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RESEARCH ARTICLE
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RANDOMIZED CONTROLLED TRIAL COMPARING EFFICACY BETWEEN A VAGINAL MISOPROSTOL LOADING AND NON-LOADING DOSE REGIMEN FOR SECOND-TRIMESTER PREGNANCY TERMINATION

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Abstract

Objective: To compare the efficacy between a vaginal misoprostol loading and non-loading dose regimen for second trimester pregnancy termination.

Methods: A randomized controlled trial was conducted among women undergoing mid-trimester abortion MTA. At enrollment, 60 women were randomized (group A: loading dose [mifepristone 200 mg, then 48 h later 800 µg loading dose vaginal misoprostol followed by 400 µg vaginal misoprostol every 3 h for 5 doses] versus group B: non-loading dose [mifepristone 200mg, then 400 µg vaginal misoprostol every 3h for 5 doses]. Demographic and clinical data were collected at enrollment and abortion.

Results: Women in group A had statistically significantly shorter Induction-abortion interval IAI (7.88h vs. 13.21h, for group A and group B, respectively; $p < 0.001$). All the women in group A had complete abortion within 12 hours, compared to 11 women (36.7%) in group B ($p < 0.001$). Median number of doses of vaginal misoprostol required in group A were 3 (IQR: 3–4) versus 5 (IQR: 4–5) in group B ($p < 0.001$). Fewer women required additional oxytocin for complete abortion (group A vs. group B; 1 vs. 4, respectively, $p = 0.161$). In our study, all women had complete abortion. There were no significant differences with respect to maternal complications.

Conclusions: Loading dose of vaginal misoprostol significantly shortens the IAI ($p<0.001$) in women undergoing mid-trimester abortion.

Trial Registration: Clinical Trial Registry of India www.ctri.nic.in CTRI/2023/09/057640 (date; 14-09-2023).

KEYWORDS: Misoprostol, mifepristone, loading dose, early mid trimester abortion (13–20 weeks), induction abortion interval

Introduction

Women seek termination in second trimester of pregnancy for a variety of social and medical reasons which has recently increased because of widespread implementation of prenatal screening programs. In India, 11-14% of women undergo MTA, though these numbers are significantly under reported in official data[1].

It is reported that unsafe abortions cause the deaths of ten women each day in India[2]. This underscores potential gaps in healthcare accessibility and quality, highlighting the need for improved support and resources in this area. Addressing these challenges requires comprehensive strategies that prioritize patient safety, access to reliable information and compassionate care.

Ideally any medical method of abortion should have an overall efficacy comparable to that of surgical method, i.e. a rate of complete abortion of more than 95% and an ongoing pregnancy rate of less than 1%[3].

Misoprostol's efficacy, ease of administration, cost-effectiveness, stability at room temperature and versatility in administration routes (vaginal, oral, or sublingual) make it a preferred choice[4–6].The combination of mifepristone (RU486) and misoprostol is widely recognized as an effective method for medical abortion in the second trimester[7]. It reduces the incidence of nausea and vomiting compared to misoprostol alone due to a shorter induction-abortion interval[8]. There is a continuous need to refine these techniques to reduce both the duration of the procedure and the risk of complications. Medical abortion has become the preferred treatment due to a shortage of trained personnel capable of performing Dilatation and Evacuation[6].

This study was conducted in search for a protocol that maximizes efficacy while minimizing side effects and improving patient tolerance. This study compared the efficacy of a loading dose regimen versus non-loading dose regimen of vaginal misoprostol after pre-treatment with mifepristone for MTA.

Material and methods

This prospective randomized controlled trial RCT was carried out in the labour ward of the Department of Obstetrics & Gynecology, Dr Rajendra Prasad Government Medical College, Kangra at Tanda (HP), India, a tertiary care teaching and training hospital. Institutional ethics committee approval was obtained (letter no. HFW- HDRPGMC/ Ethics/2023/099 dated August 23, 2023). The study was also registered prospectively in the Clinical Trial Registry of India (CTRI) www.ctri.nic.in (registration number CTRI/2023/09/072474, dated; 14/09/2023).

