Mifepristone and misoprostol compared to osmotic dilators for cervical preparation prior to surgical abortion at 15–18 weeks' gestation: a randomised controlled non-inferiority trial

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ABSTRACT:

Objective Cervical preparation is recommended prior to second-trimester surgical abortion. Osmotic dilators are an effective means to prepare the cervix, but require an additional procedure and may cause discomfort. We compared cervical preparation with mifepristone and misoprostol to preparation with osmotic dilators.

Study design A randomised, controlled, non-inferiority trial was performed to compare cervical preparation with mifepristone and misoprostol to preparation with osmotic dilators in women undergoing surgical abortion between 15 and 18 weeks gestation. The medication group (n=29) received mifepristone 200 mg orally 24 hours prior to uterine evacuation and misoprostol 400 µg buccally 2 hours before the procedure. The dilator group (n=20) underwent osmotic dilator insertion 24 hours prior to the procedure. The primary outcome was total procedure time, from insertion to removal of the speculum. Secondary outcomes included operative time (from intrauterine instrumentation to speculum removal), initial cervical dilation, nausea, pain, ease of procedure, and whether participants would choose the same modality in the future.

Results For mean total procedure time, medication preparation (14.0 min, 95% CI 12.0–16.1) was not inferior to dilators (14.3 min, 95% CI 11.7 to 16.8, p<0.001). Mean operative time and ease of procedure were also similar between groups. More women in the medication group than the dilator group would prefer to use the same method in the future (86% vs 30%, p=0.003).

Conclusion Prior to surgical abortion at 15–18 weeks, use of mifepristone and misoprostol did not result in longer procedure times than overnight osmotic dilators.

Trial registration number NCT01462.

Key messages

- Mifepristone and misoprostol for cervical preparation prior to surgical abortion between 15 and 18 weeks' gestation did not increase procedure times when compared with dilators.
- Surgeons' assessment of ease of procedure, as well as patient-reported side effects, were similar for both groups.
- Women in the medication group were more likely to prefer their modality of cervical preparation than those in the dilator group.

INTRODUCTION

Cervical preparation is recommended before second-trimester surgical abortion in order to soften and open the cervix so that instruments can be safely introduced and manipulated.[1 2] Osmotic dilators are highly effective for this purpose and include laminaria tents and Dilapan-S.[2] Laminaria are made from dehydrated seaweed, while Dilapan-S is made of synthetic hydrogel. Both dilators swell by absorbing water from the cervical stroma and applying radial force to the walls of

the cervical canal as they expand; in addition, laminaria induce the local production of prostaglandins. Osmotic dilators require a trained provider for insertion, and many women experience pain during insertion, as well as afterwards, while the dilators are in place. In addition, osmotic dilators require at least several hours of use, and are often used overnight. To avoid these disadvantages of dilator insertion, pharmaceutical alternatives such as mifepristone and misoprostol have been used.[2 3]

Mifepristone, a progesterone receptor modulator, is used in the first and second trimester as part of medical abortion procedures. Mifepristone alone is not an efficient pharmacological abortifacient in either the first or second trimester, and therefore misoprostol is used after mifepristone to complete a medication abortion.[4] Mifepristone alone has also been shown to be effective for cervical preparation before first-trimester surgical abortion.[5–8]

There is limited published experience comparing modalities of cervical preparation in the second trimester. Goldberg *et al*[9] compared women at 13–16 weeks of gestation who were randomly assigned to receive osmotic dilators the day before abortion or misoprostol 3 hours before abortion. Starting cervical dilation was greater in the dilator group, and procedures were shorter and less likely to be classified as difficult by the operator. However, women preferred misoprostol. In a small randomised study, use of mifepristone alone at 14–16 weeks resulted in less cervical dilation than osmotic dilators, although operating times were similar.[10]

Carbonell *et al*[11] randomly assigned women with pregnancies of 14–18 weeks to receive mifepristone or not to receive mifepristone 48 hours before abortion; all women received misoprostol prior to the procedure. They found that the women who received mifepristone had greater cervical dilation at the start of the procedure compared with women who received misoprostol alone. Searle *et al*[12] reported a historical cohort study comparing women who received overnight laminaria to women who received mifepristone, the day before, and misoprostol, on the morning of, abortion at 16–19 weeks. The primary outcome of operator-rated ease of procedure was the same in the two groups.

