Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion

A Randomized Controlled Trial

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OBJECTIVE: To study the efficacy, safety, and acceptability of oral immediately swallowed and buccal misoprostol 800 mcg after mifepristone 200 mg for terminating pregnancy through 63 days since the last menstrual period (LMP).

METHODS: This seven-site study randomly assigned 966 women seeking abortions to oral or buccal misoprostol 800 mcg 24–36 hours after mifepristone 200 mg with 7–14-day follow-up.

RESULTS: Success rates in the oral and buccal groups were 91.3% (389 of 426) and 96.2% (405 of 421), respectively (*P*=.003; relative risk [RR] 0.95, 95% confidence interval [CI] 0.92–0.98). Ongoing pregnancy occurred in 3.5% (15 of 426) of women who took oral misoprostol compared with 1.0% (4 of 421) of women in the buccal group (*P*=.012; RR 3.71, 95% CI 1.24–11.07). Through 49 days since the LMP, oral and buccal regimens performed similarly, but success with oral misoprostol decreased as pregnancy advanced. In pregnancies of 57–63 days since the LMP, success with oral misoprostol fell below 90%, whereas that with buccal remained high (oral 85.1% [97 of 114], buccal 94.8% [109 of 115], *P*=.015, RR 0.90, 95% CI 0.82–0.98). Furthermore, in this gestational age group, there were significantly more ongoing pregnancies among women who took misoprostol orally (7.9% [9 of 114]) compared with buccally (1.7% [2 of 115]; *P*=.029, RR 4.54, 95% CI 1.0–20.55). Adverse effect profiles were similar, although fever and chills were reported approximately 10% more often among women who took buccal misoprostol. Satisfaction and acceptability were high for both methods.

CONCLUSION: Buccal misoprostol 800 mcg after mifepristone 200 mg is a good option for medical abortion through 63 days since the LMP. Oral misoprostol 800 mcg is also a safe and effective alternative, although success rates diminish with increasing gestational age.

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LEVEL OF EVIDENCE: I

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After mifepristone was approved by the United States Food and Drug Administration in 2000, vaginal use of misoprostol 800 mcg became almost a standard of care in early medical abortion.[1–3] However, nonvaginal routes of misoprostol administration are now of increasing interest to women and providers because of 1) lower acceptability of vaginal administration[4,5]; 2) legal peril to women where abortion is clandestine and pill remnants may remain in the vagina; and 3) concern about infection, specifically,

very rare but fatal clostridial infections[6,7] (although no association between such infections and use of vaginal misoprostol has been found). In March 2006, Planned Parenthood Federation of America changed its national guidelines to avoid vaginal administration of misoprostol, but the scanty evidence supporting a nonvaginal regimen through 63 days since the last menstrual period (LMP) meant that medical abortion was no longer an option for women with pregnancies of more than 56 days since the LMP.

Oral (immediately swallowing pills), buccal (holding pills in the cheek) and sublingual (holding pills under the tongue) misoprostol administration after mifepristone has been studied as an alternative to vaginal administration in early medical abortion. Encouraging but equivocal findings of studies on 800 mcg oral misoprostol[8–10] and unpublished claims of high clinical success and tolerance of adverse effects with this regimen in a large United Kingdom system (January 2006, Dr. Kate Worsley, personal communication) suggested the need for a more definitive trial. Similarly, because an 800 mcg buccal regimen had been shown to be as effective as a 800 mcg vaginal regimen through 56 days since the LMP[11] and the pharmacokinetic profiles and effect on uterine contractility were similar,[12,13] we decided that buccal administration was also a likely candidate for use through 63 days since the LMP. We conducted a randomized trial to explore whether 800 mcg oral and buccal misoprostol 24–36 hours after mifepristone 200 mg are effective regimens for routine clinical use in medical abortion through 63 days since the LMP.

MATERIALS AND METHODS

We report an open-label, randomized trial to characterize oral and buccal misoprostol administration after mifepristone in women with pregnancies through 63 days since the LMP. The study was implemented in seven facilities in the United States: Family Planning Associates Medical Group (Chicago); Institute of Urban Family Health (New York); Magee Womens Hospital/University of Pittsburgh (Pittsburgh); Parkmed (New York); Planned Parenthood League of Massachusetts (Boston); Planned Parenthood of Waco (Waco); and Whole Woman's Health (Austin). The Western Institutional Review Board and the institutional review boards at the University of Pittsburgh and the Institute for Urban Family Health approved the protocol.

