Contraception 100 (2019) 445–450

Contents lists available at ScienceDirect

Contraception

journal homepage: www.elsevier.com/locate/con

A factorial-design randomized controlled trial comparing misoprostol alone to Dilapan with misoprostol and comparing buccal to vaginal misoprostol for same-day cervical preparation prior to dilation & evacuation at 14 weeks 0 days–19 weeks 6 days gestation☆,☆☆

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ARTICLE INFO

Article history:
Received 11 January 2019
Received in revised form 4 September 2019
Accepted 4 September 2019

Keywords:
Second-trimester abortion
Surgical abortion
Dilation and evacuation
Cervical preparation
Osmotic dilators
Misoprostol

ABSTRACT

Objectives: To compare procedure times following same-day cervical preparation using misoprostol 400 mcg alone or misoprostol 400 mcg plus hygroscopic dilators for dilation and evacuation (D&E) before 20 weeks gestation and to compare side effects of buccal and vaginal misoprostol administration.
Study Design: We randomized women undergoing D&E at 14 weeks 0 days–19 weeks 6 days gestation to receive (1) hygroscopic dilators or not and (2) buccal or vaginal misoprostol using a 2 × 2 factorial design. We assessed two primary outcomes: (1) total procedure time, defined as time to insert hygroscopic dilators plus D&E time, and (2) side effects of misoprostol 4–6 h after initiation of cervical preparation using a 5-point Likert scale assessing nausea, emesis, diarrhea, chills and cramps.
Results: We randomized 163 women and 161 completed the study. We completed all procedures in one day. Mean total procedure time was 14.0 and 10.8 min. with and without hygroscopic dilators (difference 3.2 minutes, 95% CI 1.7, 4.6). Mean D&E procedure time was 0.7 (95% CI −0.8, 2.1) min longer without hygroscopic dilators. Initial cervical dilation was 15.6 and 11.7 mm with and without hygroscopic dilators (difference 3.9 mm, 95% CI 3.1, 4.8). Participants receiving buccal misoprostol reported less chills (1.9) than women receiving vaginal misoprostol (2.3), $p = 0.04$.
Conclusions: Hygroscopic dilators with misoprostol requires more time and increases cervical dilation without shortening D&E time when used for cervical preparation 4–6 h prior to D&E before 20 weeks. Women receiving vaginal misoprostol may have more chills compared to buccal misoprostol.
Implications: Adding hygroscopic dilators to misoprostol for same day D&E procedures at less than 20 weeks gestation increases total intervention time without reducing D&E time and is less favored by patients. Clinical judgment requires balancing relative effectiveness with patient preference. Further studies should evaluate the side effect profile of vaginal misoprostol.

1. Introduction

Dilation and Evacuation (D&E) is the most commonly performed method of second trimester abortion in the United States [1]. Adequate cervical preparation is required prior to second-trimester D&E to minimize uterine and cervical trauma [1,2]. Traditionally, cervical preparation starts the day before D&E with hygroscopic dilators, although recent Society of Family Planning guidelines state that evidence supports same-day cervical preparation up to 18 weeks gestational age [1]. Overnight dilation is fre-

☆ *Conflict of Interest/Disclosures*: Matthew F. Reeves, MD MPH is a consultant for ContraMed LLC and Cooper Surgical. Pamela S. Lotke, MD MPH is on an international advisory board for Bayer Healthcare. The other authors have no conflicts of interest to disclose.
☆☆ *Funding*: This work was supported by the Society of Family Planning Research Fund, grant number: SFPR14-22.
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https://doi.org/10.1016/j.contraception.2019.09.001
0010-7824/

quently recommended after 18 weeks [3–5]. While misoprostol alone is safe and effective through 19 weeks 6 days gestation, the majority of this data is up to 18 weeks gestation, with some using multiple doses of misoprostol [6,7]. Additionally, a same-day regimen of misoprostol and hygroscopic dilators 3–4 h prior to D&E procedures in gestations up to 21 weeks 6 days is both safe and feasible for experienced providers [8].

