

Misoprostol for 1st Trimester Miscarriage: Efficacy of Vaginal Versus Oral Misoprostol

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ABSTRACT

Aim: This study was conducted to compare the efficacy and safety of vaginal versus oral misoprostol in 1st trimester miscarriage.

Study Design: It was a quasi-experimental interventional study.

Place and Duration of Study: Our study was conducted in Sharif Medical City Hospital affiliated with Sharif Medical and Dental College, Lahore from August 2015 to July 2017.

Methodology: Women with 1st trimester miscarriage were admitted. Gestational age was assessed by menstrual history and the size of gestation was estimated on recent ultrasound. They were assigned randomly to vaginal and oral group. These patients were given tablet misoprostol (200 microgram) four hourly up to a maximum of four doses if needed. Side effects were noted. After 4th dose, patients were observed for next 24 hours and pelvic ultrasound was done. Medical evacuation was considered successful if ultrasound showed empty uterus. If patient did not miscarry at all or the ultrasound showed retained products of conception or endometrial thickness of 1.5 cm or more, evacuation and curettage was performed.

Results: Although there was no statistically significant difference in the start of miscarriage in vaginal 40(80%) and oral 42(84%) groups ($p=0.603$) but need of evacuation and curettage was less in the oral 20(40%) as compared to vaginal 30(60%) group ($p=0.046$). Doses of misoprostol needed in vaginal (3.58 ± 0.785) and oral (3.62 ± 0.697) groups showed no statistically significant difference ($p=0.788$). Misoprostol to miscarriage interval in vaginal (14.65 ± 4.769 hours) and oral (13.69 ± 4.285) groups was also not statistically different ($p=0.340$).

The percentage of complications and side effects on the whole was 12(24%) in vaginal group and 10(20%) in oral group. In vaginal group excessive bleeding was the most frequent complication 5(10%), followed by vomiting 3(6%), excessive abdominal pain 3(6%) and diarrhoea 1(2%). In oral group excessive abdominal pain was the commonest side effect 4(8%), followed by excessive bleeding 3(6%), fever 2(4%) and diarrhoea 1(2%). No cases of uterine rupture or sepsis were seen in either group. There was no statistically significant difference in any of these complications and side effects (all having $p>0.05$).

Conclusion: Although the need of surgical evacuation was more in the vaginal group but there was no statistically significant difference in other parameters of outcome including miscarriage rate, number of misoprostol doses needed and time interval from misoprostol to miscarriage. The complication and side effect rate was also found to be comparable in both groups.

Keywords: Misoprostol; Missed miscarriage; Efficacy; Vaginal versus oral routes

INTRODUCTION

Miscarriage, the natural death of an embryo or foetus before the age of viability or independent survival, is the most common complication of early pregnancy. About 10-15% of clinical pregnancies result in miscarriage and 80% of these occur in 1st trimester¹. Missed miscarriage is an ultrasound diagnosis when there is empty gestational sac of 25mm or more/ foetal pole of 7mm or more without fetal cardiac activity². A repeat scan should be done after a minimum of 7 days in case of transvaginal ultrasound and 14 days in case of transabdominal route to confirm the diagnosis. Various methods are used for expulsion or evacuation of products of conception in missed miscarriage with main concern being to provide an effective, safe, acceptable and cost effective method with least side effects³. For decades, dilatation and evacuation has been the standard management for 1st trimester missed

miscarriage. It carries the risks of cervical injury, uterine perforation, excessive haemorrhage, infection, complications of anaesthesia and maternal death.

In recent times, medical evacuation has been largely accepted as an effective and safe management with higher acceptability and increased privacy⁴. As compared to surgical evacuation, it does not increase the future risk of ectopic pregnancy, miscarriage, low birth weight or preterm birth. It does not compromise the long term fertility potential⁵. It offers economic benefits from reduction in the number of operations. Various preparations have been used largely for termination of pregnancy with different results⁶. Misoprostol and gemeprost are two synthetic prostaglandin E1 (PGE1) compounds widely used for this purpose. Gemeprost (vaginal pessary) is costly, not available widely and needs to be refrigerated. Misoprostol (also used for peptic ulcer caused by nonsteroidal anti-inflammatory drugs) is not only inexpensive but can be stored at room temperature and is also available in many countries. Prostaglandin F2 α (PGF2 α injection) is also highly effective, convenient, safe and simple method used in the first and second trimester termination of pregnancy⁷. But again, it is expensive, requires refrigeration and needs higher doses (associated with higher incidence of side

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effects such as severe nausea, vomiting, diarrhoea and fever as compared to misoprostol^{8,9}.

