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IMPROVING MATERNAL HEALTH

Misoprostol for prevention and treatment of postpartum hemorrhage: What do we know? What is next?

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ABSTRACT

Misoprostol is an effective and safe uterotonic for the prevention and treatment of postpartum hemorrhage (PPH). A 600-μg oral dose of misoprostol has been shown to prevent PPH in community-based randomized controlled trials. An 800-μg sublingual dose of misoprostol appears to be a good first-line treatment for controlling PPH. Adverse effects after use of misoprostol for PPH prevention or treatment may include shivering and fever. These effects are transient, resolve on their own, and are not life threatening. Misoprostol can play an important role in settings with limited access to oxytocin, and where there is no other option for PPH care.

1. Introduction

Misoprostol, an E1 prostaglandin analogue, induces uterine contractions and, because of this property, has several important uses in women's reproductive health programs. Originally registered for preventing gastric ulcers due to chronic use of nonsteroidal anti-inflammatory drugs, misoprostol has proven to be effective in preventing and treating postpartum hemorrhage (PPH) resulting from the failure of the uterus to contract fully after delivery [1,2]. While oxytocin is the gold standard drug for use in PPH prevention and treatment, it requires cool storage, sterile equipment, and trained personnel, so that routine use of oxytocin in low-resource settings may be difficult [1,2]. Misoprostol offers several advantages over oxytocin in such settings. It is formulated as a tablet, stable at ambient room temperature, widely available and affordable, and does not require any special skills, equipment, or facilities for its use [1].

The efficacy of misoprostol for PPH prevention has been well documented over the past decade [1,3,4]. This body of knowledge resulted in the addition of misoprostol to the World Health Organization's (WHO) Model List of Essential Medicines (EML) in 2011 for PPH prevention (600-μg oral dose) [5]. The evidence on misoprostol for PPH treatment shows that it is effective in curbing excessive postpartum bleeding [6,7] and suggests that misoprostol can fill a service delivery gap in settings where women and providers are unable to access oxytocin.

The present paper provides an overview of the evidence on misoprostol for prevention and treatment of PPH. It also identifies clinical and programmatic research questions that need to be addressed to help decision makers and service providers integrate misoprostol effectively into service delivery programs for the management of PPH.

2. Misoprostol for prevention of PPH

2.1. What do we know?

Systematic reviews of randomized controlled trials (RCTs) comparing misoprostol with injectable uterotonics indicate that oxytocin is the preferred uterotonic for use in active management of the third stage of labor [1,8]. However, in the absence of oxytocin, misoprostol is a suitable alternative. Four RCTs offer evidence that misoprostol administered to women immediately after delivery of the baby is safe and effective for use in community settings to reduce the risk of PPH [3,4,9,10]. Table 1 lists the key findings of these trials, which compared misoprostol with either placebo or oral ergometrine.

The evidence-based misoprostol regimen for PPH prevention is a single 600-μg dose (3 tablets, 200 μg) administered orally to women immediately after vaginal delivery of the baby (or babies, in the case of multiple births) [1,11]. Breastfeeding is not contraindicated when misoprostol is used for PPH prevention [1,3].

The WHO, the International Federation of Gynecology and Obstetrics (FIGO), the International Confederation of Midwives (ICM), and the Royal College of Obstetricians and Gynaecologists (RCOG) all support the use of misoprostol for PPH prevention and recommend that where oxytocin is not available or where birth attendants' skills are limited, misoprostol can be used to prevent PPH [12–14].

2.2. Safety profile of misoprostol for PPH prevention

All reported adverse effects after misoprostol prophylaxis have been transient, manageable by providers, and, in the vast majority of

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Table 1
Misoprostol for prevention of PPH: community-based RCTs.

Reference	No. in misoprostol arm	Misoprostol dose and route	Control group	Provider type and setting	Primary outcome(s) + other blood loss or hemoglobin(Hb) outcomes	Summary of results
Derman et al. [3]	812	600 μg oral	Placebo	Auxiliary-nurse midwives Sub-center and homebirth	Blood loss ≥ 500 mL Blood loss ≥ 1000 mL Mean blood loss	RR: 0.53 (0.39–0.74) RR: 0.02 (0.04–0.91) 214.3 mL vs 262.3 mL, $P<0.0001$
Mobeen et al. [4]	514	600 μg oral	Placebo	Traditional birth attendant Homebirth	Blood loss ≥ 500 mL Drop in Hb < 2 g/dL	RR: 0.76 (0.59–0.97) RR: 0.79 (0.62–1.02)
Hoj et al. [10]	330	600 μg sublingual	Placebo	Auxiliary-nurse midwives Primary health center	Blood loss ≥ 500 mL Blood loss ≥ 1000 mL Decrease in hemoglobin concentration after delivery	RR: 0.89 (0.76–1.04) RR: 0.66 (0.45–0.98) Mean diff 0.16 mmol/L (−0.01 mmol/L to 03.2 mmol/L)
Walraven et al. [9]	630	600 μg oral	2 mg ergometrine oral	Traditional birth attendant Homebirth	Blood loss > 1000 mL Postpartum Hb < 8 g/dL	RR: 0.91 (0.67–1.24) RR: 0.84 (0.67–1.05)