We designed a prospective, randomised trial of cervical preparation with mifepristone and misoprostol compared with preparation with osmotic dilators prior to surgical abortion at 15–18 weeks' gestation. The primary hypothesis was that procedures performed after preparation with medications would not take longer than those performed after dilators.

METHODS

Women aged 18–45 years requesting an induced abortion between 15 weeks 0 days and 18 weeks 0 days, confirmed by ultrasound dating (consistent with biparietal diameter 30–40 mm), were eligible for the study. After they had completed counselling and given consent for surgical abortion, women were approached by a research assistant and asked if they were interested in the study. Women who indicated interest were screened by the research assistant. Women were excluded from the study if they had fetal demise, ruptured membranes, spontaneous abortion, active substance abuse or intoxication, or did not speak English or Spanish. They were also excluded if they had serious underlying medical illnesses, a body mass index >45 kg/m^2, or contraindications to any of the study medications or procedures. Written informed consent was obtained from all participants prior to the start of study procedures by one of the investigators. The study was approved by the Boston University Medical Center Institutional Review Board, and all study procedures were conducted at Boston Medical Center.

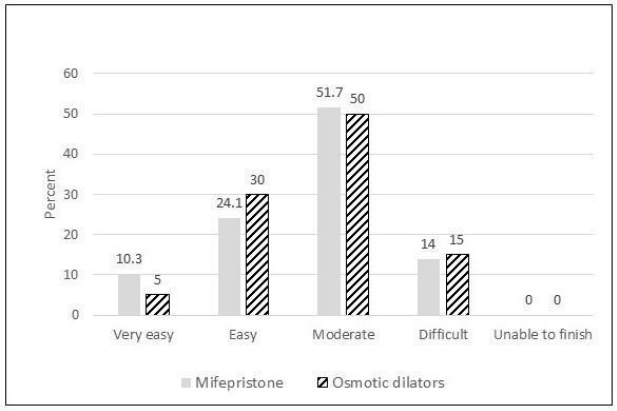
Study procedures began on the day prior to the abortion. Women were allocated 3:2 to one of two groups, the medication group or the dilator group, respectively. The randomisation scheme was computer-generated, using a block size of 10. Allocation was carried out using sequentially numbered sealed opaque vials which contained either the mifepristone tablet or the assignment to dilators; the vials concealed the group assignment until they were opened. The vials were prepared by the research pharmacy. Once allocation had occurred, treatment was not blinded.

Women in the dilator group had osmotic dilators placed on the day before abortion. Prior to insertion they received ibuprofen 800 mg orally. The cervix was cleansed with povidone-iodine solution and infiltrated with 10 mL 1% lidocaine. Laminaria (2 mm and 4 mm) (Medgyn, Addison, IL, USA), and 4 mm Dilapan-S (Medicem s.r.o., Prague, Czech Republic) dilators were used. Mechanical pre-dilation was not used. Doxycycline 200 mg orally was given after the dilators were inserted.

Women in the medication group received mifepristone 200 mg orally with ingestion observed, on the day prior to the abortion. No antibiotics or other medications were used at this time. All women were instructed to take ibuprofen if they had pain overnight.

Women in both groups were scheduled to return 20–24 hours after treatment for their abortion procedure. Women in the medication group were given 400 μg misoprostol buccally 2 hours before the expected time of procedure.

