WHO recommendation on the uterotonic drug of choice for the prevention of postpartum haemorrhage in caesarean section

22 September 2012

Recommendation

Oxytocin (IV or IM) is the recommended uterotonic drug for the prevention of PPH in caesarean section.

*(Strong recommendation, moderate-quality evidence)*

Publication history

First published: September 2012

Updated: Update planned for 2018

Assessed as up-to-date: September 2012

Remarks

- The GDG noted that, in terms of blood loss, there was not enough evidence to recommend oxytocin infusion over IV bolus injection. However, due to concerns regarding adverse haemodynamic effects, the GDG considered that if an IV bolus injection is used, a slow injection rate is preferred and a rapid injection rate should be avoided.
- The GDG noted that the combination of an oxytocin infusion after an initial IV bolus of oxytocin after caesarean delivery reduces the need for additional uterotonic agents but does not affect the overall occurrence of major obstetric haemorrhage.
- The GDG noted that carbetocin is associated with a reduction in the use of additional uterotonic agents but with no difference in the occurrence of major obstetric haemorrhage. In addition, the GDG noted that the use of carbetocin is considerably more expensive than oxytocin. This remark is equally applicable to vaginal deliveries.

Background

Postpartum haemorrhage 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.

It is generally assumed that by preventing and treating PPH, most PPH-associated deaths could be avoided. The prevention and treatment of PPH are therefore vital steps towards improving the health care of women during childbirth and the achievement of the Millennium Development Goals. To reach these objectives, health workers in developing countries should be given access to appropriate medications and be trained in procedures relevant to the management of PPH. Countries also need evidence-based guidance to inform their health policies and improve their health outcomes.

Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, based on the GRADE approach. (2,3) Outcomes used for this recommendation were the prioritized outcomes from the WHO recommendations on prevention and treatment of postpartum haemorrhage (2012).(4)

Three systematic reviews provided evidence. (4-6). 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, magnitude of effect, balance of benefits versus disadvantages, resource usage, and feasibility, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

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

Recommendation question

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

- For all women after caesarean section (P), does oxytocin administration (I) compared to placebo, other uterotonic drugs or no treatment (C) improve maternal outcomes, including postpartum haemorrhage prevention (O)?

Evidence Summary

Part of the evidence supporting this recommendation has been extrapolated (but downgraded for indirectness) from studies investigating the use of oxytocin in vaginal deliveries.

A systematic review included 39 trials (>7900 women) which addressed the use of different drugs, routes and doses for the prevention of PPH both at elective and emergency caesarean sections. In general, all the sample sizes of the studies were very small, except for the study by Sheehan (2011) which had a sample size of 2069 women.
**Oxytocin at different doses and routes (14 trials, 4002 women)**

Two trials compared the use of an oxytocin bolus of 5 IU with the use of a 10 IU oxytocin bolus administered as a 5-minute or 15-minute infusion. Only one trial (102 women) reported clinical outcomes. No differences were found in the use of additional uterotonic. Other outcomes of interest could not be evaluated. Three studies (almost 2900 women) compared the use of a bolus of 5 IU oxytocin only followed by an infusion of 30 IU and 40 IU of oxytocin versus a single bolus of 5 IU of oxytocin. The studies found a significant reduction in the use of additional uterotonic (RR 0.54; 95% CI 0.36 to 0.79), but not in blood loss >1000 ml, the use of blood transfusions, or in side-effects.

Two other studies (217 women) compared the use of a bolus of 5 IU of oxytocin followed by an infusion of 5 IU or 20 IU of oxytocin versus an infusion of 5 IU or 20 IU of oxytocin. No differences were found for any of the priority outcomes. There were fewer cases of hypotension in the group not receiving the bolus (RR 0.44; 95% CI 0.23 to 0.87).

Oxytocin administered as a bolus was compared at doses of 5 IU versus 10 IU in two trials (137 women). There was an increase in the use of additional uterotonic when a bolus of 5 IU rather than 10 IU was used (RR 17.35; 95% CI 2.18 to 137.83).

Different doses of oxytocin administered by infusion only were compared in two trials. The first of these (321 women) compared 10 IU versus 80 IU, while the second trial (40 women) compared 5 IU versus 10 IU versus 15 IU versus 20 IU. No conclusions could be drawn for any of the priority outcomes.

One small study (40 women) compared the use of 20 IU of intramyometrial oxytocin versus a bolus of 5 IU of IV oxytocin. Two other trials (139 women) compared the use of lower doses (1 IU to 3 IU) versus higher doses (5 IU) of oxytocin using a bolus in women also receiving oxytocin administered by IV infusion.