RR, Relative Risk.

cases, women have found them to be tolerable [8]. Transient fever and shivering are the most frequent adverse effects, commonly occur together, and are dose and route dependent [15]. Other less frequent adverse effects include nausea, vomiting, and diarrhea. Nausea and vomiting typically resolve in 2–6 hours after misoprostol administration and diarrhea usually resolves within a day [1]. Rates of shivering and fever reported in studies of 600 μg of oral misoprostol vary across studies (shivering 18%–71%; fever 1%–38%) [16,17]. There have been rare cases of hyperpyrexia (>40 °C) reported in published studies after a 600-μg oral misoprostol prophylactic dose. These fevers were transient and did not result in further complications [18].

3. Misoprostol for treatment of PPH

3.1. What do we know?

In 2007, a FIGO expert panel reviewed the published literature on misoprostol for treatment of PPH, including 7 case reports and 3 RCTs. The panel recommended that in the absence of standard uterotonics, misoprostol can be used for the primary treatment of PPH [2]. Since then, 2 large-scale double-blind placebo-controlled randomized trials comparing 800 μg of sublingual misoprostol with 40 IU of intravenous oxytocin have demonstrated that 9 out of 10 women with PPH due to suspected uterine atony had their bleeding controlled successfully within 20 minutes of treatment with either drug [6,7]. These trials screened 41,000 women in total and enrolled 1786 women for excessive bleeding after delivery at tertiary and secondary hospitals in multiple sites in 5 countries. Hemorrhage was diagnosed either by the provider's clinical estimation or when blood loss reached 700 mL on a calibrated delivery drape within 1 hour after delivery.

The RCTs were designed as complementary studies and investigated the efficacy of misoprostol for treatment of PPH in women who received routine oxytocin prophylaxis and in women who did not receive prophylaxis for PPH. In women receiving prophylactic oxytocin, misoprostol and oxytocin for PPH treatment worked equally well in stopping postpartum bleeding (89% vs 90%) with no significant differences in the primary or secondary outcomes (Table 2) [7]. Among women not receiving prophylactic oxytocin, misoprostol and oxytocin also effectively controlled PPH (90% vs 95%), although most of the primary and secondary outcomes were statistically better with oxytocin (Table 3) [6].

The evidence suggests that 800 μg of sublingual misoprostol is a safe and effective first-line treatment alternative for controlling PPH, when intravenous oxytocin is unavailable. The sublingual route is recommended because it is the only treatment route tested in RCTs. To date, all published studies and case reports on misoprostol for treatment of PPH have reported on the rectal or sublingual route. However, evidence on rectal administration is limited because no double-blind RCT has assessed the efficacy of administering misoprostol via this route to treat PPH. The pharmacokinetic data show that compared with the rectal route, the sublingual route has the advantage of rapid onset of action [19]. Furthermore, the sublingual route is easy to administer, has the fastest absorption, highest serum levels, greatest bioavailability, and more sustained effect compared with all other routes [20].

Misoprostol as an adjunct treatment option for PPH has also been studied. Meta-analysis of data from 2 small RCTs that provided misoprostol following standard PPH treatment with oxytocin showed a significant reduction in blood loss greater than or equal to 500 mL (n = 397) [2]. However, a large multisite double-blind placebo RCT

Table 2
Double-blind RCT of misoprostol as a first-line treatment for PPH in women exposed to prophylactic oxytocin: Key outcomes.[a]

