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Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion

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Abstract

Mifepristone was recently approved in the United States. Regimens with shorter intervals may be more acceptable. The objective of this study was to determine whether the oral route of misoprostol was as effective as the vaginal route of misoprostol 1 day after mifepristone. A prospective, open-labeled, randomized trial of healthy adult women up to 63 days pregnant and wanting a medical abortion were randomized to use either two doses of oral misoprostol 400 μg taken 2 h apart or misoprostol 800 μg vaginally. Women self-administered misoprostol 1 day after taking one-third of the standard dose of mifepristone (200 mg) orally. Women then returned to the clinic up to 5 days later for a repeat sonogram evaluation. A dose of vaginal misoprostol was administered to women with a continuing pregnancy who then returned 1 day later to Day 15. The primary outcome measures were a complete medical abortion by the first or by the second follow-up visits. Surgical intervention was indicated for continuing pregnancy at the second follow-up visit, excessive bleeding, or persistent products of conception 5 weeks later. One thousand one hundred sixty-eight women were enrolled. Of the 1144 (98%) women who complied with their random assignment, two oral doses of misoprostol (800 μg total) were 90% effective at inducing an abortion by the first follow-up visit, compared with one dose of misoprostol by vagina of 97% (χ^2 = 23.95, p = 0.001). By the second follow-up visit, the complete abortion rate was 95% for oral misoprostol and 99% for vaginal misoprostol (χ^2 = 21.76, p = 0.001). There were minimal differences in side effects. Women preferred the oral route. The trial demonstrated that although two doses of oral misoprostol were effective, the vaginal misoprostol was more effective at inducing an early medical abortion at 1 day after low-dose mifepristone, and the regimen could be extended to 63 days gestation.

Keywords: Abortion; Mifepristone; Misoprostol

1. Introduction

Mifepristone has been available in France since 1989 and, when followed by oral misoprostol, has been an effective abortifacient up to 7 weeks of pregnancy [1–3]. Studies have demonstrated the effectiveness of a lower dose mifepristone, i.e., 200 mg [4–7]. The regimen has also been effective up to 9 weeks of pregnancy when misoprostol is administered by the vaginal route [8,9]. A recent trial found that vaginal misoprostol is effective from 1 to 3 days after a low-dose mifepristone for up to 8 weeks of pregnancy and the women preferred the shortest interval [10].

Although oral misoprostol peaks in 20 min and is metabolized in the next hour, vaginal misoprostol's effectiveness is due to the sustained blood level rather than the quick peak and rapid metabolism noted after oral misoprostol [11]. Despite the advantages of vaginal administration of misoprostol, oral administration is still the most common mode of use in Europe and is the recommendation of the US Food and Drug Administration (FDA).

There continues to be a question regarding the most effective route of administering misoprostol after mifepristone. Although women prefer an oral rather than a vaginal route of a medication, vaginal misoprostol has been more effective than the oral route [8]. Would increasing the oral dose of misoprostol improve the regimen's effectiveness to equal that of the vaginal route? Would timing a second dose of oral misoprostol 2 h after the first dose, when the serum level is reaching a trough, provide similar pharmacokinetics and uterine contractions to that of the vaginal route? This study attempted to answer these questions by investigating whether, 1 day after mifepristone, giving two 400 μg oral

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doses of misoprostol (800 μg total) taken 2 h apart was as effective as one 800 μg vaginal dose of misoprostol, and whether the regimen could be extended to 9 weeks gestation.

2. Method

This was a multicenter, prospective, open-label, randomized trial that occurred from July 1999 through February 2000. There were 15 sites including hospital abortion services, private and nonprofit abortion facilities, and private family practice and gynecology offices. Eighty-four percent of the women were enrolled at seven sites: Rochester, New York; Cherry Hill, New Jersey; Brooklyn, New York; San Francisco, California; New York City, New York; South Bend, Indiana; and Cleveland, Ohio. All sites had institutional review board approval.

