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Mifepristone and Misoprostol Compared with Misoprostol alone for Delivery after Fetal Death between 14 and 28 Weeks of Gestation

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Abstract: ***Objective: To assess the efficacy of pretreatment with mifepristone before misoprostol, compared with misoprostol alone, for termination of pregnancy after a fetal death in the second trimester. Methods: This prospective, double blind, placebo-controlled trial randomized women requiring a termination of pregnancy after fetal death between 14 and 28 weeks of gestation to placebo or 200 mg mifepristone orally 24-48 hours before the termination of pregnancy with misoprostol (400 micrograms every 6 hours vaginally for women at 24 weeks of gestation or less, and 200 micrograms every 4 hours vaginally for women at 24 weeks of gestation or more). Based on a median labor with misoprostol alone in the second trimester of 13 hours, a sample size of 66 women per group was planned to compare the primary outcome of time from administration of misoprostol to delivery. Results: From April 2021 to October 2022, 66 women were randomized (34 to placebo and 32 to mifepristone). There were no differences in the characteristics between the two groups. The median time for the primary outcome of administration of misoprostol to delivery in the placebo group was 10.5 hours, compared with 6.8 hours in the treatment group (hazard ratio 2.41 95% CI 1.39-4.17, P5.002). Women in the placebo group required more doses of misoprostol (3.4 vs 2.1, P5.002) and more misoprostol overall (1,181.8 micrograms, vs 767.7 micrograms, P5.003). There was no difference in maternal complications between the two groups. Women in the mifepristone group reported improved perception of the procedure. Conclusion: The sequential use of mifepristone and misoprostol for the termination of pregnancy after fetal deaths between 14 and 28 weeks of gestation reduces the time to delivery, compared with the use of misoprostol alone, with no worsening of maternal complications.***

Keywords: Mifepristone, Misoprostol, Termination of Pregnancy

1. Introduction

The use of mifepristone across the gestational spectrum has increased since the first clinical trials in the 1980s investigating its use as an abortifacient in early pregnancy.[1] Mifepristone (a competitive progesterone antagonist) primes the myometrium and cervix to respond to prostaglandins and is, therefore, used in combination with a prostaglandin analogue (e.g., misoprostol). Mifepristone has been safely and efficaciously used in medical termination of pregnancy in the first and second trimesters [2, 3].

Several randomized trials have demonstrated the usefulness of mifepristone before prostaglandin use for second trimester termination where the fetus is alive. Mifepristone priming results in a shortened induction to abortion interval and a reduced dosage of prostaglandins required to achieve delivery.[3-6] There are fewer data available on the role of mifepristone in termination of pregnancy after fetal death, and the relevance of blocking the effect of residual progesterone in a nonviable pregnancy is unclear. Two randomized controlled trials completed since commencement of this study demonstrated a reduction in the time to delivery after misoprostol administration with preceding mifepristone priming in the setting of fetal death in the second and third trimesters [7, 8]. The randomized trial of Chaudhuri and Datta[7] investigated women with a fetal death after 20 weeks of gestation (median gestational age 32 weeks) using a regimen of 50-100 micrograms of vaginal misoprostol every 6 hours for a maximum of four doses and reported a significant reduction in delivery interval in those women randomized to mifepristone, compared with placebo.

The recent trial of Bracken et al[8] used 200 micrograms of buccal misoprostol every 3 hours for a maximum of 16 doses in pregnancies at 14-28 weeks of gestation, with a significant reduction in the fetal expulsion time for the women receiving mifepristone priming. There are also several cohort studies supporting the use of misoprostol after mifepristone priming in the setting of fetal death after the first trimester.

Our institution typically has used vaginal misoprostol after mifepristone priming following a randomized trial[9] and wished to extend this experience to women with a fetal death. Therefore, to assess the efficacy of mifepristone, we conducted a randomized double blind placebo-controlled trial that compared misoprostol alone with misoprostol after mifepristone priming for the termination of a pregnancy after fetal death in women between 14-28 weeks of gestation. Our primary study hypothesis was that pretreatment with mifepristone would significantly decrease the delivery interval after prostaglandin commencement.

2. Methods

From April 2021, to October 2022, women with a fetal death between 14-24 weeks of gestation who were admitted to santhiram medical college were screened for enrollment in this randomized trial. The initial gestational age inclusion criteria were determined by usual practice in our unit for the management of a fetal death at less than 24 weeks up to 28 weeks of gestation was eligible to be recruited. All participants provided written consent.

Aims

The primary aim of this trial was to compare the time interval from commencement of misoprostol to delivery of the fetus between the two study regimens. Secondary aims were to assess the incidence of maternal side effects, including postpartum blood loss, placental retention rates, the need for manual removal of placenta, the need for blood transfusion, the incidence of febrile illness, and the need for antiemetic and analgesic treatment. Women's satisfaction was also assessed. A secondary arm of this trial (with the results to be published separately) was to assess the circulating progesterone and estrogen levels in the trial patients as well as a cohort of women undergoing induced abortion of pregnancy with a live fetus. The aim of this was twofold: to consider whether the efficacy of mifepristone is related to the concentration of progesterone in the setting of fetal death, and to analyze the usual range of both progesterone and estrogen levels in pregnancy.

Women with gestational ages of 14 0/7 to 28 6/7 weeks and a confirmed fetal death in utero were invited to participate in the trial. If the gestational age was unknown, an ultrasonogram-confirmed crown-rump length of 85 mm was considered as the lower limit to allow inclusion. Women were excluded if they were taking corticosteroids (see below), had a documented allergy to misoprostol or mifepristone, had a history of more than three previous cesarean deliveries, presented with ruptured membranes, presented in spontaneous labor, or were unable to provide written consent.

After obtaining written consent, one of the study investigators allocated a unique study participant number to the woman. This was sequential and documented in the study data set, as well as in the patient notes and in the inpatient medication chart. The medication chart was then provided to the pharmacy. Before the study commenced, the pharmacist (A.M.W.) had used a random sampling program to allocate participants to the case and control groups to the unique study identifiers, with 1:1 randomization. On receiving the medication chart, the trial pharmacist used the unique study participant number to provide the trial drug, ensuring that the study investigators, the participants, and the staff who administered the treatment remained blinded to the patient's allocated study group.

Women were randomized to receive either 200 mg of mifepristone or placebo 24-48 hours before misoprostol. The mifepristone was placed in capsules identical to the placebo capsules. The women were directly observed swallowing the trial medication. The women were discharged with safety advice and then admitted to the hospital 24-48 hours later for standard management of termination of pregnancy after a fetal death. According to standard unit proto- cols, women between 14 and 24 weeks of gestation received 400 micrograms of misoprostol vaginally every 6 hours, and women between 24 and 28 weeks of gestation were given 200 micrograms vaginally every 4 hours. Women who had not delivered within 24 hours of misoprostol administration were reviewed by a consultant obstetrician for decision on the requirement for additional misoprostol.

In all groups, management of the placenta after delivery of the fetus followed the standard hospital protocol, with 10 units of oxytocin administered intramuscularly after delivery of the fetus. If expulsion of the placenta did not occur within 60 minutes of delivery (or if heavy vaginal bleeding occurred before this time) then manual removal of the placenta in the operating room was undertaken.

Hemoglobin and hematocrit were measured before administration of the trial drug and in the 24 hours after delivery. Maternal pulse, blood pressure, and temperature were recorded every 3 hours during the termination. A visual analogue scale was used at 3-hour intervals to assess nausea and pain. Estradiol and progesterone levels before administration of the trial drug were assessed on maternal serum. Objective documentation of vomiting and diarrhea was made by the nursing staff. The nature, frequency, and dosage of analgesia were recorded. At time of discharge, patients completed a four question visual analogue questionnaire (used in previous similar randomized trials conducted by our group[9]) with answers obtained using a visual analogue ruler scaled from 0 to 10, with 0 perceived as "much better than expected" and 10 as "much worse than expected", for the following questions: What did you think of the procedure? How would you rate your pain during the procedure? Would you recommend this method of termination to a friend in a similar situation? How much control did you feel you had?

3. Results

Sixty-six women were randomized to placebo or treatment. The flow diagram for patient accrual is shown in Figure 1. Eleven women declined to participate in the trial, 19 women were unable to provide consent, and 15 women were unable to be recruited (for example attended out of hours). One woman withdrew after randomization but before treatment started, and another woman delivered between randomization and treatment. A further four women started treatment but experienced the delivery outcome before misoprostol was used. Baseline characteristics did not differ between groups and are shown in Table 1.

Women in the treatment group had fewer doses of misoprostol (2.1 vs 3.4, *P*5.002) and less total misoprostol (a mean of 767.7 micrograms vs 1,181.8 micrograms, *P*5.003). The median time from misoprostol to delivery in the placebo group was 10.5 hours, compared with 6.8 hours in the treatment group (hazard ratio 2.41 95% CI 1.39-4.17, *P*5.002) (Fig. 2). The effect of mifepristone on time from misoprostol to delivery did not seem to vary among women with gestational ages of less than 20 weeks compared with those with 20 weeks or more (*P*5.795). However, owing to the relatively small study sample size, we lacked statistical power to detect any small differences in time to delivery. Parous women in the mifepristone group had a significantly shorter time to delivery after misoprostol compared with parous women in the placebo group (hazard ratio 2.81 95% CI 1.412-5.57, *P*5.003).

Table 1: Baseline Characteristics

Completion status

Characteristic	Placebo (n534)	Mifepristone (n532)
Completion status		
Completed as planned	31 (91.2)	29 (90.6)
Delivered before treatment	0 (0.0)	1 (3.1)
Delivered before misoprostol	2 (5.9)	2 (6.3)
Withdrew postrandomization	1 (2.9)	0 (0.0)
Age group (y)		
Younger than 25	4 (11.8)	7 (21.9)
25-34	20 (58.8)	15 (46.9)
35 or older	10 (29.4)	10 (31.3)
BMI (kg/m2)		
18.5-24.9	8 (23.5)	7 (21.9)
25-29.9	7 (20.6)	6 (18.8)
30 or higher	7 (20.6)	6 (18.8)
Missing	12 (35.3)	13 (40.6)
Gestational age (wk)		
Less than 16	5 (14.7)	3 (9.4)
16 to less than 20	15 (44.1)	17 (53.1)
20 to less than 24	10 (29.4)	6 (18.8)
24 to less than 28	2 (5.9)	5 (15.6)
28 or more	1 (2.9)	0 (0.0)
Missing Parity	1 (2.9)	1 (3.1)
0	12 (35.3)	10 (31.3)
1	4 (11.8)	7 (21.9)
2	9 (26.5)	9 (28.1)
3	3 (8.8)	3 (9.4)
4	3 (8.8)	2 (6.3)
5	1 (2.9)	0 (0.0)
6	1 (2.9)	0 (0.0)
Missing	1 (2.9)	1 (3.1)
No. previous cesareans		
0	24 (70.6)	24 (75.0)
1	5 (14.7)	4 (12.5)
2	3 (8.8)	3 (9.4)
3	1 (2.9)	0 (0.0)
Missing	1 (2.9)	1 (3.1)

BMI, body mass index

There was no evidence that time to delivery after misoprostol varied between mifepristone and placebo in nulliparous women; however, the numbers of women included in this subgroup analysis is small (n522).

There was no difference in the time from administration of mifepristone or placebo to delivery (median of 40.1 hours in the placebo group vs 42.3 hours in the treatment group). Nor was there any difference in the time from either admission to the hospital to discharge (median of 29.5 hours in the placebo group vs 28.3 hours in the treatment group), or from the commencement of misoprostol to discharge (median of 27.8 hours in the placebo group vs 26.3 hours in the treatment group).

Four women in the placebo group and no women in the mifepristone group took longer than 24 hours after misoprostol to deliver. Their gestational ages ranged from 16 to 22.1 weeks, and the total doses of misoprostol received were between 6 and 10. There were no apparent differences between these women and those who delivered in less than 24 hours.