	Misoprostol (n = 407)	Oxytocin (n = 402)	Relative Risk (95% CI)	*P* value
Active bleeding controlled within 20 minutes with initial uterotonic treatment	363 (89.2)	360 (89.6)	0.99 (0.95–1.04)	0.867
Additional blood loss ≥ 500 mL after treatment	58 (14.4)	53 (13.2)	1.09 (0.77–1.54)	0.713
Additional blood loss ≥ 1000 mL after treatment	11 (2.7)	3 (0.7)	3.62 (1.02–12.89)	0.062
Drop in Hb ≥ 2 g/dL or blood transfusion	152 (37.6)	142 (35.7)	1.06 (0.88–1.27)	0.567
Drop in Hb ≥ 3 g/dL or blood transfusion	104 (25.7)	90 (22.6)	1.14 (0.89–1.46)	0.301
Shivering	152 (37.3)	59 (14.7)	2.54 (1.95–3.32)	–
Fever	88 (21.6)	59 (14.7)	1.47 (1.09–1.99)	–
Temp ≥ 40 °C	5 (1.2)	1 (<1)	4.94 (0.58–42.09)	–
Additional uterotonics	40 (9.8)	46 (11.5)	0.86 (0.58–1.28)	0.260
Blood transfusion	24 (5.9)	18 (4.5)	1.32 (0.73–2.39)	0.229
Hysterectomy	4 (1.0)	2 (0.5)	1.98 (0.36–10.73)	0.350
Maternal death	1 (0.2)	1 (0.2)	0.99 (0.06–15.74)	0.747

Source: Blum et al. [7].
[a] Values are given as number (percentage) unless otherwise indicated.

Table 3
Double-blind RCT of misoprostol as a first-line treatment for PPH in women not exposed to prophylactic oxytocin: Key outcomes.[a]

	Misoprostol (n = 488)	Oxytocin (n = 490)	Relative Risk (95% CI)	*P* value
Active bleeding controlled within 20 minutes with initial uterotonic treatment	440 (90.2)	468 (95.5)	0.94 (0.91–0.98)	0.001
Additional blood loss ≥ 500 mL after treatment	53 (10.9)	20 (4.1)	2.84 (1.63–5.01)	<0.0001
Additional blood loss ≥ 1000 mL after treatment	5 (1.0)	3 (0.6)	1.67 (0.40–6.96)	0.360
Drop in Hb ≥ 2 g/dL or blood transfusion	250 (51.2)	230 (46.9)	1.09 (0.96–1.24)	0.101
Drop in Hb ≥ 3 g/dL or blood transfusion	199 (40.8)	148 (30.2)	1.35 (1.14–1.60)	<0.0001
Shivering	229 (46.9)	82 (16.8)	2.80 (2.25–3.49)	–
Fever	217 (44.5)	27 (5.5)	8.07 (5.52–11.8)	–
Temp ≥ 40 °C	66 (13.5)	0 (0.0)	–	
Additional uterotonics	61 (12.5)	31 (6.3)	1.98 (1.31–2.99)	0.001
Blood transfusion	41 (8.4)	26 (5.3)	1.58 (0.98–2.55)	0.036
Hysterectomy/other surgery	0 (0.0)	0 (0.0)	–	–
Maternal death	0 (0.0)	0 (0.0)	–	–

Source: Winikoff et al. [6].
[a] Values are given as number (percentage) unless otherwise indicated.

showed that there is no clinical advantage to providing misoprostol (600 μg sublingually) in addition to standard treatment [21].

WHO, FIGO, RCOG, and the American College of Obstetricians and Gynecologists (ACOG) acknowledge that misoprostol is effective in treating PPH and recommend that it be used for treatment in situations where standard uterotonics are unavailable or unfeasible to use [12–14,22]. These international guidelines were all issued prior to the 2010 publication of the 2 trials comparing misoprostol with intravenous oxytocin for the treatment of PPH. WHO and FIGO are expected to publish revised guidelines on PPH treatment in 2011–2012 (not available at the time of this publication) [23].

3.2. Safety profile of misoprostol for PPH treatment

Adverse effects of misoprostol following its postpartum administration are similar to those described after its prophylactic use. The most frequent adverse effects are fever and shivering, which commonly occur together. Other less frequent adverse effects include nausea, vomiting, and diarrhea [6,7]. In the 2 RCTs in which women received 800 μg of sublingual misoprostol for treatment of PPH, fever (≥40 °C) was observed to have a high incidence at 1 location (Quito, Ecuador: 35.6%). In these cases, fevers peaked 1–2 hours post treatment and gradually declined over 3 hours [18]. All fevers were transient, self-limiting, and did not result in additional health complications or require hospitalization. In the same trials, the rate of high fever in the other 8 hospitals ranged from 0%–10% [18], suggesting that the genetic make-up of the population may be a factor. Further research is being undertaken to explore this hypothesis. Tables 1 and 2 list the rates of adverse effects and adverse events documented in the 2 RCTs that compared misoprostol with oxytocin as treatment for PPH [6,7].

