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REVIEW ARTICLE

Treatment of postpartum hemorrhage with misoprostol

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Recommended Dosage
Oral misoprostol 600 μg as a single dose

KEYWORDS
Misoprostol;
Postpartum hemorrhage

Abstract

A literature review was conducted to determine whether misoprostol is an effective treatment for postpartum hemorrhage (PPH) and in what dose. All English language articles published before March 2007 reporting on misoprostol for treatment of PPH were reviewed. Unpublished data previously presented at international scientific meetings were also included in the review. Little evidence exists in support of misoprostol for treatment of postpartum hemorrhage (PPH). Nonetheless, PPH remains a major killer of women worldwide, and new treatment options are widely sought. For this reason, we recommend a single dose of misoprostol 600 μg oral or sublingual for PPH treatment in instances when other treatments have either failed to work or are not available.

1. Background

Postpartum hemorrhage (PPH) is a major cause of maternal death worldwide. When postpartum hemorrhage occurs, a number of medical and surgical interventions are used to control the bleeding [1,2]. A crucial aspect of postpartum hemorrhage treatment is uterotonic therapy. The most commonly used agents are injectible oxytocin and/or ergometrine. They both require parenteral administration, and ergometrine requires refrigeration. Parenteral prostaglandins have shown promise [3], but their use has been limited by side effects. In dire situations, intramyometrial injection of prostaglandin F2-alpha has been used with apparently dramatic effects [4,5] but this method has not been assessed in a controlled trial, and serious side effects have been reported [6,7]. Intrauterine irrigation with prostaglandin F2 alpha has also been used [8].

To date, there is insufficient evidence to support the use of misoprostol for routine treatment of PPH. Nonetheless, misoprostol has been used as a last resort for treatment of severe PPH cases and its effectiveness has been reported in seven uncontrolled studies [9–15]. These studies used a range of doses (200 μg to 1200 μg) and routes (rectal, oral, and intrauterine) and reported dramatic responses to the drug (Table 1). Three randomized controlled trials (RCTs) also studied misoprostol for PPH treatment [16–18]. An RCT by Lokugamage et al. [16] suggests that 800 μg rectal misoprostol may be more effective than syntometrine for treatment of PPH; however this study was single blinded and the outcome was subjective assessment of response, and is therefore prone to assessment bias. Two RCTs compared misoprostol with placebo, following routine PPH treatment with oxytocics among women who had received routine prophylactic oxytocin

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Table 1 Summary of reports on misoprostol for PPH treatment

Uncontrolled reports

Authors	Subjects	Misoprostol regimen	Outcomes	Success *N* (%)
O'Brien et al. [9]	14 women, atonic primary PPH unresponsive to first line uterotonics (3 cesarean sections)	1000 μg rectally	Hemorrhage, controlled and sustained uterine contraction within 3 min	14/14 (100%)
Ozan et al. [10]	2 women with atonic PPH unresponsive to conventional therapy	400 μg orally, repeated 2-hourly once or twice	Decreased bleeding within 30 min of first dose	2/2 (100%)
Abdel-Aleem et al. [11]	18 women with atonic PPH (5 cesarean section)	600 μg (n=4) or 1000 μg (n=14) rectally soon after other uterotonics	Prompt response (30 s to 3 min)	16/18 (88%)
Shojai et al. [12]	5 women with severe delivery-induced hemorrhage due to uterine atony unresponsive to oxytocin	200 μg rectally	Cessation of hemorrhage within 5 min	5/5 (100%)
Adekanmi et al. [13]	1 woman, para 3, atonic hemorrhage after evacuation of retained placental tissue several days after delivery, unresponsive to conventional treatment	800 μg intrauterine plus bimanual compression of uterus	Prompt contraction of uterus and reduction of bleeding	1/1 (100%)
Oboro et al. [14]	1 woman, para 4, atonic uterine bleeding after evacuation of the uterus 5 days after delivery, unresponsive to conventional therapy.	800 μg intrauterine + bimanual compression of uterus	Uterus became firm and bleeding was significantly reduced	1/1 (100%)
Shojai et al. [15]	41 women with PPH unresponsive to oxytocin.	1000 μg rectally	Bleeding controlled within 10 min of miso	26/41 (63%)

Randomised controlled trials

Authors	Subjects	Misoprostol regimen	Outcomes	Success RR
Lokugamage et al. [16]	64 women with primary PPH > 500 mL	800 μg rectal vs. sytometrine + IV syntocinon	PPH stopped within 20 min of txt	RR 0.18 (0.04–0.76)
Hofmeyr et al. [17]	238 women bleeding more than expected at least 10 min after delivery and thought to be experiencing PPH	200 μg oral, 400 μg sublingual, 400 μg rectal vs. standard oxytocics	Blood loss ≥ 500 mL or more in 1 h	RR 0.56 (0.21–1.46)
Walraven et al. [18]	160 with measured postpartum blood loss of ≥ 500 mL	200 μg oral, 400 μg sublingual vs. standard oxytocics	Blood loss ≥ 500 mL or more in 1 h	RR 0.58 (0.32–1.06)

in the third stage of labor. Hofmeyr et al. [17] tested a 1000 μg misoprostol regimen (200 μg orally + 400 μg sublingually + 400 μg rectally) in 238 women and found a trend towards reduced blood loss ≥ 500 mL in 1 h after treatment among the misoprostol group. Walraven et al. [18]tested 600 μg misoprostol (200 μg orally + 400 μg sublingually) among 160 women; this pilot trial was not powered to detect significant differences between misoprostol and placebo. Meta-analysis of data from these two trials shows a significant reduction in blood loss > 500 mL (n=397, RR 0.57, 95% CI 0.34 to 0.96)[19]. No other clinical outcomes were significantly improved. Based on these data, it has been advocated that misoprostol should be available to women who do not have access to conventional peripartum care.