Consultant surgeons or family planning fellows at Boston Medical Center performed all procedures. Moderate sedation was available. A cervical block of 20 mL 1% lidocaine with 4 units of vasopressin was used for all women.[13–15] Cervical dilation was measured with Pratt dilators, starting with a 63 French (F) size. If the 63F dilator did not pass without resistance, sequentially smaller dilators were used until the largest size that passed without resistance was identified. If



Percentage of surgeons giving each response.
P = 0.96, chi-square test

Figure 1 Surgeon's rating of ease of procedure.

the 63F dilator did pass, larger dilators were passed until resistance was encountered. Initial dilation was recorded by a research assistant. The operator could then use additional mechanical dilation as desired, according to his or her standard clinical practice.

The primary outcome was the time from speculum placement to speculum removal ('total procedure time'). Secondary outcomes included the length of time from the initial insertion of cannula or forceps to speculum removal ('operative time') and cervical dilation at the beginning of the procedure. A research assistant recorded time points during the procedure.

A research assistant interviewed participants to obtain secondary outcome data regarding their experience at three different time points: immediately after dilator placement (dilator group) or immediately prior to procedure (medication group), on admission the morning of the abortion procedure, and just prior to discharge. Pain immediately after dilator placement (dilator group) or prior to procedure, after misoprostol (medication group), was assessed on a 10-point Likert scale and categorised as none (0), mild (1–3), moderate (4–6) or severe (7–10). On the morning of admission for abortion, participants were asked to rate overnight pain, nausea and bleeding as either none, mild, moderate or severe. Just prior to discharge, participants were asked to agree or disagree on a five-point Likert scale with statements regarding their satisfaction with cervical preparation. After the procedure, surgeons were also asked to rate the its ease on a five-point scale and to make note of any intraoperative or immediate complications, such as the need for additional surgical intervention, medications or blood products.

The study was structured with a non-inferiority design. The primary outcome, total procedure time, was defined as inferior if procedures in the medication group were more than 3 min longer than those in the dilator group. We rationalised that a 3-min increase in procedure time would be noticeable to the operator, and would affect acceptability. The total procedure time for the dilator group was expected to be 10 min with a SD of 4 min, based on our prior study.[10] With a 3:2 randomisation scheme, 29 women assigned to the medication group and 20 women to the dilator group gave >80% power to detect a 3-min difference between groups, assuming an alpha error of 0.05.

Data were analysed as intent-to-treat using SAS (Version 9.3; SAS Institute, Inc., Cary, NC, USA). Kolmogorov-Smirnov test of normality was done for the primary outcome, Wilcoxon test was performed for testing medians and t-tests were used for testing means. A non-inferiority test was done to assess the likelihood that the mean of the medication group was at least 3 min longer than the mean of the dilator group. Secondary outcomes were evaluated with Chi-square and Fisher's exact tests or t-tests as appropriate. Bivariate analyses were performed to evaluate the relationship between the primary outcome and covariates, namely parity, prior abortion, ethnicity, the woman's age and gestational age. A value of $p<0.05$ was considered significant.

Patient and public involvement

Patients were not involved in the design of the study.

RESULTS

Fifty women were enrolled from October 2011 to August 2013 (figure 1). One woman was enrolled in error after a failed attempt to insert dilators and was removed from the study. Forty-nine women were analysed. Characteristics of enrolled women are presented in table 1. The groups had similar baseline characteristics. All women received their assigned treatment and all procedures were completed successfully. There were no immediate complications, including incomplete abortion, cervical laceration, repeat procedure, infection or excessive blood loss.

Most women in the dilator group had a combination of Dilapan-S and laminaria placed. The median number of total dilators placed was 5 (IQR 4, 6). Nineteen of the 20 women had discomfort or pain during insertion.

The abortion procedure began at a mean of 22.0±2.0 (range 18–27) hours after osmotic dilator placement and 24.6±1.7 (range 21–30) hours after mifepristone ingestion. In the medication group, the mean interval between misoprostol and the procedure was 2.6±0.4 (range 1.7–3.0) hours. Two women, both in the medication group, had their procedure with local anaesthesia only; the remaining 47 women had intravenous sedation and local anaesthesia. The mean amount of midazolam (3.1 vs 2.9 mg) and fentanyl (104 vs 105 μg) was similar in the two groups.