Women were ≥18 years old, healthy, ≤63 days pregnant confirmed by sonogram, and desiring an abortion. The inclusion and exclusion criteria and method of routine gestational dating by sonogram have been previously reported [4]. All women had a vaginal probe sonogram for dating and monitoring their abortions. On Day 1, after informed consent, women drew their computer-generated randomized assignments of either misoprostol orally or vaginally at 1 day after mifepristone (at least 24 h after mifepristone up to midnight of Day 2). Women then received mifepristone 200 mg orally in the office and used misoprostol the following day at home. All women using misoprostol were required to have an emergency plan with the clinic site to seek medical care in the case bleeding became excessive. Women assigned to oral misoprostol were instructed to take two 200 μg (400 μg total) tablets, followed by two more tablets (400 μg total) 2 h later, with the last dose no later than midnight on Day 2. Women taking vaginal misoprostol were instructed on how to insert four dry 200 μg (800 μg total) misoprostol tablets into the vagina with their finger. Women returned for their follow-up visit at their discretion from Day 3 to 8 after mifepristone.

At the first follow-up visit, the main outcome was the absence of the gestational sac on sonogram. A repeat dose of vaginal misoprostol 800 μg was given to all nonresponders, defined as women who had a persistent gestational sac on sonogram. These women then returned from 1 day later to Day 15 after mifepristone. At this second follow-up visit up to Day 15, if there was a continuing pregnancy on sonogram, a surgical abortion was performed. If there was a gestational sac present but no interval growth, women had the option for an aspiration curettage or waiting up to Day 36 after mifepristone for the gestational sac to spontaneously pass.

Women were interviewed regarding when bleeding and cramping began and kept a diary regarding symptoms and days of bleeding. They were to call or send a postcard when bleeding stopped. Women completed a symptom questionnaire at each visit and an acceptability questionnaire at the time of a sonogram documenting an absent gestational sac. The questionnaire used a Likert scale (*strongly disagree, disagree, neutral, agree,* or *strongly agree*) to rate the acceptability of the (a) overall procedure, (b) cramping pain, (c) bleeding, (d) side effects from the medications, (e) time waiting until the abortion was over, (f) willingness to recommend using misoprostol at home, (g) willingness to recommend the procedure to another woman, and (h) willingness to choose medical abortion again. Women were also asked how they would have preferred to use misoprostol, either "by mouth" or "by vagina." We combined *agree* and *strongly agree* for our analysis. If needed, women reported by mail or phone when their vaginal bleeding stopped.

Women were considered lost to follow-up if there was no documentation of their outcome after multiple attempts by study personnel to contact them by phone and certified letter. Outcome measures included (a) effectiveness rates at first follow-up visit (Pearson chi-square test), (b) reasons for surgical intervention, (c) side effects (Pearson chi-square test), (d) acceptability of the procedure (Pearson chi-square test, logistic regression), and (e) adverse outcomes. The acceptability results were stratified by gestational age groups up to 49 days, 50–56 days, and 57–63 days. A logistic regression was performed to measure the influence of misoprostol assignment, waiting for the procedure to end; the acceptability of pain, bleeding, and home use of misoprostol; and the patients' race, age, prior abortions, prior births, and gestational age on the acceptability of pain and the overall procedure.

To detect a 5% difference from 95% to 90% efficacy among the two groups with a power of 95%, two-tailed, $\alpha = 0.05$, required 582 women in each randomized group. The actual sample analyzed had the power to detect any significant differences between the oral and vaginal groups greater than ± 2.86% at the 95% confidence level. Data were analyzed with Statistical Analysis System (Cary, North Carolina).

3. Results

Of 1168 women enrolled, 19 (2%) were lost to follow-up and 5 used the misoprostol contrary to their assignment, leaving 1144 (98%) women remaining for analysis: 548 women in the oral misoprostol group and 596 in the vaginal misoprostol group (Table 1). There were no differences noted in age, race, parity, and gestational age of the two groups (Table 2).

