



Review article

A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks of gestation

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Abstract

Objectives: This review aimed to assess the effectiveness, acceptability and safety of regimens that include mifepristone and multiple misoprostol doses for abortion up to 10 weeks of gestation.

Methods: We searched MEDLINE and reference lists for English-language reports (published between January 1990 and September 2005) of trials evaluating a medication abortion regimen consisting of mifepristone and multiple doses of misoprostol. Eligible trials had to either be restricted to women with less than 10 weeks' gestation or report stratified results that allowed the extraction of data for this subset.

Results: Although we identified 26 eligible studies, only 3 were randomized controlled trials (RCTs), comparing regimens that differed in the repeat-dose misoprostol component. These trials did not detect differences in effectiveness between the randomized groups. One RCT found evidence of higher effectiveness from repeat misoprostol doses among a subgroup of women with more advanced gestations.

Conclusions: Although clinicians often prescribe a repeat dose of misoprostol to increase effectiveness in medication abortion, the effect of the repeat dose has not been established. Because mifepristone followed by a single misoprostol dose is highly effective in inducing abortion, determining the effect of a repeat misoprostol dose would require a large sample size. The resource expenditure on such large trials might not be warranted. Any future studies should use induction-to-completion time to measure effectiveness and should assess acceptability and side effects.

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1. Introduction

Although mifepristone followed by a single misoprostol dose causes a high complete abortion rate (92–99%) among women with early pregnancies [1], some clinicians administer additional misoprostol doses in an attempt to improve abortion effectiveness. Clinical practices should be based, though, on sound evidence. If repeat misoprostol does not improve effectiveness, then its administration would expose women to unnecessary risks of dose-dependent side effects or unnecessary office visits.

Determining whether repeat misoprostol dose (or doses) improves effectiveness is complicated by the variety of regimens and measures used. The effect of the repeat misoprostol dose could be influenced by the mifepristone

dose, as well as by the mode of administration, timing and individual and cumulative doses for the misoprostol component. Furthermore, given that a single misoprostol dose administered after mifepristone is highly effective in causing abortion, any possible influence of a repeat misoprostol dose on the effectiveness rate would have to be small. Consequently, a large sample size would be required to detect the limited potential contribution of the repeat dose. When assessing such a small possible effect, bias or residual confounding could be particularly influential and possibly lead to spurious conclusions.

Thus, the choice of the appropriate control group for assessing the effectiveness of the repeat misoprostol dose is paramount. Ideally, randomized controlled trials (RCTs) would be conducted to compare mifepristone and misoprostol regimens that differed only in that one regimen included a repeat misoprostol dose while the other used a placebo. This design would demonstrate the marginal increase in effec-

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tiveness from a repeat misoprostol dose. RCTs also could be used to evaluate the relative effectiveness of repeat doses in order to establish the optimal number, dose, timing and route for the additional misoprostol.

We conducted a review of trials of any design evaluating mifepristone and misoprostol regimens that included more than one misoprostol dose for inducing abortion in women before 10 weeks' gestation.

2. Methods

2.1. Search strategy

We searched MEDLINE via PubMed using the terms “mifepristone,” “misoprostol” and “abortion” for studies of medication abortion regimens that included more than one dose of misoprostol. We also searched the references of eligible trials for additional studies. Thus, the search strategy was an iterative process.

Only English-language reports (published between January 1990 and September 2005) of studies evaluating a medication abortion regimen consisting of mifepristone and a repeat dose of misoprostol were eligible for the review. We defined a “repeat dose” as the administration of at least 200 µg of misoprostol, via any route, initiated at least 2 h after an initial bolus of at least 400 µg. In addition, eligible

studies had to either be restricted to women with less than 10 weeks' gestation or report stratified results that would allow the extraction of data on the study women meeting this gestational age criterion.

2.2. Outcome measures

Our primary outcome measure was abortion effectiveness, defined as time from induction to complete expulsion. However, we were limited in this review to report the measures of effectiveness described in the eligible trial reports. Some studies required complete abortion within a certain time frame to be considered a successful event; others used a less rigorous (or inadequately described) protocol employed over an unspecified time frame. A regimen that requires less time to completion — even if it does not affect the overall complete abortion rate — would likely be viewed more favorably by women [2]. Evaluating differences in the time from treatment initiation to expulsion using survival analysis would give more information about the regimen's effectiveness than a dichotomous outcome based on the proportion having a complete abortion. This survival analysis approach also reduces attrition bias by including women in the analysis up to the time that they were lost to follow-up [3,4]. Studies also differed in their methods for determining complete expulsion; criteria included review of products of conception, absence of gestational sac, endome-

