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ORIGINAL RESEARCH

A comparative study to evaluate the efficacy of vaginal versus oral prostaglandin E1 analogue (Misoprostol) in the management of first-trimester missed abortions at a tertiary centre

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ABSTRACT
Background: Missed miscarriages in the first trimester are characterised by the arrest of embryonic or foetal development with ultrasound findings of an empty gestational sac or an embryo or foetus without cardiac activity.
Methods: Comparing the efficacy of misoprostol, by vaginal and oral routes, for termination of first trimester missed abortion was conducted in the department of obstetrics and gynaecology. 2 groups were made as group A and group B which had 60 participants in each group and a total of 120 participants, in which group A was given misoprostol 400 mcg orally, maximum up to 3 doses and group B was given misoprostol 400 mcg vaginally maximum up to 3 doses and outcome was documented. Primary outcome expecting drug induced complete expulsion of products of conception (POCs). Secondary outcomes measured were induction expulsion interval, number of doses required, classification of failures, cervical canal permeability in women requiring surgical evacuation, side effects.
Results: Both oral and vaginal routes are highly effective (oral=73.33% , vaginal=90%, p<0.001), safe and acceptable with tolerable side effects. The mean time to expulsion was longer (11.06 hours) in the oral than vaginal group (9.05 hours). All unsuccessful cases, 2 out of 6 in vaginal group and 12 out of 16 in oral group had permeable cervices prior to surgical evacuation. Most of the side effects were tolerable in both groups. **Conclusions:** Vaginal route of misoprostol is more effective than oral misoprostol for first trimester missed abortion.
Keywords: Misoprostol, First trimester abortion, Gestational sac, Surgical evacuation

Introduction

Missed miscarriages in the first trimester are characterised by the arrest of embryonic or foetal development with ultrasound findings of an empty gestational sac or an embryo or foetus without cardiac activity.[1] Misoprostol is a PGEI analogue (15-deoxy, 16-hydroxy, and 16-methyl PGE1) extensively used for termination of pregnancy, despite it being an "off-label use" , since it is effective, inexpensive, has a long shelf life (2 years) at room temperature, and requires no needles for administration.[2-4] It also has fewer side effects than PGE2 analogues.[5] Although it can be used vaginally and orally, most women choose the oral route to avoid the uncomfortable vaginal examination. The vaginal method is preferred and is thought to reduce gastrointestinal adverse effects. It results in a slower rise and lower peak plasma concentration of misoprostol acid than oral administration, but the overall medication concentration reaching the target organ is higher when using the vaginal route.[7] According to several studies, women with missed abortions who get mifepristone and misoprostol medical treatment are more likely to experience severe bleeding.[6,7]
Expectant management has the downsides of ambiguity in the timing of expulsion and the need for surgical backup. Therefore, the thrust today is being directed towards utilising medical methods to treat non-traumatic cervical dilatation, separation of products, and their expulsion.[8,9]
Aims and Objectives: to evaluate and compare safety and efficacy of 400µg misoprostol administered orally and intravaginally routes in missed miscarriage upto 12 weeks period of gestation. Oral and vaginal routes of misoprostol in missed miscarriage.

Materials and Methods

The present randomized prospective control trial, included 120 women with first missed miscarriage ≤12 weeks of gestation attending the OPD/Emergency, Department of Obstetrics and Gynaecology, Government Medical College and Hospital, Purnea, Bihar, India, after getting ethical clearance over a period from October 2022 to July 2023. The study was conducted at Department of Obstetrics and Gynaecology, Government Medical College and Hospital, Purnea, Bihar, India.

Inclusion criteria
Mild vaginal bleeding or spotting per vaginum; Fetal, Gestational age ≤12 weeks by last menstrual period (LMP), females of age group 18-45 years, diagnosis of missed abortion on USG, closed cervix on bimanual pelvic examination, haemoglobin ≥9 gm/dl.