Women seeking medical abortion were eligible if they did not have U.S. Food and Drug Administration–labeled contraindications to the method, were at least 18 years old, and had an intrauterine pregnancy not exceeding 63 days since the LMP on the day of the medical abortion. Gestational age was determined by LMP, clinical examination, and/or ultrasonography, as needed. Participants had to be willing and able to sign consent forms, have access to a telephone and emergency transportation, speak and read English or Spanish, and agree to comply with the study procedures. Screening and enrollment generally occurred during the same visit, except when state-mandated 24-hour waiting periods after informed consent required a second visit.

On day 1, participants swallowed mifepristone 200 mg (Mifeprex; Danco Laboratories, New York, NY) in the clinic and then were provided with misoprostol 800 mcg (Ivax Pharmaceuticals, Miami, FL) to take 24–36 hours later at home, either orally or buccally according to random assignment. Women assigned to take misoprostol buccally were instructed to hold two 200-mcg pills in each cheek pouch for 30 minutes and then to swallow any remnants. Women were offered prescriptions for oral narcotics to manage pain and antidiarrheal and antinausea medications, according to local standards at each facility. Participants maintained a diary for up to 15 days to record misoprostol administration, pain, bleeding, adverse effects and medications taken.

Participants returned to the study site 7 to14 days after taking mifepristone for clinical assessment, including transvaginal ultrasonography, except at one site where ß-hCG levels were routinely monitored and ultrasonography was employed only when needed. Women with ongoing pregnancies were recommended suction aspiration. Women with nonviable pregnancies (eg, sac or other evidence of products of conception, but no gestational growth and no cardiac activity on ultrasonography) could opt for suction aspiration, expectant management, or a second misoprostol dose administered by the same route as the initial dose. If either of the latter two options was chosen, women were asked to return 7 days later. If a persistent nonviable pregnancy was diagnosed at the extended follow-up visit, a suction aspiration was recommended. Providers also could intervene surgically if deemed medically necessary (eg, for excessive bleeding) or at the participant's request. After expulsion was confirmed, women responded to a semi-structured interview about the experience overall, the acceptability of the procedure, and adverse effects.

Allocation to study group was determined by computer-generated assignment concealed in sealed opaque envelopes. Randomization sequence (using random blocks of eight and stratified by study center) and envelopes were prepared by Gynuity Health Projects staff unrelated to the clinical conduct of the

study. Envelopes were assigned to study participants in numerical sequence. Both providers and participants became aware of group assignment when the envelopes were opened.

The primary objective of the study was twofold: 1) to estimate the effectiveness of each regimen among women with gestations 57 to 63 days since the LMP and 2) to compare their effectiveness among all women. In determining the sample size, recruitment of women in the 57–63 day gestational age group was a limiting factor, and therefore the sample size calculation was based on the first stated objective. We determined that a sample of 105 women in the gestational age range of 57–63 days was required in each study arm to be able to estimate efficacy at 93% with a 95% confidence interval (CI) of ±5% (assuming a 5% rate of loss to follow-up). Based on U.S. abortion clinic statistics, we estimated that 15–20% of all participants would fall in the 57–63 day gestational age group, and anticipated enrolling a total of 1,200 women. With at least 425 women per arm, and assuming a 95% efficacy for the buccal regimen,[11] we would be able to detect a 5% difference between the study arms with 80% statistical power at the 95% confidence level—a difference we considered clinically important for formulating practice guidelines.

Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL). An interim analysis was conducted when approximately 50% of the study sample completed participation to assess safety. Baseline demographic variables were compared according to treatment group to test randomization, using the Student *t* test or the Mann-Whitney *U* test for continuous variables and χ^2; or Fisher exact test (where cell sizes were 5 or less) for categorical variables. Normality of continuous variables was assessed by graphic display.