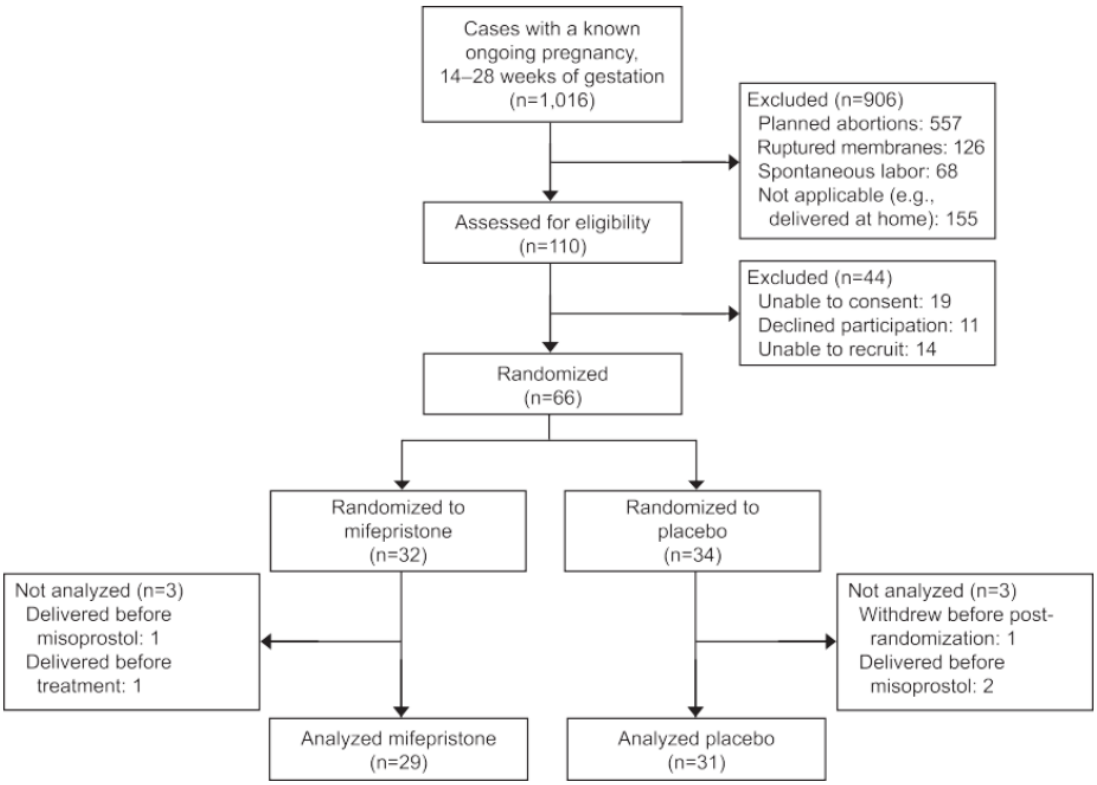

Figure 1: Flow diagram for patient accrual

Table 2: Maternal Complications

Complication	Placebo	Mifepristone	P*
No	9 (27.3)	2 (6.5)	.055
Yes	23 (69.7)	28 (90.3)	
Missing	1 (3.0)	1 (3.2)	
Retained Placenta			
No	23 (69.7)	22 (71.0)	1.000
Yes	10 (30.3)	9 (29.0)	
Manual removal of placenta			
No	23 (69.7)	24 (77.4)	.577
Yes	10 (30.3)	7 (22.6)	
Blood loss greater than 500 mL			
No	25 (75.8)	24 (77.4)	.740
Yes	5 (15.2)	6 (19.4)	
Missing	3 (9.1)	1 (3.2)	
Blood transfusion			
No	32 (97.0)	30 (96.8)	.738
Yes	0 (0.0)	1 (3.2)	
Missing	1 (3.0)	0 (0.0)	
Need for antiinflammatory			
No	16 (48.5)	19 (61.3)	.327
Yes	17 (51.5)	12 (38.7)	
Need for			
intramuscular			
analgesia	12 (36.4)	9 (29.0)	.601
No			
Yes	21 (63.6)	22 (71.0)	
Need for antiemetic			
No	8 (24.2)	11 (35.5)	.415
Yes	25 (75.8)	20 (64.5)	
Febrile illness			
No	32 (97.0)	28 (90.3)	.347
Yes	1 (3.0)	3 (9.7)	
Readmission after discharge			
No	29 (87.9)	29 (93.5)	1.000
Yes	3 (9.1)	2 (6.5)	
Missing	1 (3.0)	0 (0.0)	

