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REVIEW ARTICLE

Prevention of postpartum hemorrhage with misoprostol

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Recommended Dosages

Oral (or sublingual)
misoprostol 600 µg as
a single dose. Do not
repeat for 2 hours

KEYWORDS

Misoprostol;
Postpartum hemorrhage

Abstract

As a stable, orally active and cheap uterotonic, misoprostol would appear ideally suited to the prevention of postpartum hemorrhage (PPH) in the developing world. Following numerous clinical trials, it appears that misoprostol prophylaxis using an oral or sublingual dose of 600 µg is more effective than placebo at preventing PPH in community births (relative risk 0.59, 95% confidence intervals 0.41–0.84), but not in hospital settings (RR 1.23, 95% CI 0.86–1.74). It is, however, not as effective as injectible oxytocin (RR 1.34, 95% CI 1.16 to 1.55). Misoprostol is therefore indicated for prevention of PPH in settings where injectible conventional uterotonics are not available. In the event of continued hemorrhage, a minimum of 2 h should lapse after the original dose before a second dose is given. If the initial dose was associated with pyrexia or marked shivering, at least 6 h should lapse before the second dose is given.

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1. Background

Postpartum hemorrhage (PPH) is the most important direct cause of maternal mortality in low-income countries, and one of the most preventable. As the most common cause of PPH is the failure of the uterus to contract adequately (atonic uterus), a key aspect in prevention of PPH is uterotonic therapy. The most widely used agents are injectible oxytocin and/or ergometrine. They require parenteral administration, and therefore skills to give injections as well as sterile needles and syringes. In addition, ergometrine requires refrigeration and oxytocin may

be inactivated if exposed to high ambient temperatures. For this reason the use of misoprostol to prevent PPH has attracted considerable attention [1]. A recent guideline on PPH prevention developed by the World Health Organization recommended the use of oxytocin or misoprostol 600 µg orally for prevention of PPH in settings in which active management of labor is not practiced [2].

1.1. Misoprostol versus conventional injectible uterotonics in the prevention of PPH

A systematic review of 7 randomized controlled trials of misoprostol 600 µg versus injectible uterotonics, involving a total 22 749 women showed that oral misoprostol is less effective than injectible uterotonics in preventing severe PPH (blood loss > 1000 mL: 3.6% vs 2.7%, relative risk 1.34, 95% confidence interval 1.16 to 1.55) [3].

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Therefore, for the primary prevention of postpartum haemorrhage, there is good evidence to recommend injectible conventional uterotonics rather than misoprostol.

1.2. Misoprostol in the prevention of PPH in situations without access to conventional uterotonics

Early trials of misoprostol versus placebo conducted in hospital settings had variable results, and meta-analysis of all trials to date showed no significant effect on blood loss >1000 mL (in one trial >500 mL was used) (Fig. 1, 7 trials, 4979 women, RR 0.86, 95% CI 0.67 to 1.10).

Recently, the first three relatively large, randomized controlled trials using misoprostol 600 µg orally or sublingually in community or primary health care settings without access to conventional injectible uterotonics, have been published [4–6].

The first was conducted in Guinea-Bissau, where a randomized trial of 661 women found that sublingual misoprostol 600 µg was significantly better than placebo for reduction of severe postpartum blood loss (blood loss ≥1000 mL) [4]. The second was a community-based randomized controlled study in The Gambia ($n=1229$ women) comparing 600 µg orally with the standard treatment of 2 mg oral ergometrine. This showed significantly lower pre-delivery to post-delivery hemoglobin drop in the misoprostol compared to ergometrine arm but no statistically significant differences on greater blood loss (≥750 and ≥1000 ml) [5]. Finally, a placebo-controlled trial, undertaken in 1620 women in rural India showed the efficacy of misoprostol in significantly reducing most indicators of postpartum hemor-

rhage: blood loss ≥500 ml, ≥1000 ml, need for transfer to a health facility, blood transfusion, and surgical interventions [6]. Meta-analysis of these community and primary health care-based studies shows a reduction in blood loss >1000 mL (Fig. 1, 3 trials, 3509 women, 2.3% versus 5.7%, RR 0.59, 95% CI 0.41 to 0.84). Trials reported to date are too small to draw conclusions on the effect of misoprostol on maternal deaths [7]. At least one large trial is currently in progress which will strengthen the evidence for or against the effectiveness of misoprostol considerably. Results from this trial are expected in 2008.

Known side effects with the use of misoprostol include shivering, pyrexia, nausea, vomiting and diarrhea. The most common side effects are shivering and pyrexia, which are dose-related. Systematic review of randomized comparisons between misoprostol 600 µg versus 400 µg for the prevention of PPH found the rate of fever >38 °C to be 17% for 600 µg versus 8% for 400 µg (2 trials, 794 women, RR 2.12, 95% CI 1.44 to 3.12) [3].

If used routinely for PPH prevention, misoprostol would be given to very large numbers of women, even though the drug would not be needed for over 90% of them. Given the uncomfortable side effects and the possibility of serious harm due to hyperpyrexia or fetal and maternal death if misoprostol is inadvertently given before birth of the baby or a second twin, caution should be advised if considering routine use of the drug for this indication.

