Original Research

Cervical Preparation Before Dilation and Evacuation Using Adjunctive Misoprostol or Mifepristone Compared With Overnight Osmotic Dilators Alone

A Randomized Controlled Trial

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OBJECTIVE: To evaluate operative time after adjunctive misoprostol or mifepristone compared with overnight osmotic dilators alone for cervical preparation before dilation and evacuation at 16–23 6/7 weeks of gestation.

METHODS: This double-blind, three-arm, multicenter, randomized trial compared overnight osmotic dilators alone, dilators plus 400 micrograms buccal misoprostol 3 hours preoperatively, and dilators plus 200 mg oral mifepristone during dilator placement for dilation and evacuation. Our primary outcome was dilation and evacuation operative time within two cohorts: 16–18 6/7 weeks of gestation (N=150) and 19–23 6/7 weeks of gestation (N=150). Three hundred women were required for 80% power to detect a 2-minute difference in operative time. Secondary outcomes included initial cervical dilation, side effects, physician satisfaction by Likert scale, and complications.

RESULTS: Between February 2013 and February 2014 we randomized 300 women evenly across treatment arms. Group demographics were similar. We found no difference in operative time in either gestational cohort (early cohort [minutes]: 5.11±3.0 dilators alone, 4.99±3.3 misoprostol, 4.33±2.0 mifepristone, P=.34; late cohort [minutes]: 7.50±3.7 dilators alone, 7.62±5.4 misoprostol, 6.74±3.2 mifepristone, P=.53). In the early cohort, initial dilation was greater with misoprostol than dilators alone (2.4 compared with 2.0 cm, P=.007). Patients given misoprostol had significantly more pain, fever, and chills. In the late cohort, dilation and evacuation procedures were less difficult after mifepristone (4.1%, 95% confidence interval [CI] 0.0–9.6) than misoprostol (18.8%, 95% CI 7.7–29.8) or dilators alone (18.8%, 95% CI 7.7–29.8; P=.04). We had inadequate power to infer differences in complications: dilators alone (10%, 95% CI 4.2–16.0) compared with misoprostol (2%, 95% CI 0–4.7) compared with mifepristone (2%, 95% CI 0–4.8).

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CONCLUSION: Despite no difference in operative time, adjunctive mifepristone facilitates later dilation and evacuation compared with osmotic dilators alone and is better tolerated than misoprostol.

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In 2011, approximately 40,000 second-trimester abortions were completed by suction curettage or dilation and evacuation in the United States.[1] Dilation and evacuation is a safe procedure and complications are uncommon[2,3]; however, the risk of complications increases with gestational duration.[2] Preoperative cervical preparation is used routinely to reduce procedural risks, especially cervical laceration and uterine perforation.[4,5]

Osmotic cervical dilators are used routinely for cervical preparation and are effective.[6–8] The prostaglandin, misoprostol, is widely used with osmotic dilators before second-trimester dilation and evacuation,[9–11] yet limited data support this practice beyond 16 weeks of gestation.[12] One study gave adjuvant buccal misoprostol 90 minutes preoperatively and showed no benefit between 16–19 weeks of gestation but increased dilation at 19–21 weeks of gestation, suggesting a gestational effect.[13] The other study gave adjuvant buccal misoprostol 3 hours preoperatively and found no significant difference in dilation and evacuation procedure times at 21–23 weeks of gestation.[14] In the first trimester, misoprostol has no effect on cervical dilation after 60 minutes,[15] yet multiple studies show benefit after 3 hours.[16,17]

Mifepristone is effective for cervical preparation before first-trimester abortion.[18] A recent randomized trial compared overnight osmotic dilators plus mifepristone and misoprostol with 2 days of osmotic dilators plus misoprostol before dilation and evacuation at 19–23 6/7 weeks of gestation and found no difference in procedure time or initial cervical dilation between groups.[19]

We hypothesized that adjunctive misoprostol 3 hours preoperatively or mifepristone at the time of osmotic dilator placement would improve cervical preparation before dilation and evacuation at 16–23 6/7 weeks of gestation, making surgery easier and faster than preparation with osmotic dilators alone.

MATERIALS AND METHODS

We conducted a multicenter, three-arm, double-blind, randomized controlled trial of 300 women seeking surgical abortion. Enrollment was stratified by gestation into two groups: 16–18 6/7 weeks of gestation (N=150) and 19–23 6/7 weeks of gestation (N=150). Using computer-generated blocked randomization with a block size of six, women were assigned in a one-to-one-to-one ratio to receive: 1) overnight osmotic dilators alone; 2) overnight osmotic dilators plus adjunctive misoprostol; or 3) overnight osmotic dilators plus adjunctive mifepristone.