The primary outcome variable—treatment success—was assessed both by per-protocol and intention-to-treat analyses; because no significant differences were found using the χ^2 test, only the per-protocol analysis is presented. Per-protocol analysis has been deemed more appropriate for an exploratory efficacy trial[14] and more valuable to clinicians and clinic managers who want to understand the true efficacy of the two regimens; moreover, it is commonly presented in medical abortion trials.[10] In both analyses, we included in-clinic or telephone follow-up adequate to determine that a woman's pregnancy had been terminated; for per-protocol analysis, adherence to the regimen was determined according to information provided at the follow-up visit. Successful medical abortion was defined as a complete abortion without surgical intervention at any point, regardless of the number of doses of misoprostol taken. For the final analysis of the primary outcome variable, the alpha was reduced to 0.0479, as a result of the interim analysis and according to the O'Brien and Fleming method.[15]

Secondary outcome variables were the effect of a second dose of misoprostol, adverse effects, patient satisfaction and acceptability of each of the regimens, adverse effects, and pain; these outcomes were assessed according to treatment group using χ^2 test or Fisher exact test. Finally, the effect of gestational age on primary and secondary outcome variables was assessed by χ^2 test for trend, and post-hoc, pair-wise comparisons were conducted using the Tukey HSD test, where results were significant. Efficacy within groups by site was assessed using χ^2 test or Fisher exact test. For secondary analyses, two-tailed values of $P<.05$ were considered significant.

RESULTS

Between September 2006 and May 2007, the study sites enrolled 966 participants (Fig. 1). Enrollment was discontinued after 265 women with pregnancies between 57 and 63 days since the LMP were randomly assigned, ensuring at least 210 analyzable cases. The two treatment groups were similar with respect to education level, marital status, gravidity, gestational age, and previous abortions, but there was a statistically significant difference in mean age (25.8 years for oral compared with 26.7 years for buccal $P=.02$) (Table 1).

Five participants (0.5%) withdrew from the study after randomization and 92 (9.5%) were lost-to-follow-up. The experiences of 847 women were analyzed for efficacy (Fig. 1). Overall the efficacy after buccal misoprostol administration was greater than that of oral administration (96.2% compared with 91.3%, $P=.003$) (Table 2). An intention-to-treat analysis was also conducted, which yielded no difference in conclusions (96.1%, buccal compared with 91.0%, oral, $P=.003$, RR 1.06, 95% CI 1.02–1.09). One percent of the women assigned to buccal misoprostol and 3.5% of the women assigned to oral misoprostol had a surgical intervention due to ongoing pregnancy (RR 3.71; $P=.012$). Other reasons for surgical intervention included persistent nonviable pregnancy or sac (n=14), medical indications (n=19), or woman's request (n=1), none of which varied significantly by study group. Efficacy did not vary significantly by study group among all women with gestations 56 days since the LMP or less, but among women with pregnancies 57–63 days since the LMP, efficacy was higher after buccal administration (85.1% compared with 94.8%, RR 0.90; $P=.015$). Fur-

