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Review Article

Active management of third stage of labour with special reference to misoprostol

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ABSTRACT

Active management of third stage of labour is an effective method of preventing postpartum hemorrhage. It includes administration of uterotonic immediately after delivery of the baby, delaying cord clamping for at least 1-3 minutes to reduce rates of infant anaemia, performing controlled cord traction for removing the placenta and postpartum vigilance, ie, assess the uterine tone to ensure a contracted uterus; and continue to check every 15 minutes for 2 hours. If there is uterine atony, fundal massage should be performed and patient should be monitored more frequently. Though oxytocin is the best drug for routine prophylaxis, misoprostol is a relatively newer drug which is now included in the various guidelines for prevention and treatment of postpartum hemorrhage. It can be used as an effective and safe drug in areas with poor access to skilled healthcare providers and facilities.

Keywords: Active management, Misoprostol, Maternal deaths, Postpartum hemorrhage, Third stage

INTRODUCTION

Postpartum haemorrhage is one of the leading causes of maternal death worldwide; it occurs in about 10.5% of births and accounts for over 130 000 maternal deaths annually.¹ Primary postpartum haemorrhage (PPH) is the most common form of major obstetric haemorrhage.

The traditional definition of primary PPH is the loss of 500 ml or more of blood from the genital tract within 24 hours of the birth of a baby.² PPH can be minor (500–1000 ml) or major (more than 1000 ml). Major can be further subdivided into moderate (1001–2000 ml) and severe (more than 2000 ml). In women with lower body mass (e.g. less than 60 kg), a lower level of blood loss may be clinically significant.³

Secondary PPH is defined as abnormal or excessive bleeding from the birth canal between 24 hours and 12 weeks postnatally.⁴

Oxytocin, methargin and prostaglandins like carboprost are in use for active management of third stage of labour. But of late, another prostaglandin, misoprostol, is being used for the same purpose, by various routes. It is also used for the management of atonic PPH. This article throws light on this drug, its onset of action, efficacy, side effects, etc.

ACTIVE MANAGEMENT OF THIRD STAGE OF LABOUR

Active management of the third stage of labour is highly effective at preventing postpartum haemorrhage among facility-based deliveries. It is more effective than physiological management in preventing blood loss, severe postpartum haemorrhage (>500 ml) and prolonged third stage of labour.⁵ International Federation of Gynecologists and Obstetricians (FIGO), the International Confederation of Midwives (ICM), as well as by WHO recommend routine use of active

management of labour for all vaginal singleton births in health facilities.^{6,7}

The FIGO–ICM definition includes use of a uterotonic immediately following delivery of the fetus, controlled cord traction and fundal massage immediately after delivery of the placenta, followed by palpation of the uterus every 15 minutes for 2 hours to assess the continued need for massage.⁸ Cord clamping is excluded based on research indicating that delayed clamping benefits preterm (and probably term) infants.⁹

The NICE guideline on intrapartum care (2014) recommends administration of 10 IU of oxytocin by intramuscular injection with the birth of the anterior shoulder and that the umbilical cord should not be clamped earlier than 1 minute from delivery of the baby if there are no concerns over cord integrity or the baby's wellbeing.

Use oxytocin as it is associated with fewer side effects than oxytocin plus ergometrine.¹⁰

OTHER DRUGS FOR PPH

The use of prostaglandins for the prevention of PPH has been the subject of two Cochrane reviews.¹¹ Neither intramuscular prostaglandins (such as carboprost, a 15-methyl prostaglandin F_{2α} analogue) nor misoprostol (a prostaglandin E₁ analogue given orally or sublingually) were preferable to conventional injectable uterotonics (oxytocin and/or ergometrine) for routine prophylaxis.¹²

A Cochrane review has addressed the use of a longer-acting oxytocin derivative, carbetocin, in the prevention of PPH.¹³ Carbetocin is licensed in the UK specifically for the indication of prevention of PPH in the context of caesarean delivery. Use of carbetocin resulted in a statistically significant reduction in the need for further uterotonics compared with oxytocin for those undergoing a caesarean, but not for vaginal delivery.

The use of tranexamic acid in the prevention of PPH in women considered to be at low risk of PPH was addressed in a Cochrane review.¹⁴ This found that blood loss greater than 400 or 500 ml was less common in women who received tranexamic acid in addition to the usual uterotonic agent after vaginal birth or caesarean section in a dosage of 1 or 0.5 g intravenously.

ROLE OF MISOPROSTOL

Misoprostol, an E₁ prostaglandin analogue, is a potent uterotonic agent whose usefulness is increasingly recognized in obstetric and gynecologic practice, including in the control of PPH.^{15,16} Misoprostol can be administered orally, rectally, vaginally, or sublingually without syringes or intravenous equipment, and it is inexpensive, easy to store and stable at room temperature. