Treatment of Post-Partum Haemorrhage with Misoprostol

FIGO GUIDELINE
ANNOTATED VERSION

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Background Evidence

Post-partum haemorrhage (PPH) is a major cause of maternal death worldwide. When PPH occurs due to uterine atony, a number of medical and surgical interventions are used to control the bleeding [Mousa 2001, Ramanathan 2006]. A crucial aspect of PPH treatment is uterotonic therapy and the gold standard is oxytocin. However, it is often not available in low resource settings due to parenteral administration and cool storage requirements. Ergometrine is also commonly used for treatment of PPH, but needs to be given by injection and is unstable in heat and light. It is also contraindicated in women with hypertension and cardiac disease. It may not, therefore, be suitable for certain low resource settings.

Misoprostol, an E1 prostaglandin analogue, has been studied as an alternative to oxytocin due to its low cost, stability at room temperature, and ease of administration. Three randomised controlled trials (RCTs) have assessed the effectiveness of misoprostol for treatment of PPH [Winikoff 2010, Blum 2010, Lokugamage 2001]. Two compared 800 µg sublingual misoprostol with 40 IU intravenous oxytocin [Winikoff 2010, Blum 2010]. In the first trial, involving 978 women diagnosed with PPH, oxytocin prophylaxis was not given [Winikoff 2010]. Results indicated IV oxytocin was more effective at controlling active bleeding within 20 minutes (96% vs. 90% of women) and preventing additional blood loss of 300 mL or more (17% vs. 30%). The second trial involved 809 women diagnosed with PPH, all of whom were given oxytocin prophylaxis (IV or IM) [Blum 2010]. Results indicated misoprostol was non-inferior to oxytocin at controlling active bleeding within 20 minutes (90% vs. 89%) and preventing additional blood loss of 300 mL or more (31% vs. 34%). The third RCT compared 800 µg rectal misoprostol with IM syntometrine plus IV syntocinon, also following receipt of oxytocin prophylaxis [Lokugamage 2001]. Results suggested that misoprostol may be more effective than syntometrine/syntocinon for treatment of PPH. However, this study was single blinded and the outcome was subjective assessment of response, and, therefore, prone to assessment bias.

Four RCTs have assessed the adjunct (simultaneous) use of misoprostol when given in conjunction with conventional uterotonics for treatment of PPH [Widmer 2010, Zuberi 2008, Walraven 2004, Hofmeyr 2004]. Two trials compared adjunct use of

600 µg sublingual misoprostol with placebo for treatment of PPH [Widmer 2010, Zuberi 2008]. Widmer et al. enrolled 1,422 women and found no differences between the misoprostol and placebo groups in terms of blood loss ≥ 500 mL, blood loss ≥ 1000 mL or post-partum haemoglobin changes. However, there was a higher incidence of side effects among those given misoprostol [Widmer 2010]. Zuberi et al. enrolled 61 women who had also received uterotonic prophylaxis for management of the third stage. Due to a lower than expected rate of PPH, the trial was unable to obtain statistical significance in any of the outcomes studied. There were non-significant trends, however, towards reduced post-partum blood loss, smaller drops in post-partum hemoglobin, and need for fewer additional interventions [Zuberi 2008]. A third trial by Walraven et al. compared adjunct use of 600 µg misoprostol (200 µg orally + 400 µg sublingually) with placebo among 160 women who had also received uterotonic prophylaxis. However, this pilot trial was not powered to detect significant differences between misoprostol and placebo [Walraven 2004]. Hofmeyr et al. compared adjunct use of a 1000 µg misoprostol regimen (200 µg oral + 400 µg sublingual + 400 µg rectal) with placebo in 238 women with uterotonic prophylaxis, and found no significant differences in blood loss ≥ 500 mL within one hour after treatment [Hofmeyr 2004].

No study has looked at the effectiveness of repeat doses of 800 µg sublingual misoprostol for treatment of PPH and as a result there is insufficient information about the risks and benefits of additional doses. Given documented side effects after a single dose of misoprostol for PPH treatment [Winikoff 2010, Blum 2010, Lokugamage 2001, Widmer 2010, Zuberi 2008, Walraven 2004, Hofmeyr 2004, Durocher 2010] and the absence of evidence of effect, repeat doses are not advised.

Regimen

One dose of misoprostol **800 µg sublingually** is indicated for treatment of PPH when 40 IU IV oxytocin is not immediately available (irrespective of the prophylactic measures). The recommended dose does not change according to the woman's weight.

Course of Treatment

Once PPH is diagnosed, the treatment should be given immediately.

Repeat or Consecutive Doses

There is insufficient information about the effect of two or more consecutive doses of misoprostol for treatment of PPH. In absence of such information, repeat doses of misoprostol for PPH treatment are not recommended.

If oxytocin is already being provided for treatment of PPH, evidence suggests that adjunct (simultaneous) use of misoprostol has no added benefit.

Since the known side effects of misoprostol appear to be dose related, repeat or consecutive doses of misoprostol may increase the incidence of side effects.

Contraindications

History of allergy to misoprostol or other prostaglandin.

Precautions

1. Caution is advised in instances where the woman may have already received misoprostol as prophylaxis for PPH prevention, especially if an initial dose of misoprostol was associated with pyrexia or marked shivering.
2. After provision of uterotonics, the need for other steps to stop the bleeding should be explored, and causes of PPH other than uterine atony should be considered.

Effects and Side Effects

Prolonged or serious effects and side effects are rare.

The most common known side effects associated with misoprostol are:

Temperature changes: Shivering, chills and/or fever are all commonly associated with use of misoprostol. Shivering has been reported in 37-47% of women following administration of 800 µg sublingual misoprostol, fever in 22-44%, and hyperpyrexia (>40 degrees Celcius) in 1-14% [Blum 2010, Winikoff 2010, Durocher 2010]. The shivering is self-regulating and even if high temperatures occur, they are transient and settle with reassurance and symptomatic treatment.

Gastro-intestinal effects: Nausea occurs in 10-15% of women given 800 µg sublingual misoprostol and vomiting in about 5% [Winikoff 2010, Blum 2010]. Both should resolve within two to six hours. An anti-emetic can be used if needed, but in general no action is required except to reassure the woman and her family. Diarrhoea may also occur in about 1% of women but should resolve within a day.

Breast feeding: Small amounts of misoprostol or its active metabolite may appear in breast milk. No adverse effects on nursing infants have been reported.

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Abbreviations

FIGO	International Federation of Gynecology and Obstetrics
IM	intramuscular
IU	international unit
IV	intravenous
µg	microgramme
PPH	post-partum haemorrhage
RCT	randomised controlled trial

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