prostaglandins were excluded. Written informed consent was taken in each case. All women had their blood group, hemoglobin estimation, and hepatitis B and C screening. Coagulation profile was performed in patients who were selected for termination of pregnancy because of intra uterine fetal demise. One unit of blood was cross-matched. The subjects were randomly allocated into two groups. The patients receiving Misoprostol as oral dose were labeled as group A, while those given vaginally were labeled as group B. The dose of 400µg of Misoprostol every 6 hours orally and 400µg every 6 hours vaginally and maximum 4 doses in 24 hours was given. Both

groups were followed for efficacy i.e. induction to delivery interval and complete expulsion. Primary outcome measures were induction to expulsion interval and complete expulsion and need for surgical evacuation, while secondary outcomes were maternal satisfaction with induction process, nausea, vomiting, diarrhea and any serious complication like uterine rupture.

Regular monitoring of patients for blood pressure, pulse, temperature at 4 hourly intervals was carried out. Patients were observed for abdominal pain, uterine contractions and vaginal bleeding. If delivery had not been achieved by the last dose of misoprostol in spite of cervical dilatation a Syntocinon infusion was started after 6 hours of last dose to expedite the process of expulsion.

After delivery of fetus all patients received 30 units of syntocinon in 5% dextrose. When placenta was expelled within 1 hour of expulsion of fetus, abortion was considered complete while expulsion was considered incomplete. If the placenta did not expel within 1 hour and was removed manually or evacuation was performed for retained product of conception diagnosed on the basis of clinical signs and ultrasonography. The patients who did not respond to four doses of Misoprostol were subjected to some alternate method of termination of pregnancy after 24 hours period of rest.

Patients were observed for maternal complications for 24 hours after expulsion and discharged subsequently. Data was collected on pre-designed proforma in each case and analyzed by SPSS software version 10. Descriptive statistics were used for maternal age, gestational age and induction to expulsion interval and were calculated as mean \pm SD. The mean induction expulsion interval in both the groups was compared. The student t-test was used as test of significance with p-value <0.05 as level of significance. For indications of induction and side effects of the drugs, proportions and percentages were calculated. Complete expulsion, augmentation with oxytocin, need of surgical evacuation and failed termination was compared in both the groups; chi square was used as test of significance with p-value <0.05 as level of significance.

RESULTS

During the study period, 110 women were assigned into two groups. Group A received oral misoprostol, while in the group B, misoprostol was administered vaginally. The groups were comparable with regard to age, parity, gestational age and indications for termination, the mean induction-expulsion interval in the group A and B was 22.87 \pm 7.74 and

19.15±8.24hours respectively p-value (0.016) which was statistically significant. Out of 55 patients included in each group, 21(38%) in group A and 32(58%) in group B patients had complete expulsion with 1 to 4 doses of misoprostol and remaining 34(62%) in group A and 23(42%) in group B either needed syntocinon for delivery after four doses of misoprostol ,post expulsion evacuation for retained product of conceptions or did not respond to four doses of misoprostol at all.

Table 1: Demographic data of study subjects

Characteristics	Group 1	Group 2	p-value
Maternal age (years)	26.55±5.30	26.00±5.75	0.016
Parity (range)	0-4	0-4	
Gestational age (weeks)	19.60±2.94	18.55±3.94	0.114 (NS)

Data given as mean + SD, n= Number of cases

Table 2: Indications for termination of pregnancy in two groups (n=110)

Indications for termination of pregnancy	Group 1	Group 2
fetal demise	17(30%)	17(30%)
Structural anomaly	31(56%)	32(58%)
Preterm premature rupture of membranes	7(12%)	6(10%)

Table 3: Primary outcome measures

Primary outcome	Group A	Group B	P value
Induction – expulsion interval	22.87±7.7	19.15±8.24	0.016 Significant (student t test)
Complete expulsion achieved with 1-4 doses of misoprostol	21(38%)	32(58%)	0.036 Significant (Chi-square test)
Needed syntocinon, post expulsion evacuation or alternative method for termination	34(62%)	23(42%)	0.036 Significant (chi-square test)

Chi-square test was applied as test of significance and p-value was 0.036. There was statistical difference in the two groups in terms of efficacy (P<0.05). There was no reported case of nausea, diarrhea, headache, dizziness, shivering, and hyperstimulation in both the groups. However, a case of vomiting in vaginal group and two cases of pyrexia in oral group were observed.

DISCUSSION

Misoprostol is safe and efficacious agent for medical termination of pregnancy in second trimester because of cervical ripening and uterotonic properties. Before misoprostol widespread use in mid 1990's, other prostaglandins such as PGE2, vaginal pesseries and PGF2 alpha were used for pregnancy termination, although efficacious, these were associated with side effects such as nausea ,vomiting ,diarrhea and fever in high percentage of patients 7.