Women prefer a pharmacological method for cervical preparation prior to D&E [9]. A survey of second-trimester abortion practices among US providers reported the majority (85%) of clinicians use osmotic dilators for cervical preparation, and nearly three-quarters use both misoprostol and osmotic dilators [10]. Only one randomized trial directly compared same day misoprostol to Dilapan® but was limited to 12–15 weeks gestational age. [11] National Abortion Federation members administer misoprostol both buccally (57%) and vaginally (52%) for cervical preparation [12]. These two routes of administration have not been compared for D&E with respect to clinical outcomes, including side effects.

We conducted a factorial-designed randomized controlled trial to evaluate the effect of same-day cervical preparation using misoprostol-hygroscopic dilators (henceforth referred to as "dilators") versus misoprostol alone on procedure times and to compare side effects of buccal and vaginal misoprostol. Secondarily, we evaluated initial cervical dilation and participant and provider acceptability.

2. Materials and methods

We recruited healthy English-speaking women 18 years or older presenting for a same-day abortion between 14 and 19 6/7 weeks of gestation by ultrasound at MedStar Washington Hospital Center (MWHC) and Planned Parenthood of Metropolitan Washington, DC (PPMW) from January 2015 to June 2016. We excluded non-English speaking women, those with emergent need for D&E or fetal demise, and women with an intolerance, allergy or contraindication to misoprostol or hygroscopic dilators. The MedStar Health Institutional Review Board approved the study protocol and Planned Parenthood Federation of America reviewed the protocol for acceptability.

A research staff member at the MedStar Health Research Institute uninvolved in study recruitment or analysis created two computer-generated randomization sequences with 1:1 allocation: one for cervical preparation (misoprostol vs. misoprostol-dilators) and one for misoprostol administration route (buccal vs. vaginal). Sequentially numbered opaque envelopes with the assigned groups were prepared and opened after eligibility was confirmed. Neither the investigators nor research coordinators were involved in the randomization generation or creation of the envelopes.

We offered study participation to all women meeting eligibility criteria who had already provided informed consent for same-day D&E. After consenting to the study, participants completed a baseline questionnaire including demographics and reproductive history. Research staff then opened the next randomization envelope which assigned women to receive (1) hygroscopic dilators or not and (2) buccal or vaginal misoprostol 4–6 h prior to the procedure. Women in the misoprostol-only arm self-administered two misoprostol 200 mcg tables. We instructed women assigned vaginal misoprostol to insert the tablets "as high as possible" in the bathroom. We instructed women assigned buccal misoprostol to place two tablets buccally (one tablet in each cheek or both tablets in one cheek) and swallow the remaining misoprostol after 30 min with water. We observed participants entering/leaving the bathroom or placing the buccal misoprostol and recorded the time. For participants randomized to hygroscopic dilators, we inserted a standardized number of dilators based on gestational age, after a lidocaine 1% 20 mL paracervical block: (a) 14–15 6/7 weeks: 1–2 Dilapan and 1 laminaria; (b) 16–17 6/7 weeks: 2–3 Dilapan and 1 laminaria; (c) 18–19 6/7 weeks: 3–4 Dilapan and 1 laminaria. After insertion of the osmotic dilators, women randomized to vaginal misoprostol had one misoprostol 200 mcg tablet placed in each lateral vaginal fornix. Women randomized to buccal misoprostol initiated use (with the same instructions as the misoprostol-only group) after sitting up upon completion of dilator placement. Women had 4×4 gauze placed in the vagina after insertion of hygroscopic dilators, for those assigned buccal misoprostol, or after placement of vaginal misoprostol, for those assigned to vaginal misoprostol. Neither providers nor participants were blinded to the treatment arm. We administered an oral non-steroidal anti-inflammatory drug, an opioid analgesic such as tramadol, an anxiolytic such as alprazolam, an antiemetic (most commonly promethazine), as well as an antibiotic at the time of cervical preparation. We brought participants back to the procedure room 4–6 h later to complete a side effect survey, initiate intravenous sedation, and perform the D&E procedure. Intravenous sedation included initial doses of fentanyl 100 mcg and midazolam 2 mg, at the discretion of the provider, increasing as needed to a maximum of fentanyl 200 mcg and midazolam 4 mg. A family planning fellow or attending physician performed all procedures using standard extraction techniques.