On day 1, after obtaining informed consent, research staff confirmed gestational duration by transabdominal ultrasound (biparietal diameter between 33.3 and 58.2 mm). Women in arms 1 (dilators alone) and 2 (misoprostol) received an oral placebo and women in arm 3 received 200 mg oral mifepristone. Within 30 minutes of medication administration, all women underwent osmotic dilator insertion according to standard clinical practice at each site utilizing laminaria (4 mm, medium) and Dilapan-S (a synthetic cervical dilator, 4×55 mm or 4×65 mm). The number and mix of osmotic dilators were at the discretion of the health care provider placing them, but only one set of dilators was permitted. No patients received a feticidal injection. On day 2, women in arms 1 and 3 received a placebo and women in arm 2 received 400 micrograms buccal misoprostol. All women held the two tablets buccally for 30 minutes and then swallowed any remaining fragments. The placebo and active study drug tablets were nearly identical in appearance and were administered by a staff member not involved in study dilation and evacuations. Study staff not involved in trial conduct prepared the sequentially numbered, opaque randomization envelopes containing the study medications. Patients, operating physicians, and research staff collecting data were blinded to treatment arm.

Abortions were started 3 hours (±30 minutes) after day 2 medication administration. After completing initial intraoperative outcome measurements, gynecologists experienced in providing dilation and evacuations completed all dilation and evacuations according to each site's standard clinical practices. Immediate postabortion intrauterine contraception was provided per the site's usual practices.

The protocol was approved by a central institutional review board (New England institutional review board) along with five individual academic institutional review boards. Patients were recruited at Family Planning Associates Medical Group, Chicago, Illinois; Planned Parenthood of New York City, New York; Women's Options Center, San Francisco General Hospital, San Francisco, California; Lovejoy Surgicenter, Portland, Oregon; Magee-Women's Hospital

of the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and Brigham and Women's Hospital and Boston Medical Center, Boston, Massachusetts. An independent data safety monitoring committee reviewed serious adverse events and overall study conduct.

We recruited English- or Spanish-speaking women ages 18 years and older seeking an abortion between 16 0/7 and 23 6/7 days of gestation who were able to give informed consent and eligible to have an outpatient surgical abortion at the clinical site. We excluded women if they were incarcerated or if they had a spontaneous fetal demise, chorioamnionitis, active heavy bleeding or hemodynamic instability, active labor or cervical insufficiency, or an allergy or contraindication to mifepristone or misoprostol.

Our primary outcome was dilation and evacuation operative time. We used a stopwatch to measure the time from the first instrument into the uterus until the last instrument was removed from the uterus. This outcome measures the time needed for complete uterine evacuation as well as additional cervical dilation if required. As a secondary outcome, the total procedure time was measured as the time from speculum insertion to removal of all instruments from the vagina. Total procedure time included time spent managing bleeding or other immediate complications. When an intrauterine device was inserted, the time was recorded to enable calculation of total procedure time that excluded the intrauterine device placement.

We measured initial cervical dilation as a secondary outcome. Starting with a 79-French Pratt dilator and moving sequentially to smaller dilators, the largest dilator to pass easily through the internal os without force was recorded as the initial cervical circumferential dilation. For women with initial dilation greater than 79 French, ovum forceps were placed within the internal os and opened to the widest diameter the cervix allowed. A sterile ruler was used to measure the distance between the thumb holes at the widest point. The physician then removed the forceps and opened the forceps again outside the patient to the recorded distance between the thumb holes. The distance between the tips of the forceps was measured from outer edge to outer edge and recorded as the diameter of initial cervical dilation. To provide a continuous measure of initial cervical dilation combining those measured with Pratt dilators and those measured with ovum forceps, we mathematically converted French units to diameter in millimeters. The physician next removed the speculum to complete a digital examination to assess cervical dilation, length, and consistency. The speculum then was reinserted and the timer started to measure both operative and total procedure time with the physician completing the dilation and evacuation as usual.

Study staff uninvolved in the abortion administered five serial questionnaires to assess patient pain, side effects, and acceptability at baseline, after osmotic dilator insertion, on arrival on day 2, after completion of the 3-hour waiting period, and postoperatively immediately before discharge. After each dilation and evacuation, the operating surgeon assessed satisfaction with the cervical preparation, overall procedural difficulty, and ease of additional dilation if required using a 5-point Likert scale: 1) very easy or very satisfied; 2) somewhat easy or satisfied; 3) moderate or neither satisfied nor dissatisfied; 4) somewhat difficult or dissatisfied; or 5) very difficult or very dissatisfied. Physicians were also asked to classify cervical preparation for each case either as adequate or inadequate. Blinding was assessed by asking patients and physicians to guess treatment arm. We recorded acute complications on the day of procedure. To capture additional complications, we contacted patients at 1 week and reviewed medical records at 1 week and 1 month postabortion.

We calculated sample size for the primary outcome of operative time. Allowing for missing data on 5% of the sample, to have 80% power to detect a 2-minute difference in operative time in each gestational cohort with a two-sided 0.05 significance level, we required a total sample size of 300 women: 150 between 16–18 6/7 weeks of gestation and 150 between 19–23 6/7 weeks of gestation.

