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Journal

Contraception, 104(4)

ISSN

0010-7824

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Publication Date

2021-10-01

DOI

10.1016/j.contraception.2021.04.023

Peer reviewed

HHS Public Access

Author manuscript

Contraception. Author manuscript; available in PMC 2023 June 28.

Published in final edited form as:

Contraception. 2021 October ; 104(4): 432–436. doi:10.1016/j.contraception.2021.04.023.

The effect of mifepristone pretreatment on bleeding and pain during medical management of early pregnancy loss

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Abstract

Objectives: To compare participant-reported bleeding and pain with two medication regimens for early pregnancy loss (EPL).

Study Design: We performed a secondary analysis of a randomized trial in which participants took either mifepristone 200 mg orally followed by misoprostol 800 mcg vaginally 24 hours later or misoprostol alone for medical management of EPL. Participants reported bleeding and pain (Numeric Pain Rating Scale, NPRS, 0–10) with daily paper diaries and at study visits on trial days 3, 8, and 30. We used, Fisher's exact, Pearson chi-square, Wilcoxon rank sum, and Student's *t* -tests to compare onset, duration, and severity of bleeding and pain symptoms between trial arms after misoprostol administration.

Results: Among 291 participants who submitted diary data, 143 received mifepristone pretreatment. A larger proportion of this group reported moderate or heavy bleeding on trial day 2, the day of misoprostol administration, compared with those who did not receive pretreatment (73% vs 47%, $p < 0.01$). Between days 4 and 8, more mifepristone-pretreatment participants reported mild or no bleeding, compared with the misoprostol-only arm (78% vs 61%, $p < 0.01$). Average pain score for trial days 2–4 was higher for the pretreatment group compared with the misoprostol-only group (6.9 vs 6.0, $p = 0.01$), and there was a trend toward shorter total duration of pain (15 vs 19 hours, $p = 0.08$). These differences remained after controlling for treatment success across arms.

Conclusions: Mifepristone pretreatment increased the severity of pain but not bleeding and resulted in a shorter trajectory of symptoms during medical management of EPL.

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Declaration of Competing Interest

Dr. Schreiber has received consulting fees from Danco Laboratories. No other potential conflict of interest relevant to this article was reported.

Implications: Mifepristone pretreatment decreases the duration of heavy bleeding and there was a trend toward decreased duration of pain during medical management of miscarriage, indicating that this medication improves the efficiency, in addition to the efficacy, of this treatment.

Keywords

Bleeding; Early pregnancy loss; Mifepristone; Miscarriage; Misoprostol; Pain

1. Introduction

First-trimester early pregnancy loss (EPL) occurs commonly, and hemodynamically stable patients may opt for active medical or surgical management [1]. Medication is a safe, expedient, and private management option. Compared with suction curettage, individuals undergoing medical management with misoprostol report heavier, prolonged bleeding and have lower hemoglobin levels two weeks after treatment (−0.7 vs −0.2 g/dL, $p < 0.01$) [2]. Individuals undergoing misoprostol treatment reported abdominal pain more frequently (99% vs 95%, $p < 0.01$) and rated pain severity higher within two days of treatment (5.7 vs 3.2 on a 10-cm visual analog pain scale) compared with aspiration [3]. These data can inform anticipatory guidance about bleeding and pain when using misoprostol for medical treatment of EPL, which can confirm that medication is the appropriate treatment choice, as well as provide safety thresholds for when to seek medical care.

A randomized controlled trial demonstrated that a combined regimen of mifepristone pretreatment and misoprostol therapy improves treatment success compared with misoprostol alone [4]. Mifepristone pretreatment has thus become the standard of care [1]. However, whether mifepristone modulates bleeding and pain during EPL management is unknown.

2. Material and methods

2.1. Study design

We performed a secondary analysis of data from a randomized clinical trial of medical management of EPL, the Comparative Effectiveness of Pregnancy Failure Management Regimens (PreFaiR) trial [4]. In this multisite clinical trial, 300 women diagnosed with EPL between 5 and 12 completed weeks' gestation desiring medical management were randomized to mifepristone 200 mg oral pre-treatment, or no medication, on trial day 1. Women with incomplete or inevitable abortion or with a hemoglobin level below 9.5 g/dL were excluded. Participants were instructed to self-administer misoprostol 24 hours after mifepristone, on trial day 2. Although some variability existed in the actual timing of misoprostol administration [5], for simplicity and clarity in this secondary analysis, we have described the day of misoprostol administration as trial day 2 throughout this manuscript.