We chose total procedure time as our primary outcome for the misoprostol versus misoprostol-dilators cervical preparation comparison based on the assumption that inadequate cervical preparation would manifest itself as longer procedure times. We defined total procedure time as the time required for hygroscopic dilator insertion plus the D&E time. We defined dilator insertion time from the insertion of the speculum prior to hygroscopic dilator placement to the speculum removal time after hygroscopic dilators were placed. D&E procedure time began at either the time of speculum placement after manual removal of the dilators, or, if manual removal could not be accomplished, at the time after dilator removal after placement of the speculum. D&E procedure time ended at time of speculum removal, excluding the time needed to assess initial cervical dilation. For participants receiving an intrauterine device (IUD) insertion, the opening of the IUD package indicated the end of the procedure. D&E time also included any additional mechanical dilation necessary to complete the procedure. Secondary outcomes included initial cervical dilation, determined by Hegar dilators beginning with 20 mm and working down, as well as participant and provider acceptability and satisfaction. We assessed participant experience at enrollment, immediately before D&E, and after the D&E when participants were ready for discharge per site protocol. Both sites had previously established protocols to determine whether patients were appropriate for discharge, using vital sign criteria as well as the Aldrete score [13]. Providers completed their satisfaction assessment immediately after the procedure.

We used the average procedure time in a prior study conducted at the same sites with a provider- and gestational-age-adjusted standard deviation (SD) of 5.0 minutes. [4]. We estimated that 80 women in each group were required to show a mean difference in total procedure time of 2.0 min, with a two-sided alpha of 0.05, and a power of 80%. We chose a difference of 2 min. because it is clinically noticeable to both provider and participant; additionally this difference allowed comparison to other studies evaluating cervical preparation with a primary outcome of operative time [14]. In the buccal versus vaginal misoprostol comparison, we had 88% power to detect a clinically significant difference of 25% in reported symptoms with 160 women randomly allocated between the groups and a two-sided alpha of 0.05.