Use of 3rd stage oxytocics

Although not significant, women in the placebo group were more likely not to receive oxytocics in the third stage, and the reasons for this were not recorded. There was, however, no difference in the length of third stage, estimated blood loss, pre-delivery or post-delivery hemoglobin and hematocrit, or temperature at any time point. One woman in the mifepristone arm required a blood transfusion. Of the five women readmitted, four were for retained products of conception requiring suction curettage in the operating room (four in the placebo group and one in the mifepristone group) and one was for endometritis requiring intravenous antibiotics (in the mifepristone group). Only the patient with endometritis was admitted for longer than a day (Table 2). There was no significant difference between the treatment and placebo groups at the time of trial enrollment in the mean estradiol levels (15,418.1 pmol/L vs 9,860.5 pmol/L, *P*5.137) or mean progesterone levels (166.6 nmol/L vs 101.0 nmol/L, *P*5.164) at the time of enrollment in the trial.

Satisfaction scores (from a scale of 0-10 with 0 perceived as "much better than expected" and 10 as "much worse than expected") differed between the two groups for question of "what did you think of the procedure," with women in the placebo group rating it worse than women in the mifepristone group (mean score 7.8 vs 6.3, *P*5.035). There was no difference in the other three questions about perception (Table 3).

4. Discussion

This randomized trial demonstrates that the use of mifepristone before misoprostol administration for termination of pregnancy after fetal death between 14 and 28 weeks of gestation significantly reduces the time from the commencement of misoprostol to delivery, with no difference in adverse maternal events. Despite the early termination of our trial, we achieved our planned outcome of a 30% reduction in the median duration of labor. Parity (vs nulliparity) but not gestational age affected the time to delivery in this study. Unlike other randomized trials on the use of mifepristone in termination of pregnancy, [9] our trial did not show any effect of gestational age on the primary outcome. It may be that this is a consequence of the small numbers of women in each gestational age group.

Table 3: Women's Perceptions of the Procedure

Perception	n	Mean±SD	P*	Median (IQR)	P†
Opinion of Procedure					
Placebo	22	7.8±2.3	0.035	8 (5-10)	0.016
Mifepristone	21	6.3±2.3		5 (5-9)	
Perception of pain					
Placebo	22	6.0±2.6	0.027	5 (5-8)	0.313
Mifepristone	22	5.0±2.6		5 (3-7)	
Recommendation					
Placebo	21	8.4±2.0	0.15	10 (7-10)	0.131
Mifepristone	22	7.4±2.4		8 (5-10)	
Impression of control					
Placebo	22	7.2±2.2	0.8	7 (5-10)	0.849
Mifepristone	22	7.0±2.8		7 (5-10)	

* *t* test.

† Wilcoxon rank sum test.

Our trial adds to the data of the two existing randomized controlled trials.[7, 8] Chauduri and Datta randomized 110 women with fetal death after more than 20 weeks of gestation (including those in the third trimester) to 200 mg of mifepristone followed by a misoprostol regimen of 100 micrograms vaginally every 6 hours in women at a gestational age of less than 26 weeks and 50 micrograms vaginally every 6 hours in women at a gestational age of more than 26 weeks. Despite a differing misoprostol regimen, they also found a reduction in time to delivery of the fetus after the commencement of misoprostol (16.3 hours compared, with 9.8 hours when mifepristone used, *P*,.001). [7]

A further randomized trial was published in 2020 by Bracken et al that used 200 micrograms of buccal misoprostol every 3 hours after mifepristone pretreatment at a gestational age range of 14-28 weeks. The authors reported completion of the delivery process by 48 hours in 82.2% of women in the mifepristone arm compared with 81.4% of women in the placebo trial arm (*P*5.887); however, the median duration of delivery was significantly shorter in the mifepristone arm (7 hours vs 12 hours, *P*,.001).