Exclusion criteria
Excessive uterine bleeding; Fetal gestational age >12 weeks; Any degree of cervical dilatation; Haemoglobin concentration < 9gm/dl); Haemodynamic instability; Blood pressure ≥160/90 mmHg; Poor general health of any cause; Deranged coagulation profile (defined as PTI≤85%); Maternal history of asthma or cardiac disease or cerebral disease; Known allergy to or C/I to misoprostol use; Any prior medical or surgical treatment to interrupt current pregnancy; Inability or refusal of patient to adhere to follow-up.

Sampling size determination and sampling technique
The following simple formula would be used for calculating the adequate sample size in prevalence study
$n= Z^2 P (1-P)/d^2$
n= sample size, Z= level of confidence, P= prevalence, d= Absolute error or precision
Z = Is standard normal variate (at 5% type 1 error (P< 0.05) it is 1.96 and at 1% type 1 error (P<0.01) it is 2.58). As in majority of studies P values are considered significant below 0.05 hence 1.96 is used in formula. p = Expected proportion in population based on previous studies or pilot studies. d = Absolute error or precision The sample size was calculated using a single population proportion formula, by considering, 95% confidence level, a 5% margin of error, and a 8% estimated proportion of incidence of first trimester missed miscarriage among patients.
Sample size = $1.96^2 \times 0.08 (1-0.08)/0.05^2$
=113.09
Considering 5% non-response rate, the total minimum sample size for study was 119 patients.
We included 120 women with first missed miscarriage ≤12 weeks of gestation in present study.
Hundred twenty eligible women were hospitalized after ultrasonography confirmation of missed abortion. Women were then randomly assigned to one of the two groups, to receive 400µg oral or vaginal misoprostol.
Group A: sixty women with confirmed missed abortion with ultrasonography were administered 400µg of misoprostol intravaginally into posterior fornix (soaked in normal saline solution), repeated 4-6 hourly up to a maximum of three doses. Vaginal cleansing had been performed before insertion with 10% povidone iodine (Betadine).
Group B: sixty women with confirmed missed abortion with ultrasonography were administered 400µg of misoprostol of oral misoprostol, repeated every 4-6 hourly for a maximum of three doses. Women swallowed the pills with sips of water under guidance of the doctor. All patients were monitored for vitals. The baseline investigations were carried out. If POCs had been expelled, it was examined grossly. Also, a bimanual pelvic examination was performed to determine any retained gestational material. If POCs had been left, administration of further doses of misoprostol was continued until the tissue was expelled completely or maximum dose of misoprostol had been given. If patient aborted earlier completely, no further doses were given. Before beginning the study, the following clinical outcomes had been defined: a) Success was defined as non-surgical evacuation of POCs confirmed by absence of echogenic structure measuring≥15mm in AP diameter on USG; b) Failure was defined as any recourse to surgical abortion; c) Abortion was considered incomplete when POC was not completely expelled or the echogram was not an archetypal image of an empty uterine cavity. The outcome was documented 12 hours after the last dose of misoprostol to facilitate sufficient time for the drug to be effective. Surgical evacuation was performed in case of heavy vaginal bleeding, severe pain or infection and in patients who failed to abort or abort completely even then. The patients were observed for a period of 24 hours after complete abortion or surgical evacuation and then discharged. They received prophylactic antibiotics and analgesics for 5 days. All women were then asked to return to hospital 14 days post discharge when they underwent bimanual pelvic examination, USG and an interview to assess quantity of post-aborted bleeding. The second follow-up visit was scheduled at 6 weeks to determine the time taken for resumption of menses, any other side effects (if experienced) and overall acceptability to treatment. However, all women were advised to return to hospital at any time if any complications or questions arose.

Statistical Analysis
Statistical analysis was performed on the obtained data by using SPSS version 22.0 (IBM Corp., 2016) and Microsoft 16, P value < 0.05 was considered significant.

