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Original Research Article

Two prophylactic pain management regimens for medical abortion ≤63 days' gestation with mifepristone and misoprostol: A multicenter, randomized, placebo-controlled trial

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ABSTRACT

Objective: To determine if either prophylactic tramadol 50 mg or ibuprofen 400 mg/metoclopramide 10 mg result in lower maximal pain compared to placebo in women ≤63 days' gestation having a mifepristone-misoprostol medical abortion.

Study design: We conducted a randomized, placebo-controlled trial in Nepal, South Africa, and Vietnam. Participants seeking medical abortion received active treatment or placebo, taken at time of misoprostol and repeated 4 hours later. All had access to additional analgesia. The primary outcome was mean maximum pain score within 8 hours. Participants self-assessed maximum pain using an 11-point numeric rating scale recorded in paper diaries; we analyzed these data using intention-to-treat analysis. Secondary outcomes included use of additional analgesia, side effects, and satisfaction.

Results: We enrolled 563 patients between June 2016 and October 2017; 5 participants failed to follow up. Mean adjusted maximum pain scores within 8 hours in both active arms were lower than placebo (tramadol: $n = 188$, 6.78 (95% confidence interval [CI] 6.46, 7.11); ibuprofen/metoclopramide: $n = 187$, 6.43 (95% CI 6.10, 6.75); placebo: $n = 188$, 7.42 (95% CI 7.10, 7.74); $p = 0.0001$). Additional analgesia was used by 97 (52.2%) participants in the tramadol group, 80 (43.0%) in the ibuprofen/metoclopramide group, and 103 (55.7%) in the placebo group, $p = 0.04$. More dizziness ($p = 0.004$), headache ($p = 0.03$), and vomiting ($p < 0.001$) occurred in the tramadol group. More participants reported experienced pain was the same or less than expected in the ibuprofen/metoclopramide group ($p = 0.05$); overall abortion satisfaction did not differ by group ($p = 0.44$).

Conclusions: Compared with placebo, tramadol or ibuprofen/metoclopramide co-administered with misoprostol and repeated 4 h later resulted in lower mean maximum pain scores that failed to achieve clinical significance. Women who received ibuprofen/metoclopramide were least likely to use additional analgesia and reported fewer side effects.

Implications: Given that tramadol, ibuprofen, and metoclopramide are inexpensive, globally available; and, ibuprofen and metoclopramide are included on the World Health Organization Essential Medicines List, these medicines could be considered for prophylactic pain management during medical abortion.

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1. Introduction

The recommended regimen for medical abortion through 10 weeks' gestation is mifepristone 200 mg orally followed 24 to 48 hours later with misoprostol 800 mcg via buccal, vaginal, or sublingual routes [1]. This regimen is highly effective and safe, and home use offers flexibility and privacy to individuals seeking services. Treatment with mifepristone and misoprostol results in uterine contractions to expel a pregnancy; these contractions also cause pain. While women generally report tolerating pain accompanying medical abortion, it can be quite severe [2]. Options for pain management are varied; and studies have not identified a definitive regimen [3–6]. However, nonsteroidal anti-inflammatory drugs (NSAIDs) are routinely provided for pain management and typically initiated once pain begins [1,3,5]. Supplemental narcotics may also be prescribed, though they have limited value [6].

The emphasis on NSAIDs, particularly ibuprofen, as first-line treatment for pain accompanying medical abortion reflects current recommendations from the World Health Organization (WHO) and other public health and professional medical societies. WHO also identified that research to inform more pain management options for medical abortion, including additional medicines and evaluation of the timing of pain medication administration, is a priority [1]. We aimed to evaluate whether prophylactic administration of tramadol or ibuprofen plus metoclopramide are superior to placebo combined with analgesia administration after pain begins during the medical abortion process [7].

2. Materials and methods

We conducted a randomized, placebo-controlled trial in Nepal, South Africa, and Vietnam. Participants seeking medical abortion received active treatment or placebo, taken at time of misoprostol and repeated 4 hours later. All had access to additional analgesia. The primary outcome was mean maximum pain score within 8 hours. Participants self-assessed maximum pain using an 11-point numeric rating scale (NRS) recorded in paper diaries; we analyzed these data using intention-to-treat analysis. Secondary outcomes included use of additional analgesia, side effects, and satisfaction. The full study protocol has been published [7].

2.1. Study design

From June 2016 through October 2017, we conducted a multicenter, three-arm, randomized, placebo-controlled trial to examine whether the proposed pain management options reduce maximum reported pain scores associated with medical abortion compared to placebo. We stratified enrollment by parity and site. HRP (the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction) in Geneva, Switzerland, coordinated the trial centrally in collaboration with Gynuity Health Projects (New York, NY, USA), University of California San Francisco, and Ibis Reproductive Health (Cambridge, MA), and was implemented at 3 health centers in Nepal (Paropakar and Women's Hospital, Kathmandu), South Africa (Thlabane Health Center, Rustenburg), and Vietnam (National Hospital of Obstetrics and Gynecology, Hanoi).

