ORIGINAL ARTICLE

Efficacy of Mifepristone and Misoprostol Compared to Misoprostol Alone in the Medical Management of the First-trimester Missed Miscarriages

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Abstract

Introduction: Misoprostol, a prostaglandin analog, is frequently used to treat miscarriages medically by causing myometrial contractions that help the pregnancy tissue to be expelled. Mifepristone, a competitive progesterone receptor antagonist, primes the myometrium for prostaglandin exposure.

Aim: By contrasting mifepristone combined with misoprostol with misoprostol alone in first-trimester missed miscarriage, to evaluate the potential challenges such as the requirement for an operation.

Objective: To reduce the chances of surgical intervention in first-trimester missed miscarriage.

Study design and participants: This study was done in the Saveetha Medical College and Hospital, Chennai, in two years of duration from September 2020 to August 2022.

Materials and methods: In the first 13 weeks + 6 days of pregnancy, 150 women who had first-trimester missed miscarriages confirmed by pelvic ultrasound were recruited. Seventy-five women (group A) were randomly allocated to receive mifepristone 200 mg, 48 hours later 400 µg misoprostol per vaginally at 3 hourly intervals to a maximum of three doses were given. Seventy-five women (group B) were randomly allocated to receive 400 µg misoprostol per vaginally at 3 hourly intervals to a maximum of three doses were given.

Results: In total 29.33% of 75 women within the mifepristone plus misoprostol group required surgical intervention to complete the miscarriage, versus 56% of 75 women within the misoprostol alone group.

Conclusion: We recommend that women with a first-trimester missed miscarriage should be offered mifepristone pretreatment before misoprostol to increase the chance of successful miscarriage management, while reducing the necessity for surgical evacuation like D&E especially in primigravidas.

Keywords: Dilatation, Evacuation, Mifepristone, Misoprostol.

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Introduction

First-trimester missed abortions, also known as missed miscarriages, are defined by the arrest of embryonic or fetal development and ultrasound findings of an empty gestational sac or an embryo or fetus without cardiac activity. They occur in up to 12–15% of all clinically recognized pregnancies. In missed abortion, pregnancies simply stop growing without obvious symptoms, with a delay within the expulsion of the conceptus. One of the following three approaches can be used to treat a first-trimester missed miscarriage: expectant, medical or surgical. Expectant management, during which women wait for the uterus to naturally evacuate the pregnancy tissue for a period of 7–14 days, is the first-line treatment for missed miscarriage that is advised. Medical management is preferred if expectant management fails or is not acceptable to the woman. With the aid of medicinal medications, medical care hastens the ejection of retained pregnancy tissue. Many women choose medical management as their best option, and this is supported by international clinical recommendations. Misoprostol, a prostaglandin analog, is frequently used to treat miscarriages medically by causing myometrial contractions that help the pregnancy tissue to be expelled. Misoprostol is not always effective, though, and 15–40% of women need an extra dose, prolonging the course of treatment. Mifepristone, a steroidal antiprogesterone, is occasionally used with misoprostol to enhance its effects. A competitive progesterone receptor antagonist called mifepristone prepares the myometrium for exposure to prostaglandins. It is recommended that misoprostol (PGE1 analog) should be used in medical treatment of missed miscarriages. However, there is evidence to suggest that combining this drug with mifepristone (RU 486 antiprogestin—an oral tablet that reduces pregnancy hormones) acts on the pregnant uterus by causing decidual necrosis, cervical softening, and increases uterine

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contractility. Prostaglandin sensitivity may be more effective in treating miscarriage if mifepristone is given 48 hours prior to misoprostol. Mifepristone and misoprostol combined treatment for missed abortions has been shown to be between 64 and 95% successful.

We investigated whether using mifepristone in addition to misoprostol would increase the completion rate of missed miscarriages compared with using misoprostol alone. The need for surgery and other important outcomes will be evaluated.