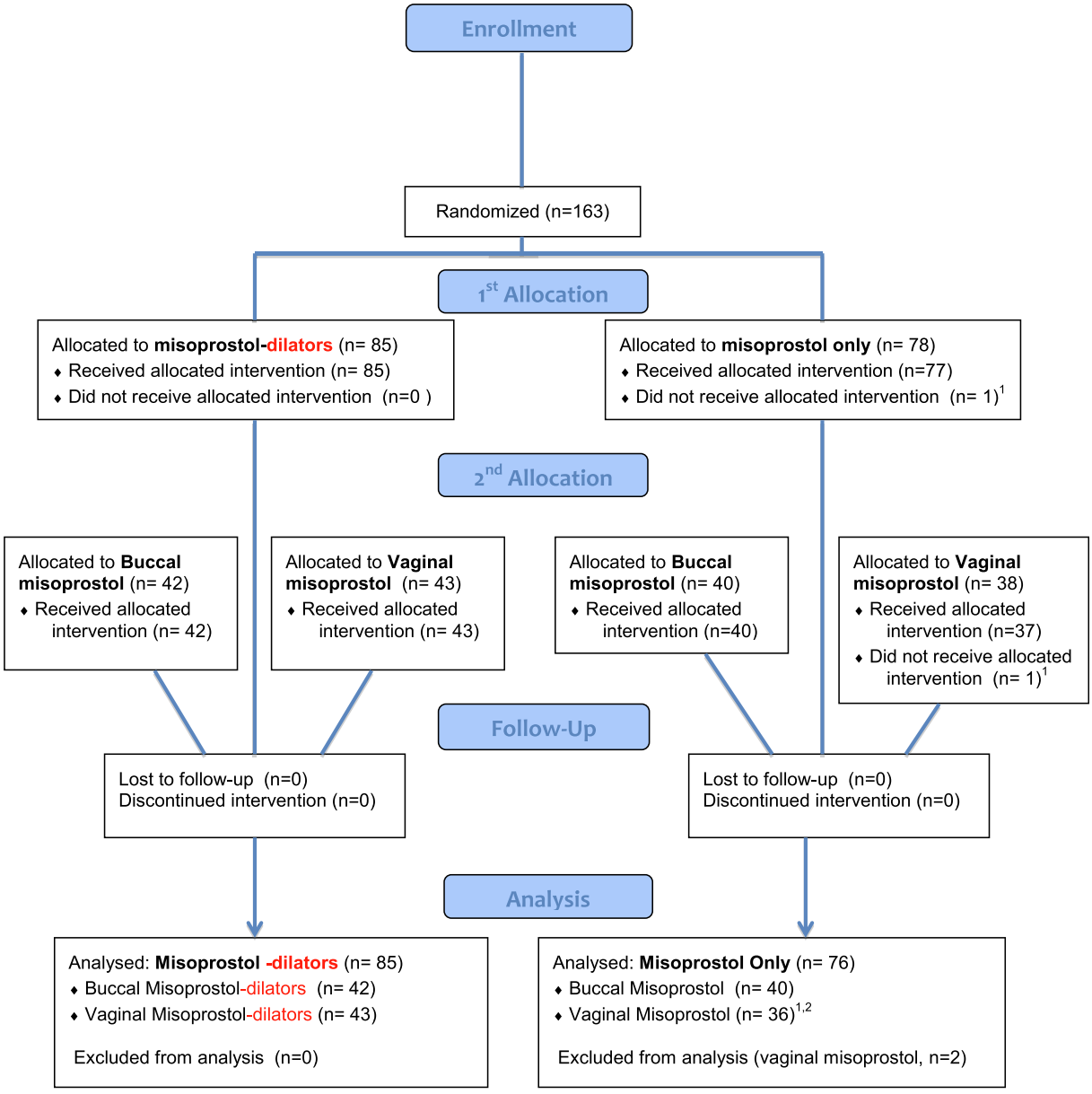
We conducted per-protocol statistical analyses using Stata MP/13.1 statistical software (StataCorp LP, College Station, TX,

www.stata.com), and significance was set at $p < 0.05$. We performed descriptive analysis comparing the baseline demographic and clinical characteristics of participants in each treatment arm. We summarized continuous variables using means, medians, and SDs. We analyzed normally distributed continuous variables with Student's *t*-tests; otherwise we used Wilcoxon rank-sum test. We used chi-square and Fisher's Exact test to analyze categorical variables as appropriate, including misoprostol side effects.

3. Results

We randomized 163 women from January 2015 through June 2016. Fig. 1 demonstrates the 4 treatment arms. We excluded two women in the misoprostol only group (both vaginal): one declined the D&E procedure after randomization and the second had her D&E performed outside the 4–6 h window. We conducted a per-protocol analysis. Baseline demographic characteristics were similar between the two groups (Table 1), with the majority being young, parous, and African-American.

We completed all 161 procedures successfully on the same day. Procedure times and cervical dilation are presented in Table 2. Mean total procedure time was longer in the misoprostol-dilator group, taking 3.2 min (95% CI 1.7, 4.6 min) longer versus misoprostol alone. However, D&E procedure times trended longer in the misoprostol-only group by 0.7 min (95% CI −0.8, 2.1 min). Eleven of 85 participants (13%) required hygroscopic dilator removal after speculum placement due to difficulty with manual removal, with a



[1] Pt decided not to have D&E procedure after randomization (misoprostol only & vaginal misoprostol)
[2] Protocol deviation: (D&E procedure performed outside the 4-6 hrs. for cervical preparation)

Fig. 1. Study flow diagram and randomization scheme.