The WHO Ethics Review Committee (Geneva, Switzerland), Nepal Health Research Council (Kathmandu, Nepal), Ministry of Health in Vietnam (Hanoi, Vietnam), Human Research Ethics Committee of the University of Witwatersrand (Johannesburg, South Africa), and Allendale Investigational Review Board (USA) approved the trial. We previously published the study protocol [7].

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2.2. Participants

On the day of service, we informed healthy patients requesting abortion about the study; if interested, we screened for eligibility. Inclusion criteria were age ≥18 years; intrauterine singleton live pregnancy ≤63 days' gestation via ultrasound; no allergies or other contraindications to study medicines; access to a time-keeping device; ability to adhere to study procedures, including home completion of a study diary to document symptoms; and, willingness to complete telephone/in-clinic follow-up; and provision of written informed consent. We recruited patients at sites where medical abortion services were well-established. We gave participants minimal remuneration for expenses related to telephone and clinic follow-up.

2.3. Randomization and masking

At enrollment, we sequentially assigned participants a unique subject ID according to parity, previously generated by the coordinating center. Each participant received a sealed, opaque bag, prelabeled with their corresponding subject ID containing misoprostol, study treatments, and supplemental analgesia for use as needed, all individually labeled and color-coded with instructions for use. Before the participant left the health center, research staff reviewed contents with participants using a sample package and provided detailed information about how to use the medicines; participants did not open the outer sealed opaque bag with study staff.

We randomly assigned treatments in a 1:1:1 ratio to either active treatment or placebo. The randomization sequence was stratified by parity and site and computer-generated using random permuted block sizes by the trial statistician at WHO/HRP. We communicated treatment assignments according to subject ID to a central supervising trial pharmacist and in-country partners who oversaw preparation of the sealed, pharmacy-grade treatment packages. Health care personnel and research staff were unaware of group assignment, as were participating patients.

2.4. Study procedures

At enrollment, participants provided demographic, medical, obstetric, and gynecological histories; we also recorded clinical information, including ultrasound results to confirm gestational age and exclude abnormal pregnancies. All participants took mifepristone 200 mg orally in clinic to initiate medical abortion and received instruction to use misoprostol 800 mcg at home 24 to 48 hours later via buccal, sublingual or vaginal routes according to standard practice at the site and participant preference.

Participants' treatment package contained misoprostol 800 mcg (4 × 200 mcg tablets), 2 doses of one of the following oral study treatments to be taken immediately prior to misoprostol and repeated 4 hours later: (1) tramadol 50 mg and one placebo pill; (2) ibuprofen 400 mg and metoclopramide 10 mg; or (3) 2 placebo pills. The package also included additional oral analgesia for use every 4 hours, as needed, including ibuprofen 400 mg (4 tablets) for mild to moderate pain and acetaminophen 500 mg/codeine 10 mg (2 tablets) for moderate to severe pain. All medicines were registered products in the country and produced by GMP-certified manufacturers (see Appendix A for details). Research staff counseled participants on use of the medicines, performance of periodic pain assessments, completion of the medication and symptom diary, and when and how to contact the facility in case of emergency.

Research staff contacted participants by telephone 3 to 5 days after enrollment to determine the maximum level of pain participants recorded during the first 8 and 24 hours after misoprostol, assess adherence to the treatment regimen, and use of sup-

plemental analgesia. We asked participants to return to clinic 14 days postenrollment (range 10–21 days) to determine abortion status via clinical assessment with or without ultrasound, review and collect their diary, and complete a questionnaire about the acceptability of the abortion process and study drugs. At the follow-up visit, we resolved any discrepancies in data collected at the time of telephone contact, recorded in the participant diary, or reported in person. If the abortion was not complete at the follow-up visit, some participants returned for subsequent visits.

Research staff recorded data on paper forms and then double-entered data into OpenClinica, a GCP-compliant, password-protected, web-based application for data entry and management. Queries for missing data, data errors, and inconsistencies were automatically generated and resolved accordingly by the local data manager with the assistance of the WHO/HRP clinical trial manager.

2.5. Outcomes

The primary outcome was maximum self-reported pain during the first 8 hours after misoprostol. Participants rated their pain using an eleven-point (0–10) NRS. Secondary outcomes included maximum self-reported pain during the first 24 hours after misoprostol, any use of supplemental analgesia, and the effectiveness of the medical abortion regimen, defined as successful completion without additional intervention. We also evaluated acceptability of the pain management regimen and abortion process.