The mean dilation at the start of the procedure was 42F±11 in the medication group and 56F±5 in the dilator group. After mechanical dilation, if done, the final dilation values were 58F±8 and 60F±3,

Table 1 Characteristics of study participants

Characteristic	Medication group (n=29) (n (%))	Dilator group (n=20) (n (%))
Age* (years)	26±6	26±5
Gravidity		
1	7 (24)	2 (10)
>1	22 (76)	18 (90)
Parity		
0	10 (34)	5 (25)
1	5 (17)	4 (20)
>1	14 (48)	11 (55)
Previous abortions		
None	14 (48)	10 (50)
Any prior abortion	15 (52)	10 (50)
Prior second-rimester abortion	6 (21)	4 (20)
Prior caesarean delivery	7 (24)	3 (15)
Gestational age* (days)	115±5	113±6
Ethnic group		
Caucasian	5 (17)	4 (20)
African American	14 (48)	6 (30)
Hispanic	6 (21)	7 (35)
Other	4 (14)	3 (15%)

*Mean±SD.

respectively. Further dilation was more often required in the medication group (25/29, 86%) than the dilator group (9 /20, 45%, p<0.0025).

The total procedure time, from speculum placement to speculum removal, was 14.0 (95% CI 12.0 to 16.1) min in the medication group and 14.3 (95% CI 11.7 to 16.8) min in the dilator group. Inferiority of the medication group was rejected (p<0.001). The operative time, from the start of aspiration or intrauterine instrumentation until speculum removal, was 7.3 (95% CI 5.43 to 9.19) and 9.1 (95% CI 6.78 to 11.42) min, respectively.

Bivariate analysis did not show an association for parity, prior abortion, women's age, gestational age at the time of the abortion, or ethnic group with either total procedure time or operative time.

Surgeons rated the difficulty of each procedure (figure 1). The distribution of ratings was similar. No procedure was rated as 'very difficult' or unable to be finished.

During the night after insertion, women in the dilator group were more likely to take pain medication (12 (60%) vs 4 (14%), p<0.01); ibuprofen was the most common medication. Although there were trends toward more moderate or severe pain, nausea and/or vomiting in the dilator group, these differences were not statistically significant (table 2).

Overnight spotting or light bleeding was more common in the dilator group, eight women (40%) compared with none in the medication group (p<0.003). No woman had moderate or heavy bleeding overnight.

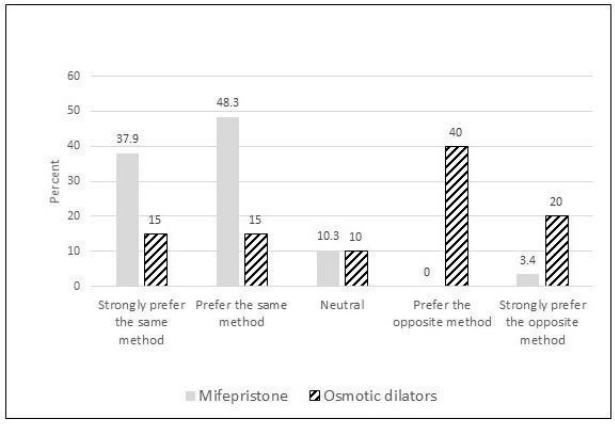
On the morning before the abortion procedure, the incidence of nausea was similar between the two groups, and half of the women in each group had no pain at all (table 2). After misoprostol, immediately before the procedure, 16 of the women (55%) in the medication group had moderate or severe pain. No woman aborted prior to her planned surgical procedure.