Study Design and Participants

This study was carried out in the Saveetha Medical College and Hospital, Chennai, in two years of duration from September 2020 to August 2022. Women who opt for medical miscarriage management after being diagnosed with missed miscarriage by pelvic ultrasound scan within the first 13 weeks + 6 days of pregnancy between the ages of 18 and 30 years.[1] Pregnancy inside the womb with a gestational sac larger than 20 mm and no sign of an embryo or yolk sac. Crown-rump length (CRL) greater than 6 mm during intrauterine pregnancy without heart activity. Intrauterine pregnancy with a gestational sac that is less than 20 mm in diameter and a CRL that is less than 6 mm, with no growth after 7 days. Other radiographic indicators of an unhealthy pregnancy include an irregular gestational sac and debris inside. Able and willing to provide informed consent. Willingness to comply with follow-up schedule. Closed cervix on bimanual pelvic examination. Hemoglobin is more than equal to 9 g/dL. If an ultrasound revealed a nonviable pregnancy with a gestational sac present, qualified ultrasonographers at early pregnancy units would diagnose a missed miscarriage. After another 7 days, an ultrasound scan was performed again to confirm the miscarriage's initial diagnosis and treatment.[2]

Women choosing alternative miscarriage management techniques (expectant or surgical), incomplete or inevitable miscarriages, life-threatening bleeding, cervical dilatation of any degree, twin gestation, molar pregnancy, hemoglobin 9 g/dL, hemodynamic instability, blood pressure greater than 160/90 mm Hg, abnormal coagulation profile, and mifepristone contraindications such as chronic adrenal failure, known drug hypersensitivity, hemorrhagic disease and anticoagulant therapy, prosthetic heart valves, history of endocarditis, pre-existing cardiovascular illnesses, untreated asthma, and genetic porphyria were excluded from the study.

Materials and Methods

Around 150 women who had missed miscarriages confirmed by pelvic ultrasound within the first 13 weeks + 6 days of pregnancy were sought out. Seventy-five women (group A) were randomly allocated to receive mifepristone 200 mg, 45 hours later 400 µg misoprostol per vaginally at 3 hourly intervals to a maximum of three doses were given. Seventy-five women (group B) were randomly allocated to receive 400 µg misoprostol per vaginally at 3 hourly intervals to a maximum of three doses were given. The patient has been reviewed after two weeks with transvaginal ultrasound endometrial thickness lesser than 15 mm indicates successful medical management. Patients who failed to expel the products of conception within 48 hours, who bleed heavily, or endometrial thickness greater than 15 mm after two weeks were taken up for surgical management method such as D&E.

Table 1: Misoprostol alone for primigravida

Doses	*How many patients required suction and evacuation?*
Three doses	9 of 12
Two doses	8 of 15
One dose	5 of 5

Table 2: Combination of mifepristone and misoprostol for primigravida

Doses	*How many patients required suction and evacuation?*
Three doses	2 of 2
Two doses	5 of 18
One dose	2 of 10

Table 3: Misoprostol alone for multiparous women (previous vaginal delivery)

Doses	*How many patients required suction and evacuation?*
Two doses	2 of 5
One dose	10 of 18 (underwent suction and evacuation due to ET >15 mm)

Table 4: Combination of mifepristone and misoprostol for multiparous (previous vaginal delivery)

Doses	*How many patients required suction and evacuation?*
Two doses	2 of 16
One dose	6 of 18

Table 5: Misoprostol alone for previous cesarean delivery

Doses	*How many patients required suction and evacuation?*
Three doses	8 of 8
Two doses	4 of 9
One dose	3 of 3

Table 6: Combination of mifepristone and misoprostol for previous cesarean delivery

Doses	*How many patients required suction and evacuation?*
Three doses	4 of 7
Two doses	1 of 4

Based on the above samples given under both the study groups, patients required suction and evacuation for each category of patients were analyzed (Tables 1 to 6).

With the help of IBM SPSS Statistics for Windows, version 23.0, the acquired data were analyzed (IBM Corp, Armonk, NY). For categorical variables, frequency analysis and percentage analysis were used to provide descriptive statistics about the data. Chi-square test was applied to categorical data to determine the significance. The probability value of 0.05 is regarded as a significant level in all of the aforementioned statistical techniques.