2.6. Statistical analysis

Previous research reported maximum pain scores with early medical abortion with mifepristone and misoprostol at 7, ranging from 5 to 8 [5,8,9]. Studies have also reported that the minimally clinically significant difference in pain scores to be between 1.5 and 2 [10]. In order to detect a 1.5 point-reduction in maximum pain scores in the first 8 hours, using a 2-sided alpha of 0.05 and power of 90% while accounting for 10% loss to follow-up, we needed 96 women in each study arm. To stratify by parity, we planned to enroll a total of 576 women: 192 patients per treatment arm, half of whom would be nulliparous. Each of our 3 sites planned to recruit a total of 192 participants, 64 to each treatment arm, half nulliparous.

We used SAS (Version 9.4) to conduct analyses. [11] We used an intention-to-treat approach for analysis of the primary outcome. One-way Analysis of Variance (ANOVA) was applied to compare crude group mean differences in primary and secondary continuous outcomes when assumptions were met. Median and interquartile range (IQR) were reported for non-normal continuous outcomes, with the Kruskal-Wallis test applied to test for significance comparing median outcomes. We used the generalized linear model with a normal distribution and an identity link to compare continuous pain score outcomes. For comparison of binary outcomes, a Chi-square test and a log-binomial multivariable regression model were applied to adjust for covariates. If the log-binomial model did not converge, a modified Poisson regression model with robust variance was used. *A priori* we planned for adjustment by site and parity in the multivariable model because of randomization stratification based on these factors. We excluded missing data from the analysis. Detailed statistical analyses have been described elsewhere [7].

An independent data safety and monitoring committee comprised of individuals with expertise in medical abortion, biostatistics, epidemiology, and ethics met to review results from an interim analysis according to the Haybittle-Peto rule and advised study continuation. We prospectively registered the trial with the Australian New Zealand Clinical Trials Registry, number ACTRN12613000017729.

3. Results

Of 694 patients screened, 131 (19%) were ineligible; we enrolled 563 patients and randomly assigned them to tramadol, ibuprofen plus metoclopramide, or placebo (Fig. 1). Though our target sample was 576, we halted recruitment early due to slow recruitment of nulliparous women in South Africa. Overall, only 5 (0.9%) participants failed to follow-up and 2 (0.3%) participants withdrew.

Participants' baseline characteristics were similar across treatment groups (Table 1). Nulliparous women tended to be younger with lower BMI, more frequently single, and reported greater educational attainment than their parous counterparts (see Appendix B). Nulliparous participants also reported higher average pain scores for menstrual cramps with more frequent use of medicines to manage this pain. Fewer nulliparous participants reported a prior abortion or medical abortion, and, among those that had, average pain scores with the experience were higher than those reported by parous participants.

Table 1 also shows participant characteristics at initiation of medication abortion. The majority was pregnant at ≤49 days' gestation and denied having pain at the time of mifepristone ingestion. Just over one-third of all participants received progestin-only contraception, predominantly a progestin-only injectable, on the day of mifepristone prior to leaving health centers.

Table 2 shows the unadjusted maximum pain scores in the first 8 and 24 hours after misoprostol, as well as use of any additional analgesia. Fewer women receiving either tramadol or ibuprofen plus metoclopramide reported severe pain with their medical abortion (score ≥8) in either interval, as well as use of supplemental analgesia—particularly those receiving ibuprofen plus metoclopramide. The number of additional tablets of analgesia taken did not differ by treatment group. Table 3 shows the maximum pain scores in the first 8 and 24 hours after misoprostol adjusted for center and parity. Participants receiving tramadol (mean adjusted pain score 6.78, 95% confidence interval [CI] 6.46, 7.11) or ibuprofen plus metoclopramide (mean adjusted pain score 6.43, 95% CI 6.10, 6.75) reported significantly lower mean maximum pain scores compared with women receiving placebo (mean adjusted pain score 7.42, 95% CI 7.10, 7.74, $p = 0.0001$) within 8 hours of misoprostol use. Maximum pain scores in the first 24 hours were similar to those reported in the first 8 hours. Nulliparous women reported higher maximum pain scores compared to parous women in all treatment arms. A sensitivity analysis for participants using only sublingual misoprostol found no significant differences from the overall results using all routes of administration (see Appendices C-E for secondary analysis of primary and secondary outcomes among the sublingual misoprostol group).