**Ergometrine versus oxytocin (3 trials, 239 women)**

A four-arm trial (136 women) compared: (i) a bolus of 10 IU of oxytocin versus (ii) a 10 IU infusion lasting 5 minutes versus (iii) a 10 IU infusion lasting 15 minutes versus (iv) a bolus of 0.2 mg methylergonovine. One small study (55 women) compared the use of an oxytocin bolus of 10 IU IV and methylergonovine maleate 0.2 mg IV bolus followed by 0.125 mg oral methylergonovine repeated at 8-hourly intervals and oxytocin infusion versus oxytocin bolus 10 IU IV and oxytocin infusion. Another small trial (48 women) compared a 0.25 mg dose of ergometrine and 20 IU oxytocin infusion versus 20 IU oxytocin infusion. The latter reported an increased risk in the use of additional uterotonic in the oxytocin group (RR 2.14; 95% CI 1.07 to 4.30) and fewer cases of nausea (RR 0.20; 95% CI 0.05 to 0.82).

**Misoprostol versus oxytocin or placebo (11 trials, 1580 women)**

Misoprostol was compared with oxytocin in seven trials (762 women). Misoprostol was given orally, sublingually or rectally in doses ranging from 400 to 800 ?g. Oxytocin was administered as a bolus of 10 IU, as an infusion of 10 IU or 20 IU, or as an intramyometrial injection. No additional benefits were found in the misoprostol group for the priority outcomes and an increase in shivering was reported in the vaginal delivery group.

Four trials (819 women) compared misoprostol and oxytocin versus oxytocin. Misoprostol was given orally, rectally, or as intrauterine tablets in doses of 200 ?g, 400 ?g, or 800 ?g. Oxytocin in the misoprostol group was administered as a bolus or infusion of 5 IU to 20 IU, and in the control group as an IV infusion of 20 IU.

Again, no difference was reported for the priority outcomes, but an increase in pyrexia >38 °C and shivering was noted.

Misoprostol only was compared with misoprostol and 20 IU of intramyometrial oxytocin in a 3-arm trial.
(124 women) and no differences in priority outcomes were reported.

Injectable prostaglandins versus oxytocin (3 trials, 575 women)

No differences were found for any of the priority outcomes for the use of carboprost only or combined with oxytocin versus oxytocin [only]. A small trial (60 women) of prostaglandin F2 alpha versus oxytocin did not report any outcomes relevant to this guideline.

Carbetocin versus oxytocin or placebo (6 trials, 1407 women)

Five trials (nearly 1300 women) compared carbetocin 100 μg IV versus oxytocin (5 IU of IV bolus or IM, 5 IU or 10 IU of IV infusion, or 2.5 IU bolus followed by a 30 IU IV infusion of 16 hours). As stated previously, carbetocin was superior to oxytocin only for reducing the use of additional uterotonics.

One trial compared carbetocin 100 μg IV versus placebo (119 women) and reported a reduced risk for the additional use of uterotonics.

Other drugs (2 trials, 180 women)

Oral methergine administered every 6 hours was compared with no methergine (one study, 80 women). A second trial (100 women) compared the use of 1 g of tranexamic acid IV versus no tranexamic acid, with both groups receiving adjunct oxytocin. No differences in the priority outcomes were found.

Haemodynamic effects

The haemodynamic effects related to the use of oxytocin bolus injections have been evaluated in numerous studies ranging from randomized controlled trials to case reports. The magnitude and clinical significance of haemodynamic effects remain controversial. Generally, randomized studies have reported that the use of oxytocin bolus injection has resulted in milder and transitory haemodynamic effects, while case reports have tended to note more severe effects, including severe hypotension, cardiac arrest, pulmonary oedema, and maternal deaths. The difficulty of interpreting the data derived from case reports is due to the challenge of establishing the causality between the bolus infusion and the reported effects, and in disentangling the role of confounders.

The use of carbetocin

One systematic review was found which evaluated 11 trials (2635 women). The trials evaluated the effect of using carbetocin (100 μg as an IV bolus or IM injection) for the prevention of PPH. The trials evaluated the effect of both forms of administration after both vaginal delivery and caesarean section, and compared the results to the use of oxytocin, fixed dose oxytocin-ergometrine, and placebo.