We assessed the effect of mifepristone pretreatment on the individual experience of bleeding and pain. We collected variables at several time points during follow-up. First, starting on trial day 1, participants filled out once daily paper diaries, which they submitted at study visits, and stopped once treatment was determined to be successful (which, for the

majority of participants, occurred at their trial day 3 study visit). In these daily diaries, participants reported onset, duration, severity of vaginal bleeding and pelvic pain, as well as usage of pain medications. Participants were eligible for this secondary analysis if they submitted diary data on trial day 2. Second, participants presented in person on trial day 3, at which time we used ultrasound to evaluate for treatment success, defined as absence of a gestational sac on ultrasound. Third, participants had telephone follow-up on trial days 8 and 30, at which points they reported a cumulative presence and severity of bleeding and pain since the previous evaluation. Participants reported, both in their daily diaries and at their study visits, if they called a doctor, visited an outpatient clinic, or went to an emergency room ("need for medical attention"), and study staff classified these events as bleeding-related, pain-related, or due to other reasons.

2.2. Bleeding outcome variables

In each daily diary on trial days 2, 3, and 4, participants recorded the severity of their bleeding as "none," "spotting," "light," "moderate," or "heavy." We grouped "spotting" and "light" into a single category that we considered "mild" and compared proportions of participants reporting bleeding in each category on each trial day. On trial day 2, participants recorded the time of misoprostol administration and the time of onset of bleeding; the hours elapsed until bleeding onset was calculated as the difference between these times. On day 8, participants reported a cumulative assessment of bleeding since day 3, which was categorized as "none," "mild," "moderate," or "severe," and we compared proportions of participants reporting bleeding in each of these categories. On day 30, participants reported the presence of any bleeding since day 8. We also report the maximum category of reported bleeding – none, mild, moderate, heavy or severe – from either the daily diaries or the day 8 survey) and the first trial day that this was reported. Transfusion information was recorded as part of our assessment of serious adverse events and was verified via medical records review.

2.3. Pain outcome variables

In each daily diary on trial days 2, 3, and 4, participants recorded time of onset, duration, and severity of pain. On trial day 2, participants recorded the time of misoprostol administration and the time of onset of pain; the hours elapsed until pain onset was calculated as the difference between these times. Pain severity was reported using a Numeric Pain Rating Scale (NPRS, 0–10), and we calculated an average over trial days 2, 3, and 4. We also determined the highest recorded pain score and report the trial day on which participants reported that score. Participants recorded the number of hours of pain that they had each day, and the total duration of pain was calculated as a sum of these numbers over trial days 2, 3, and 4. In each daily diary, participants also reported the quantity of pain medication prescribed by the study clinicians (ibuprofen and acetaminophen with codeine) that they used.

2.4. Statistical approach

We used Student's t-tests or Wilcoxon rank sum tests to compare continuous variables and Pearson chi-square or Fisher's exact tests to compare categorical variables across treatment arms. We tested for differences in demographic and baseline factors between the study groups and performed bleeding analysis comparisons while controlling for treatment success

using logistic regression and generalized linear models. Analyses were performed using Stata 14.2 (StataCorp, College Station, TX).

3. Results

We received complete diary data on trial day 2 from 291 participants, all of whom also completed the day 30 assessment. We received diary data from 265 participants on trial day 3 and from 182 participants on trial day 4. Missing data were excluded from the analyses. The study arms were similar with respect to age, race, and other baseline variables (Table 1).

3.1. Bleeding outcomes

Bleeding severity differed between arms at trial day 2 and from 4 to 8 (Fig. 1). On the day of misoprostol administration, trial day 2, 105 (73%) reported moderate or heavy bleeding in the mifepristone-pretreatment arm, compared with 69 (47%) in the misoprostol-only arm ($p < 0.01$). Between days 4 and 8, moderate or severe bleeding was reported by 31 (22%) in the mifepristone-pretreatment arm and 58 (39%) in the misoprostol-alone arm ($p < 0.01$). The same proportion (26%) of participants across arms reported maximum bleeding by day 8 as heavy or severe, while participants in the mifepristone-pretreatment arm were more likely to report mild maximum bleeding compared with those in the misoprostol-only arm (49% vs 36%, $p = 0.05$) (Table 2). Time to onset of maximum bleeding was shorter in the mifepristone-pretreatment arm (77% vs 51% reaching maximum bleeding on trial day 2, $p < 0.01$). Bleeding-related need for medical attention did not differ by arm and primarily represented participant concerns that were managed by telephone. Three (2.1%) participants in the mifepristone-pretreatment arm required a blood transfusion, compared with one (0.7%) in the misoprostol-only arm ($p = 0.31$).