Differences in mean maximum pain scores adjusted for center and parity were statistically significant for participants exposed to either treatment versus placebo at 8 and 24 hours (Fig. 2). This difference was larger for participants randomized to ibuprofen and metoclopramide compared to tramadol users, and it was highly significant across parity groups. Mean maximum pain scores were lower in the tramadol group compared to placebo only among parous participants. While pain scores among ibuprofen and metoclopramide users were lower than those reported by tramadol users, these differences were not statistically significant.

We found no differences in median time to pregnancy expulsion (tramadol: 3.6 hours, IQR 2.6, 5.8; ibu/met: 3.8 h, IQR 2.5, 5.8; placebo: 3.6, IQR 2.6, 5.0, $p = 0.90$) or complete medical abortion, defined as successful pregnancy expulsion without need for surgical intervention (tramadol: 173/185, 93.5%; ibu/met: 178/186, 95.7%; placebo: 177/184, 96.1%, $p = 0.71$). Table 4 shows reported

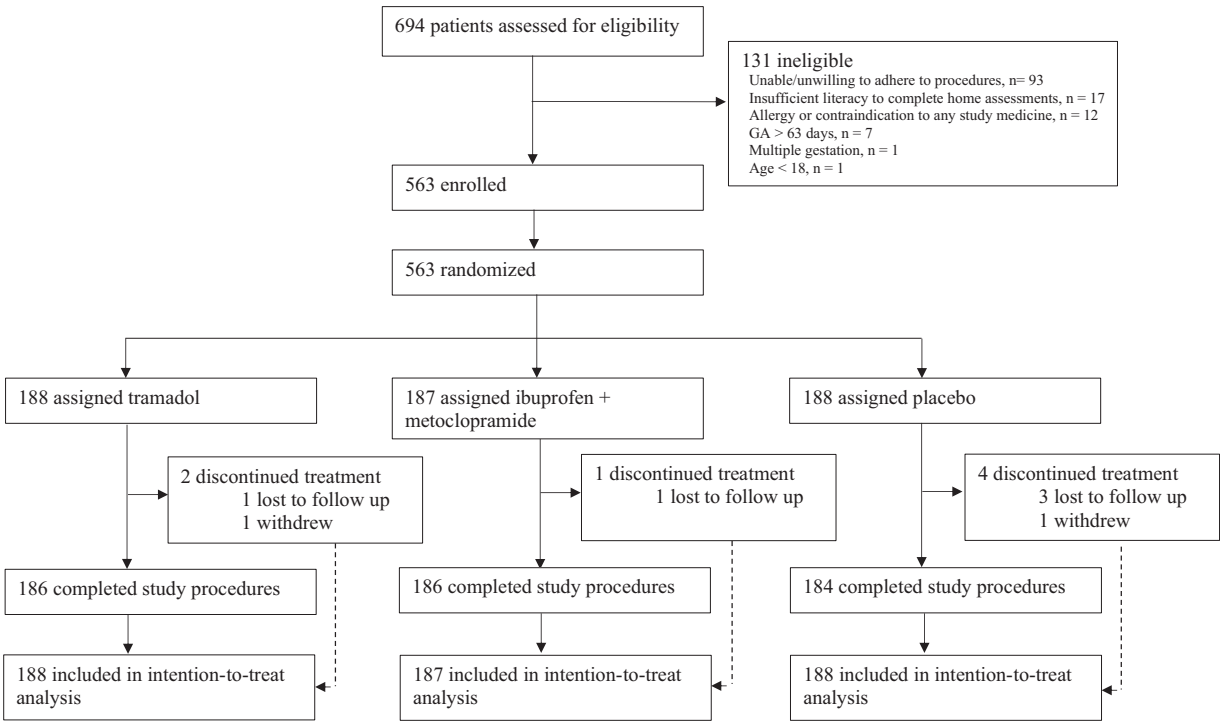


Fig. 1. Flow of participants through the trial of 2 prophylactic pain management regimens for medical abortion ≤63 days' gestation with mifepristone and misoprostol.

Table 1
Baseline characteristics of study participants seeking medical abortion and randomized to prophylactic administration of tramadol, ibuprofen plus metoclopramide, or placebo