National Institute for Health and Care Excellence (NICE) recommends medical management with misoprostol once missed miscarriage is confirmed¹⁰. Surgical management using either manual vacuum aspiration under local anaesthesia in the outpatient / clinic or dilatation and evacuation in theatre under general anaesthesia may be offered, where clinically appropriate¹⁰.

Studies have been done in the past to evaluate efficacy and safety of misoprostol with only few studies available comparing different routes of misoprostol. So this study was planned to compare the efficacy and safety of vaginal versus oral misoprostol in 1st trimester miscarriage so that recommendations can be made about the better route of administration of misoprostol.

METHODS

This quasi-experimental interventional study was conducted in Sharif Medical City Hospital affiliated with Sharif Medical and Dental College, Lahore from August 2015 to July 2017. Ethical approval was taken. Sample size of hundred patients was calculated with 50 patients being allocated to each vaginal and oral group. It was a non-probability purposive sampling technique. Women presenting with 1st trimester missed miscarriage who gave consent were enrolled in this study. But women having incomplete miscarriage, suspected or proven ectopic pregnancy, irregular and unexplained vaginal bleeding, pelvic inflammatory disease or medical disorder like diabetes or hypertension were excluded.

Detail history was taken and clinical examination performed. Gestational age was assessed by menstrual history and the size of gestation was estimated on recent ultrasound. These patients were given 200 microgram of tablet misoprostol either vaginally or orally, four hourly up to a maximum of four doses if needed. Patients were observed for side effects associated with misoprostol (nausea & vomiting, diarrhoea, abdominal pain, fever, excessive bleeding, uterine rupture and sepsis). Excessive vaginal bleeding for this study was defined as soakage of two maternity pads, each one within 30 minute of use, or a fall in haemoglobin by one gm/dl or more. After the last dose, patients were observed for next 24 hours and pelvic ultrasound was done. Medical evacuation was considered successful if ultrasound showed empty uterus. If patient did not miscarry at all or the ultrasound showed retained products of conception or endometrial thickness of 1.5 cm or more, evacuation and curettage was performed. The collected data was analysed using SPSS 23. The maternal age, parity, gestational age, size of gestation on ultrasound, doses of misoprostol given and misoprostol to miscarriage interval in hours were calculated as mean with standard deviation and compared using t test. Rates of miscarriage achieved, need of evacuation and occurrence of complications & side effects were calculated as percentages and compared using Chi-square. P value of < 0.05 was taken as significant.

RESULTS

The mean age of women in the vaginal and oral group was 27.22±5.148 and 25.32±4.033 respectively (P=0.043).

Comparison of means of parity, gestational age and size on ultrasound is given in Table 1. In these parameters, there was no statistically significant difference between the two groups (all having p>0.05).

Table 1. The Comparison of variables in two groups

Variables	Vaginal Group	Oral Group	P value (t test)
Age in years as mean with SD	27.22±5.148	25.32±4.033	0.043
Parity as mean with SD	1.58±1.263	1.32±1.504	0.352
Gestational age as mean with SD	11.17±2.192	11.19±2.211	0.975
Size on Ultrasound as mean with SD	8.80±2.060	9.24±2.684	0.360
Doses of misoprostol as mean with SD	3.58±0.785	3.62±0.697	0.788
Misoprostol to miscarriage interval in hours as mean with SD	14.65±4.769	13.69±4.285	0.340

Table 2: Comparison of the Frequency of Response to Treatment in Two Groups

	Vaginal Group	Oral Group	P value (Chi-square)
Miscarriage started			
Yes	60	40	0.046
No	40	60	
Evacuation needed			
Yes	60	40	0.046
No	40	60	
Any complication			
Yes	24	20	0.629
No	76	80	
Diarrhoea			
Yes	2	2	1
No	98	98	
Vomiting			
Yes	6	0	0.079
No	94	100	
Excessive pain			
Yes	6	8	0.695
No	94	92	
Excessive Haemorrhage			
Yes	10	6	0.461
No	90	94	
Uterine Rupture			
Yes	0	0	
No	100	100	
Sepsis			
Yes	0	0	
No	100	100	
Fever			
Yes	0	4	0.153
No	100	96	

Comparison of response to treatment in terms of start of miscarriage process and need of evacuation and curettage is shown in Table 2. Although there was no statistically significant difference in the start of miscarriage in vaginal 40(80%) and oral 42(84%) groups (p=0.603) but need of evacuation and curettage was less in the oral 20(40%) as compared to vaginal (60%, n=30) group

($p=0.046$). Doses of misoprostol needed in vaginal (3.58 ± 0.785) and oral (3.62 ± 0.697) groups showed no statistically significant difference ($p=0.788$). Misoprostol to miscarriage interval in vaginal (14.65 ± 4.769 hours) and oral (13.69 ± 4.285) groups was also not statistically different ($p=0.340$).