Table 1
Characteristics and results for RCTs with groups that differed with respect to repeat misoprostol dose

| Reference | Trial design | Gestational restriction | Intervention | | Results | | |
|----------------------------|------------------|-------------------------|---|---|---|--|---|
| | | | Initial treatment | Repeat miso dose(s) and indication for use | Repeat miso dose(s) data | Complete abortion rate | Induction-to-expulsion times |
| Creinin et al. [7] | Unblinded RCT | ≤49 Days | Mife 600 mg+miso 400 µg PO after 6–8 h (n=42) Mife 600 mg+miso 400 µg PO after 48 h (n=44) | Miso 6–8 h: miso 400 µg PO 48 h after mife use for gestation sac Miso 48 h: no repeat miso dose | 18 Women in miso 6–8 h group used a second miso dose | Miso 6–8 h: 95% (95% CI, 89–100%) Miso 48 h: 98% (95% CI, 93–100%) | Not reported |
| Hamoda et al. [8] | Unblinded RCT | ≤63 Days | Mife 200 mg+miso 600 µg SL after 36–48 h (n=53) Mife 200 mg+miso 800 µg PV after 36–48 h (n=69) | Miso 400 µg SL or PV (route same as that of initial treatment) 3 h after first miso dose for all participants | SL group: mean no. of miso doses used, 1.3 (S.D., 0.5) PV group: 1.4 (S.D., 0.5) | SL group: 100% PV group: 98.6% | SL group: median time, 3.3 h (range, 0.4–8.2) PV group: median time, 3.4 h (range, 1.1–63.3) |
| von Hertzen et al. [2,5,6] | Double-blind RCT | ≤63 Days | PO–PO: Day 1: mife 200 mg. Day 3: miso 800 µg PO and placebo PV (n=740) PV–PO: Day 1: mife 200 mg. Day 3: miso 800 µg PV and placebo PO (n=741) PV only: Day 1: mife 200 mg. Day 3: miso 800 µg PV and placebo PO (n=738) | PO–PO and PV–PO: Days 4–10: miso 400 µg PO bid PV only: Days 4–10: placebo PO bid | Same as for overall rates | PO–PO: 92.3% (95% CI, 90.1–94.1) PV–PO: 94.7% (95% CI, 92.9–96.2) PV only: 93.5% (95% CI, 91.5–95.2) | Not reported |

Miso, misoprostol; mife, mifepristone; PO, orally; SL, sublingually; PV, vaginally; CI, confidence interval; bid, twice a day.

trial thickness, pelvic exam or simply the proportion of cases that did not undergo evacuation.

Secondary outcomes included measures of acceptability and side effects. Assessing these outcomes is important because, for example, a slight increase in effectiveness achieved at the cost of a substantial increase in negative side effects might not be a worthy trade-off. Again, we report the outcomes included in the eligible articles.

3. Results

The MEDLINE search yielded 335 articles. We retrieved complete articles for the citations that appeared potentially eligible based on the electronic database search or the review of the reference lists of the included articles. After eliminating those that did not meet the eligibility criteria, we included 28 reports on 26 studies in the present review. Three were RCTs that differed regarding the repeat misoprostol doses. The remaining trials had methodological issues or study designs that were inadequate for answering the research question.

3.1. RCT with groups that differed regarding repeat misoprostol doses

The search strategy yielded three RCTs that evaluated regimens that differed with respect to the repeat misoprostol dose (Table 1). The World Health Organization (WHO) conducted a large ($N=2219$), multicenter RCT, which was described in three reports [2,5,6]. Both the participants and the investigators were blinded as to group assignment. The women were to use mifepristone 200 mg on Day 1 and then one of the following regimens starting on Day 3: (a) misoprostol 800 μg po and vaginal placebo followed by misoprostol 400 μg po bid for 7 days (oral/oral), (b) vaginal misoprostol 800 μg and placebo po followed by misoprostol 400 μg po bid for 7 days (vaginal/oral) and (c) vaginal misoprostol 800 μg and placebo po followed by placebo po bid for 7 days (vaginal only).

The complete abortion rate, measured on Days 15 and 43, did not differ between groups. Subgroup analyses among women with more advanced gestations (>57 days) showed that those in the vaginal-only group had a statistically significantly lower complete abortion rate (92.1%) than those in the vaginal/oral group (96.5%). The relative risk (RR) for failure to achieve complete abortion for the vaginal-only group was 2.2 times (95% CI, 1.0–4.7) that of the vaginal/oral group.