	Tramadol (n = 188)	Ibu + Met (n = 187)	Placebo (n = 188)
Site			
Nepal	64 (34.0)	64 (34.2)	64 (34.0)
South Africa	60 (31.9)	59 (31.6)	60 (31.9)
Vietnam	64 (34.0)	64 (34.2)	64 (34.0)
Age (y)	25.6 ± 5.3	26.3 ± 5.8	25.6 ± 5.6
BMI (kg/m^2)	22.8 ± 4.8	22.8 ± 5.1	22.7 ± 5.1
Highest level of education			
Primary school	0 (0.0)	2 (1.1)	2 (1.1)
Secondary school	56 (29.8)	58 (31.0)	57 (30.3)
More than secondary	132 (70.2)	127 (67.9)	129 (68.6)
Currently in school	53 (28.2)	38 (20.3)	54 (28.7)
Partnership status			
Single	59 (31.4)	50 (26.7)	56 (29.8)
Married	100 (53.2)	100 (53.5)	95 (50.5)
Partnered	29 (15.4)	35 (18.7)	32 (17.0)
Divorced/Separated/Widowed	0 (0.0)	2 (1.1)	5 (2.7)
Nulliparous	92 (49.0)	91 (49.0)	92 (49.0)
Ever had vaginal birth	87 (46.2)	88 (47.0)	80 (42.5)
Ever had cesarean delivery	12 (6.3)	11 (5.9)	17 (9.0)
Ever had abortion	38 (20.2)	41 (21.9)	42 (22.3)
Ever had medical abortion	19 (10.1)	13 (6.9)	21 (11.2)
Mean pain score for menstrual cramps	3.2 ± 2.7	3.2 ± 2.7	3.5 ± 2.7
Mean pain score for most recent birth	7.4 ± 3.0	7.4 ± 3.0	7.0 ± 3.1
Mean pain score for prior medical abortion	6.1 ± 2.1	5.7 ± 2.3	6.8 ± 2.8
Expected mean pain score for index medical abortion	6.7 ± 1.9	6.8 ± 2.0	6.8 ± 2.0
Ever use of pain medicines for menstrual cramps	48 (25.5)	43 (23.0)	41 (21.8)
Ever use of pain medicines for other pain	89 (47.3)	84 (44.9)	93 (49.5)
Gestational age of index pregnancy (days)			
Up to 49 d	108 (57.4)	104 (55.6)	111 (59.0)
50–56 d	47 (25.0)	51 (27.3)	40 (21.3)
57–63 d	33 (17.6)	32 (17.1)	37 (19.7)
Contraception initiated on day of mifepristone			
Injectable	60 (31.9)	60 (32.1)	60 (31.9)
Implant	7 (3.7)	9 (4.8)	6 (3.2)
Route of misoprostol			
Buccal	4/187 (2.2)	2/186 (1.1)	3/185 (1.6)
Sublingual	172/187 (91.9)	172/186 (92.5)	173/185 (93.5)
Vaginal	11/187 (5.9)	12/186 (6.4)	9/185 (4.9)

BMI, body-mass index, Ibu, ibuprofen, Met, metoclopramide.
Data are presented as n (%), n/N (%) or mean ± standard deviation; all pain scores reported using a numeric rating scale, 0 to 10.

Table 2
Crude estimates of maximum pain scores and use of supplemental analgesia during the first 8 and 24 hours following misoprostol for participants undergoing medical abortion and randomized to prophylactic administration of tramadol, ibuprofen plus metoclopramide, or placebo

	Tramadol (n = 188)	Ibu + Met (n = 187)	Placebo (n = 188)	p-value
Interval: Misoprostol to 8 h				
Maximum pain score	6.75 ± 2.50	6.37 ± 2.64	7.38 ± 2.36	<0.001[a]
Maximum reported pain score ≥8	90/187 (48.1)	76/186 (40.9)	107/185 (57.8)	0.005[b]
Use of any supplemental analgesia	97/186 (52.2)	80/186 (43.0)	103/185 (55.7)	0.04[b]
Use of any ibuprofen	69/186 (37.1)	63/186 (33.9)	89/185 (48.1)	0.01[b]
Use of any codeine/acetaminophen)	59/186 (31.7)	45/186 (24.2)	56/185 (30.3)	0.24[b]
Number of supplemental ibuprofen tablets used				
0	117/186 (62.9)	123/186 (66.1)	96/185 (51.9)	0.06
1	53/186 (28.5)	49/186 (26.3)	66/185 (35.7)	
2 or more	16/186 (8.6)	14/186 (7.5)	23/185 (12.4)	
Number of supplemental codeine/acetaminophen tablets used				
0	127/186 (68.3)	141/186 (75.8)	129/185 (69.7)	0.34
1	46/186 (24.7)	37/186 (19.9)	40/185 (21.6)	
2 or more	13/186 (7.0)	8/186 (4.3)	16/185 (8.7)	
Interval: Misoprostol to 24 h				
Maximum pain score	6.76 ± 2.50	6.42 ± 2.66	7.43 ± 2.35	<0.001[a]
Maximum reported pain score ≥8	90/186 (48.1)	80/186 (43.0)	108/185 (58.4)	0.01[b]
Use of any supplemental analgesia	105/186 (56.2)	89/186 (47.9)	112/185 (60.5)	0.04[b]
Use of any ibuprofen	81/186 (43.3)	71/186 (38.2)	98/185 (53.0)	0.02[b]
Use of any codeine/acetaminophen	64/186 (34.2)	52/186 (28.0)	64/185 (34.6)	0.31[b]

Data are presented as n (%), n/N (%) or mean ± standard deviation; all pain scores reported using a numeric rating scale, 0 to 10. Participants could use ibuprofen and/or codeine/acetaminophen and had access to 4 doses of ibuprofen and 2 doses of codeine/acetaminophen.
h, hour, Ibu, ibuprofen, Met, metoclopramide, SD, standard deviation.
[a] ANOVA test p-value.
[b] Chi square p-value.