Table 1
Baseline characteristics of participants randomized to misoprostol versus misoprostol-dilators for cervical preparation ($N = 161$).[1]

Variable	Misoprostol only $n = 76$	Misoprostol-dilators $n = 85$	p-value
Age (yr)			0.56
18–24	39(51)	52(61)	
25–29	21(28)	21(25)	
30–34	12(16)	9(11)	
>35	4(5)	3(4)	
Parity			0.52
Nulliparous	32(42)	32(38)	
Primiparous	18(24)	27(32)	
2 or more	26(34)	26(31)	
Gestational Age (weeks)			0.33
14–16 6/7	24(32)	21(25)	
17–19 6/7	52(68)	64(75)	
Prior induced abortion	34(45)	34(40)	0.54
Prior cesarean delivery	9(12)	14(16)	0.40
Body mass index (kg/m^2)			0.40
Underweight (below 18.5)	1(1.3)	3(3.5)	
Normal weight (18.5–24.9)	32(42)	27(32)	
Overweight (25–29.9)	22(29)	24(28)	
Class 1 Obesity (30.0–34.9)	7(9)	15(18)	
Class 2 Obesity (35.0–39.9)	14(19)	16(19)	
Race			0.34
White, not Hispanic	9(12)	10(12)	
Black, not Hispanic	55(72)	55(65)	
Hispanic	4(5)	6(7)	
Asian or Pacific Islander	3(4)	1(1)	
Multiracial/Other	5(7)	13(15)	
Current insurance			0.53
Private	23(30)	24(28)	
Public	34(45)	33(39)	
None	19(25)	28(33)	

Chi squared.
[1] Totals for each category may not add up to 100% secondary to rounding.
[2] All data presented as n(%).

Table 2
Procedure characteristics by relevant subgroup.[1]

	Misoprostol only $n = 76$	Misoprostol-dilators $n = 85$	p-value*
Total procedure time (min)			
Overall	10.8 ± 3.9	14.0 ± 5.3	<0.0001
Nulliparous	10.9 ± 3.9	15.3 ± 6.8	
Parity = 1	10.2 ± 3.9	13.5 ± 4.0	
Parity ≥ 2	11.1 ± 4.2	12.8 ± 4.1	
Total procedure time (min)			0.0001
14–16 6/7 weeks	9.6 ± 3.6	12.8 ± 6.8	
17–19 6/7 weeks	11.3 ± 4.0	14.3 ± 4.7	
Dilator insertion time (min)	N/A	3.8 ± 0.1	
Dilator removal time (min)	N/A	0.6 ± 0.3	
D&E procedure time (min)			
Overall	10.8 ± 3.9	10.1 ± 5.3	0.41
Nulliparous	10.9 ± 3.9	11.3 ± 7.0	
Parity = 1	10.2 ± 3.6	9.5 ± 3.8	
Parity ≥ 2	11.1 ± 4.2	9.2 ± 4.0	
D&E procedure time (min)			0.3
14–16 6/7 weeks	9.6 ± 3.6	9.4 ± 6.6	
17–19 6/7 weeks	11.3 ± 4.0	10.3 ± 4.8	
Initial cervical dilation (mm)			
Overall	11.7 ± 2.5	15.6 ± 2.7	<0.0001
Nulliparous	11.0 ± 2.4	14.8 ± 2.4	
Parity = 1	11.4 ± 2.0	16.1 ± 2.5	
Parity ≥ 2	12.6 ± 2.6	16.2 ± 3.1	
Initial cervical dilation (mm)			<0.0001
14–16 6/7	11.7 ± 2.8	14.6 ± 2.4	
17–19 6/7	11.7 ± 2.3	16.0 ± 2.7	
Total fentanyl given (μg)	104 ± 20.1	103 ± 15	0.9
Total midazolam given (mg)	2.37 ± 0.68	2.34 ± 0.68	0.7

* Student's t-test.
[1] All data presented as mean ± standard deviation.

mean dilator removal time of 0.5 ± 0.3 min. Sixty-three of 76 (83%) of participants in the misoprostol only group required additional mechanical cervical dilation compared to 54 out of 85 (64%) in the misoprostol-dilator group. Average cervical preparation time did not differ between the misoprostol-only group (281 ± 35.6 min) and the misoprostol-dilator group (281 ± 31.8 min), $p = 0.99$. One subject in the buccal misoprostol-dilator group experienced a significant complication of hysterectomy secondary to an occult uterine perforation which was identified after leaving the facility.