Women were asked whether, if they had another procedure, they would use the same method or try another method. Twenty-five women (86%) in the medication group compared with six women (30%) in the dilator group either preferred or strongly preferred to use the same method again, while only one woman (3.4%) in the medication group compared with 12

Table 2 Secondary outcomes: pain and nausea before the abortion procedure

	Night prior to abortion*			Morning of abortion procedure		
Secondary outcome	Medication group (n=29) (n (%))	Dilator group (n=20) (n (%))	P value†	Medication group (n=29) (n (%))	Dilator group (n=20) (n (%))	P value†
Pain			0.051			0.77
None	18 (62)	7 (35)		14 (48)	10 (50)	
Mild	7 (24)	6 (30)		10 (34)	5 (25)	
Moderate	4 (14)	3 (15)		3 (10)	2 (10)	
Severe	0 (0)	4 (20)		2 (7)	3 (15)	
Nausea			0.24			0.86
None	21 (73)	10 (50)		22 (73)	16 (80)	
Mild	2 (7)	4 (20)		1 (3)	1 (5)	
Moderate	1 (3)	0 (0)		6 (23)	3 (15)	
Severe and/or vomiting	5 (17)	6 (30)		0 (0)	0 (0)	

*On the morning of admission for abortion, participants were asked to rate pain,and nausea experienced overnight.
†Fisher's exact test.



Percentage of women giving each response.
P = 0.003, chi-square test

Figure 2 Women's preferences if a repeat procedure were needed.

women (60%) in the dilator group would prefer the other method (p=0.003, figure 2). Six women with a previous second-trimester abortion with dilators were randomised to the medication group; all of these preferred medications to dilators.

DISCUSSION

We found that procedures performed at 15–18 weeks' gestation after cervical preparation with mifepristone and misoprostol did not take significantly longer to complete than those performed after overnight preparation with osmotic dilators. This is consistent with findings in a study of surgical abortion after 19 weeks, in which mifepristone in combination with misoprostol had similar operative times compared with preparation with osmotic dilators.[16]

More women in the medication group said they would use their method of cervical preparation again. An advantage of using medications for cervical preparation is that women did not need to have a pelvic examination and procedure for the purpose of inserting dilators. This is a saving in time for both clinicians and patients, and may be preferred by some women. For women who are very apprehensive about pelvic examinations or procedures, avoidance of a pelvic procedure might be important. Medication preparation was preferred by the few women who had experience with both methods.

Our sample size was too small to assess whether characteristics of the woman affected her experience and preference. Comparison of various techniques is limited by the variety of outcome measures, which include cervical dilation, surgeon assessment of ease, patient assessments, and the time to perform the procedure. Another limitation of our study was the lack of blinding, which could have led to bias by both patients and surgeons. Finally, our primary outcome, procedure time, is a proxy for procedure complexity. An ideal outcome in a study comparing cervical preparation methods would be incidence of procedure complications, but our sample size was too small to measure differences in complications.

A disadvantage of using mifepristone is that it requires medication the day prior to abortion.[17] However, same-day procedures using same-day osmotic dilators or same-day misoprostol require a longer period of time on the day of abortion, and are not available in all settings.

Selection of the method for cervical preparation is multifaceted and may include time, facility, cost issues, and personal preference, all of which may vary in importance from site to site. The combination of mifepristone and misoprostol may be an alternative to overnight osmotic dilators for cervical preparation prior to surgical abortion in the second trimester. Comparative studies of the multiple methods of cervical preparation in the second trimester are needed to assess the relative advantages and disadvantages of each method at various gestational ages. Acceptability, both to providers and women undergoing procedures, should be evaluated further to be able to offer the optimal method to each woman.

Contributors LB was the principal investigator; she planned and designed the study, participated in data collection, interpretation of results, and preparation of the manuscript. AP was a co-investigator who participated in subject recruitment, data collection, interpretation of data, and preparation of the manuscript including final submission. SS and MF were co-investigators who collaborated on study design, subject recruitment, data collection, interpretation of results, and manuscript preparation. OV collaborated on study design, devised and performed statistical analysis, data interpretation and participated in manuscript preparation. All authors read and approved the final manuscript.

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