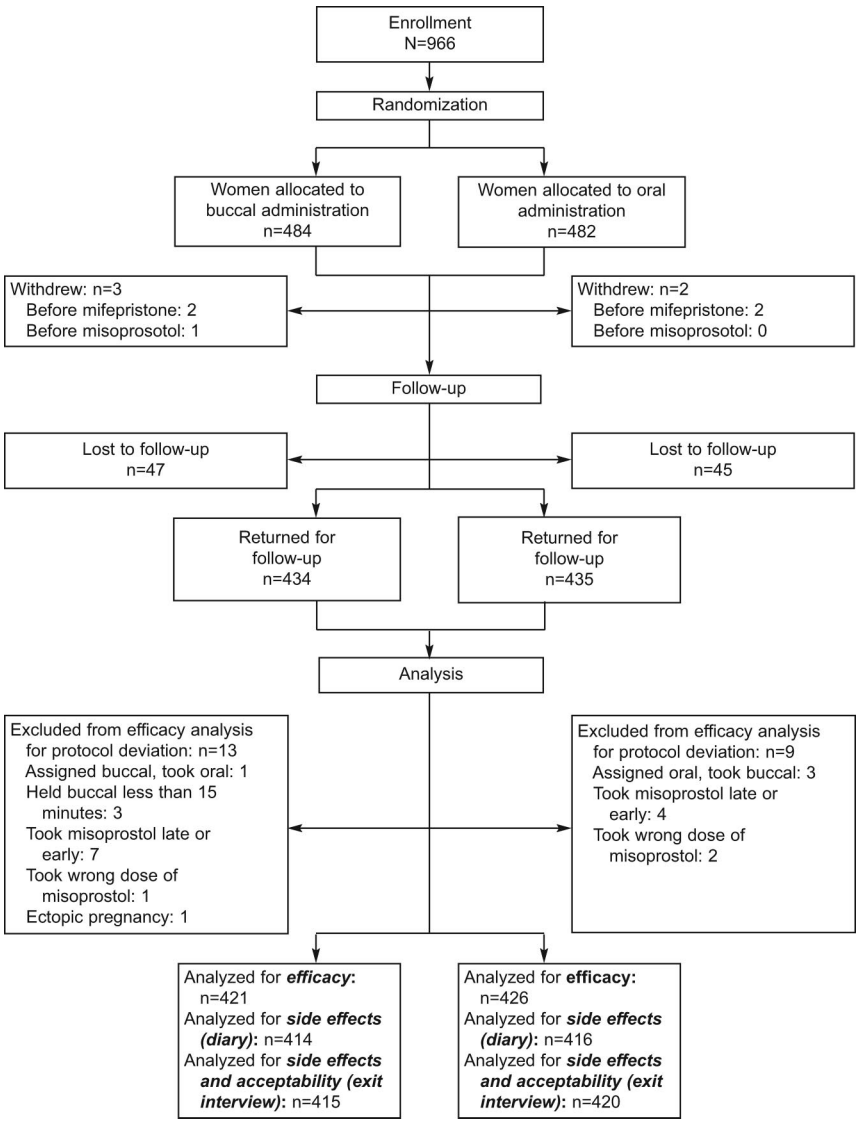

Fig. 1. Illustration of the flow and numbers of study participants through each phase of the study (enrollment, randomization, follow-up and analysis). *Winikoff. Misoprostol by Mouth in Medical Abortion. Obstet Gynecol 2008.*

ther, the frequency of ongoing pregnancy was significantly higher in that gestational age group among women administering misoprostol orally (7.9% compared with 1.7%, RR 4.54; P=.029). The success of buccal administration did not vary significantly with gestational age (χ^2 for trend 1.776; P=.183), although there was some decline in success with advancing gestational age (Fig. 2). Success after oral administration, however, was high (96.1%) among women with gestations 49 days since the LMP or less, but declined to 85.1% among those 57–63 days (P<.001).

The frequency of use of a second dose of misoprostol at follow-up to treat women with persistent nonviable pregnancies or uncertain outcomes did not vary between women in the buccal (n=14) and oral (n=12) groups (P=.668). Nonetheless, more women in the buccal group who took a second dose achieved a successful outcome (92.9% compared with 50.0%, P=.026). After a second dose of misoprostol, the success rate among women using misoprostol buccally increased by 3.1%, whereas the success rate was improved by only 1.5% for women in the oral group. This difference in improved outcome was not statistically significant.

Women reported adverse effects in diaries and in semistructured interviews at the follow-up visit (Table 3). The differences between what women recorded in diaries and what they reported in interviews were less than 10% for all effects except weakness, and approximately 80% of women's responses were consistent between the two sources (data not shown). Regardless of the source of report, the adverse effect profiles of

Table 1. Participant Characteristics by Study Group

	Oral (n=435)	Buccal (n=434)
Age (y)*	25.8 (±5.8)	26.7 (±6.1)
Educational level		
Less than high school	7.6 (33)	7.4 (32)
High school graduate	53.1 (231)	52.3 (227)
University graduate	33.8 (147)	32.0 (139)
Postgraduate degree†	3.9 (17)	6.9 (30)
Unknown	1.6 (7)	1.4 (6)
Currently married	14.1 (61)	16.8 (73)
Gravidity	3 (1–13)	3 (1–11)
Previous abortions	50.5 (219)	46.4 (201)
Gestational age (d)	49.7 (±8.3)	49.9 (±8.1)

Data are mean (±standard deviation), % (n), or median (1st quartile–3rd quartile).
* P=.02.
† P=.05.

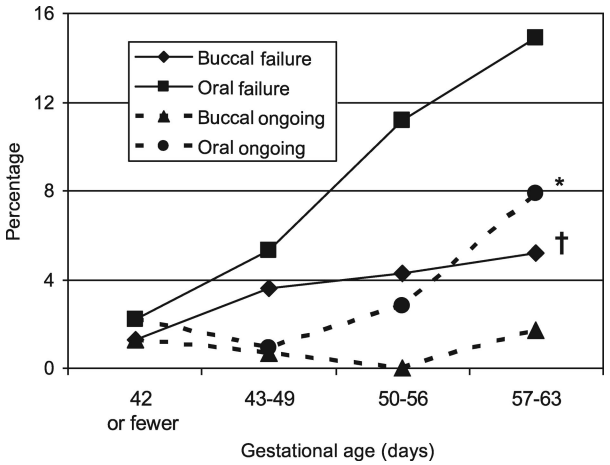

Fig. 2. Illustration of how failure rates and, more specifically, ongoing pregnancy rates increased with gestational age, particularly in the group of women that took oral misoprostol. * Difference between ongoing pregnancy rates by regimen is statistically significant at 57–63 days since the LMP (P=.029). † Difference between failure rates by regimen is statistically significant at 57–63 days since the LMP (P=.015).