Summary

Approximately 26.67% of participants required three doses, 38.67% required two doses, and 34.67% required one dose in the misoprostol alone group.[3] Whereas 12% required three doses, 50.67% required two doses, and 37.34% required one dose among the mifepristone and misoprostol group (Table 7 and Fig. 1). The probability value of less than 0.05 indicates that it is significantly

Table 7: Describes doses of misoprostol required in each group

Methods used	*3 Doses required by*	*2 Doses required by*	*1 Dose required by*
Misoprostol alone	26.67%	38.67%	34.67%
Combination of mifepristone and misoprostol	12%	50.67%	37.34%

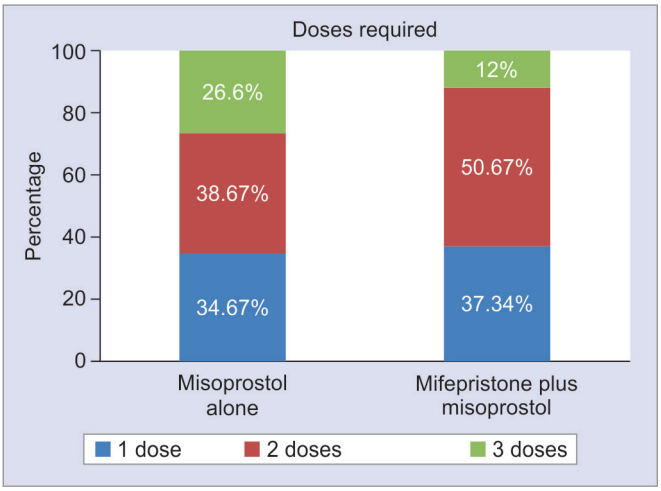

Fig. 1: Doses required for both groups

- In comparison to the misoprostol alone group, which included 75 women, 30.61% of those in the mifepristone plus misoprostol group required further doses of the drug till discharge.
- In the group receiving both misoprostol and mifepristone as opposed to misoprostol alone, the mean period from admission to discharge was 4 days as opposed to 6 days.
- In both study groups, the frequency of unfavorable side effects and the need for blood transfusions was comparable.

Discussion

This descriptive analysis study shows that the incidence of surgical management reduces in mifepristone and misoprostol combination than within the misoprostol alone group. Requirements for more than two doses of misoprostol are observed more among the misoprostol alone group. In this study, the dose of mifepristone was 200 mg and the dose of misoprostol was 400 µg. The outcome of miscarriage care was evaluated in this study using a variety of techniques, including clinical and ultrasound examination, and at several time periods.[5] In the Cochrane meta-analysis, which compared the efficacy of misoprostol alone against misoprostol plus mifepristone for the medical management of miscarriage, we included the findings from our study. For the treatment of missed miscarriage, mifepristone + misoprostol was found to be more effective than misoprostol alone [relative risk (RR) 1–15, 95% confidence interval 1-01-130)].[6] The results of our study emphasize the importance of maximizing medical management of missed miscarriage using the combined mifepristone and misoprostol

Table 8: Compares parity, mode of previous delivery, and number of patients who underwent surgical intervention among two groups

How many underwent suction and evacuation?	*Primigravida*	*Multiparous*		*Total*
		Previous vaginal delivery	*Previous cesarean delivery*	
Misoprostol alone	68.75%	21.74%	75%	56%
Combination of mifepristone and misoprostol	30%	23.53%	45.45%	29.33%

requires fewer doses among combined group compared with misoprostol alone group.

A total of 68.74% of primigravida, 21.74% of previous vaginal delivery, and 75% of previous cesarean delivery in the misoprostol alone group. Thirty percent of primigravida, 23.53% of previous vaginal delivery, and 45.4% of previous cesarean delivery among mifepristone and misoprostol combined group (Table 8 and Fig. 2). The *p*-value > 0.05 indicates that it has no significant correlation.

