Oxytocic Agents for the Management of Postpartum Haemorrhage

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Postpartum haemorrhage (PPH) or excessive bleeding at or after childbirth is a potentially life-threatening complication and is one of the major contributors to maternal mortality and morbidity worldwide. Primary PPH, defined as bleeding from the genital tract of 500 ml or more in the first 24 hours following the delivery, occurs in 5% to 15% of all deliveries while severe PPH (blood loss >1000 ml) occurs in 1-6%. The most frequent cause for PPH is uterine atony (>50%). Oxytocic agents administered prophylactically during the third stage of labour have been shown to reduce the risk of PPH by about 40%. There is no difference in the risk of PPH, placental retention and use of additional oxytocics when the drug is administered as the anterior shoulder of the baby presents or after delivery of the placenta.

Oxytocin

Oxytocin (Syntocinon®) is the most widely used oxytocics. It has a short half-life, approximately 3–5 minutes, and is used as an infusion to maintain uterine contraction. Oxytocin can be used in a solution or administered intramuscularly, but not orally. It should not be given intravenously as a large bolus as severe hypotension may occur. Because of its anti-diuretic effect, water intoxication can occur with prolonged infusion of oxytocin.

Compared with placebo, prophylactic oxytocin showed a lower incidence of post-partum blood loss >500mL (RR 0.50, 95% CI 0.43-0.59) and less need for therapeutic oxytocics (RR 0.50, 95% CI 0.39-0.64). There was no difference between oxytocin and ergot alkaloids (ergometrine or methylergonovine maleate). However, oxytocin was associated with fewer manual removals of the placenta (RR 0.57; 95% CI 0.41 to 0.79), and with the suggestion of less raised blood pressure (RR 0.53; 95% CI 0.19 to 1.52). The RCOG recommends intravenous oxytocin 5 units (with the option of repeated doses) as the first-line drug treatment for PPH.

Ergot Alkaloids

Ergometrine is the most common ergot alkaloids used. Its half-life is approximately 32 minutes, and it produces long sustained uterine contractions. Administration is most commonly intramuscular, although oral and intravenous administrations are also possible. These drugs are contraindicated in patients with hypertension, migraine, and Raynaud’s syndrome. Reported side effects include nausea, vomiting, tinnitus, headache, and increased blood pressure.

Parenteral administration of ergot alkaloid reduced the mean blood loss and the rate of PPH (RR 0.38, 95% CI 0.21-0.69). However, ergot alkaloids increased the risk of vomiting (RR 11.81, 95% CI 1.78 to 78.28), elevation of blood pressure (RR 2.60, 95% CI 1.03 to 6.57) and pain after birth requiring analgesia (RR 2.53, 95% CI 1.34 to 4.78). Oral ergometrine did not show a reduction in PPH when compared to placebo. The available evidence provides no support for the prophylactic use of ergometrine alone.

Syntometrine

Syntometrine is a mixture of 5 IU oxytocin and 0.5 mg ergometrine. It is the most commonly used oxytocics for the prevention and management of post-partum haemorrhage. It is administrated intramuscular and combines the rapid onset of action of oxytocin with the prolonged action of ergometrine. Intravenous administration enhances the side effects of hypertension, nausea and vomiting without the benefit of its sustained action.

Compared with oxytocin, syntometrine was associated with a small reduction in the risk of PPH (OR 0.82, 95% CI 0.71 to 0.95) with no difference in the risk of severe PPH. Syntometrine was also associated with a reduced need for additional oxytocics (OR 0.83, 95% CI 0.72 to 0.96) with no difference in the risk of manual removal of placenta (OR 1.03, 95%CI 0.80 to 1.33). However, syntometrine was more likely to cause adverse effects of vomiting (OR 4.92, 95%CI 4.03 to 6.0), nausea (OR 4.07, 95% CI 3.43 to 4.84) and hypertension (OR 2.40, 95% CI 1.58 to 3.64). Intramuscular syntometrine is an alternative to intravenous oxytocin for the management of PPH.

Misoprostol

Misoprostol is a prostaglandin E1 analog and is registered for the prevention and treatment of gastric ulcers. It is well known for its off-label use as a uterotonc agent. It is available as a 200μg tablet and can be administered orally, vaginally, rectally, sublingually or via the buccal route; the rate and extent of absorption vary between routes. Oral and sublingual routes have the advantage of rapid onset of action, while the sublingual, vaginal and rectal routes result in prolonged activity and greater bioavailability. Side effects include diarrhoea, abdominal pain, nausea and vomiting, shivering and pyrexia.
Compared with conventional oxytocics for prevention of PPH, oral misoprostol was associated with a higher risk of severe PPH (RR 1.32; 95% CI 1.16 to 1.51). There was a trend towards lesser use of additional oxytocics and fewer blood transfusions with misoprostol (RR 0.81; 95% CI 0.64 to 1.02). When combined with oxytocin, oral misoprostol was more effective than placebo and oxytocin in decreasing severe PPH (RR 0.38; 95% CI 0.15 to 0.97), and PPH (RR 0.44; 95% CI 0.23 to 0.84).

When used as a first line treatment for PPH in women who had not received prophylactic oxytocics, fewer women who were given misoprostol had active bleeding controlled within 20 minutes (RR 0.94, 95% CI 0.91 to 0.98) and more had additional blood loss of at least 300 ml (RR 1.78, 95% CI 1.40 to 2.26) when compared with oxytocin. In women who had received prophylactic oxytocin, there was no difference in the 2 outcome parameters after misoprostol or oxytocin. Misoprostol is less effective than oxytocin for prophylaxis of post-partum haemorrhage and has more side effects with no adjunctive effect if the woman has already been given oxytocin.

**Carbetocin**

Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties. It has a rapid onset of action and a prolonged duration of action relative to oxytocin. It is administered as a single-dose of 100μg either intravenously or intramuscularly. Irrespective of the route of administration, carbetocin produces tetanic uterine contractions within 2 minutes. However, the tetanic contractions last for 11 minutes followed by rhythmic contractions for 120 minutes after intramuscular injection, which are both twice as long when compared with that following intravenous injection (6 minutes and 60 minutes respectively).

When compared with intravenous oxytocin in women delivered vaginally, the use of intramuscular carbetocin resulted in significant reduction in the need for additional oxytocics and uterine massage. When given intramuscularly, carbetocin was as effective as syntometrine. However, it was associated with a significantly lower incidence of nausea, vomiting, and hypertension, but a significantly higher incidence of tachycardia.

When used in women after Caesarean section, Boucher et al. did not find any difference between intravenous carbetocin and oxytocin while Dansereau et al demonstrated a reduction in the need for additional oxytocics in the carbetocin group (4.7% versus 10.5%, P<0.05). In both studies, a continuous dose of oxytocin was administered after the initial dose, likely improving effectiveness of oxytocin beyond that of a bolus dose alone.

The use of carbetocin resulted in a significant reduction in the need for additional oxytocics agent (RR 0.44, 95% CI 0.25 to 0.78) compared to oxytocin for those who underwent Caesarean section, but not for vaginal delivery.

**References**