Results

Table 1: Demographic and baseline characteristics of study participants

Baseline characteristics	Oral (Group A) (n=60)	Vaginal (Group B) (n=60)	p-value
Age (years) (Mean ± SD)	24.8 ± 2.7	23.5 ± 2.5	0.82
Parity			
Primigravida	18	16	0.67
Multigravidas	42	44	
Gestational age (weeks)			
<6 weeks	02	04	0.73
6-12 weeks	58	56	
Previous cesarean section	14	10	0.58
Previous spontaneous abortion	16	22	0.58
BMI (Kg/m2) (Mean ± SD)	21.89 ± 1.63	22.50 ± 1.45	0.10

Mean age of patients was 24.8 ± 2.7years in oral group and 23.5 ± 2.5 years in vaginal group and (ranging from 18-35 years). Most patients were multigravida in both groups 70% in group A and 73.33% (20) in group B. Previous spontaneous abortion was present in 26.67% in group A and 36.67% in group B. The mean BMI of patients was 21.713 ± 2.2017 kg/m2 in Group A and 22.50 ± 1.45 kg/m2 in Group B(Table 1).

Table 2: Incidence of side-effects and complications

Side effects/ Complications	Oral (Group A) (n=60)	Vaginal (Group B) (n=60)
Nausea /vomiting	41 (68.33%)	37 (61.67%)
Headache	14 (23.33%)	9 (15%)
Dizziness	15 (25%)	10 (16.67%)
Severe Crampy Pain	26 (43.33%)	16 (26.67%)
Fever	5 (8.33%)	3 (5%)
Diarrhoea	9 (15%)	7 (11.67%)
Excessive bleeding	4 (6.67%)	9 (15%)
Discharge per vaginum	3 (5%)	2(3.33%)
Cervical tear	0	0
Uterine Rupture	0	0
Death	0	0

Table 2, showing all side effects of misoprostol were more common with oral group. Side effects and Complications of misoprostol were more common with oral group (the difference was statistically not significant; p-value=0.65).

Table-3: Comparison of clinical outcome in study participants

Outcome	Oral (Group A) (n=60)	Vaginal (Group B) (n=60)
Success	44 (73.33%)	54 (90%)
Failure	16 (26.67)	6 (10%)

Clinical outcome and its relationship with number of doses of misoprostol in successful cases: In Group B, success rate was 90% as against 73.33% in Group A [Table 3/Fig-1].

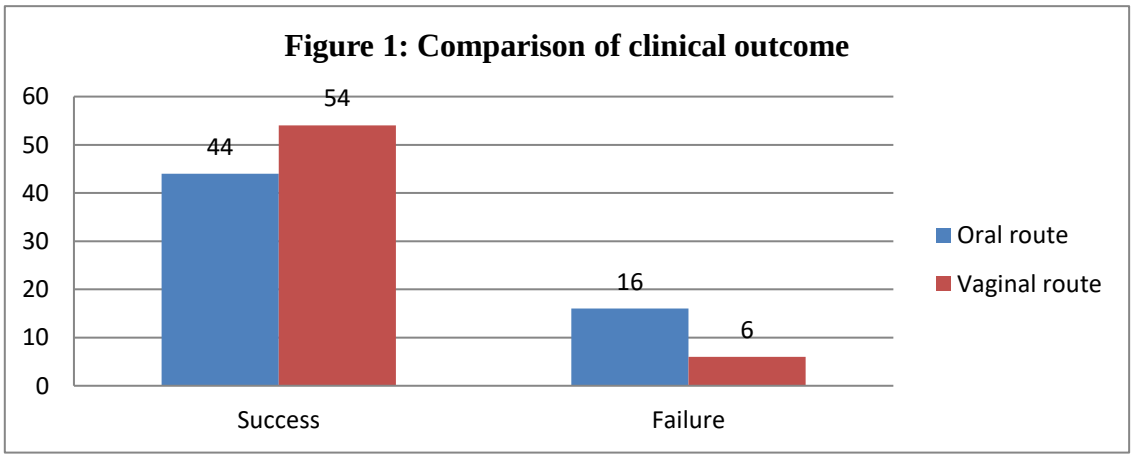
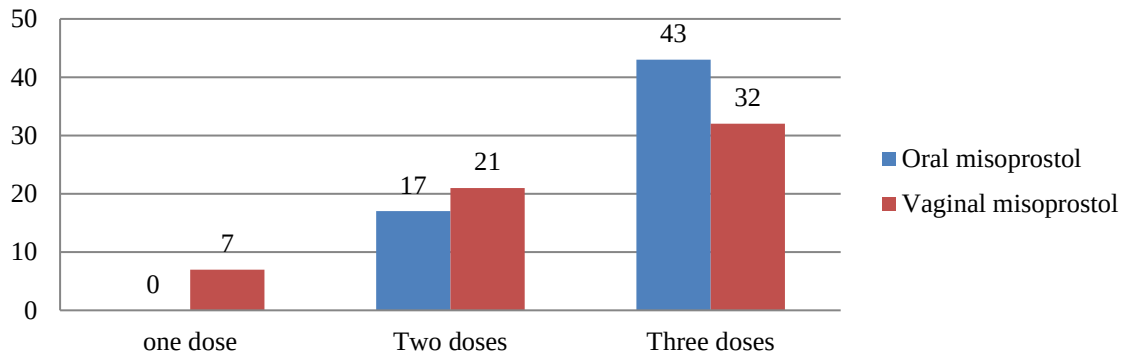