The randomized groups did not differ during the interval between the misoprostol visit and the follow-up visit at Day 15 in bleeding duration or side effect outcomes, except for diarrhea and rash. More women in the oral/oral group (27%) and the vaginal/oral group (26%) reported diarrhea than the vaginal-only group (9%) for this interval. While rash was a rare outcome ($<1\%$ overall), the vaginal/oral group was statistically significantly more likely to report this outcome than the other two groups.

The other two RCTs did not include a placebo group for the repeat dose [7,8]. Furthermore, they were small trials that likely had insufficient power to detect any differences that might have existed between groups. Creinin et al. [7] conducted an unblinded trial to compare two groups that used the same initial regimen (mifepristone 600 mg and misoprostol 400 μg po) but then differed in the timing of the misoprostol dose (6–8 vs. 48 h). The group using misoprostol ($n=42$) after the shorter interval was to receive a repeat misoprostol dose (same amount and route) if the gestational sac was still present 48 h after mifepristone use. The second group ($n=44$) did not receive more misoprostol. No difference in effectiveness between the groups was detected at the 2-week follow-up visit; the effectiveness rate was 95% (95% CI, 89–100%) for the repeat-dose group and 98% (95% CI, 93–100%) for the single-dose group. The repeat-dose group was statistically significantly less likely to report vomiting (RR 0.2; 95% CI, 0.0–0.7), spotting (RR 0.1; 95% CI, 0.0–0.4) or bleeding (RR 0.6; 95% CI, 0.5–0.8) than the comparison group.

In the most recent RCT, women under 9 weeks' gestation received mifepristone 200 mg followed after 36–48 h by either (a) misoprostol 600 μg used sublingually ($n=53$) or (b) misoprostol 800 μg used vaginally ($n=69$) [8]. After an additional 3 h, the groups received misoprostol 400 μg sublingually or vaginally, respectively. The median induction-to-expulsion times were similar for the two groups: 3.3 h (range, 0.4–8.2) for the sublingual group and 3.4 h (range, 1.1–63.3) for the vaginal group.

3.2. RCTs with groups that did not differ in regard to repeat misoprostol dose

We found four RCTs comparing medication abortion regimens that did not differ in terms of the repeat misoprostol dose [9–12]. Although these trials provide useful data on the effectiveness of the mifepristone and initial misoprostol dose, they do not allow us to assess any marginal increase in effectiveness attributable to the repeat misoprostol dose (Table 2).

3.3. Nonrandomized, comparative studies

Our search revealed five comparative, nonrandomized studies that compared regimens with a repeat misoprostol dose [13–17]. The nonrandomized, comparative trials did not show any statistically significant differences in improvements in effectiveness (or other outcomes) with repeat misoprostol doses. Systematic differences between the groups could have led to biased results in these trials, though, because the group selection was based either on the time interval in which the woman sought care [13–15] or participant preferences [16,17].

For example, Aubény [15] conducted a trial in which the repeat misoprostol dosage was based on whether the woman attended during the 1993–1994 or 1995–1997 time period. However, if their experience with medication abortion led providers in the second time period to wait longer before

Table 2
Attributes of study designs for evaluating repeat misoprostol doses

| | RCTs with groups that differ regarding repeat misoprostol dose | RCTs with groups that do not differ in regard to repeat misoprostol dose | Nonrandomized, comparative studies | Noncomparative studies |
|-------------------|---|---|--|---|
| Published reports | [2,5–8] | [9–12] | [13–17] | [18–31] |
| Advantages | Strongest study design to answer research question regarding effect of repeat dosing Randomization controls for unmeasured confounding | Randomization controls for unmeasured confounding | Potentially more acceptable to women Less expensive and difficult to conduct | Potentially more acceptable to women Less expensive and difficult to conduct |
| Disadvantages | Expensive to conduct Potential ethical issues regarding assigning regimen to participants Limited generalizability to nonresearch populations | Does not answer study question Expensive to conduct Potential ethical issues regarding assigning regimen to participants Potentially unacceptable to participants Limited generalizability to nonresearch populations | Residual confounding or selection bias could mask the effectiveness of repeat dose or lead to spurious conclusions | Does not answer study question. (Without a control group, we do not know how effective the regimen would be without the repeat dose.) |

surgically intervening, then any improvements in effectiveness might be incorrectly attributed to the change in the medication regimen rather than the differences in provider management. Gestational age also could act as confounding if women in the later time period presented at the clinic with earlier gestations (perhaps due to improved access to early pregnancy testing) and if gestational age is associated with regimen effectiveness. These examples underscore the importance of either having an appropriate control group or controlling for confounding. Because the researchers in these five trials did not adequately assess the possible role of confounders, these trials do not provide evidence regarding the effect of the repeat misoprostol dose.