Side effect profiles in the buccal and vaginal misoprostol groups are demonstrated in Fig. 2. Of note, subjects receiving vaginal misoprostol reported chills more frequently than subjects receiving buccal misoprostol (mean Likert scores 2.3 vs. 1.9, $p = 0.04$). However, the rates of moderate to severe chills did not differ with 44/77 (57%) of subjects receiving vaginal misoprostol reporting moderate to severe chills versus 36/82 (43%) receiving buccal misoprostol ($p = 0.16$). Additionally, placement of hygroscopic dilators just prior to placement of vaginal misoprostol did not worsen reports of symptoms, as 20/43 (46%) of vaginal misoprostol-dilator patients reported moderate to severe chills compared to 24/36 (67%) of those receiving vaginal misoprostol only ($p = 0.07$).

Participant and provider satisfaction is presented in Figs. 3 and 4, respectively.

4. Discussion

We found that total procedure time took 3.2 min longer in patients receiving hygroscopic dilators with misoprostol for cervical preparation prior to D&E, a result we did not anticipate. We expected that the additional time to insert hygroscopic dilators would result in higher initial cervical dilation, leading to a shorter D&E procedure time compared to misoprostol-only cervical preparation. Although initial cervical dilation was indeed greater by 3.9 mm and D&E procedure time trended shorter in the misoprostol-dilator group, the possible reduction in D&E time did not offset the 3.8 min needed to place hygroscopic dilators. Total and D&E procedure time increased with increasing gestational age, but decreased with parity as expected. Neither gestational age nor parity altered D&E procedure time. Providers preferred cervical preparation with misoprostol-dilators, while patients found the pharmacologic-only method of cervical preparation more acceptable, which is consistent with previous studies.

Misoprostol worked equally well for cervical preparation, regardless of route of administration. We also found no difference in most of the reported side effects from misoprostol by route of administration, except increased chills in the vaginal misoprostol group. However, patients in each group reported similar severity when limited to moderate or severe chills. While our high frequency of chills is similar to the proportion of patients complaining of chills in other studies who received both hygroscopic dilators and misoprostol [14,15], these studies used buccal misoprostol.