Questions remain over whether a lower misoprostol dose (600 μg) could be as effective for treatment of PPH as an 800-μg sublingual dose and result in fewer adverse effects. Since a reduced dose might benefit only a small number of special populations, efforts to prove the efficacy of lower doses may not be feasible. Any rigorous trial to compare the efficacy of 800 μg with 600 μg of misoprostol for PPH treatment would require extensive resources that might be better utilized in other efforts to combat maternal mortality and morbidity.

4. Misoprostol for prevention and treatment of PPH

4.1. What is next?

While the clinical evidence on misoprostol for PPH prevention is well established, there are operational elements of misoprostol use that need to be documented at the community level. Programmatic information on ease of use, storage, acceptability among providers and women, and cost-effectiveness of misoprostol can help inform decision makers on the feasibility of its community-wide use and distribution for PPH prevention. There is theoretical concern that community-wide distribution of misoprostol may dilute national efforts to promote skilled birth deliveries and use of oxytocin as a first-line uterotonic drug. On the other hand, while efforts may be underway to promote use of oxytocin, in reality the drug is often unavailable in health facilities or stored in unfavorable conditions that may diminish efficacy. Intravenous infusion is not always feasible, and there are few data on the efficacy of intramuscular oxytocin for PPH care. In these contexts, it is conceivable that misoprostol can fill a void. Efforts are underway to compare misoprostol with intramuscular oxytocin for PPH prevention at the community level. Several countries are also exploring the provision of misoprostol prophylaxis for self-administration by women in homebirth settings.

While we know that prophylaxis reduces postpartum blood loss, some proportion of women (3% to 16.5%) will go on to experience PPH [3,4,7,9]. Any comprehensive model of maternal care therefore needs to include simple, accessible, and effective options for treatment of PPH, as well as for prevention.

While misoprostol for PPH treatment has been studied at the hospital level, no RCTs have assessed its role at lower levels of health care or the community level, where in many settings the only available treatment option is to transfer a woman to a higher-level health facility. In places where geographic, financial, and infrastructure constraints often hinder these efforts, misoprostol could potentially have a significant impact on maternal morbidity and mortality. It will be useful to develop service delivery models that engage lower-level healthcare providers to diagnose excessive bleeding, administer treatment, and manage any potential adverse effects.

In some places, misoprostol may be the only drug available to providers for prevention and treatment of PPH. Concern over possible adverse effects, as well as lack of information about efficacy after sequential use of misoprostol for PPH prevention and treatment, has resulted in reluctance to recommend a comprehensive misoprostol program using evidence-based regimens (600 μg oral for prevention followed by 800 μg sublingual for treatment). Data on the safety and efficacy profile of sequential use of misoprostol for the management of PPH, if encouraging, may alleviate these concerns. Efforts to collect such data will help inform international and national reproductive health policies and guidelines and allow for the creation of more comprehensive PPH care programs.

Information on service delivery models that selectively offer misoprostol to a subset of women experiencing heavy bleeding (in contrast to universal prophylaxis) may also help Ministries of Health determine how best to invest resources and develop PPH programs. This alternative model would involve offering a "first aid" dose to women who appear to be bleeding more than usual. Such strategies would medicate fewer women, thereby exposing fewer women to possible adverse effects, and lower drug costs in

Table 4
Recommended evidence-based regimens of misoprostol for PPH.

Indication	Recommended regimen
Prevention of PPH	600 μg oral
Treatment of PPH	800 μg sublingual

settings where this is a limitation. Current research efforts are underway to evaluate alternative service delivery models and to identify meaningful diagnostic indicators to trigger administration of a misoprostol dose.

5. Conclusion

The published literature on misoprostol for prevention and treatment of PPH, coupled with growing program experience worldwide, offers strong support for its use in PPH care. Use of various misoprostol doses and routes by providers is ad hoc in many places. However, the largest amount of clinical data supports the safety and efficacy of a 600 μg oral dose for prevention and an 800 μg sublingual dose for treatment of PPH (Table 4). As new regimens and service delivery models are tested, the international community needs to make a concerted effort to update recommendations and promote evidence-based guidelines and practices. Ministries of Health interested in promoting misoprostol in PPH programs can establish a dedicated supply system in public facilities and develop training programs for healthcare providers.

The simplicity and ease with which misoprostol can be administered suggest it can have wide application in low-resource settings. Inclusion of misoprostol as part of the package of PPH interventions available to practitioners can help reduce the incidence of PPH and will undoubtedly improve access to care for women and enhance the quality of maternal health services.

Conflict of interest

The authors confirm that they have no conflicts of interest to disclose.

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