We compared the primary outcome of operative time (three-arm comparison) using analysis of variance within each gestational cohort. Pairwise comparisons (one arm compared with another) were conducted using post hoc Tukey tests within each gestational age cohort. To adjust for multiple comparisons, the three pairwise treatment contrasts were made at the 0.017 (0.05/3) level. Analyses were adjusted for study site but not for any baseline variables. However, because prior vaginal delivery and prior cesarean delivery are thought likely to influence cervical priming, we examined the sensitivity of the treatment comparisons within each gestational cohort through an analysis of covariance that adjusts for these two factors.

Similarly, for analyses of secondary outcomes, we used analysis of variance and *t* tests to compare other approximately normally distributed continuous outcomes and used χ^2 and Fisher's exact tests to compare binary and ordinal outcomes in separate analyses

within each gestational cohort. Because complications were uncommon, to avoid problems of sparseness, we combined data across gestational strata for the purpose of treatment comparisons. A κ statistic was used to assess blinding and compare subject and physician guesses with actual treatment assignments. We used SAS 9.3 for all statistical analysis.

RESULTS

Between February 2013 and February 2014, we enrolled 300 participants who were randomly assigned to osmotic dilators alone (n=100), osmotic dilators plus adjunctive misoprostol (n=100), or osmotic dilators plus adjunctive mifepristone (n=100) (Fig. 1). Enrollment was stratified by gestation with 152 patients in the early gestational cohort (16 0/7–18 6/7 weeks of gestation) and 148 in the later cohort (19 0/7–23 6/7 weeks of gestation). We excluded five patients from the intent-to-treat analysis; one withdrew consent, one was found to be ineligible after randomization, and three were missing data for the primary outcome. One of the three with missing operative time data expelled the pregnancy on initial examination in the procedure room (misoprostol arm, early cohort); this was the only expulsion. The other two missing operative time data had inadequate dilation on initial evaluation; one received an additional set of overnight osmotic dilators and the other misoprostol for several hours. When the delayed dilation and evacuations were completed, operative time was not recorded. Two other patients received repeat overnight osmotic dilators for inadequate dilation. When these two delayed dilation and evacuations were completed, operative time was recorded and they are included in the intent-to-treat analysis. Participants in the three treatment arms were similar in demographic and reproductive characteristics and in the number and type of osmotic dilators used with synthetic osmotic dilators used predominantly in the majority of patients (Table 1).

Intent-to-treat analysis by gestational cohort revealed no difference among treatment arms in dilation and evacuation operative time (first instrument in to last instrument out of the uterus) (Table 2). Per-protocol analysis of dilation and evacuation operative time similarly revealed no difference between arms (data not shown). A sensitivity analysis adjusting for prior vaginal and cesarean delivery showed no difference in operative time. However, when we stratified by gestational cohort and parity (post hoc analysis), we found treatment effects differed by parity only for the later gestational cohort ($F=3.36$, $P=.038$); specifically, dilation and evacuations in nulliparous women in the later gestational cohort were slowest after adjunctive misoprostol (Table 2), whereas no significant differences in operative time were observed in multiparous women. Treatment effects did not differ by parity in the early gestational cohort ($F=2.05$,

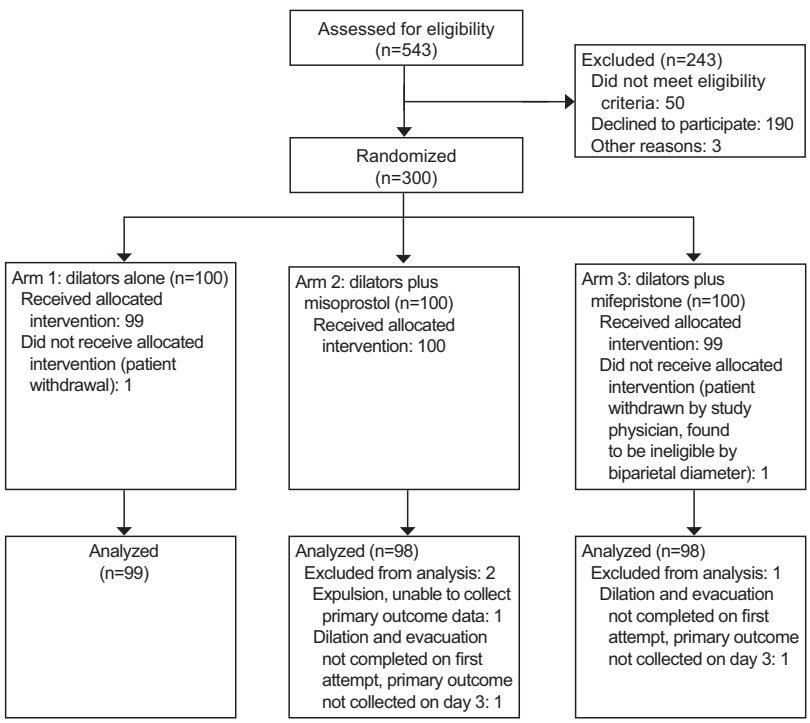

Fig. 1. Flowchart of study participants.
Goldberg. Adjunctive Mifepristone or Misoprostol Before Dilation and Evacuation. Obstet Gynecol 2015.