3.2. Pain outcomes

The maximum reported pain (7.7 vs 7.3, $p = 0.17$) was similar across treatment arms, but mean daily NPRS score during trial days 2, 3, and 4 was higher in the mifepristone-pretreatment arm (NPRS score 6.9 vs 6.0, $p = 0.01$) (Table 2). Mifepristone pretreatment had a trend toward a shorter total duration of pain during trial days 2, 3, and 4 (15 vs 19 hours, $p = 0.08$). Proportion of participants who used the prescribed ibuprofen and acetaminophen with codeine to manage pain did not differ by study arm (Table 2). Pain-related need for medical attention also did not differ by arm.

4. Discussion

In this study, we compared self-reported bleeding and pain in women undergoing medical management for EPL with mifepristone pretreatment versus those using misoprostol alone. We found that mifepristone pretreatment reduced the time to maximum bleeding, with three-quarters of participants in this arm reporting maximum bleeding on the day of misoprostol administration, and may reduce total duration of pain (by 4 hours, $p = 0.08$), suggesting that, in addition to increasing the efficacy of medical management of EPL, it also increases its efficiency.

Mifepristone is a competitive antagonist at the progesterone receptor; it increases uterine contractility and sensitizes the myometrium to prostaglandin, priming the uterus for misoprostol administration [6]. These mechanisms of action may explain why on-set to maximum bleeding was quicker and average NPRS scores higher in the mifepristone-pretreatment arm compared with the misoprostol-alone arm. In addition, these effects may induce the uterus to expel pregnancy tissue more efficiently, ultimately shortening the time to maximum bleeding and total duration of pain after misoprostol administration.

Previous prospective studies on medical management of EPL with misoprostol have described average bleeding durations of 7 to 12 days after misoprostol use [2,7,8,9,10]. However, these likely underestimate true durations of bleeding due to their short follow-up periods. Davis et al. found that 90% of participants using misoprostol 800 mcg vaginally for EPL reported any bleeding after 1 week, with 1/3 reporting heavy bleeding, and half of participants reported any bleeding between days 15 and 30 after misoprostol administration [2]. Our results were comparable and had similar limitations, as we collected data prospectively until ultrasound confirmation of the gestational sac expulsion; as a result, neither of our studies adequately measured total bleeding duration. It is possible that mifepristone has an effect on this outcome, but this needs to be better assessed prospectively.

Studies of vaginal misoprostol for EPL have reported single visual analog scale scores (VAS) of 5.7 and 5.9 within 1 or 2 days after treatment [3,7], although they do not specify whether this describes average or maximum pain. Our NPRS scores exceeded these values, both on average and at their maximum. This may be due to differences in timing of pain reporting in relation to misoprostol administration, or to our use of the NPRS rather than the VAS. These two pain scales are usually highly correlated, but discrepancies can occur and usually involve higher NPRS compared with VAS scores [11]. The maximum pain we observed (NPRS score of 7.5 across all participants, with no difference between arms) was comparable to the maximum pain described during medication abortion (NPRS score 8) [12].

The majority of our participants used both the prescribed ibuprofen and acetaminophen with codeine. Pain medication regimens have not been well studied in medical management of miscarriage and no standard protocol exists [1]. However, opioids do not improve pain with medication abortion and given the overdose risks with these medications, we have extrapolated from these data and now prescribe ibuprofen alone without routine opioids for medical management of miscarriage. Mifepristone appears to slightly worsen overall pain severity after misoprostol, although it does not affect the maximum pain reported, highlighting the need to identify a superior analgesic regimen to ibuprofen for patients using medication to manage EPL.

This study had the following limitations. First, our prospective follow-up through daily diaries was truncated after determination of treatment success, as described above, which prevented us from measuring the total number of bleeding days and from fully describing the trajectory of bleeding severity. We attempted to estimate this trajectory by using data from the day 8 assessment, but this was retrospective, cumulative, and used different terminology from the daily diary assessments (e.g. “severe” rather than “heavy”). Second,

the daily diary assessments themselves required recall of timing and duration of bleeding and pain over the day; real-time reporting rather than paper diaries might provide more exact estimates of these events. Third, participant bleeding severity was self-reported and subjective. We did not collect hemoglobin levels after enrollment and thus cannot report a quantitative measure of blood loss. Finally, serious adverse outcomes during EPL medical management are rare and our sample size was not large enough to detect differences in rates of clinically significant events, such as hemorrhage, blood transfusion, emergency room visit, and hospital admission that also contribute to the patient experience of bleeding and pain.

