WHO recommendation on the use of uterotonics for the treatment of postpartum haemorrhage if intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin

01 September 2012

Recommendation

If intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin, the use of intravenous ergometrine, oxytocin-ergometrine fixed dose, or a prostaglandin drug (including sublingual misoprostol, 800 µg) is recommended.

(Strong recommendation, low-quality evidence)

Publication history

First published: September 2012

Updated: Updated planned for early 2018

Assessed as up-to-date: September 2012

Remarks

- The GDG recognized that IV oxytocin may not be available in all settings. It encourages health care decision-makers in these settings to strive to make oxytocin available.
- In settings where IV oxytocin is unavailable to women who have received prophylactic IM oxytocin during the third stage of labour, the GDG considered misoprostol to be a valid alternative.
- If PPH prophylaxis with misoprostol has been administered and if injectable uterotonics are unavailable, there is insufficient evidence to guide further misoprostol dosing and consideration must be given to the risk of potential toxicity.
- There is no added benefit to offering misoprostol simultaneously to women receiving oxytocin for the treatment of PPH (i.e. adjunct misoprostol).
- The GDG noted that the two largest trials of misoprostol for the treatment of PPH (Winikoff 2010, Blum 2010)(1,2) reported the use of a 800 µg dose administered sublingually. The majority of the GDG members agreed that 800 µg is an acceptable sublingual misoprostol dose for the treatment of PPH, though some members of the GDG expressed concern related to the risk of hyperpyrexia associated with this dosage.
- If IV oxytocin has been used for the treatment of PPH and the bleeding does not stop, there is a paucity of data to recommend preferences for second line uterotonic drug treatment. Decisions in such
situations must be guided by the experience of the provider, the availability of the drugs, and by known contraindications.

- In situations in which IM oxytocin can be administered and there is no possibility of IV treatment with ergot alkaloids/injectable prostaglandins, there is a paucity of data to recommend a preference of IM oxytocin over misoprostol or other uterotonics. Decisions in such situations must be guided by the experience of the provider, the availability of the drugs, and by known contraindications.

Background

Postpartum haemorrhage (PPH) is defined as blood loss of 500ml or more within 24 hours after birth. PPH is the primary cause of nearly one-fifth of all maternal deaths globally. Most of these deaths occur during the first 24 hours after birth. The majority could be prevented through the use of prophylactic uterotonics during the third stage of labour, and by timely and appropriate management. The use of uterotonics (oxytocin alone as the first choice) plays a central role in the treatment of PPH.

Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach.(3,4) Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of postpartum haemorrhage (2012).(5)

Six Cochrane systematic reviews provided evidence.(6-11) Randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting in March 2012. This group of independent experts used the evidence profiles to assess evidence on effects on the pre-specified outcomes. GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to finalize the recommendation and remarks.

Further information on procedures for developing this recommendation are available here.

Recommendation question

For this recommendation, we aimed to answer the following question:

- For women with postpartum haemorrhage, which is the uterotonic of choice to improve outcomes?

Evidence summary

One Cochrane systematic review was conducted to assess the effectiveness and safety of any intervention used for the treatment of primary PPH. This review of ten randomized controlled trials (4052 women) provided evidence related to the effect of misoprostol on the management of PPH.
**Misoprostol versus oxytocin**

- Among those women not exposed to prophylactic oxytocin, the use of misoprostol was associated with an increased risk of blood loss >500 ml (RR 2.66; 95% CI 1.62 to 4.38), the increased use of uterotonics (RR 1.98; 95% CI 1.31 to 2.99), and an increased risk of shivering, hyperthermia and vomiting.

- Among those women exposed to prophylactic oxytocin, and despite the very small number of events (8 in total), an increased risk of blood loss >1000 ml with marginal statistical significance was observed (RR 3.62; 95% CI 1.02 to 12.88) for those women who received misoprostol. In addition, an increase in the risk of shivering was associated with the use of misoprostol (RR 2.54; 95% CI 1.95 to 3.32).

- The use of misoprostol as an adjunct for the treatment of women who received therapeutic oxytocin for PPH added no benefit. An increased risk of hyperthermia, vomiting and shivering was observed.

Evidence related to the use of various uterotonics was extrapolated from research on the prevention of PPH. Systematic reviews comparing the effects of oxytocin versus ergometrine, a fixed dose combination of oxytocin versus ergometrine, and carbetocin versus prostaglandins for the prevention of PPH were reviewed.

**Oxytocin versus ergometrine**

One Cochrane systematic review investigated the effects of prophylactic oxytocin versus placebo or no treatment versus ergot alkaloids:

- There was no observed difference in the incidence of blood loss >1000 ml reported (RR 1.09; 95% CI 0.63 to 1.87).

- No differences in blood transfusion in women receiving oxytocin compared with women receiving ergometrine (RR 3.74; 95% CI 0.34 to 40.64).

- No significant difference was observed in the use of additional uterotonics in the four trials included the systematic review.

- Among the adverse outcomes rated as important, the comparison of oxytocin versus ergometrine (or derivatives) showed a lower rate of adverse effects in women treated with oxytocin only, as well as lower rates of nausea (RR 0.13; 95% CI 0.08 to 0.21), vomiting (RR 0.08; 95% CI 0.05 to 0.14), and headache (RR 0.03; 95% CI 0.01 to 0.14).

- There was no observed difference reported in high blood pressure in women treated with oxytocin only (RR 0.53; 95% CI 0.19 to 1.52), though the quality of evidence was noted to be low.

**Oxytocin-ergometrine (fixed dose combination) versus oxytocin**

One Cochrane systematic review investigated the effects of IM ergometrine-oxytocin versus IM or IV oxytocin in reducing the risk of PPH (>8000 women). Doses of oxytocin used ranged from 2 IU to 10 IU, while the fixed drug combination doses consisted of 5 IU of oxytocin and 0.5 mg of ergometrine. Of the five identified studies in which IM oxytocin was used as a comparator (8000 women), three of these studies (6000 women) compared the fixed dose combination of oxytocin-ergometrine versus 10 IU of IM oxytocin.
• There was no observed difference in the incidence of blood loss >1000 ml between the two groups (RR 0.80; 95% CI 0.60 to 1.07) although there was a reduction in blood loss ≤500 ml (RR 0.85; 95% CI 0.73 to 0.99).

• In the three studies that reported on the use of blood transfusion, the effect was uncertain as the confidence interval included both benefit and harm (RR 1.25; 95% CI 0.77 to 2.05).

• Two studies reported a statistically significant lower use of additional uterotonics in the group receiving the fixed dose oxytocin-ergometrine combination (RR 0.78; 95% CI 0.66 to 0.91).

• Among the adverse outcomes rated as important, higher rates of nausea (RR 4.18; 95% CI 3.51 to 4.99) and vomiting (RR 4.97; 95% CI 4.06 to 6.08) were reported in women treated with the fixed dose combination only (two studies, >4000 women).

Two studies (6000 women) were identified which compared IV oxytocin versus a fixed dose IM oxytocin-ergometrine combination.

• There was no statistically significant difference between the two groups with regard to blood loss, the use of blood transfusion, or the use of additional uterotonics.

• Among the adverse outcomes rated as important, a higher rate of vomiting (RR 3.33; 95% CI 1.21 to 9.2) was observed in the group treated with the fixed dose combination only.

**Oxytocin-ergometrine IM (fixed dose combination) versus ergometrine IM (any dose)**

Evidence was extrapolated from one systematic review of five PPH prevention trials (>4000 women).

• While a significant difference was observed in blood loss ≤500 ml (RR 0.57; 95% CI 0.4 to 0.81) in the group treated with ergometrine only, this difference was not seen for blood loss >1000 ml (RR 1.67; 95% CI 0.4 to 6.94) evaluated in one trial only (1120 women).

• Of the reported critical outcomes, there was no difference in the need for blood transfusion between the groups, or for the manual removal of the placenta.

• Other important adverse effects were not reported.

**Carbetocin versus oxytocin**

Evidence came from one systematic review of 11 trials (2635 women) which evaluated the effect of carbetocin (100 mcg as an IV bolus or IM injection) for the prevention of PPH after vaginal delivery and caesarean section versus oxytocin, fixed dose oxytocin-ergometrine, and placebo.

• When compared to oxytocin, carbetocin was associated with a reduced use of additional uterotonic drugs after caesarean delivery (RR 0.64; 95% CI 0.51 to 0.81) in four trials (>1000 women).

• This association was not apparent for vaginal delivery (RR 0.93; 95% CI 0.44 to 1.94) but this finding was evaluated in only one study (160 women) and the quality of the evidence was very low.