Table 1. Baseline Characteristics

	Arm 1, Dilators Alone (N=100)	Arm 2, Dilators Plus Misoprostol (N=100)	Arm 3, Dilators Plus Mifepristone (N=100)
Age (y)	24.6±5.7	25.9±5.9	25.3±5.8
Race			
Hispanic or Latina	19 (19.0, 11.3–26.7)	18 (18.0, 10.5–25.5)	22 (22.0, 13.9–30.1)
African American or black	39 (39.0, 29.4–49.3)	48 (48.0, 38.2–57.8)	36 (36.0, 26.6–45.4)
White or European American	31 (31.0, 21.9–40.1)	22 (22.0, 13.9–30.1)	29 (29.0, 20.1–37.9)
Other	11 (11.0, 4.9–17.1)	12 (12.0, 5.6–18.4)	13 (13.0, 6.4–19.6)
Marital status	N=99	N=99	N=100
Married	10 (10.1, 4.2–16.0)	8 (8.1, 2.7–13.5)	3 (3.0, 0.0–6.3)
In a relationship	33 (33.3, 24.1–42.6)	32 (32.3, 23.1–41.5)	44 (44.0, 34.3–53.7)
Single	56 (56.6, 46.8–66.3)	59 (59.6, 49.9–69.3)	53 (53.0, 43.2–62.8)
Education			
Less than high school	18 (18.0, 10.5–25.5)	13 (13.0, 6.4–19.6)	9 (9.0, 3.4–14.6)
High school or graduate equivalency degree	35 (35.0, 25.7–44.4)	33 (33.0, 23.8–42.2)	34 (34.0, 24.7–43.3)
Some college or 2-y college	38 (38.0, 28.5–47.5)	44 (44.0, 34.3–53.7)	45 (45.0, 35.3–54.8)
4-y college and greater	9 (9.0, 3.4–14.6)	10 (10.0, 4.1–15.9)	12 (12.0, 5.6–18.4)
Payment for this abortion (not mutually exclusive)			
Government health plan	50 (50.0, 40.2–59.8)	52 (52.0, 42.2–61.8)	46 (46.0, 36.2–55.8)
Private insurance plan	12 (12.0, 5.6–18.4)	15 (15.0, 8.0–22.0)	17 (17.0, 9.6–24.4)
Out of pocket	38 (38.0, 28.5–47.5)	32 (32.0, 22.9–41.1)	36 (36.0, 26.6–45.4)
Borrowed money	25 (25.0, 16.5–33.5)	26 (26.0, 17.4–34.6)	29 (29.0, 20.1–37.9)
Abortion fund	25 (25.0, 16.5–33.5)	22 (22.0, 13.9–30.1)	25 (25.0, 16.5–33.5)
Reproductive history			
Gravidity	2 [1, 4]	3 [2, 5]	3 [2, 5]
Parity	1 [0, 2]	1 [0, 2]	1 [0, 2]
Any prior vaginal delivery	48 (48.0, 38.2–57.8)	59 (59.0, 49.4–68.6)	56 (56.0, 46.3–65.7)
Any prior cesarean delivery	13 (13.0, 6.4–19.6)	14 (14.0, 7.2–20.8)	17 (17.0, 9.6–24.4)
Gestation and osmotic dilators			
Group I (early)	(n=51) 17 wk 6 d±6.12 d	(n=51) 17 wk 7 d±7.32 d	(n=50) 17 wk 6 d±6.53 d
Dilators placed	5.2±1.8	5.7±2.0	5.5±2.0
Greater than 60% synthetic dilators	29 (56.9, 43.3–70.5)	31 (60.8, 47.4–74.2)	27 (54.0, 40.2–67.8)
Group II (late)	(n=49) 21 wk 1 d±9.23 d	(n=49) 21 wk 2 d±9.31 d	(n=50) 21 wk 1 d±8.44 d
Dilators placed	7.6±2.0	7.7±2.2	8.0±2.5
Greater than 60% synthetic dilators	33 (67.4, 54.2–80.5)	30 (61.2, 47.6–74.9)	34 (68.0, 55.1–80.9)

Numerical variables presented as mean±standard deviation or median [quartile 1, quartile 3]. Categorical variables presented as frequency (%, 95% confidence interval). $P>.05$, all nonsignificant.

$P=.133$). Supplementary analyses, examining medians as well as log-transformed times to assess sensitivity of results to outliers and skewness qualitatively, yielded the same results.

We also measured the total procedure time (from speculum insertion to removal of all instruments from the vagina, including time spent managing bleeding and other immediate complications), minus the time for intrauterine device insertion, controlling for site. When including all patients, the total procedure time was significantly shorter in the mifepristone arm (Table 2). In the early gestational cohort, there was no difference in total procedure time between treatment arms; however, in the later cohort, dilation and evacuations were fastest after adjunctive mifepristone and slowest after dilators alone with the pairwise comparison significant only for mifepristone compared with dilators alone (Table 2). In a post hoc analysis, when the 14 patients with acute procedure-related complications were removed, no difference remained in total procedure time between arms in the late cohort, suggesting that complication management may have been responsible for much of the observed difference (data not shown).