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each study group were similar. Nausea vomiting, and diarrhea were reported equally frequently by women in each group. Fever/chills were also reported about 10% more frequently among women who took misoprostol buccally, whether reported in the diary (47.6 compared with 36.1, P=.001) or during the exit interview (41.4% compared with 33.3%, P=.020).

Twenty-six (3.0%) women made visits to an emergency room during the study period (14 from the oral group and 12 from the buccal group), 21 of whom were not admitted, primarily for pain and bleeding. Three participants from the buccal group were hospitalized during the study period for reasons that were unrelated to the study protocol (pulmonary embolus, ruptured ectopic pregnancy, and right hip pain).

Participants were highly satisfied with the procedure, regardless of the route by which they administered misoprostol: 91.9% of women were either satisfied or very satisfied (Table 4). Satisfaction decreased significantly with increasing gestational age in the oral

Table 2. Treatment Outcomes by Study Group and Gestational Age (Days)

Gestational Age (d)	Oral	Buccal	RR (95% CI)
Success*	91.3* (389/426) (88.2–93.8)	96.2* (405/421) (93.9–97.8)	0.95 (0.92–0.98)
42 or less	97.8 (90/92) (92.4–99.7)	98.7 (75/76) (92.9–100.0)	0.99 (0.93–1.03)
43–49	94.7 (107/113) (88.8–98.0)	96.4 (132/137) (91.7–98.8)	0.93 (0.86–1.00)
50–56	88.8† (95/107) (81.2–94.1)	95.7† (89/93) (89.4–98.8)	0.69 (0.56–1.04)
57–63	85.1* (97/114) (77.2–91.1)	94.8* (109/115) (89.0–98.1)	0.90 (0.82–0.98)
Failure	8.7* (37/426) (6.2–11.8)	3.8* (16/421) (2.2–6.1)	2.29 (1.29–4.04)
Ongoing pregnancy	3.5* (15/426) (2.0–5.7)	1.0* (4/421) (0.3–2.4)	3.71 (1.24–11.07)
42 or less	2.2 (2/92) (0.3–7.6)	1.3 (1/76) (0.0–7.1)	1.65 (0.15–17.87)
43–49	0.9 (1/113) (0.0–4.8)	0.7 (1/137) (0.0–4.0)	1.21 (0.08–19.17)
50–56	2.8 (3/107) (0.6–8.0)	0.0 (0/93) (0.0–3.2)	–
57–63	7.9* (9/114) (3.7–14.5)	1.7* (2/115) (0.2–6.1)	4.54 (1.0–20.55)
Medically necessary	2.6 (11/426) (1.3–4.6)	1.9 (8/421) (0.8–3.7)	1.36 (0.55–3.34)
Persistent sac	2.3 (10/426) (1.1–4.3)	1.0 (4/421) (0.3–2.4)	2.47 (0.78–7.82)
Patient request	0.2 (1/426) (0.0–1.3)	0.0 (0/421) (0.0–0.7)	–

RR, relative risk; CI, confidence interval.
Data are %, (n/N), or (95% confidence interval), unless otherwise specified.
* P<.048, comparing oral and buccal groups.
† P<.10, comparing oral and buccal groups.