Results

Between September 2020 and August 2022, 150 women who met the study's eligibility requirements were found.[4] Randomly, 150 women were given either misoprostol alone or mifepristone with misoprostol.

Between the two study groups, demographic and baseline variables were comparable.

- Compared to 56% of 75 women in the misoprostol alone group, 29.33% of the 75 women in the mifepristone + misoprostol group needed surgical intervention to complete the miscarriage.
- Pregnancy tissue persisting in the uterus was documented in 12% of the 75 women who received mifepristone + misoprostol and in 26.67% of the 75 women who received misoprostol alone, among the women who underwent surgery.

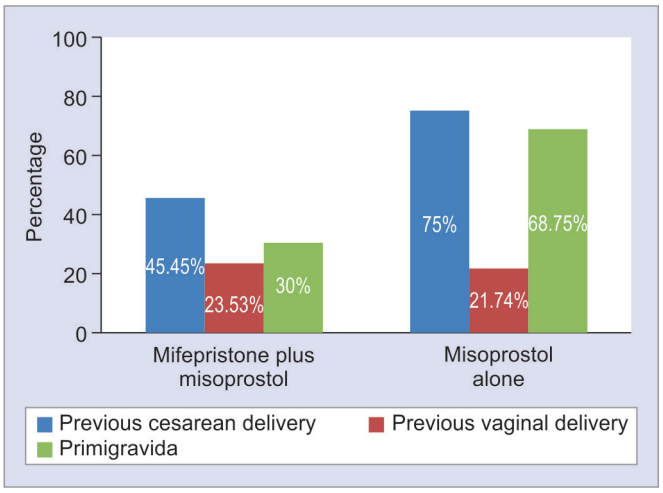

Fig. 2: How many underwent suction and evacuation?

treatment regimen. This regimen improves outcomes and safety by increasing the percentage of women who experience resolution of their miscarriage and lowering the requirement for surgical management (Table 9). The incidence of serious adverse events was generally low.[7] Frequent adverse effects were nausea, vomiting, fever, cramps in the abdomen, and diarrhea.

Table 9: Events taken into account during the study

	Number of events/total number	
Data for	*Mifepristone plus misoprostol*	*Only misoprostol*
Gestational age (weeks)		
<9	29	35
≥9, <14	46	40
Maternal age (years)		
<30	39	32
>30	36	43
Body mass index (kg/m^2)		
<35	61	70
≥35	14	5
Previous parity		
Nulliparous	32	30
Parous	43	45

The strength of this study is that all women received misoprostol via the vaginal route, hence the administration method was comparable between the two study groups.[8]

Study comparison done with Okeke et al., published in BJOG 2021, total participants of 711, primary outcome measures mifepristone 200 mg per oral followed by misoprostol (variable doses of 400–800 mcg per vaginally, sublingually, per orally).[9] These patients had 83.1% medical management and 17.8% surgical management, whereas among misoprostol alone group 76.4% medical management and 25% surgical management such as D&E.[10]

Also another study by Justin J Chu et al., published in Lancet 2020, 28 UK hospitals participated in a multicenter, double-blind, placebo-controlled, randomized experiment. A single dosage of vaginal, oral, or sublingual misoprostol 800 mg was administered to participants two days after receiving either a single dose of oral mifepristone 200 mg or an oral placebo pill, according to a 1:1 randomization scheme.[11] Mifepristone and misoprostol (357 women) or a placebo and misoprostol (711 women) were given at random (354 women). Of the 711 women, 696 (98%) had data for the main outcome. Compared to 82 (24%) of the 348 women in the placebo plus misoprostol group, 59 (17%) of the 348 women in the mifepristone plus misoprostol group did not spontaneously pass the gestational sac within 7 days.[12,13]

Conclusion

In contrast to misoprostol treatment alone, according to our research, pretreatment with mifepristone and misoprostol increased the rate of missed miscarriage resolution by 7 days. To maximize the likelihood of successful miscarriage management and decrease the need for surgical evacuation, like D&E particularly in primigravidas, we advise offering mifepristone pretreatment before misoprostol to women who have had a missed miscarriage.

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