Four dilation and evacuations were unable to be completed on the first attempt as a result of insufficient dilation: dilators alone one of 99 (1%); adjunctive misoprostol two of 100 (2%); and adjunctive

Table 2. Procedure Time: Intent-to-Treat Analysis

	Arm 1, Dilators Alone (n=99)	Arm 2, Dilators Plus Misoprostol (n=98)	Arm 3, Dilators Plus Mifepristone (n=98)	*P*, Pairwise Analysis
Dilation and evacuation operative time (min)				
Overall	6.27±3.5 (range 1.7–19.9)	6.28±4.6 (range 1.2–27.3)	5.53±2.9 (range 1.4–15.4)	.28
Early cohort	5.11±3.0 (range 1.7–14.8)	4.99±3.3 (range 1.2–15.8)	4.33±2.0 (range 1.4–10.7)	.34
Late cohort	7.50±3.7 (range 2.4–19.9)	7.62±5.4 (range 1.8–27.3)	6.74±3.2 (range 1.6–15.4)	.53
Controlled for site				
Early cohort	5.54 (4.8–6.3)	5.41 (4.6–6.2)	4.77 (4.0–5.5)	.28
Late cohort	8.26 (6.9–9.6)	8.17 (6.8–9.5)	7.14 (5.8–8.5)	.29
Stratified by parity, gestation (post hoc analysis)				
Nulliparous				
Early (N=56)	5.55±3.1 (range 2.8–14.8)	6.18±3.9 (range 2.0–15.8)	4.53±1.8 (range 1.4–7.7)	.29
Late (N=50)	6.83±3.3 (range 2.9–13.0)	10.38±6.7 (range 2.3–27.3)	6.54±3.4 (range 1.9–12.5)	.04*
Multiparous				
Early (N=94)	4.77±2.9 (range 1.7–11.4)	4.38±2.9 (range 1.2–14.1)	4.23±2.1 (range 1.6–10.7)	.71
Late (N=95)	8.02±3.9 (range 2.4–19.9)	6.60±4.5 (range 1.8–15.5)	6.83±3.2 (range 1.6–15.4)	.33
Total procedure time (min)				
Overall	11.58 (10.0–13.1)	10.13 (8.6–11.6)	9.12 (7.7–10.6)	.01* Arm 1 vs 2: .08 Arm 1 vs 3: .003† Arm 2 vs 3: .22
Early cohort	8.19 (6.7–9.7)	8.27 (6.8–9.8)	6.97 (5.5–8.4)	.33
Late cohort	13.39 (11.2–15.6)	10.35 (8.2–12.6)	9.42 (7.2–11.6)	.007* Arm 1 vs 2: .02 Arm 1 vs 3: .003† Arm 2 vs 3: .47

Early cohort=16–18 6/7 weeks of gestation and late cohort=19–23 6/7 weeks of gestation. Variables presented as mean±standard deviation and as least square mean (95% confidence interval) when adjusted for site. All comparisons performed using analysis of variance. Dilation and evacuation operative time: stopwatch time from first instrument into the uterus to last instrument out of the uterus. Total procedure time: clock time from speculum in to speculum out, including time spent managing immediate complications, subtracting time for intrauterine device insertion, and controlling for site.

* Three-way comparisons (arm 1 compared with arm 2 compared with arm 3), significant if $P<.05$.

† Pairwise comparisons (one arm compared with another), significant if $P<.017$.

mifepristone one of 99 (1%). Although not significantly different, we have inadequate power to definitively compare this uncommon outcome.

In the early gestational cohort, initial cervical dilation was greatest in the adjunctive misoprostol arm and smallest in the dilators-alone arm. In the early cohort, additional mechanical dilation was required for 35.3% of women who received dilators alone, significantly more often than for those who received adjuvants (Table 3). We observed no difference in initial cervical dilation or need for additional mechanical dilation in the later gestational cohort. When patients in either gestational cohort required additional dilation, the frequency of difficult or very difficult dilation did not differ significantly by treatment arm (Table 3). Reports of difficult dilation were infrequent.