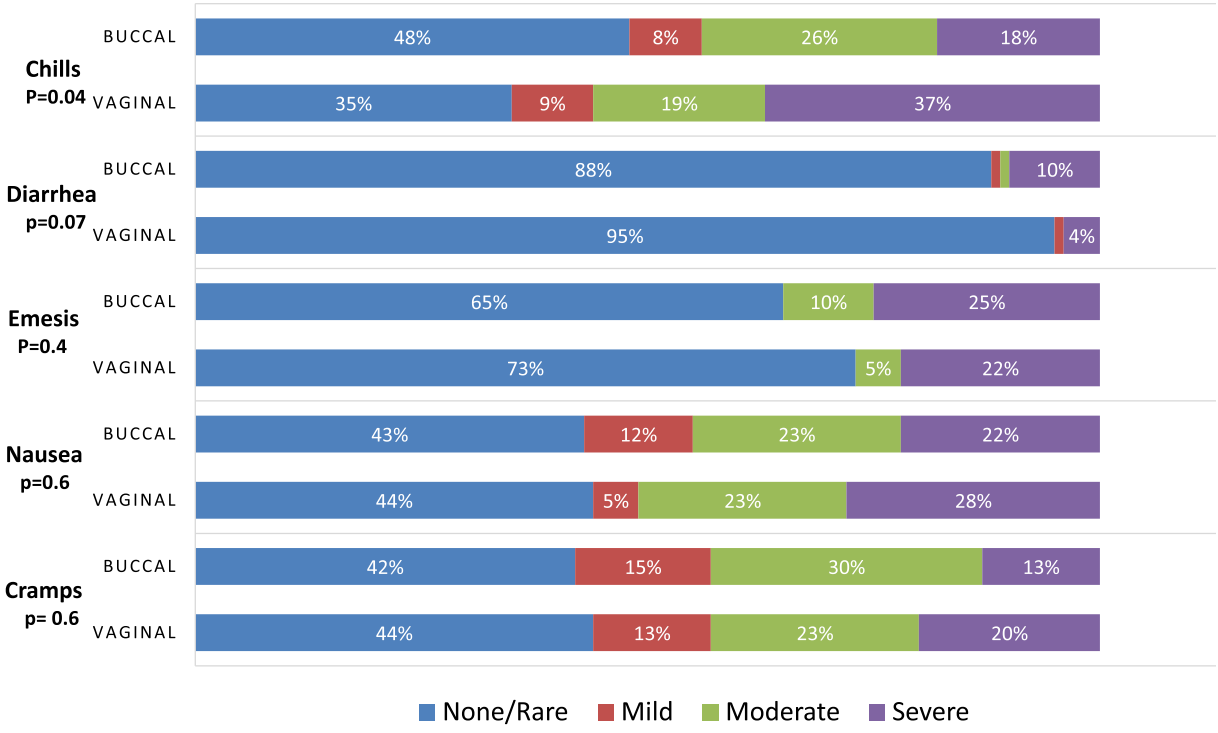


Fig. 2. Buccal vs. Vaginal misoprostol participant side-effects.

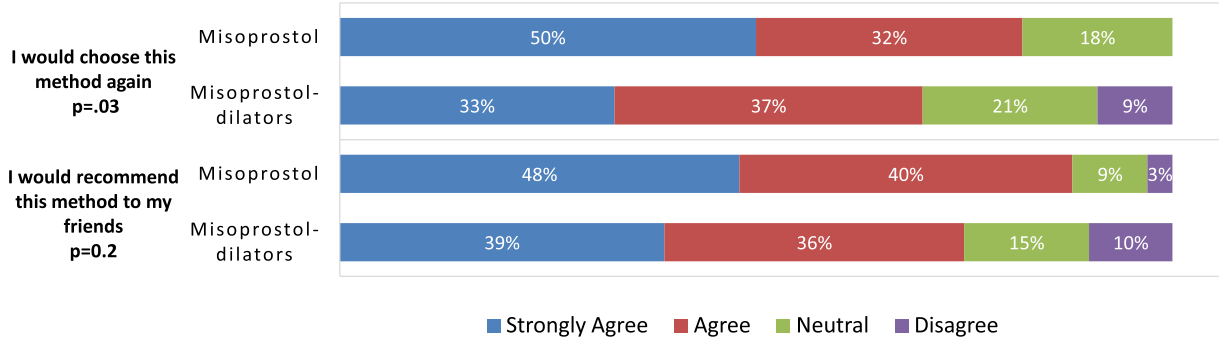


Fig. 3. Participant acceptability.