Table-4: Comparison of number of doses of misoprostol in successful expulsion in study participants

Number Of Doses	Oral (Group A) (n=60)	Vaginal (Group B) (n=60)
One	0	7 (11.67%)
Two	17 (28.33%)	21 (36.67%)
Three	43 (71.67%)	32 (53.33%)

Amongst these, 0 % patients in Group A and 7 (11.67%) in Group B expelled completely with single dose whereas 17 (28.33%) in Group A and 21 (36.67%) in Group B expelled after two doses. 43 (71.67%)in Group A and 32 (53.33%)in Group B expelled after three doses [Table-4/Fig-2]. Therefore Vaginal administration of misoprostol was thus found to be more effective than oral for complete uterine evacuation ($p<0.001$).
Mean Induction-expulsion interval (I-E interval - in hours from administration of first dose to complete expulsion) was11.06±2.72 hours in group A (oral) and 9.05±2.03 hours in group B (vaginal), difference being statistically not significant (p=0.82).

Figure 2: Comparison of number of doses of Mioprostol in successful expulsion



Discussion

Patients in the present study were younger than those in American and European studies, reflecting early marriage and first conception ages common in India.[7-10] The majority of the study participants were illiterate, from lower socioeconomic backgrounds, from rural areas, working in the home, and had normal BMI. In our study, a complete uterine evacuation without the need for surgical intervention for any cause, including endometrium thickness (ET) of 15 mm, was defined as the final success rate, and assessed by trans-vaginal solography (TVS). When compared to the majority of research in the literature, this boosted our success rates without placing an additional load on healthcare institutions.[11-13] Misoprostol is an effective non-surgical approach with high effectiveness in missed miscarriage, with higher overall efficacy of vaginal route, as evidenced by 73.33% and 90% success rates in group A and group B. similar to study done by Ngoc NTN et al.[14] and Marwah Sheeba et al.[15]. Ngoc NTN et al., (2004) study on two hundred women with confirmed missed abortion received 800 mcg misoprostol either orally or vaginally. Efficacy was high in both groups and not statistically different (oral=89.0%, vaginal=92.9%). While the groups did not differ in terms of the completion rate by day 2 (oral=41.6%, vaginal=52.7%), the mean time to expulsion was longer (21.04 h) in the oral group than the vaginal group (13.47 h), $p = 0.041$. Marwah Sheeba et al.[15] observed that both routes were highly effective (vaginal = 92%, oral = 74%, p = 0.032), safe, and acceptable with tolerable side effects. The mean time to expulsion was longer (13.24 hours) in the oral than vaginal group (10.87 hours). All four unsuccessful cases in the vaginal group and 12 of the 13 in the oral group had permeable cervices prior to surgical evacuation.
This provided more evidence for the idea that because progesterone levels are often low and uterine contractions and gestational sac evacuation are initiated by PGs rather than antigestagens in missed miscarriages. Misoprostol success rates depend to a number of factors such as route of delivery, various dosing regimens, repeated dosing regimens, prolonging follow-up (waiting for 3-15 days was found to be related with better success rates), patient selection, Use of USG prior to beginning treatment is associated with higher success rates, small sample size creating bias, criteria used to define success (waiting period of 24 hours or more, cut-off for ET presumed to be 15 mm or until 30 mm to rule out RPOC), type of PG analogue used, such as sulprostone or PGE2 analogues along with misoprostol or simultaneous use of mifepristone in other studies. In comparison to group A, group B had a much higher percentage of patients who miscarried within the first 12 hours. These results, which showed a lower mean I-E interval in the vaginal group, were consistent with the work of the majority of researchers.[16 -17] The mean gestational age was 68.84 + 1.468 days in Group A and 68.74 + 1.34 days