Overall, physician satisfaction with cervical preparation was highest after mifepristone, then misoprostol, then dilators alone ($P<.001$, comparing the 5-point Likert scale, percentages for each category on the 5-point scale not shown). When dichotomized into very satisfied or satisfied compared with all other ratings (shown on Table 3), satisfaction was; 86.8% (95% confidence interval [CI] 80.0–93.5) with mifepristone,

Table 3. Initial Cervical Dilation, Additional Dilation Required, and Procedural Difficulty

	Arm 1, Dilators Alone (N=99)	Arm 2, Dilators Plus Misoprostol (N=97)	Arm 3, Dilators Plus Mifepristone (N=98)	*P*, Pairwise Analysis
Initial cervical dilation (cm)				
Overall	2.2±0.5	2.5±0.9	2.4±0.5	.009* Arm 1 vs 2: .003† Arm 1 vs 3: .04 Arm 2 vs 3: .32
Early cohort	2.0±0.4	2.4±1.0	2.2±0.4	.02* Arm 1 vs 2: .007† Arm 1 vs 3: .23 Arm 2 vs 3: .13
Late cohort	2.4±0.5	2.5±0.8	2.6±0.5	.19
Additional dilation required	N=98	N=99	N=99	
Overall	26 (26.5, 17.8–35.3)	9 (9.1, 3.4–14.8)	16 (16.2, 8.9–23.4)	.005* Arm 1 vs 2: .001† Arm 1 vs 3: .08 Arm 2 vs 3: .13
Early cohort	18 (35.3, 22.2–48.4)	5 (9.8, 1.6–18.0)	7 (14.3, 4.5–24.1)	.003* Arm 1 vs 2: .002† Arm 1 vs 3: .02 Arm 2 vs 3: .49
Late cohort	8 (17.0, 6.3–27.8)	4 (8.3, 0.5–16.2)	9 (18.0, 7.4–28.7)	.34
Physician satisfaction	N=99	N=99	N=98	
Satisfied or very satisfied with preparation	71 (71.7, 62.9–80.6)	78 (78.8, 70.7–86.8)	85 (86.7, 80.0–93.5)	.03*
Early cohort	N=51	N=51	N=49	
Procedure difficult or very difficult	6 (11.8, 2.9–20.6)	2 (3.9, 0.0–9.3)	1 (2.0, 0.0–6.0)	.15
Inadequate cervical preparation	12 (23.5, 11.9–35.2)	7 (13.7, 4.3–23.2)	4 (8, 0.5–15.8)	.10
Dissatisfied or very dissatisfied with preparation	8 (15.7, 5.7–25.7)	6 (11.8, 2.9–20.6)	0	.009*
Additional dilation difficult or very difficult	4/18 (22.2, 6.4–47.6)	2/5 (40.0, 5.3–85.3)	0/7	.24
Late cohort	N=48	N=48	N=49	
Procedure difficult or very difficult	9 (18.8, 7.7–29.8)	9 (18.8, 7.7–29.8)	2 (4.1, 0.0–9.6)	.04*
Inadequate cervical preparation	8 (16.7, 6.1–27.2)	7 (14.6, 4.6–24.6)	4 (8.2, 0.5–15.8)	.44
Dissatisfied or very dissatisfied with preparation	6 (12.5, 3.1–21.9)	5 (10.4, 1.8–19.1)	2 (4.1, 0.0–9.6)	.32
Additional dilation difficult or very difficult	2/8 (25.0, 3.2–65.1)	2/4 (50.0, 1.0–99.0)	1/9 (11.1, 0.3–48.3)	.27

Early cohort=16–18 6/7 weeks of gestation and late cohort=19–23 6/7 weeks of gestation. Numerical variables presented as mean±standard deviation, compared using analysis of variance. Categorical variables presented as frequency (%, 95% confidence interval), compared using χ^2 and Fisher's exact tests. Satisfaction and difficulty: 5-point Likert scale, collapsed to binary outcomes, frequency (%, 95% confidence interval). Inadequate cervical preparation: binary outcome, frequency (%, 95% confidence interval).

* Three-way comparisons (arm 1 compared with arm 2 compared with arm 3), significant if $P<.05$.

† Pairwise comparisons (one arm compared with another), significant if $P<.017$.

78.8% (95% CI 70.7–86.8) with misoprostol, and 71.7% (95% CI 62.9–80.6) with dilators alone ($P<.03$). In the early cohort, physicians reported no subjective difference in the overall procedural difficulty by treatment arm but were least likely to be dissatisfied or very dissatisfied with the cervical preparation after mifepristone (Table 3). In the later cohort, physicians reported dilation and evacuations to be easier (significantly lower percentage of dilation and evacuations rated as difficult or very difficult) after adjunctive mifepristone than dilators alone and reported no difference in overall procedural difficulty comparing dilators alone with adjunctive misoprostol or comparing mifepristone with misoprostol (Table 3). Physicians were adequately blinded (κ statistic for agreement between guess and actual treatment, 0.23).

There were no additional side effects from adjunctive mifepristone; however, women had significantly more pain, fever, and chills after misoprostol (Table 4). Despite this, overall participant satisfaction with the cervical preparation was similar with all regimens (Table 4). Patients were also adequately blinded (κ statistic for agreement between guess and actual treatment, 0.20).