Table 3. Adverse Effects (% Reporting Ever Experiencing)*

	Reported on Diary				Reported During Exit Interview			
Adverse Effect	Oral (n=416)	Buccal (n=414)	RR (95% CI)	*P*	Oral (n=420)	Buccal (n=415)	RR (95% CI)	*P*
None	2.6 (11)	4.9 (21)	1.67 (0.99–2.83)	.132	7.1 (30)	8.0 (33)	0.90 (0.56–1.46)	.680
Nausea	68.5 (285)	75.1 (311)	0.92 (0.84–1.01)	.067	63.6 (267)	66.0 (274)	0.97 (0.88–1.07)	.559
Vomiting	43.5 (181)	47.6 (197)	0.92 (0.79–1.07)	.228	39.5 (166)	40.2 (167)	0.99 (0.84–1.17)	.901
Diarrhea	38.7 (161)	43.0 (178)	0.91 (0.77–1.07)	.257	35.0 (147)	33.7 (140)	1.05 (0.87–1.26)	.646
Fever/chills	36.1 (150)	47.6 (197)	0.76 (065–0.90)	.001	33.3 (140)	41.4 (172)	0.81 (0.68–0.97)	.020
Headache	38.5 (160)	41.1 (170)	0.95 (0.80–1.12)	.517	31.0 (130)	34.0 (141)	0.92 (0.75–1.12)	.393
Dizziness	37.5 (156)	39.4 (163)	0.96 (0.81–1.14)	.658	29.8 (125)	32.8 (136)	0.91 (0.75–1.12)	.389
Weakness	53.6 (223)	58.0 (240)	0.93 (0.83–1.06)	.274	42.9 (180)	45.1 (187)	0.96 (0.82–1.12)	.588

RR, relative risk; CI, confidence interval.
Data are % (n) unless otherwise specified.
* Responses were consistent between reports on diaries and in exit interviews for 83% of women reporting nausea, 87% reporting diarrhea, 83% reporting dizziness, 83% reporting headache, 79% reporting weakness, and 85% reporting fever/chills.

group (χ^2 for trend 8.708, P=.003) but not in the buccal group (χ^2 for trend 3.495, P=.062). Participant satisfaction was significantly related to success, regardless of study group (χ^2 136.8, P<.001, oral; χ^2 50.1, P<.001, buccal).

Of women having successful abortions, overall satisfaction was higher among those who took misoprostol orally (96.9% compared with 92.8%, P=.009). Among women whose abortions were successful, the difference in the acceptability of adverse effects between the study groups was statistically significant, with more women in the oral group finding the effects acceptable (78.5% compared with 72.1%, P=.037). In both study groups, pain, the time to completion, and adverse effects were considered acceptable or very acceptable to the majority of women (Table 4). In general, women's expectations of the procedure were similar to their experiences, with the majority of women experiencing the same or less pain (70.7%) and bleeding (72.5%) than expected. There was no difference between study groups in expectations of bleeding, but women were more likely to have less pain than expected with oral than with buccal administration (38.6% compared with 29.6%, P=.006). When asked about regimen preference for a future medical abortion, 93.6% of women in the oral group responded that they preferred to take misoprostol orally, whereas only 34.0% of women in the buccal group would prefer buccal administration. The primary complaint about the buccal route was a bitter

Table 4. Women's Experience With the Procedure and Its Acceptability*

	All Women		Successes	
	Oral (n=420)	Buccal (n=415)	Oral (n=386)	Buccal (n=401)
Satisfaction with procedure	92.6 (389)	91.1 (378)	96.9† (374)	92.8† (372)
Procedure not/slightly difficult	71.2 (299)	70.4 (292)	72.8 (281)	71.3 (286)
Amount bleeding				
Less than expected	28.3 (119)	28.9 (120)	25.9 (100)	27.4 (110)
Same as expected	44.0 (185)	43.6 (181)	45.9 (177)	45.1 (181)
More than expected	26.0 (109)	25.3 (105)	26.4 (102)	25.7 (103)
Amount pain				
Less than expected	38.6† (162)	29.6† (123)	37.3† (144)	29.2† (117)
Same as expected	34.3 (144)	38.8 (161)	34.7 (134)	39.2 (157)
More than expected	25.7 (108)	29.9 (124)	26.4 (102)	30.2 (121)
Pain acceptable	68.3 (287)	64.8 (269)	68.4 (264)	65.3 (262)
Adverse effects acceptable	76.4 (321)	71.3 (296)	78.5† (303)	72.1† (289)
Time acceptable	83.3 (350)	82.7 (343)	85.5 (330)	84.0 (337)

Data are % (n).
* Satisfied means responded that procedure was either very satisfactory or satisfactory; acceptable means that women reported adverse effects, pain, or time of procedure was either acceptable or very acceptable.
† P<.05 comparing oral and buccal groups.

and chalky taste of the misoprostol, mentioned by 24% of women who administered it that way.