• The systematic review reported a reduction in the risk of PPH, with the use of carbetocin versus oxytocin for women who underwent caesarean section. However, these results were greatly influenced by the definition of PPH in the trial as blood loss >500 ml, which may have biased the findings significantly.
The authors of the systematic review did not include data from one trial (Attilakos 2010, 9/186 versus 9/189) in the meta-analysis. Including this trial in the meta-analysis changes the results (RR 0.60; 95% CI 0.34 to 1.07).

- No difference in [the risk of] PPH was reported for vaginal delivery (RR 0.95; 95% CI 0.43 to 2.09).

**Carbetocin versus oxytocin-ergometrine fixed dose combination**

Evidence for this comparison was extrapolated from one systematic review which evaluated four trials (>1000 women).

- No significant difference was observed between the two groups with regard to blood loss, the use of blood transfusion, or the use of additional uterotonics.

- Among the important adverse maternal outcomes reported, lower rates of nausea (RR 0.24; 95% CI 0.15 to 0.4) and vomiting (RR 0.21; 95% CI 0.11 to 0.39) were observed among the group given carbetocin, compared with the group given fixed dose oxytocin-ergometrine.

**Intramuscular prostaglandins versus injectable uterotonics**

Evidence was extrapolated from one systematic review of 10 trials (>1300 women) which compared intramuscular prostaglandins (sulprostone, carboprost, and prostaglandin F2 alpha) versus injectable uterotonics.

- No difference was observed in the risk of blood loss, the additional use of uterotonics, or the need for blood transfusion.

- Among the important adverse effects reported, IM prostaglandins were associated with a higher risk of vomiting (RR 2.33; 95% CI 1.06 to 5.11), diarrhoea (RR 12.28; 95% CI 4.47 to 33.70), and abdominal pain (RR 4.99; 95% CI 1.46 to 17.05).

**Carboprost versus misoprostol**

One trial within one systematic review (<120 women), reported no difference between those treated with rectal misoprostol (400 mcg) versus intramuscular prostaglandins (prostaglandin F2 alpha), either in terms of blood loss or the use of blood transfusion. Of the 60 patients in the group receiving IM prostaglandin, two required the use of additional uterotonics, compared to 10 of the 60 patients who received rectal misoprostol (RR 0.20; 95% CI 0.05 to 0.87). However, these findings should be viewed with caution due to the low event rate, the small sample, and the very low quality of the evidence.

**Misoprostol (any route) versus injectable uterotonics**

Evidence was extrapolated from one systematic review which evaluated a number of routes and doses of misoprostol versus injectable uterotonics for the prevention of PPH.
There was no difference in the risk of blood loss >1000 ml in women receiving 600 mcg of misoprostol orally or sublingually, 400 mcg rectally, or 800 mcg rectally, compared with those receiving injectable uterotonics. The trials did not report the outcome of invasive or surgical treatment.

Further information on evidence supporting this recommendation are available [here](#).

**Implementation considerations**

The successful introduction of evidence-based policies related to the prevention and management of PPH into national programmes and health care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of national guidelines or protocols based on this recommendation.

The recommendation should be adapted into locally-appropriate documents and tools that are able to meet the specific needs of each country and health service. Modifications to the recommendation, where necessary, should be justified in an explicit and transparent manner. An enabling environment (for example, by widening the availability of uterotonics), should be created for the use of this recommendation (for example, by widening the availability of crystalloid solution), including changes in the behaviour of health care practitioners to enable the use of evidence-based practices.

Local professional societies may play important roles in this process and an all-inclusive and participatory process should be encouraged.

**Related Links**

- WHO recommendations on prevention and treatment of postpartum haemorrhage (2012) - [full document](#) and [evidence tables](#)
- [Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors](#)
- [Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice](#)

**Links to the supporting systematic reviews:**


Related resources

VIDEO: Active management of third stage of labour

Education material for teachers of midwifery. Managing postpartum haemorrhage.

Research implications

The GDG identified these research priorities related to this recommendation:

What is the minimum effective dose of misoprostol for the treatment of PPH?

What are effects and safety of misoprostol as treatment for PPH, in women who received misoprostol as PPH prophylaxis?

References


8. Brass E, Cotter AM, Ness A, Tolosa JE, Westhoff G. Prophylactic oxytocin for the third stage of
labour. Cochrane Database of Systematic Reviews. Art. No.: CD001808.

9 McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database of Systematic Reviews.


Citation: WHO Reproductive Health Library. WHO recommendation on the use of uterotonics for the treatment of postpartum haemorrhage if intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin (September 2012). The WHO Reproductive Health Library; Geneva: World Health Organization.


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