Acute complications were not significantly different between arms or by site (Table 5); however, we did not have adequate power to detect small differences in complications. Overall, 10 patients in the dilators-alone arm (10%, 95% CI 4.2–16.0), two in the misoprostol arm (2%, 95% CI 0–4.7), and two in the mifepristone arm (2%, 95% CI 0–4.8) had acute complications. Four patients were hospitalized for acute management of uterine bleeding, all in the later gestational cohort. Three of the four were treated with uterotonics, uterine reaspiration, and an intrauterine balloon, which was left in situ overnight. These three had the balloon removed the next morning and were discharged home without further intervention (two in dilators-alone arm, one in mifepristone arm). The fourth participant (misoprostol arm) had a uterine perforation, received a blood transfusion, and underwent hysterectomy to control bleeding. Two additional dilators-alone patients with heavy bleeding were managed with intrauterine tamponade (balloon or packing) but did not require hospital admission.

There was no significant difference in estimated blood loss among treatment arms (median mL estimated blood loss [range]: 100 [25–400] dilators alone compared with 100 [15–2,000] misoprostol compared with 100 [35–800] mifepristone, $P=.51$), in the frequency of estimated blood loss 200 or greater (18% compared with 10% compared with 10%, $P=.15$), or in the frequency of uterine reaspiration (4% compared with 1% compared with 2%), cervical laceration requiring sutures (3% compared with 0% compared with 0%), or hemorrhage requiring any intervention beyond uterotonics and uterine massage (4% compared with 1% compared with 1%). We did not have adequate statistical power to make a definitive statement about each individual complication. Of the 14 procedure-related acute complications, 10 (71%) occurred in the later gestational cohort and 10 (71%) occurred in the dilators-alone group (Table 5).

DISCUSSION

We found no difference in our primary outcome of dilation and evacuation operative time (first instrument in to last instrument out of uterus) with adjuvant mifepristone or misoprostol. However, our other findings suggest that adjunctive mifepristone still may be beneficial for cervical preparation before dilation and evacuation, especially among women 19–23 6/7 weeks of gestation. In the later cohort, adjunctive mifepristone shortened total procedure time (speculum insertion to last intervention per vagina) and made dilation and evacuations significantly easier compared with osmotic dilators alone based on our blinded physicians' assessments. For most subjective measures of dilation and evacuation ease or adequacy of cervical preparation, compared with dilators alone, physicians were most satisfied with mifepristone followed by misoprostol.

Women in our study experienced no additional side effects or preoperative expulsions after mifepristone. Mifepristone given at the time of osmotic dilator placement may be an especially useful adjunctive treatment for cervical preparation before dilation and evacuation because it ripens the cervix without causing marked uterine contractions resulting in pain or expulsion. However, mifepristone is expensive and data suggest it takes 16–24 hours for physiologic effect.[20,21]

By contrast, we found no operative or total procedure time benefit from adjunctive misoprostol. Although misoprostol provided significantly greater initial dilation than dilators alone among women in the early gestational cohort, it offered no such benefit in the later group. Women who received misoprostol also experienced significantly more pain, fever, and chills than other study patients. Despite this, patient satisfaction with the cervical preparation and overall abortion was similar between treatment groups. Although misoprostol is inexpensive, it is commonly given in a clinical setting to treat its associated side effects and allows for early initiation of the dilation and evacuation should expulsion be imminent.

Table 4. Pain, Side Effects, and Patient Satisfaction With Cervical Preparation

	Arm 1, Dilators Alone (N=99)	Arm 2, Dilators Plus Misoprostol (N=100)	Arm 3, Dilators Plus Mifepristone (N=99)	*P*
Pain overnight after dilators and d 1 medication (mifepristone compared with placebo)				
Pain scale	45 [15, 75]	30 [10, 70]	35 [10, 70]	.17
Pain unacceptable or very unacceptable*	19 (19.2, 11.4–27.0)	17 (17.0, 9.6–24.4)	17 (17.2, 9.7–24.6)	.86
Took medication for pain or cramping	84 (84.8, 77.8–91.9)	80 (80.0, 72.2–87.8)	73 (73.7, 65.1–82.4)	.10
Pain after d 2 medication (misoprostol compared with placebo)				
Pain scale	10 [0, 35]	42.5 [15, 75]	15 [0, 30]	<.001†
Pain unacceptable or very unacceptable*	9 (9.1, 3.4–14.8)	37 (37.0, 27.5–46.5)	8 (8.1, 2.7–13.5)	<.001†
Took medication for pain or cramping	9 (9.1, 3.4–14.8)	25 (25.0, 16.5–33.5)	12 (12.1, 5.7–18.6)	.04†
Side effects after d 2 medication				
Chills				
Any*	12 (12.1, 5.7–18.6)	39 (39.0, 29.4–48.6)	18 (18.2, 10.6–25.8)	<.001†
Fever				
Any*	0	8 (8.0, 2.7–13.3)	0	<.001†
Satisfaction with cervical preparation				
Very satisfied	32 (33.0, 23.6–42.4)	42 (42.9, 33.1–52.7)	33 (33.7, 24.3–43.0)	.77
Satisfied	40 (41.2, 31.4–51.0)	38 (38.8, 29.1–48.4)	47 (47.9, 38.1–57.9)	
Neutral	19 (19.6, 11.7–27.5)	14 (14.3, 7.4–21.2)	14 (14.3, 7.4–21.2)	
Dissatisfied	4 (4.1, 0.2–8.1)	2 (2.0, 0.0–4.8)	3 (3.1, 0.0–6.5)	
Very dissatisfied	2 (2.1, 0.0–4.9)	2 (2.0, 0.0–4.8)	1 (1.0, 0.0–3.0)	

Numerical variables presented as median [quartile 1, quartile 3], compared using Kruskal-Wallis tests. Categorical variables presented as frequency (%, 95% confidence interval), compared using χ^2 and Fisher's exact tests. No significant difference with nausea, vomiting, or bleeding among treatment arms either overnight or after day 2 medication with (data not shown).