Of the 1144 women who complied with their random assignment, two oral doses of misoprostol by mouth (800 μg total) were 90% effective at inducing an abortion by the first follow-up visit (by 1 week), compared with 97% with one dose of misoprostol by vagina ($\chi^2 = 23.95$, $p = 0.001$). After a repeat dose of misoprostol by vagina for those women not passing their pregnancy by the first follow-up

Table 1
Profile of randomized trial (n = 1168)

Randomized misoprostol assignments	Oral group	Vaginal group	Total
Women enrolled	561	607	1168
Women lost to follow-up	(8)	(11)	(19)
Women with complete follow-up	553	596	1149
Women with complete abortion but not requiring misoprostol	0	0	0
Women who had an aspiration curettage prior to misoprostol	0	0	0
Women who used misoprostol contrary to random assigned route of administration	(5)	0	(5)
Women who completed random assignment*	548	596	1144

* (Sample analyzed)

visit, the complete abortion rate was 95% for women receiving oral misoprostol and 99% for those receiving vaginal misoprostol ($\chi^2 = 21.76$, p = 0.001). Table 3 shows that at the first follow-up visit, two oral doses of misoprostol by mouth (800 μg total) was less effective up to 49 days, from 50–56 days, and 57–63 days by 7%, 8%, and 9%, respectively, compared with misoprostol by vagina. The administration of 800 μg of vaginal misoprostol for those women with a persistent gestational sac narrowed these differences to 4%, 6%, and 6%, respectively. Heavy bleeding was the most common reason for an aspiration curettage (16), which occurred, on average, at 34 days (SD ± 23.0) after mifepristone.

Forty-four women (8%) of the oral group had a persistent gestational sac at first follow-up visit. Of these, 42 received a second dose of misoprostol by vaginal route per protocol, and 25 (60%) had a complete abortion by sonogram on subsequent follow-up visit.

The mean number of days of bleeding was 18 (SD ± 10.4). The route of misoprostol administration had no effect on the initiation of bleeding (Table 4); nearly 89% of all women began bleeding within 4 h of taking misoprostol, another 9–10% bled between 4 and 24 h, and the last 2–3% bled more than 24 h later or not at all. Eight percent (91/1144) of women experienced some bleeding prior to misoprostol, but all used misoprostol.

Table 2
Demographic and initial clinical variables by misoprostol assignment (n = 1144)

Variable	Oral group (%)	Vaginal group	(Chi-sq) p-value
	(n = 548)	(n = 596)	
Race			2.05, p = 0.73
White	67%	68%	
Black	17%	16%	
Hispanic	7%	8%	
Asian	6%	7%	
Other	3%	2%	
Prior live births (n)	46% (254)	44% (264)	NS
Prior abortions (n)	45% (247)	45% (269)	NS
Age (years), mean (95% CI)	27 (26.9–27.9)	27 (26.8–27.7)	NS
Gestational age (days), mean (95% CI)	47 (46.5–47.7)	47 (46.3–47.5)	NS

Reported side effects are shown in Table 5. About half of the women experienced some nausea, and a quarter experienced vomiting, with only minor differences noted by route of misoprostol. Compared with vaginal administration, women using oral misoprostol reported fever and chills less frequently (25% vs 32%, $\chi^2 = 6.54$, p = 0.01) but had more diarrhea (33% vs 18%, $\chi^2 = 30.17$, p<0.001).

There were eight adverse events, all occurring in the oral misoprostol group. One woman experienced a syncopal reaction and was found to have mild hypertension that responded to medications. Another woman had urticaria after mifepristone that responded without intervention. Six women had emergency room visits for either heavy bleeding or cramping pain; three required an aspiration curettage, one had pregnancy tissue removed from the os with forceps but no curettage, and two received only intravenous fluids. There were no hospitalizations and no transfusions.

There were few significant differences reported between the oral and the vaginal misoprostol groups regarding the acceptability of the (a) overall procedure (93% vs 91%), (b) bleeding (83% vs 85%), (c) cramping pain (76% vs 69%), (d) side effects of the medications (83% vs 84%), (e) time waiting until the abortion was over (82% vs 86%), and (f) home use of misoprostol (90% vs 91%). There was also no difference in the willingness to choose the procedure again (87% vs 88%). However, in those women in the vaginal misoprostol use group with initial gestations from 57 to 63 days, the acceptability of the overall procedure dropped to 81% (p = 0.01), and the acceptability of home use of misoprostol was 80% (p = 0.02).