Table 3
Maximum pain scores during the first 8 and 24 hours following misoprostol, adjusted for center and parity, for participants undergoing medical abortion and randomized to prophylactic administration of tramadol, ibuprofen plus metoclopramide, or placebo

	Tramadol (n = 188)	Ibu + Met (n = 187)	Placebo (n = 188)	p-value[a]
Interval: Misoprostol to 8 h				
Maximum pain score (0–10), mean (95% CI)				
Overall	6.78 (6.46, 7.11)	6.43 (6.10, 6.75)	7.42 (7.10, 7.74)	<0.001
Nulliparous	7.69 (7.27, 8.10)	7.30 (6.88, 7.71)	8.13 (7.72, 8.54)	0.02
Parous	5.88 (5.40, 6.37)	5.55 (5.07, 6.04)	6.70 (6.21, 7.19)	0.004
Interval: Misoprostol to 24 h				
Maximum pain score (0-10), mean (95% CI)				
Overall	6.80 (6.47, 7.12)	6.48 (6.15, 6.80)	7.47 (7.14, 7.79)	<0.001
Nulliparous	7.70 (7.28, 8.11)	7.35 (6.93, 7.77)	8.19 (7.78, 8.61)	0.02
Parous	5.89 (5.41, 6.38)	5.60 (5.12, 6.09)	6.73(6.24, 7.22)	0.005

Data are presented as mean (95% confidence interval); all pain scores reported using a numeric rating scale, 0 to 10.
CI, confidence interval; h, hour; Ibu, ibuprofen; Met, metoclopramide.
[a] Type 3 Likelihood Ratio Test for group differences.

side effects, details of pain experience, and acceptability of the medical abortion. A lower proportion of ibuprofen plus metoclopramide users reported fever. Approximately one-third of participants reported nausea; however, fewer ibuprofen plus metoclopramide users experienced vomiting. Dizziness and headache were more common among tramadol users. More tramadol and ibuprofen plus metoclopramide users reported that the pain was about the same or less than they expected compared to placebo users. However, the majority of women were satisfied with the medical abortion process regardless of treatment; only 4 participants were somewhat or very dissatisfied.

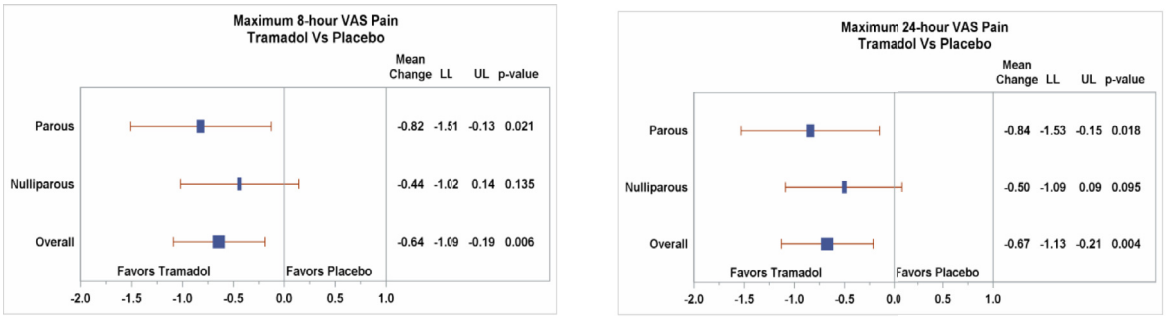
A number of participants reported other adverse effects during the trial; none exceeded a frequency of 5% (see Appendix F). One participant randomized to the placebo arm experienced a serious adverse event. After taking isoprostol and the first placebo pills, she experienced heavy bleeding which prompted her to seek hospital care. While awaiting care, she fainted and lacerated her forehead. The participant received intravenous fluids, a blood transfusion, uterine evacuation, and suturing of her wound. She was discharged in good condition.