DISCUSSION

Our study demonstrates that, after 200 mg mifepristone, a dose of 800 mcg buccal misoprostol is more effective at terminating pregnancy than an 800 mcg oral dose. The buccal regimen is superior to the oral regimen between 57 days and 63 days since the LMP, with a trend over the entire gestational age range toward superiority between 49 days and 56 days since the LMP. Our results on the performance of the 800 mcg oral misoprostol regimen corroborate previous research that demonstrates a total efficacy of 90% or greater using oral regimens through 63 days since the LMP[8,10,16–20] and also corroborates that with increasing gestational age, success decreases and ongoing pregnancies rise significantly.[9,16,17,21] However, of the studies of 800 mcg oral misoprostol, one was terminated early due to low tolerance of adverse effects and reported outcomes in only 27 women.[9] In the other study, the failure rate among women 57–63 days since the LMP who took misoprostol orally was only two percentage points higher than among those who administered it vaginally (9.8% compared with 7.8%; RR 2.8, 95% CI 1.3–5.8),[10] a difference that may not be clinically relevant.

Our data also show that efficacy with buccal administration also decreases slightly with increasing gestational age (Table 2). Similar declines in efficacy may be observable regardless of route in early medical abortion.[9,10,16,22,23] There are three published trials using buccal misoprostol for pregnancy termination,[11,24,25] one of which used methotrexate, not mifepristone,[25] another was a pilot, noncomparative trial,[24] and the last of which tested the regimen only through 56 days since the LMP.[11] Our study demonstrates clearly that buccal misoprostol 800 mcg after mifepristone 200 mg is appropriate for use between 57–63 days since the LMP, whereas oral misoprostol 800 mcg is not as effective.

Differences in pharmacokinetics between oral and buccal routes offer one possible explanation for the different success rates, because the rapid peak in serum levels after oral use has been observed to result in increased uterine tone but not sustained uterine contractions. In contrast, regular and sustained uterine contractility has been documented after buccal as well as vaginal administration.[13]

Several large randomized clinical trials suggest that a repeated misoprostol dose may have a "leveling" effect on success among regimens.[10,16] A leveling effect was not observed in our study where use of additional misoprostol doses did not differ between study groups. In fact, the effect of a second dose among women who received it was a 1.5% increment in success for the oral regimen and 3.1% increment for the buccal route, widening the difference in efficacy between the routes.

Adverse effects were acceptable to women in both study groups and did not seem to affect overall satisfaction with the method, which was very high. Moreover, adverse effects did not vary significantly by study group, with the exception of more reports of fever/chills among those who took misoprostol buccally, but which were not judged clinically important. The adverse-effects profile in the buccal group was quite similar to that published by Middleton et al.[11] Despite claims that oral misoprostol leads to more gastrointestinal adverse effects (vomiting and diarrhea)[9,26] and the fact that our oral dose was higher than that used in some studies, we observed no differences in such effects between oral and buccal administration.

Clinical practices, including the timing and length of follow-up and propensity to intervene, have an important effect on observed differences in success rates in the published literature as well as in practice. A published meta-analysis and another case series have confirmed that provider practice may affect method success.[27,28] Clinicians in our study were aware of a woman's assigned regimen, and it is possible that this knowledge inadvertently influenced patient management. However, the overall differences in the reasons for surgical intervention were neither large nor significant, with the exception of ongoing pregnancies, the diagnosis of which is not as subject to provider bias.

The consideration of provider practice is particularly relevant because most of the mifepristone–misoprostol regimens tested in randomized trials are highly effective (greater than 90% overall efficacy). Moreover, management disparities may help to explain inconsistencies among randomized controlled trials, especially those done in one or only a few sites. The effect of provider practices may be unavoidable, costly to measure, and difficult to interpret, but if trial results should guide real-world practice, there is benefit to a protocol that does not overregulate clinical management.

In addition to oral and buccal, sublingual administration is another possible nonvaginal route of drug administration in medical abortion. The two randomized trials that had reported on the sublingual route through 63 days since the LMP at the time we initiated our study[22,23] examined use in a total of only

169 women. These data were insufficient to assume that sublingual administration was a more promising route than buccal misoprostol, which had already been demonstrated to be at least as effective as vaginal misoprostol through 56 days since the LMP.[11] The sublingual route remains an alternative that warrants further investigation.

The findings of our research are important for expanding the availability of medical abortion to women with pregnancies beyond 56 days of gestation where providers or women are reluctant to use vaginal misoprostol. Our results support the offer of a highly effective, safe, and acceptable nonvaginal regimen for early termination of pregnancy.

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