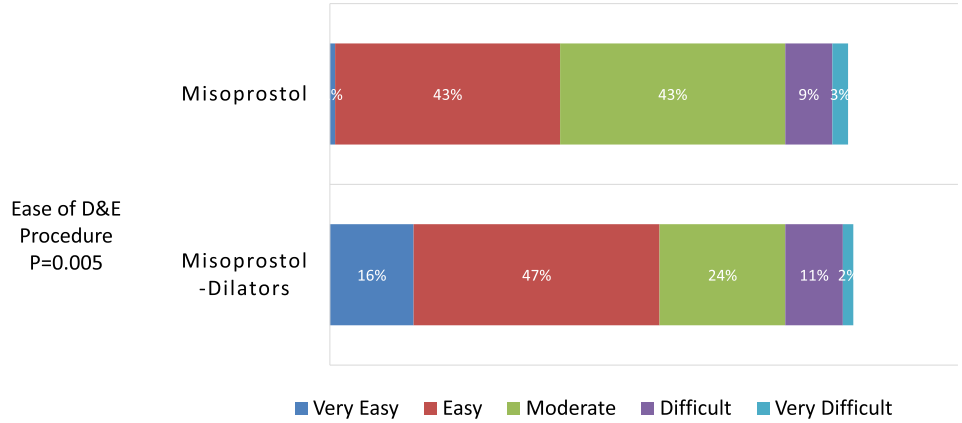


Fig. 4. Provider acceptability.

We could not find corroboration of increased chills with vaginal compared to buccal administration. The reason for this is difference is unknown, although vaginal misoprostol has higher serum peak levels than buccal misoprostol [16]. Placement of the vaginal misoprostol in the lateral vaginal fornices by a provider after cleansing of the vaginal vault during hygroscopic dilator insertion has been theorized to result in higher serum misoprostol acid concentrations and therefore could increase reported side effects compared to women who were advised to insert the misoprostol " as high as possible" [16]; however, our vaginal misoprostol-dilators group reported less severity of chills as the vaginal misoprostol-only group.

In general, misoprostol resulted in a large side effect burden, regardless of the route of administration; over 50% of participants reported nausea and chills when asked about their symptoms prior to D&E. Our data do not suggest that placement of hygroscopic dilators worsens these side effects, but further studies evaluating hygroscopic dilators alone versus misoprostol-dilators could help determine if hygroscopic dilators by themselves are sufficient as cervical preparation for same-day D&E while reducing the side effects associated with misoprostol.

This study compared different cervical ripening methods for same-day second trimester D&E. We completed all procedures successfully in one day, demonstrating that both misoprostol alone and misoprostol-dilators are feasible methods of cervical preparation prior to D&E procedures up to 20 weeks. The strengths of this study include its randomized, factorial design, which allowed for efficiency in measuring an additional outcome without recruiting an excessive number of participants. We had minimal loss to follow up as all data were collected in one day. Additionally, nearly one-third of participants were greater than 18 weeks, a group that has been less well-studied in same-day protocols.

The limitations of the study include non-blinded nature of study, relatively small study size, and wide gestational age range. Not blinding this study is unlikely to affect the primary outcomes of the study, which were measured objectively, though it could influence the subjective findings reported by patients and providers. Additionally, the number of participants excluded or declining to participate in our study is not available, which may affect its generalizability.

Our patient reported results may be impacted by the oral or IV sedation women received during the study. Patients received an oral anxiolytic, a narcotic, and an antiemetic at the initiation of cervical preparation, which may impact the validity of responses to the misoprostol side effect survey. However, a minimum of 4 h lapsed before we administered this survey, and patients in both the misoprostol-only and misoprostol-dilators group received a similar amount of total IV sedation medications, suggesting that neither group was affected more by the premedication regimen than the other. Additionally, as a randomized trial, we would expect the impact of premedication on the ability to answer survey questions to be evenly distributed between all groups. Nevertheless, our findings cannot be extrapolated to patients receiving neither oral nor IV anxiolytics. We did not define chills to patients, therefore misunderstanding may have occurred. Finally, the majority of study patients were recruited from one site (PPMW) although by research staff who rotated between MWHC and PPMW, thereby lessening the effect of any site variation on our results.

Providers' experience of ease of D&E procedures are frequently at odds with patients' experience of satisfaction and where this balance lies must include a weighing of the risks. This study adds to the body of evidence in same-day cervical preparation prior to second trimester D&E procedures, bringing us one step closer in determining an optimal cervical preparation method, and improving access to same-day D&E procedures based on evidence.

Acknowledgement

The authors acknowledge Arezou Akar for her contributions to data collection and study conduct.

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