4. Discussion

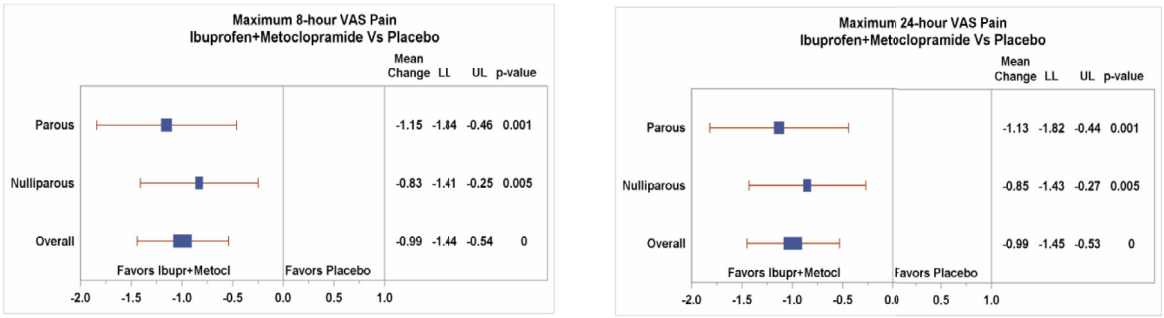
Pretreatment with tramadol or the combination of ibuprofen plus metoclopramide resulted in statistically significant lower mean maximum pain scores compared with placebo in this study but failed to achieve a clinically significant threshold (1.5 to 2 on NRS). However, participants exposed to treatment reported a maximum pain score ≥8 at a lower frequency, tended to use less additional analgesia, and more noted that their pain experience was the same or less than expected. Those randomized to ibuprofen plus metoclopramide also reported fevers and vomiting less frequently, not surprising given the antipyretic and antiemetic properties of the medicines. Taken together, it appears that participants pretreated with tramadol or ibuprofen plus metoclopramide derived some clinical benefit from their regimens.

Individual experiences with pain, responses to pain, and responses to analgesics are complex and can vary according to ethnicity, socioeconomic status, cultural factors, physiology, and genetics, among other things. Thus, the study of pain medicine regimens in diverse populations is critical to inform management. Though the report of pain is common with medical abortion, our

a.) Tramadol vs. Placebo



b.) Ibuprofen plus metoclopramide vs. Placebo



c.) Ibuprofen plus metoclopramide vs. Tramadol

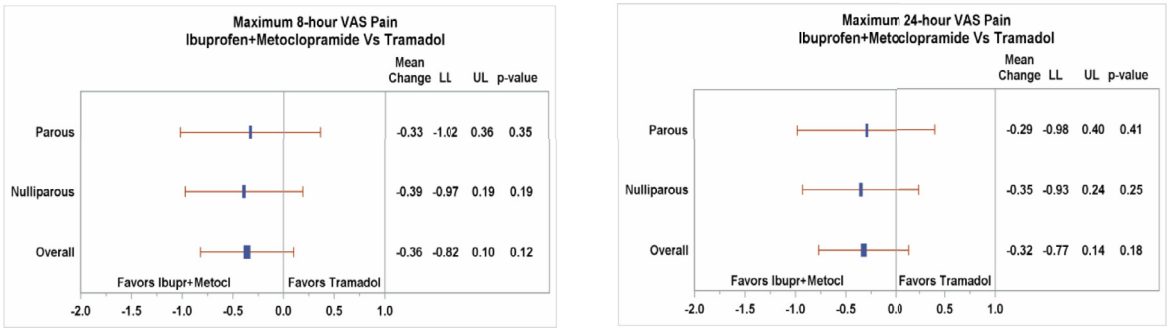


Fig. 2. Mean reduction in maximum pain scores at 8 and 24 hours among women receiving either tramadol or ibuprofen plus metoclopramide compared to placebo, and between treatment groups, overall and by parity, adjusted for center and parity. LL = lower limit, UL = upper limit.

investigation into optimal approaches to pain management is the first implemented in Africa and Asia. Prior studies have focused on populations of women in the United States, Canada, France, and Israel [3,5,12]. In a separate manuscript, we report on qualitative findings of study participants' experiences with the pain of medical abortion [13].

A priori, we planned to document pain experiences according to parity, a well-known factor influencing pain with medical abortion and other obstetrical or gynecological procedures [14]. Mean maximum pain scores among nulliparous women at both 8 and 24 hours were approximately 2 points higher compared to parous women. Interestingly, parous women experienced pain score reductions of greater magnitude with use of both treatments compared to nulliparous women.

Of the 2 treatments, we speculate prophylactic ibuprofen plus metoclopramide may offer greater advantage compared to tramadol based on trends we observed as well as likely ease of implementation. Though not statistically significant, we found that the magnitude of pain reduction was greatest among those exposed to ibuprofen plus metoclopramide compared to tramadol and the former reported a more favorable side effect profile. Additionally, ibuprofen and metoclopramide are included on the WHO Essential Medicines List, globally available, relatively inexpensive and unlike opioid medications, do not pose a risk of addiction. [15]. Given that both medicines are accessible, and ibuprofen is already endorsed for use in international and national guidelines, implementation of routine use of this regimen should be fairly easy.