Carbetocin versus placebo

The systematic review identified one trial (119 women) which compared the use of 100 μg of carbetocin for women undergoing elective caesarean versus saline as a placebo. The use of carbetocin was associated with a statistically significant reduction in the use of therapeutic uterotonic drugs (RR 0.18; 95% CI 0.09 to 0.35). However, these data came from a single small trial published as an abstract only and the risk of bias was therefore unclear. Critical or important adverse outcomes were not reported.

Carbetocin versus oxytocin

Five trials were identified (1399 women) which compared the use of carbetocin versus oxytocin for women at high risk of PPH (two trials), low risk of PPH (two trials), and both low and high risk of PPH (one trial). Oxytocin was administered as a single IV bolus of 5 IU (one trial, 377 women), as a 10 IU dose in continuous infusion (two trials, 268 women), and as an initial 2.5 IU and 5 IU bolus followed by a 20 IU
infusion (two trials, 754 women). For women who underwent caesarean section, PPH was defined as a blood loss >1000 ml (two trials, 437 women), >500 ml (one trial, 104 women), and was not defined in another (694 women). For vaginal deliveries (one trial, 164 women), PPH was defined as a blood loss >500 ml. Women underwent elective caesarean sections (two trials), elective and emergency caesarean sections (one trial), while the remaining trial[s] did not specify whether the women sampled had had elective or emergency caesareans. The results were presented separately according to the mode of delivery (caesarean or vaginal birth).

The published systematic review included only three trials that considered the risk of PPH in caesarean section. The results suggests that there is a reduced risk of PPH with the use of carbetocin versus oxytocin (RR 0.55; 95% CI 0.31 to 0.95). However, variation in the definition of PPH was noted in these trials, and the findings were influenced by the trial which had defined PPH as a blood loss of >500 ml – a claim that can be controversial in the context of caesarean section. In addition, when a trial conducted in 2010 by Attilakos , was added to the analysis, the review reported that the results were no longer statistically significant (RR 0.66; 95% CI 0.39 to 1.10). In the context of vaginal deliveries, no difference was noted in the risk of PPH defined as >500 ml (RR 0.95; 95% CI 0.43 to 2.09).

In comparison to oxytocin, carbetocin was associated with a reduced use of additional uterotonic drugs following caesarean delivery (RR 0.64; 95% CI 0.51 to 0.81) (four trials, >1100 women). This was not found to be the case for vaginal delivery (RR 0.93; 95% CI 0.44 to 1.94) although this was evaluated in only one study (164 women).

Carbetocin is also associated with a reduced use of uterine massage in both caesarean deliveries (RR 0.54; 95% CI 0.31 to 0.96) and vaginal deliveries (RR 0.70; 95% CI 0.51 to 0.94). There were no other reported differences in important adverse outcomes between the two groups, although it should be noted that the sample sizes in the trials were frequently small, and few conclusions can therefore be drawn.

**Carbetocin versus syntometrine**

Four trials were found of women (?1000) undergoing vaginal delivery. These reported the use of 100 ?g of IM carbetocin versus IM syntometrine (a fixed combination of 5 IU of oxytocin and 0.5 mg of methylergonovine). Three of the trials (910 women) were conducted on women with no risk factors for PPH, while one trial (120 women) was conducted on women with risk factors for PPH.

No difference was noted in the rates of PPH between the groups or in the additional use of uterotonics.

Among the important adverse outcomes reported, there was a reduction in risk of vomiting (RR 0.21; 95% CI 0.11 to 0.39), nausea (RR 0.24; 95% CI 0.15 to 0.4), and retching (RR 0.14; 95% CI 0.03 to 0.62) in the women receiving carbetocin. Sweating (RR 0.33; 95% CI 0.12 to 0.9) – though the event rate was low – and uterine/abdominal pain (RR 0.56; 95% CI 0.35 to 0.92) were also reported. No differences were reported for headache, facial flushing or shivering.

Two randomized controlled trials (>1600 women) observed a reduction in hypertension (blood pressure ?140/90 mmHg) in women treated with carbetocin versus syntometrine (RR 0.16; 95% CI 0.07 to 0.38)

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 should be created for the use of this recommendation, 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.

Research implications

The GDG identified these research priorities related to this recommendation:

- What are effects of ergometrine (in combination or not with oxytocin) after caesarean section for the prevention of PPH?

Related Links

WHO recommendations on prevention and treatment of postpartum haemorrhage (2012) - full document and evidence tables

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors (2nd ed)

VIDEO: Active management of third stage of labour

Education material for teachers of midwifery. Managing postpartum haemorrhage.

Links to supporting evidence:


References