Termination of pregnancy in second trimester carries importance in terms of more psychological trauma to the mother. In literature, there are several studies which have compared the efficacy of the two routes of misoprostol administration for termination of second trimester pregnancy i.e., oral route and vaginal route. Although its efficacy has been appreciated by many studies but it is not uniformly recommended globally. The present study compares the oral and vaginal routes of administration of misoprostol for second trimester termination of pregnancy in local population. The study demonstrated that misoprostol is an effective and safe drug for second trimester termination of pregnancy and vaginal route is associated with shorter induction expulsion interval. Bebbington *et al*, Dickinson and Ho *et al* also revealed a shorter induction-expulsion interval for vaginal route of the drug as compared to oral route for misoprostol^{8,9,10}.

The published results of various other authors like Pak Chung Ho, Miriam Ziemann and Eric A Schaff^{11,12,13} are all pointing toward more effectiveness of misoprostol administered vaginally than orally for termination of second trimester pregnancy. In our present study we also achieved similar encouraging results with regard the effect of misoprostol via vaginal than oral route.

Study conducted by Nuzat *et al* showed no significant difference in the induction-expulsion interval in both groups and shorter induction expulsion interval in both groups 1 and 2 of 11.8±8.3 and 12.8±8.5 hours respectively as compare to 22.87±7.74 and 19.15±8.24hours respectively in group A and B in our study, It could be due to different indications of TOP in both studies .In our study main indication for termination of pregnancy was congenital fetal anomalies while in study conducted by Nuzhat *et al* main indication for termination was intra uterine fetal demise. Second trimester pregnancy termination that is complicated by fetal demise is usually more predictable with a shorter induction-expulsion interval than that conducted when the fetus is alive. This could be due to the increased sensitivity of the uterus to prostaglandins

and the release of tissue factors following fetal demise^{14,15}.

Yazdani SH et al showed in the result of their study for comparison of oral versus vaginal route for second trimester termination of pregnancy that efficacy of both routes was comparable in context to induction expulsion interval. But most likely cause for these results was that all these patients primarily received 600mcg misoprostol through vaginal route then they were further divided into two groups for oral and vaginal administration of drug¹⁶.

Our study revealed complete expulsion in 38% in oral group versus 58 % in vaginal group with 1 to 4 doses of misoprostol while 62% pts in oral group and 42% in vaginal group needed either syntocinon to augment labor or post expulsion evacuation because of retained product of conception while study conducted by R Khurshid only 24% in oral group and 16% in vaginal group needed syntocinon to accomplish expulsion process or post expulsion evacuation. Probably the cause of this difference is dosage difference because they initially used high dosage of 800mcg of misoprostol in both groups vaginally followed by 400 mcg through oral and vaginal routes but this initial high dose of misoprostol was associated with higher chances of nausea and vomiting. In our study when both groups were compared for side effects there was no significant difference Kamal and Gilbert and Rei also reported no significant difference between side effects of misoprostol while comparing vaginal with oral route^{17,18}. In study conducted by R Kurshid, there was a trend toward more frequent nausea, vomiting and fever in oral group. Most likely cause of this increased trend was because they used 800mcg of misoprostol as a initial dose in both groups¹⁹.

There was not a single case of rupture of uterus in this study. Although, there are reports of rupture of uterus with misoprostol in the second trimester, it appears to be a less frequent event than with induction at term^{20,21}. The lower uterine segment has not thinned out to the extent as seen at term and the cervix does not need to be dilated as much to achieve expulsion of the fetus in second trimester. Therefore, the drug can be used safely for second trimester termination of pregnancy. This data suggests that misoprostol can be considered for mid-trimester pregnancy termination. Large multicentre randomized control trials are needed before adopting routine use of misoprostol for second trimester TOP.

The use of lower doses of misoprostol was associated with an increased chance of a woman not achieving vaginal birth within 24 hours, and a longer induction to birth interval, when compared with higher doses of misoprostol. In this situation, low dose medication may be ineffective in inducing labour or

result in an unacceptably long induction to delivery interval. However, the increased dose of misoprostol to effect termination must be balanced against an increase in the occurrence of maternal gastrointestinal side effects. The effect of increasing the dose misoprostol on the occurrence of rare but potentially life threatening maternal complications remains uncertain. Regarding patients satisfaction and acceptability toward route of misoprostol it was observed that that satisfaction with the induction process is more related to the duration of the induction delivery interval rather than the route of administration of medication.

CONCLUSION

The use of vaginal misoprostol for second trimester medical abortion resulted in higher success rate than oral at 24 hours. Vaginal administration of misoprostol is superior to oral misoprostol due to the achievement of complete termination of pregnancy more quickly due to improved pharmacokinetics associated with vaginal route. It is therefore recommended that when second trimester termination is to be done by medical method, vaginal route should be the preferred route, but oral route is also an effective and acceptable alternative.

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