In a cohort of 96 patients, Wagaarachchi et al[12] found that mifepristone before misoprostol for induction after a fetal death after 24 weeks of gestation resulted in an average time-to-delivery of 8.5 hours, although there was no control group. A 2007 retrospective study that compared mifepristone and misoprostol with misoprostol alone (with a variety of doses) in fetal death found a reduction in time to delivery in the mifepristone group only among those with gestational ages between 21-25 weeks.[13] In their retrospective cohort study, Fyfe and Murray[14] report a shorter duration of labor with the use of mifepris tone before induction after 20 weeks of gestation, although it should be noted that only 20% of patients in the mifepristone treatment group had experienced a fetal death before induction. In addition to this, a nonblinded trial conducted in Nepal showed that the use of mifepristone after a fetal death from 20 weeks of gestation onward decreased the dose of misoprostol required, but not the total time from commencement of misoprostol to delivery.[15] Two further prospective but nonblinded randomized trials in women with gestational ages of more than 28 weeks and with a fetal death demonstrated a shorter time to delivery and fewer doses of misoprostol needed after use of mifepristone. [16, 17]

Before conducting this trial, given the existing data for the use of mifepristone at similar gestational ages in pregnancies with a live fetus and considering the antiprogesterone action of mifepristone, we hypothesized that the potential change in maternal serum progesterone levels after the occurrence of fetal death may affect the efficacy of mifepristone. However, we found no difference in maternal serum progesterone levels between the placebo and mifepristone groups, and our findings reflect those found in similar trials with live fetuses. . In their double blinded trial, Ngoc et al[4] randomized 260 women with a live fetus between 14 and 21 weeks of gestation to 200 mg mifepristone or placebo, followed by 400 micrograms misoprostol, buccally, every 3 hours and showed a reduction in the median interval to delivery in the treatment (8.1 hours vs 10.6 hours, *P*,.001). Dabash et al[5] also used 200 mg mifepristone or placebo before 400

micrograms misoprostol buccally every 3 hours in women with a live fetus between 14 and 21 weeks of gestation and found a reduction in delivery 10.466.6 hours in the group that received mifepristone, compared with 20.669.7 hours in the misoprostol alone group (*P*,.001).

Although there was no difference in the maternal complications between the two groups, the risk and incidence of complications associated with medical termination of pregnancy in the second trimester must be an important component of clinical decision making. Our findings of a 29.7% retained placenta rate, a 26.5% need for manual removal of placenta, and 18.3% incidence of blood loss greater than 500 mL are more than what was found by Dickinson et al in women who were undergoing termination between 14 and 24 weeks of gestation[9] and need to be considered when counselling patients. Although there was an improvement in the time from misoprostol to delivery in the treatment group, there were no significant differences between the two groups in either the total amount of time spent in hospital or the time from commencing misoprostol to leaving the hospital.

Women who received misoprostol had a better opinion of the procedure than those who received placebo, although neither rate it well. This is a significant finding, although we are limited in our ability to comment on the reasons both the ratings and the differences were observed in our trial. We appreciate the clinical circumstance of an unexpected fetal death may have contributed significantly to this. Moreover, some evidence suggests that women's experience of a medical (as opposed to surgical) termination of pregnancy worsens with increasing gestational age, [18] and this may be reflected here in the scores in both groups of women. It is also plausible that the relatively short time to delivery in the mifepristone group goes some way to account for the improved perception of the procedure in these women. Perception scores in all four categories in both groups of women were worse in our trial compared with the sequential mifepristone misoprostol trial in the second trimester of Dickinson et al,[9] although with the notable difference of planned medical termination of pregnancy in that trial compared with the occurrence of unexpected fetal death in our group of women. The fact that women in our trial did not have a particularly good impression of control nor did they want to recommend the procedure to a friend may be a function of the clinical scenario that these women were experiencing.

This trial has several strengths. Randomization, allocation concealment and blinding were maintained throughout the trial. The gestational age range included is greater than any other single trial of mifepristone that includes women in the second trimester with a fetal death. Moreover, the mifepristone dose used is the same as the other randomized trial in fetal death in the second trimester, adding to the robustness of evidence for its use in this clinical scenario.

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