The regression analysis showed that women randomized to vaginal misoprostol were only 58% (95% CI, 0.43–0.80) as likely to find pain acceptable compared with the oral misoprostol group. Women with at least one live birth were 3.7 times (95% CI, 2.56–5.23) more likely to find pain acceptable. Women who had a prior abortion were only 57% (95% CI, 0.32–0.99) as likely to find the procedure acceptable.

4. Discussion

The FDA labeling of mifepristone recommends 600 mg orally followed by misoprostol 400 μg orally 2 days later. Multiple studies have supported alternative regimens. Our recent published trial demonstrated the effectiveness of mifepristone 200 mg orally followed by misoprostol 800 μg vaginally 1 and 3 days after mifepristone [10]. This trial attempted to determine whether an oral route of misoprostol could be as effective and acceptable as vaginal misoprostol at 1 day after mifepristone and whether the shorter 2-day

Table 3
Complete medical abortions and surgical interventions by three gestational age groups by misoprostol assignment at first follow-up visit (n = 1144)

	≤49 days pregnant[a] (n = 731) n, %, (95% CI)		50–56 days pregnant[b] (n = 281) n, %, (95% CI)		57–63 days pregnant[c] (n = 132) n,%, (95% CI)	
	Oral (n = 348)	Vaginal (n = 383)	Oral (n = 135)	Vaginal (n = 146)	Oral group (n = 65)	Vaginal (n = 67)
Complete medical abortion at first follow-up visit	314 90% (86.7–93.3)	371 97% (95.3–98.7)	120 89% (94–100)	141 97% (94.2–99.8)	57 88% (79.6–96.6)	65 97% (93.0–100)
Complete medical abortion at final visit	332 95% (92.7–97.3)	382 99% (98.0–100)	126 93% (90.6–99.4)	144 99% (97.4–100)	61 94% (88.1–99.9)	66 99% (96.6–100)
Surgical intervention	16 (5%)	1 (<1%)	9 (7%)	2 (1%)	4 (6%)	1 (2%)
Delayed heavy bleeding	6	1	7	1	0	1
Continuing pregnancy	4	0	1	0	1	0
Woman's request	4	0	0	0	3	0
Pain	2	0	1	1	0	0

[a] $\chi^2 = 13.62$, p = 0.001.
[b] $\chi^2 = 6.27$, p = 0.01.
[c] $\chi^2 = 4.09$, p = 0.04.

regimen could be extended to women up to 9 weeks gestation.

We found one dose of misoprostol administered vaginally was consistently more effective than twice the FDA recommended oral dose of misoprostol given 2 h apart at 1 day after mifepristone and also remained effective to 9 weeks of pregnancy. Using a repeat dose of vaginal administration for initial nonresponders increased the oral misoprostol group's effectiveness to 95%. We do not know if just waiting to Day 14 would have given similar results or whether a repeat oral dose of misoprostol would have been as effective as the repeat vaginal misoprostol dose. Although a randomized trial has not been performed regarding the benefits of a repeat dose of vaginal misoprostol versus expectant management, the repeat dose has been associated with very high effectiveness rates without associated increase in unacceptable side effects. In this trial, with a repeat dose of vaginal misoprostol, both regimens reached very high effectiveness rates in gestations 2 weeks beyond the FDA recommended 7 weeks. Repeat doses of vaginal misoprostol have been common in medical abortion trials using methotrexate [12,13].

Previous reports have found that as many as 50% of women experience some bleeding when using the FDA 3-day interval, creating some confusion for clinicians and women whether misoprostol is needed. With the shorter interval between medications, i.e. 1 day, only 8% of women experienced bleeding prior to misoprostol, leading to less confusion as to whether to use the misoprostol.

Although the vaginal misoprostol regimen being used 1 day after mifepristone was highly effective up to 9 weeks gestation, in women with gestations between 57–63 days, the reported acceptability of the overall procedure was the lowest (81%), which was likely due to increased uterine pain. All women should be counseled appropriately regarding the likely amount of pain they will experience and should be given sufficient pain medication. To maintain high patient acceptability with a 2-day regimen, clinicians may want to limit the gestational age to 8 weeks.