Among women undergoing MTA, 60 women were recruited in the study after they fulfilled inclusion and exclusion criteria. List of all abortions as per the directions of Government of India was entered in abortion register kept in Minor- OT, which was communicated to Chief Medical Officer, Kangra. Inclusion criteria were: age 18 to 40 years and singleton pregnancy. Exclusion criteria were: incomplete/ inevitable abortion, any contraindications to prostaglandins and/ or its analogues, previous scarred uterus, uterine anomaly, renal failure, respiratory distress, adrenal insufficiency, liver failure, cardiovascular diseases and uncontrolled seizures, blood clotting disease or on anticoagulant therapy and anaemia (haemoglobin <8g%).

Women were recruited into the study after evaluation by senior consultant and taking informed consent. Every time an individual was enrolled, preliminary data was entered. Each individual selected for participation was provided a serial number based on first come first serve basis. Allocation to particular group to an individual was based upon the corresponding serial number of the individual based on even-odd pattern. Serial numbers with even value were allocated to Group A

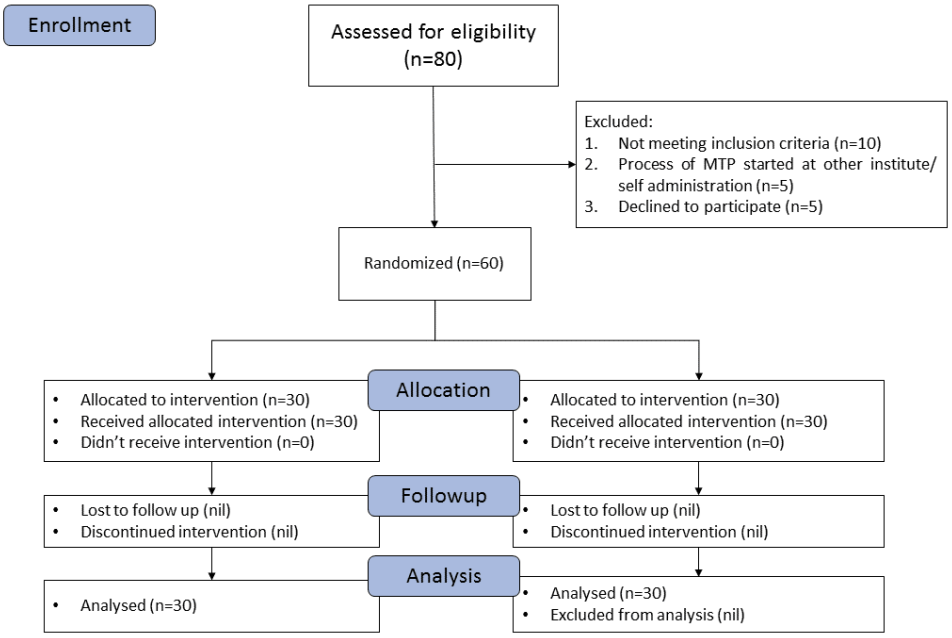
and odd serial numbers were allocated to group B. Total of 30 participants were enrolled into each group.

All women were pre-treated with 200mg mifepristone. After 48h, 800 µg loading dose of misoprostol was inserted per vaginally and was subsequently followed by 400 µg misoprostol per vaginally 3 hourly, up to maximum of five doses in Group A. In Group B, 400 µg misoprostol was inserted vaginally every 3 h, up to a maximum of five doses or until uterine contractions began, whichever was earlier). If women failed to establish uterine contractions even after five doses of vaginal misoprostol (400 µg), it was defined as failure of induction of abortion. Subsequently, patients were managed as per the discretion of the managing team of obstetricians.

Pulse rate, blood pressure, uterine contractions and adverse drug reactions (such as fever, nausea, vomiting, excessive bleeding per vaginum, etc.) were recorded 1 h and 3 h after every dose, along with any other medication given. Adverse drug reactions were treated symptomatically. A vaginal examination was performed before each dose and bleeding per vaginum and/or cervical dilation was noted. Also, the time of expulsion was recorded. The treatment was withheld if the patient had adequate uterine contractions or expulsion of products of conception.
All the women were observed for IAI (time from insertion of vaginal misoprostol to complete abortion). Additionally, the number of women having complete abortion within 12h, 12– 24h, and more than 24 h were observed. Secondary outcomes observed were number of doses of misoprostol required, failure of induction of abortion, number of women requiring additional oxytocin, number of women with incomplete abortion (retained products of conception) and subsequent need for dilatation and evacuation (D&E) (for retained products of conception or heavy vaginal bleeding).
If there were no complications during abortion procedure, the patient was discharged after 12-24 hours. Follow up was carried out 2 weeks post abortion. At the follow up visit: women were reviewed for any gastrointestinal symptoms (nausea, vomiting or diarrhea), fever, urinary tract infection, foul smelling vaginal discharge, chorioamnionitis, hemorrhage, need for subsequent hospitalization, maternal morbidity or death (admission to intensive care unit, septicemia, or any other major morbidity). Contraceptive advice was given to all the participants. Women were contacted by telephone 4 weeks later. Any complications reported were recorded as per the study protocol.