Our results add to the existing literature describing bleeding and pain during medical management of EPL by evaluating the effect of mifepristone pretreatment. Patients using this regimen can expect to have onset of bleeding within 2–3 hours of misoprostol administration and are most likely to have their heaviest bleeding and most severe pain on that day. This analysis shows that when compared with misoprostol alone, mifepristone pretreatment increases patients' initial bleeding severity and average pain severity, but reduces time to maximum bleeding and may reduce total pain duration. Thus, for patients experiencing EPL, mifepristone not only improves the likelihood of treatment success but also lessens the duration of the associated symptoms.

Acknowledgments

We would like to acknowledge our other PreFaiR trial site investigators, Dr. Mitchell Creinin (University of California, Davis) and Dr. Jessica Atrio (Albert Einstein College of Medicine).

Funding

Funded by the National Institute of Child Health and Human Development; PreFaiR ClinicalTrials.gov number, NCT02012491.

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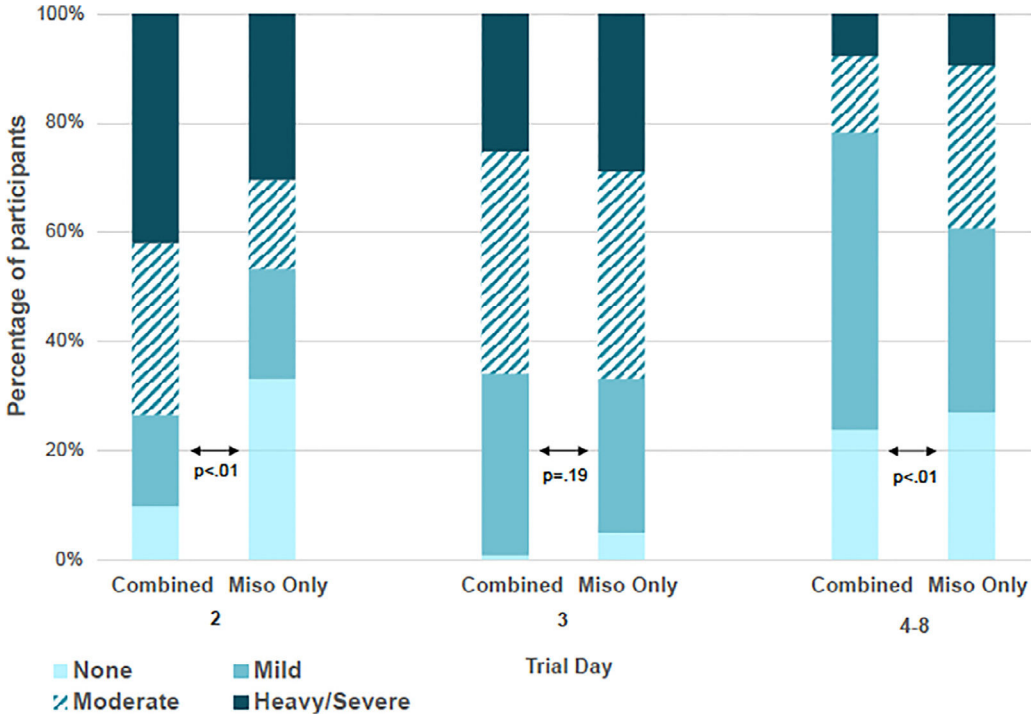

Fig. 1.

Participant-reported bleeding severity after misoprostol administration by study arm (mifepristone-pretreatment vs misoprostol-only) during medical management of early pregnancy loss. *Misoprostol administration occurred on trial day 2.