3.4. Noncomparative studies

We found 14 noncomparative studies that included the provision for a repeat dose of misoprostol [18–31]. Effectiveness rates in these single-arm studies ranged from 91.3% to 100%. None reported the time to expulsion. These studies, though, did not allow us to determine the effect of the repeat misoprostol dose. Without a comparison group, we would not be able to know if women who had a successful outcome after receiving a repeat misoprostol dose would have aborted eventually had they used only a single dose.

We cannot evaluate the effectiveness of a repeat dose simply by calculating the complete abortion rate for the subgroup of women who used the additional misoprostol. Women who accept a repeat misoprostol dose might differ systematically regarding important confounders from those who decline. For example, the decision to use a repeat dose could be influenced by the degree of negative side effects experienced, which in turn might be associated with the efficacy of the mifepristone and initial misoprostol dose within the individual woman. The results from the study by Peyron et al. [23] further illustrate this. The noncomparative, prospective study found that 98 participants were

eligible for a repeat dose. Although 38% of those who took the repeat dose had a successful outcome, 96% of those who did not take the repeat dose had a complete abortion. We cannot compare the results from these subgroups and conclude that the repeat dose prevented complete abortion; women in these two groups might have differed systematically regarding important factors.

4. Discussion

We identified 26 studies that evaluated a mifepristone and misoprostol medication abortion regimen that included the provision of a repeat misoprostol dose. Only three RCTs compared regimens that differed in the repeat-dose misoprostol component [2,5–8]. None of these trials found a difference in effectiveness rates between the randomized groups.

The WHO trial did show that the group without the repeat misoprostol dose (vaginal only) had a lower complete abortion rate than those using misoprostol vaginally followed by repeat oral doses among the subgroup of women at 57–63 days of gestation [2]. Among this subgroup, the complete abortion rate in the vaginal-only group did not differ from that of the group that used misoprostol orally followed by repeat oral doses. These results should be interpreted with caution, though, as they are based on subgroup analyses.

Results from the three RCTs do not preclude the possibility of an increase in effectiveness derived from a repeat misoprostol dose. First, because the overall success rate of medication abortion is extremely high, any marginal improvement from the repeat dose would have to be small, and the trials could have been underpowered to detect a true difference. Furthermore, a multitude of regimens exist. Regimens differ in mifepristone and initial and subsequent misoprostol dosages, timing between the drugs, route of initial and repeat misoprostol administration and location

(i.e., clinic or home) of misoprostol use. Also, population characteristics (e.g., gestational age of pregnancy) could influence the regimen's effectiveness.

Given the high effectiveness of mifepristone and misoprostol medication abortion regimens (regardless of the number of misoprostol doses), measuring the induction-to-expulsion time is important for comparing regimens. If all other factors were to remain constant, women likely would prefer a regimen that resulted in a shorter induction-to-expulsion time. However, few studies measured time to expulsion. Also, the studies differed in their reporting of measures of participant preference, acceptability and side effects. Researchers should assess these outcomes in any future studies because realizing a slight increase in effectiveness that is accompanied by decreased acceptability or increased side effects might not be regarded as an improvement. In addition, future research should assess costs. For example, the routine use of a repeat misoprostol dose at home after a specified interval possibly could reduce the total cost of medication abortion if fewer follow-up visits were needed.

Finally, we did not consider clinical significance of the repeat dose. Even if the use of additional misoprostol doses is found to improve effectiveness, the revised regimen might not have a clinically significant effect on abortion safety, acceptability or access. Before allocating substantial resources in assessing any marginal effectiveness of a repeat dose, we should consider the potential clinical impact of such a protocol change.

In conclusion, while clinicians often administer a repeat dose of misoprostol to increase effectiveness in medication abortion, the effect of the repeat dose has not been established. Determining whether a repeat misoprostol dose improves effectiveness would require a large sample size; the expense of large trials might not be warranted, given the small increase in effectiveness that potentially could be achieved. If future studies are conducted, they should evaluate effectiveness using time to complete abortion measured with survival analysis. Also, because the mifepristone plus misoprostol regimen (regardless of the repeat dose) is highly effective in inducing abortion, identifying any differences in acceptability or side effects is important for distinguishing between regimens.

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