Statistical analysis was carried out on the basis of intention- to- treat. Data were entered into software (Microsoft excel; Microsoft) and analyzed using epi- info7. Descriptive statistics, frequency percentages were determined for categorical variables with 95% confidence interval. The equivalence of the treatment outcome was assessed by computing the difference in the proportions of abortion failures between treatment groups along with 95% confidence intervals. Additionally, relative risks were computed to compare treatment failures between the groups. Interactions between treatment and parity status were assessed with a logistic regression model. In cases where the standard logistic regression model fails to produce estimates due to convergence problems, an exact logistic regression method was used to approximate the significance of the interaction terms. Time to foetal expulsion was computed and then analysed using standard survival analysis techniques. For this analysis, subjects with treatment failure was considered censored with censoring time equal to the time from onset of treatment to surgical termination of the pregnancy. Median times to expulsion were derived from Kaplan–Meier estimates of the survival function, and treatment groups were compared using the log-rank test. Interactions between treatment and parity status were assessed using the Cox regression model. Comparisons of side effects and women's perceptions on the regimens were carried out using Fisher exact tests.

Fig 1: CONSORT flow chart



Outcome in study groups

Outcome	Group A (n=30)	Group B (n=30)	P value
IAI (hours)	7.88	13.21	<0.001
Complete abortion			
Within 12 h (n)	30	11	<0.001
in 12-24h (n)	0	19	
No. of misoprostol dose required (n)	3	5	<0.001
Oxytocin requirement (n)	1	4	0.161
Adverse drug reactions			
Fever (n)	10	3	0.028
Nausea (n)	5	7	0.519
Vomiting (n)	2	3	0.640
Characteristics of abortus			
Weight (g)	273.7±136.1	298.7±144.4	0.576
Sex			
Male	19	17	0.598
Female	11	13	

Fig 1: CONSORT flow chart

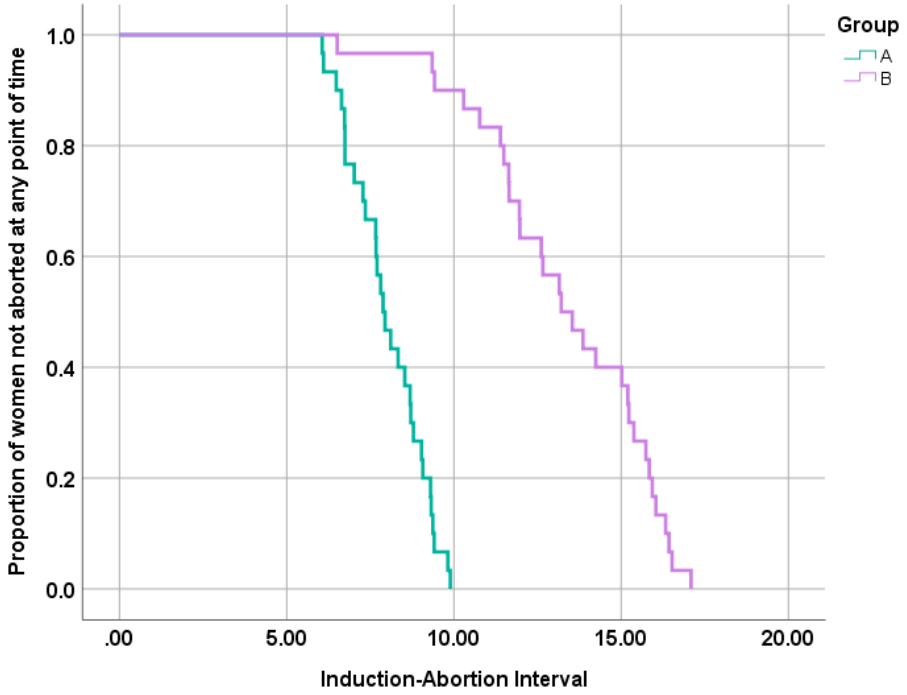


Fig 2: Kaplan Meier survival analysis curve for proportion of women not aborted at any point of time in the study period

Result

All women after enrollment were randomized as shown in fig 1 (CONSORT flow chart). A total of 60 women were randomized to either of the study group.