The reasons for surgical completions, the side effects, the adverse events, and the acceptability results were similar to other reports. Nearly all women began bleeding within 24 h of using misoprostol orally or vaginally. There was little

Table 4
Time to bleeding after misoprostol by misoprostol assignment (n = 1144)

Time to bleeding after misoprostol (h)	Oral group (n = 548)	Vaginal group (n = 596)	Total (n = 1144)	(chi-sq) p-value
<4	89% (487)	87% (521)	88% (1008)	
4 to 24	9% (52)	10% (59)	10% (111)	
>24 or no bleeding	2% (9)	3% (16)	2% (25)	1.54, p = 0.05

Table 5
Side effects reported by misoprostol assignment (n = 1144)

Side effects	Oral misoprostol group %	Vaginal misoprostol group %	(chi-sq), p-value
Cramping	92 (502/547)	93 (555/596)	$\chi^2 = 0.74$, p = 0.39
Nausea	51 (282/548)	46 (273/595)	$\chi^2 = 3.55$, p = 0.06
Diarrhea	33 (179/548)	18 (110/594)	$\chi^2 = 30.17$, p < 0.0001
Vomiting	26 (144/547)	27 (160/435)	$\chi^2 = 0.05$, p = 0.83
Dizziness	26 (142/546)	26 (153/593)	$\chi^2 = 0.00$, p = 0.94
Fever/chills	25 (136/547)	32 (188/593)	$\chi^2 = 6.54$, p = 0.01
Headaches	13 (71/548)	15 (87/594)	$\chi^2 = 0.68$, p = 0.41

difference in reported side effects between the two groups, except for more diarrhea with oral misoprostol and more fever/chills with vaginal misoprostol. Although nearly half of the women experienced some side effects, about 85% found the side effects acceptable. There were few adverse events and no hospitalization nor transfusions. In our series of studies of mifepristone for medical abortion of over 7,000 women, there have only been four women who have required a transfusion.

The trial demonstrated that mifepristone 200 mg followed by vaginal misoprostol was more effective at inducing an early medical abortion than oral misoprostol at 1 day after low-dose mifepristone and the regimen could be extended to 63 days gestation. A repeat dose of misoprostol was safe and is associated with high effectiveness. Because women prefer the shortest interval, this alternative 2-day regimen may be preferred to the FDA-approved regimen.

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References

[1] Peyron R, Aubeny E, Tarzus V, et al. Early termination of pregnancy with mifepristone (RU486) and orally active prostaglandin misoprostol. N Engl J Med 1993;328:1509–13.

[2] Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med 1998;338:1241–7.

[3] Aubeny E, Peyron R, Turpin CL, et al. Termination of early pregnancy (up to 63 days of amenorrhea) with mifepristone and increasing doses of misoprostol. Int J Fertil Menopausal Stud 1995;40(Suppl 2):85–91.

[4] Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for induced abortion. Contraception 1999;59:1–6.

[5] World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation. Termination of pregnancy with reduced doses of mifepristone. Br Med J 1993;307:532–7.

[6] World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomized trial. Br J Obstet Gynaecol 2000;107:524–30.

[7] Ashok PW, Penney GC, Flett GM, Templeton A. An effective regimen for early medical abortion: a report of 2000 consecutive cases. Hum Reprod 1998;13:2962–5.

[8] el-Refaey H, Rajaselar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU486) and oral or vaginal misoprostol. N Engl J Med 1995;332:983–7.

[9] Schaff EA, Fielding, SL, Eisinger SH, Stadalius LS, Fuller L. Low-dose mifepristone followed by vaginal misoprostol at 48 h for abortion up to 63 days. Contraception 2000;61:41–6.

[10] Schaff EA, Fielding SL, Westhoff C, et al. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion (≤56 days gestation): a randomized trial. J Am Med Assoc 2000;284:1948–53.

[11] Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997;90:88–92.

[12] Hausknecht RU. Methotrexate and misoprostol to terminate early pregnancy. New Engl J Med 1995;333:537–40.

[13] Creinin MD, Vittinghoff E, Keder L, Darney PD, Tiller G. Methotrexate and misoprostol for early abortion: a multicenter trial. I. Safety and efficacy. Contraception 1996;53:321–7.