Table 1

Demographics of participants reporting bleeding and pain experiences in a randomized controlled trial of medical management of early pregnancy loss

	Total (*N* = 291) *N* (%)	Mifepristone pretreatment (*n* = 143) *n* (%)	Misoprostol only (*n* = 148) *n* (%)	*p*-value[a]
Age				0.53
18–29	116 (40)	54 (38)	62 (42)	
30–39	157 (54)	78 (54)	79 (53)	
40+	18 (6)	11 (8)	7 (5)	
Race				0.71
Black	127 (44)	60 (42)	67 (45)	
White	107 (37)	56 (39)	51 (35)	
Other	57 (20)	27 (19)	30 (20)	
Insurance[b]				0.36
None	23 (8)	12 (8)	11 (7)	
Public	139 (48)	62 (44)	77 (52)	
Private	128 (44)	68 (48)	60 (41)	
Education[b]				0.08
Some grade/high school	27 (9)	10 (7)	17 (12)	
High school diploma	96 (33)	41 (29)	55 (37)	
Some college	167 (58)	91 (64)	76 (51)	
Parity				0.13
P0	111 (38)	61 (43)	50 (34)	
P1+	180 (62)	82 (57)	98 (66)	
Prior miscarriage				0.94
No	189 (65)	93 (65)	96 (65)	
Yes	102 (35)	50 (35)	52 (35)	
Gestational age				0.17
<7w0d	107 (37)	59 (41)	48 (33)	
7w0d to 8w6d	139 (48)	60 (42)	79 (53)	
9w0d to 12w6d	45 (15)	24 (17)	21 (14)	
Active bleeding at time of diagnosis				0.93
No	257 (88)	126 (88)	131 (89)	

	Total (*N* = 291) *N* (%)	Mifepristone pretreatment (*n* = 143) *n* (%)	Misoprostol only (*n* = 148) *n* (%)	*p*-value[a]
Yes	34 (12)	17 (12)	17 (11)	

[a] Pearson chi-square test

[b] Missing data from one participant in the mifepristone pretreatment arm.

Table 2

Participant-reported bleeding and pain experiences in a randomized controlled trial of medical management of early pregnancy loss

	Total (*N* = 291) *N* **(%), mean ± SD median [IQR]**	**Mifepristone pretreatment (*n* = 143)** *n* **(%), mean ± SD, median [IQR]**	**Misoprostol only (*n* = 148)** *n* **(%), mean ± SD, median [IQR]**	***p*-value**
Bleeding				
Hours elapsed from misoprostol administration to onset of bleeding	2.3 [1.0–3.8]	2.2 [1.0–3.4]	2.5 [1.0–4.0]	0.36[a]
Maximum category of bleeding recorded by day 8				0.05[b]
None	4 (1)	2 (1)	2 (1)	
Mild	123 (42)	70 (49)	53 (36)	
Moderate	88 (30)	34 (24)	54 (36)	
Heavy/severe	76 (26)	37 (26)	39 (26)	
Number of participants reporting onset of maximum bleeding on:				< 0.01[b]
Trial day 2	185 (64)	110 (77)	75 (51)	
Trial day 3	84 (29)	26 (18)	58 (39)	
Trial day 4 or later	22 (8)	7 (5)	15 (10)	
Any bleeding between days 8–30	138 (47)	64 (44)	74 (50)	0.34[c]
Need for medical attention due to bleeding between days 1–30	18 (6)	10 (7)	8 (5)	0.59[b]
Pain				
Hours elapsed from misoprostol administration to onset of pain	1.7 [0.8–3.0]	2.0 [0.8–3.0]	1.5 [0.8–3.0]	0.80[a]
Mean daily NPRS score during trial days 2–4	6.4 (3.0)	6.9 (2.8)	6.0 (3.1)	0.01[d]
Maximum daily mean NPRS score during trial days 2–4	7.5 (2.4)	7.7 (2.2)	7.3 (2.5)	0.17[d]
Number of participants reporting highest NPRS score on:				0.08[c]
Trial day 2	198 (68)	106 (74)	92 (62)	
Trial day 3	59 (20)	22 (15)	37 (25)	
Trial day 4 or later	34 (12)	15 (10)	19 (13)	
Duration of pain after misoprostol (hours)	16 [6–39]	15 [6–34]	19 [6–39]	0.08[a]
Ibuprofen use	243 (83)	124 (86)	119 (80)	0.19[c]
Acetaminophen with codeine use	194 (66)	96 (67)	98 (66)	0.94[c]
Need for medical attention due to pain between days 1 and 30	22 (8)	9 (6)	13 (9)	0.41[b]

SD: standard deviation

IQR: interquartile range

NPRS: Numeric Pain Rating Scale

[a] Wilcoxon rank sum

[b] Fisher's exact

[c] Pearson chi-square

[d] Student's t-test.