Recent studies suggest that intraumbilical misoprostol can also be used for retained placenta. One small trial compared misoprostol 800 μg dissolved in 30 mL saline (n=21) with oxytocin 50 units in 30 mL saline (n=20) and 30 mL saline (n=13) [20]. Manual removal of the placenta was less frequent with misoprostol than with the other two groups. Although the evidence is very limited, the likelihood of harm from an intraumbilical injection is very low, and the benefit from a conservative method of treatment of retained placenta in settings with limited facilities is high. These data suggest that in settings in which no injectible uterotonics are available, misoprostol 800 μg in 30 mL saline injected into the umbilical vein may be used for the treatment of retained placenta. Use of misoprostol for this indication needs further evaluation from both a safety and effectiveness point of view.

In the absence of systematic research to document optimal PPH treatment regimens, misoprostol has begun to enter into clinical services informally and with great variability in use.

Given the limited evidence showing the drug's safety and efficacy for this indication, the strong recommendation is that providers continue to use all available standard methods for PPH treatment and use misoprostol when other methods are not available or have failed. All potential causes for PPH should be explored by the health care provider.

2. Contraindications

The only known contraindication is a history of allergy to misoprostol or other prostaglandin.

3. Precautions

1. Caution is advised when using misoprostol for PPH in instances where the woman may have already received misoprostol as prophylaxis for PPH prevention. Misoprostol should not be used for PPH treatment if it was already given for PPH prevention within the last 2 h. If the initial dose was associated with pyrexia or marked shivering, then at least 6 h should lapse before the second dose is given. All potential causes of PPH should be explored to assure that the PPH is not due to another factor besides uterine atony.
2. The recommended dose for PPH treatment, 600 μg, should never be given *prior* to the delivery of the baby. This is especially important in settings where there may be unidentified twin pregnancies.

4. Regimen

There is currently insufficient evidence available to recommend any specific misoprostol dose for treatment of postpartum hemorrhage.

In the absence of reliable evidence on misoprostol use for PPH treatment, **we recommend using the prophylactic dose of 600 μg orally or sublingually [21–25]**. This dose was selected after careful review of the sparse data from PPH treatment and the large body of data on 600 μg oral misoprostol for PPH [19,25].

> *Misoprostol should be used only after the provider has exhausted all standard PPH treatments (oxytocin drip, uterine massage, and/or compression). All potential causes for PPH should be explored to assure that the PPH is not due to another factor besides uterine atony.*

If misoprostol has been given as prophylaxis for PPH, misoprostol should not be used for treatment within the time frames given below. Dosages above 600 μg orally or sublingually are not recommended at this time.

> *A repeat dose of misoprostol should not be given unless at least two hours have elapsed since the first dose. If the initial dose was associated with pyrexia or marked shivering, then at least six hours should lapse before the second dose is given.*

Several large multi-centre randomized controlled trials are currently underway to assess the efficacy of misoprostol at several doses for PPH treatment, and their results will be available in 2007.

5. Course of treatment

After delivery, if PPH is diagnosed, treatment should be immediate. Where available, first line treatments include administration of uterotonics, including oxytocin and ergometrine along with continued uterine massage. If these methods do not stop the bleeding, misoprostol can also be given to the woman. In settings where no other uterotonic agents are available, misoprostol 600 μg can be used for the primary treatment of PPH. The misoprostol can be given either orally or sublingually. Sublingual use might be helpful when women are unconscious or under anesthetic.

6. Effects and side effects

Prolonged or serious effects and side effects are rare.

6.1. Fever and/or chills

Fever is commonly associated with use of misoprostol. When used to treat PPH, hyperpyrexia (>40 °C) has been reported in several cases following 1000 μg (delivered orally, rectally and sublingually) [17], and hyperpyrexia with delirium and/or ICU admission has been reported following 800 μg orally or sublingually [26,27]. When used as prophylaxis for PPH prevention at a dose of 600 μg orally, 0.1% (5/9198) women [21] experienced fever >40 °C. 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 [21–24]. Fever should be carefully monitored. Women experiencing fever can be offered paracetamol and physical cooling.

6.2. Nausea and vomiting

Nausea and vomiting may occur and will resolve 2 to 6 h after taking misoprostol. An anti-emetic 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 be resolved within a day.

6.4. Pain

Pain may also occur following administration of misoprostol but should be transient and can be treated with paracetamol.

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Conflict of interest

The authors do not have any conflict of interest.

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