The percentage of complications and side effects on the whole was 12(24%) in vaginal group and 10(20%) in oral group. In vaginal group excessive bleeding was the most frequent complication 5(10%), followed by vomiting 3(6%), excessive abdominal pain 3(6%) and diarrhoea 1(2%). In oral group excessive abdominal pain was the commonest side effect 4(8%), followed by excessive bleeding 3(6%), fever 2(4%) and diarrhoea 1(2%). No cases of uterine rupture or sepsis were seen in either group. There was no statistically significant difference in any of these complications and side effects (all having $p>0.05$).

DISCUSSION

For many years, misoprostol has been used for 1st & 2nd trimester medical termination of pregnancy, missed miscarriage, intrauterine foetal death, induction of labour at or before term, cervical ripening before dilatation & curettage and prevention & treatment of postpartum haemorrhage. Despite its wide use in Obstetrics & Gynaecology, there remains a controversy regarding its preferred route of administration (vaginal, sublingual or oral).

Some studies have found that vaginal administration is more effective than oral administration¹¹. The pharmacokinetics study also showed that systemic bioavailability (area under the curve) with vaginal route was three times more than after oral administration¹². On being placed in posterior vaginal fornix, plasma concentration of misoprostol peaks in one to two hours and then slowly declines. This means slow increase and low peak plasma concentration of misoprostol after vaginal administration as compared to oral, but overall exposure to the drug is increased showed by area under the curve of serum concentration. But the absorption through vaginal route is inconsistent and may be improved by adding water to misoprostol tablets¹³.

The Misoprostol tablet is highly water soluble. It gets dissolved in 10-15 minutes when placed sublingually¹⁴ and is absorbed rapidly from the vascular mucus membrane of buccal cavity. Sublingual misoprostol has been found to be acceptable, convenient and affective route for the patients¹⁵ as it maintains privacy and avoids repeated pelvic examination (as in vaginal administration). It avoids water ingestion before anaesthesia and can be used in patients not willing to swallow a tablet or having nausea & vomiting. The rates of tachy-systole and hypertonic uterus are higher with buccal route than oral and vaginal route¹⁶.

Oral route is preferable to the patients because it limits the number of vaginal examinations and liked by the health care providers as it avoids infectious morbidity that may be associated with placement of vaginal prostaglandins after rupture of membranes.

Miscarriage rate was 80% in the vaginal group of our study which is same as reported by Fariba from Iran¹⁷ but

less than 86.7% and 83% reported by Behrashi and Hassanzadeh respectively^{18,19} and more than 75.6% reported by Ayati²⁰. In the oral group of our study, miscarriage rate was 84% which is comparable to 84.6% reported by Ayati²⁰ but higher than 82.3%, 71.1% and 43.3% reported by Fariba, Tale and Beharshi respectively^{17, 21,18}.

Complete miscarriage rate (not needing surgical evacuation) was 40% in the vaginal group of our study which is less than 87.5%, 83%, 75.6%, 57.2%, 48% and 44% reported by Jahangir, Hassanzadeh, Ayati, Fariba, Nusrat Shah and Mirmohammadi respectively^{22,19,20,17, 23, 24}. In the oral group of our study, complete miscarriage rate was 60% which was again less than the 65.7% reported by Fariba¹⁷.

The mean time interval (in hours) from misoprostol administration to expulsion of products of conception in our study was 14.65 ± 4.769 in the vaginal group and 13.69 ± 4.285 in the oral group. This is comparable to 13.29 ± 5.63 given by Nusrat Shah²³ for the vaginal group but larger than the mean interval given by many other authors. In a study by Fariba¹⁷, this mean time interval was 3.67 ± 1.40 for vaginal group and 4.09 ± 1.56 for the oral group ($p=0.28$). In another study by Kaur²⁵ this was 3.17 ± 0.17 and 2.62 ± 0.64 for the vaginal and oral groups respectively ($p=0.001$). These differences in the misoprostol administration time to expulsion of products of conception may be due to different dose regimes used in different studies.

Overall frequency of side effects and complications in our study was 24% and 20% in vaginal and oral group which is greater than 0% (for vaginal group) and 5.7% (for oral group) reported by Fariba¹⁷ for oral and vaginal groups respectively.

Being an open label study was one limitation of our study. Another limitation was its small sample size. However it can serve as a pilot study for a future large randomized double blind clinical trial to compare the efficacy of different routes of misoprostol in the management of missed miscarriage.

CONCLUSION

Although the need of surgical evacuation was more in the vaginal group but there was no statistically significant difference in other parameters of outcome including miscarriage rate, number of misoprostol doses needed and time interval from misoprostol to miscarriage. The complication and side effect rate was also found to be comparable in both groups. So the patients and healthcare provider can choose any of these routes depending on their preferences.

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