in Group B, highlighting later detection of missed miscarriage as opposed to the data from the Western countries. We observed that increasing the number of doses and reducing the dosing interval are important because the efficacy of a medical procedure depends on the dose, number of doses, mode of medication administration, and dosing interval. This could potentially boost the cumulative effects of misoprostol. However, it was lower than that of Carbonell et al.[16], which may have been due to the latter's use of a higher dose in their research. In present study, the oral group experienced more GI side effects, although these were easily managed using anti-emetic and anti-diarrheal medications. The most notable adverse reaction to misoprostol was diarrhoea, which is a normal reaction of intestinal smooth muscles to an increase in PGs. Despite prolonged treatment, diarrhoea is typically moderate and self-limiting and resolves within a few days. Hence the medication should be taken with meals to lessen any GI side effects. Similar finding by Marwah Sheebaet al.[15].Use of serum β HCG levels for demonstrating complete expulsion as opposed to USG would decrease the possibility of surgical curettage in patients with thickened endometrium even if they have otherwise completely aborted. Similarly, if serum β HCG has not declined by 50% compared to baseline, passage of pregnancy is not said to be complete. Unlike other studies, most women (12 out of 16 in Group A, and 2 out of 6 failures in Group B) underwent surgical evacuation for incomplete abortion. Also, even in women who failed treatment, we observed permeable cervices during evacuation (ability to pass no. 8 Hegar's dilator). These observations were even better than those attained by previous researchers reinforcing the utility of misoprostol for cervical dilation prior to any surgical manoeuvre's that could be applied routinely in the outpatient department patients.[17,18]Fever, requiring antipyretics, was observed in 8.33% of our subjects in Group A (oral) and 5% in the Group B (vaginal). Dizziness observed in Group A (oral) was 25% and in Group B (vaginal) was 16.67%. Headache observed in Group A (oral) was 23.33% and in Group B (vaginal) was 15%. and discharge per vaginum was 5% and 3.33% were reported in Group A (oral) and Group B respectively, more in our study due to unspecified reason. In our study, no woman had cervical tear, uterine rupture or death following the management. These inferences were far better than those by most of the reasearchers.[18] Heavy post-aborted bleeding was observed in very few women 6.67% in group A and 15% in Group B. The treatment can also be imparted on a domiciliary basis which could increase the woman's convenience and privacy, ensuring increased compliance and further reducing the cost of medical management.

Limitations of the study: Small sample size and short duration of the study

Conclusion

The present study's findings support the use of misoprostol, either vaginally or orally, as a alternative to traditional surgical evacuation in missed miscarriage, with high success rates, patient acceptability, and manageable side effects. Vaginal approach is more effective. However, it should only be provided by qualified medical professionals who are able to perform surgery in the event of a failed abortion or significant bleeding.

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