On the other hand, not giving misoprostol in settings without access to conventional uterotonics could fail to prevent maternal deaths due to PPH if misoprostol is effective. In this context, clear evidence of effectiveness would be needed to

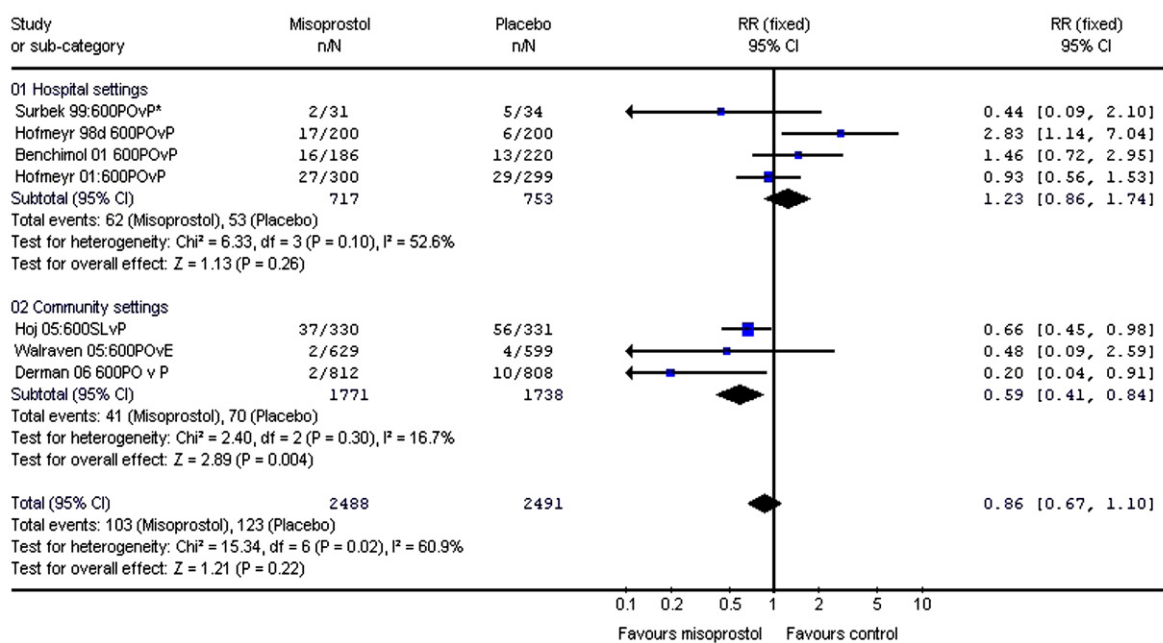


Figure 1 Randomized trials of the effect of misoprostol 600 µg orally (PO) or sublingually (SL) versus placebo (P) or oral ergometrine (E) on blood loss >1000 mL (or *500 mL for Surbek '99), subgrouped by hospital or community/primary health care settings [4–6,8,9,14,15].

justify the risks. In the absence of alternative injectible uterotonic, misoprostol 600 µg administered either orally or sublingually can be offered by a health worker trained in its use for prevention of PPH. This recommendation is pending the results of ongoing trials.

The introduction of misoprostol for prevention of PPH on a wide programmatic scale is not recommended without careful monitoring and regular evaluation as a part of a benefit-harm analysis. If possible, monitoring of overall maternal mortality as well as establishing the specific causes in the implementation settings is advocated.

Lower doses may also be effective. Four trials tested misoprostol at initial doses of 400 µg orally (3 trials) and 200 µg buccal (1 trial). In two of these trials oxytocin infusion was used routinely in both the misoprostol and the placebo group [8–11]. Although the evidence in support of a 600 µg regimen is stronger, a lower dose of 400 µg or 200 µg may also be effective regimens for PPH prevention and their use could be considered. This would result in a lower incidence of side effects.

2. Contraindication

History of allergy to misoprostol or other prostaglandin.

3. Precautions

1. Use only after the delivery of the baby, and after checking by abdominal palpation that there is not the second baby of a multiple pregnancy still *in utero*.
2. Small amounts of misoprostol or its active metabolite may appear in breast milk. There are no known consequences of this and no adverse effects on nursing infants have been reported.

4. Regimen

A single dose of misoprostol 600 µg orally or sublingually is indicated for prevention of PPH in settings where injectible conventional uterotonic are not available.

5. Course of treatment

Misoprostol should be administered by skilled attendants immediately after delivery of the newborn, and after checking that there is no multiple pregnancy. This medication should be followed 1 to 3 min later by cord clamping and controlled cord traction as part of the active management of the third stage of labor.

Unskilled providers should give misoprostol only after delivery of the placenta because of the risk of inadvertently giving the misoprostol before the delivery of a second twin.

If there is continued hemorrhage, then great care should be taken before repeating misoprostol as cumulative doses

may result in side effects. Causes of hemorrhage other than atony should be sought and the woman should be immediately transferred to a facility where PPH can be treated. In the event of continued hemorrhage, a minimum of 2 h should lapse after the original dose before a second dose is given. If the initial dose was associated with pyrexia or marked shivering, then at least 6 h should lapse before the second dose is given.

6. Side effects

Prolonged or serious side effects are uncommon.

6.1. Fever and/or chills

Fever is commonly associated with use of misoprostol. When used for PPH treatment, hyperpyrexia (>40 °C) has been reported in several cases following 600 µg, and hyperpyrexia with delirium and/or ICU admission has been reported following 800 µg orally [12,13]. Chills are a common side effect of misoprostol but are transient. In studies of misoprostol for PPH prevention, chills were reported in 32%–57% of women receiving misoprostol [4–6]. Fever should be carefully monitored. Women experiencing fever can be offered anti-pyretics and physical cooling.

6.2. Nausea and vomiting

Cramping, nausea and vomiting may occur and will resolve 2 to 6 h after taking misoprostol. An anti-emetic and paracetamol can be used if needed, but in general no action is required except to reassure the woman and her family.

6.3. Diarrhea

Diarrhea may also occur following administration of misoprostol but should resolve within a day.

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Conflict of interest

The authors do not have any conflict of interest.

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