Our study has several limitations. Although set in low- and middle-income countries, our study sample was comprised of rather well-educated participants due to the literacy required for adherence to study procedures, potentially limiting generalizability of our results. However, the education level among participants in our study was similar to that reported in other studies [5,12]. In studies evaluating predictors of pain with medical abortion, the effect of education and literacy have not routinely been studied; however, higher levels of literacy and education are frequently associated with less pain in other contexts [16,17]. It is possible that women with lower literacy might achieve different pain outcomes

Table 4
Reported side effects and acceptability of abortion and study medicines for study participants undergoing medical abortion and randomized to prophylactic administration of tramadol, ibuprofen plus metoclopramide, or placebo

	Tramadol	Ibu + Met	Placebo	*p*-value[a]
	n = 188	*n* = 187	*n* = 188	
Experience of side effects				
Fevers	56 (29.8)	38 (20.3)	64 (34.0)	0.01
Chills	107 (56.9)	100 (53.5)	119 (63.3)	0.15
Nausea	68 (36.2)	52 (27.8)	59 (31.4)	0.22
Vomiting	81 (43.1)	39 (20.9)	59 (31.4)	<0.001
Diarrhea	58 (30.9)	76 (40.6)	76 (40.4)	0.08
Dizziness	16 (8.5)	5 (2.7)	4 (2.1)	0.004
Headache	11 (5.9)	6 (3.2)	2 (1.1)	0.03
[b]Other	26	26	42	
Actual pain experience vs expectation				0.05
More than expected	61 (33.0)	42 (23.2)	68 (37.6)	
About the same	66 (35.7)	76 (42.0)	64 (35.4)	
Less than expected	58 (31.3)	63 (34.8)	49 (27.0)	
Qualitative description of overall pain experience				0.34
Mild	32 (17.3)	39 (21.5)	24 (13.2)	
Moderate	59 (31.9)	64 (35.4)	64 (35.4)	
Severe but bearable	66 (35.7)	49 (27.1)	60 (33.2)	
Unbearable	28 (15.1)	29 (16.0)	33 (18.2)	
Worst feature of medical abortion process				0.09
Nothing	88 (47.3)	106 (57.0)	86 (46.7)	
Pain	70 (37.6)	49 (26.3)	65 (35.3)	
Bleeding	15 (8.1)	25 (13.4)	26 (14.1)	
It did not work	1 (0.5)	1 (0.5)	1 (0.5)	
Other	12 (6.5)	5 (2.7)	6 (3.3)	
Overall satisfaction with medical abortion				0.44
Very satisfied	145 (77.9)	150 (80.6)	150 (81.5)	
Somewhat satisfied	36 (19.4)	30 (16.1)	26 (14.1)	
Neutral	4 (2.2)	4 (2.2)	7 (3.8)	
Somewhat dissatisfied	0 (0)	2 (1.1)	0 (0)	
Very dissatisfied	1 (0.5)	0 (0)	1 (0.5)	
Felt that study medicines improved pain				0.57
No	28 (15.1)	23 (12.4)	34 (18.5)	
Yes	141 (75.8)	143 (76.9)	134 (72.8)	
Not sure	17 (9.1)	20 (10.7)	16 (8.7)	

Data are presented as *n* (%).
Ibu, ibuprofen, Met, metoclopramide.
Columns may not total to full sample due to missing data; % is valid percent excluding missing data.
[a] Chi-square.
[b] See Appendix F for additional information.

with the same interventions. It is also possible that better pain outcomes overall might be achieved with higher doses of tramadol or ibuprofen plus metoclopramide; any improvements in pain at higher doses would need to be balanced by any increase in side effects.

Importantly, as most (81.9%) medical abortions occurred at ≤56 days in our sample; it is unclear what effects these regimens may have as gestational age increases beyond this range. In addition, most participants opted for sublingual misoprostol. This route is historically associated with more pain and side effects, perhaps explaining why we observed more pronounced effects compared to other studies of pain with medical abortion [18,19]. When we performed sensitivity analyses for participants exposed only to sublingual misoprostol, there was no significant deviation from the overall results. Despite some promise, significant proportions of participants reported severe-range maximum pain scores and used supplemental analgesia. This suggests an urgent need for further research into optimizing existing medical interventions, exploring other pharmacologic options, as well as evaluating other modalities for application to pain management during medical abortion to individualize care.

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Supplementary materials

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