The median induction-abortion interval in group A was 7.88 hours (IQR:7.02 to 9.03) and in group B was 13.21 hours (IQR:11.64 to 15.74), and the difference was statistically significant (p <0.001) as shown in Table 3. All cases in group A had a complete abortion within 12 hours, while in group B 36.7% cases had abortion in less than 12 hours and 63.3 % cases in 12 to 24 hours. The difference was statistically significant (p <0.001). The number of doses of misoprostol (p <0.001) and total dose of misoprostol required was significantly less (p 0.009) in group A than group B.

Fig 2 shows the Kaplan– Meier survival analysis of women with complete abortion. It demonstrates the proportion of women not aborted at any point of time in the two study groups. As shown in Fig 2, women in group A completed abortion faster compared with women in group B.

None of the participants required any additional intervention except oxytocin requirement i.e. 1 in Group A versus 4 in Group B. One woman in group A and four in group B required additional oxytocin which was statistically non-significant (p 0.161). No other intervention was required. Ten cases in group A and three cases in group B had complaint of fever. There was statistically significant difference between fevers in the two groups (p 0.028). No statistically significant difference was found in any other adverse drug reactions between the groups. The study observed a 100% success rate in both the groups. None of the women in our study group experienced any post abortal complications such as incomplete abortion, uterine rupture, infection or hemorrhage.

Discussion

Participants in the loading dose group experienced an induction-abortion interval that was, on an average, 5.33 hours shorter than that in the non-loading group. *All women in loading dose group aborted within 12 h of induction compared to 11 women in non-loading group (p<0.001)*. This finding aligns with study done by Promwangkwa et al where IAI was shorter by 3.2 hours. Group B reported fewer episodes of fever as compared with loading dose group. The total misoprostol

requirement was significantly lower in the loading dose regimen compared to the non-loading regimen.

Our findings of decreased IAI have also been observed by different trials using loading and non-loading dose regimen. However, there is paucity of RCTs comparing vaginal loading dose and non-loading dose regimen.

The significantly shorter IAI has tremendous implications in terms of efficient patient management and potentially higher patient satisfaction due to the reduced duration of the procedure. By shortening the induction-abortion interval, healthcare facilities enhanced operational efficiency, allowing them to serve more patients in a given timeframe. The reduced need for total misoprostol with the loading dose regimen could lower medication costs. This is especially beneficial in resource-limited settings where access to medications might be constrained. Complete abortion within 12 h of first dose might altogether eliminate the need for overnight hospitalization. Additionally, in settings with non-availability of skilled providers of D&C in MTA and need for complete fetus for autopsy, it can be a preferred method.

The latest recommendation by ACOG 2013[9], RCOG 2022[10] and WHO 2018[11] , MoHFW 2016[12] and GOI 2016 recommends loading Dose of 800 µg vaginal misoprostol followed by 400 µg 3 hourly for 5 doses.[9,10,13,14].

Misoprostol is preferred because of its efficacy, ease of administration, cost-effectiveness and non-invasiveness. Its easily available, stable at room temperature and can be used by any route i.e. vaginal, oral or sublingual[4–6]. Vaginal administration is particularly effective, offering higher bioavailability and fewer adverse effects as compared to oral administration[4,5,15]. Vaginal administration ensures more prolonged uterine contractions and is generally better tolerated, especially for nulliparous women[9,16].

Limitation of our study includes lack of blinding of women in the study, did not assess the patient satisfaction and samples were exclusively collected from a single tertiary institute. Thus, a multi-centric study on IAI in women undergoing MTA with patient centered outcomes e.g. pain perception, satisfaction with the method and willingness to have the same method again, is required.

In conclusion, our study observed that loading dose regimen is associated with statistically significant reduction in IAI. Hence, we advocate for the standard implementation of the loading dose regimen for women undergoing MTA.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare

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