* For ease of interpretation, summaries for only the extreme categories are presented.

† Three-arm comparisons significant at $P<.05$.

Clinical monitoring may add significant expense to preoperative treatment with misoprostol and many women dislike the 3-hour preoperative treatment period.

We found no significant difference in acute complications between treatment arms; however, our study was not large enough to detect small differences in complications. Serious adverse events were rare and occurred in all treatment arms with all four occurring in the later gestational cohort. Collectively more women in the dilators-alone arm had uterine reaspiration, a cervical laceration requiring sutures, or hemorrhage requiring intervention beyond uterotonics than women in the misoprostol or mifepristone arms; although warranting further investigation, these differences were not statistically significant. Although the complication rate of 10% in the dilators-alone arm appears higher than rates reported in large retrospective studies of second-trimester abortion,[3] it is comparable to rates reported in other prospective trials of cervical preparation before dilation and evacuation at 20–23 6/7 weeks of gestation.[13]

We anticipated a priori that we would have inadequate power to measure complications as our primary outcome, which is why we chose the primary outcome of operative time. Operative time is a surrogate for surgical difficulty, which may reflect complication risk. Total procedure time (speculum in to out) includes this measure of operative difficulty as well as time spent managing immediate postabortion bleeding and other complications. Given the expense of operative room time, in addition to serving as surrogates for complications, these measures of time are also useful outcomes themselves. Although we did not see a significant difference in the frequency of complications between arms, we did observe a reduction in total procedure time in the later gestational cohort with adjuvant mifepristone suggesting that adjunctive mifepristone may reduce the time spent managing immediate postprocedural bleeding and complications.

Strengths of our study include its design as a double-blind, multicenter randomized trial with diverse sites, including free-standing abortion clinics, in-hospital ambulatory surgical units, and hospital operating rooms. This variety makes our data

Table 5. Acute Complications*

	Gestational Cohort	Estimated Blood Loss	Complication
Arm 1, dilators alone (n=99)	Late	400	Reaspiration
			Heavy bleeding requiring intrauterine Foley balloon
			Suspected placenta accreta
			Hospital admission
	Late	250	Reaspiration
			Heavy bleeding requiring intrauterine Foley balloon
			Hospital admission
	Late	250	Heavy bleeding requiring intrauterine Foley balloon
			Anesthesia complications (aspiration)
	Late	200	Heavy bleeding requiring uterine or vaginal packing
	Late	350	Heavy bleeding requiring cervical stay sutures
	Late	200	Cervical laceration requiring sutures
	Late	125	Cervical laceration requiring sutures
	Early	75	Cervical laceration requiring sutures
			False passage
	Early	100	Reaspiration
	Early	200	Reaspiration
Arm 2, dilators plus misoprostol (n=100)	Late	2000	Uterine perforation
			Transfusion two units packed red blood cells
			Hysterectomy
			Hospital admission
	Early	75	Reaspiration
Arm 3, dilators plus mifepristone (n=99)	Late	800	Reaspiration
			Heavy bleeding requiring intrauterine Foley balloon
			Hospital admission
	Late	100	Reaspiration

* Acute complications include any hospitalizations, transfusions, and additional unplanned procedures (ie, laparotomy, hysterectomy, uterine artery embolization, uterine tamponade with Foley balloon or packing, uterine reaspiration, or surgical repair of cervical laceration). Heavy vaginal bleeding successfully managed with uterotonics and uterine massage and cervical lacerations or abrasions managed with ferric subsulfate (Monsel's) solution or pressure were not included. Early cohort=16–18 6/7 weeks of gestation and late cohort=19–23 6/7 weeks of gestation.

generalizable to most clinical settings. Limitations include inadequate sample size to measure complications as a primary outcome and reliance on outcomes that measure efficacy of the cervical preparation rather than its direct effect on overall safety.

Despite no difference in operative time, physicians found procedures in the later cohort easier after adjunctive mifepristone and it was well tolerated by women. Given the added cost of adjunctive mifepristone, its use should be considered for patients later in gestation or for whom the dilation and evacuation is anticipated to be difficult. Misoprostol increased initial cervical dilation in the early, but not the later, cohort, had an intermediate effect on physician satisfaction, had no benefit on operative or total procedure time, and was associated with more side effects. Individual clinical factors and service delivery issues should help guide the decision about whether to use either mifepristone or misoprostol in addition to osmotic dilators before second-trimester dilation and evacuation.

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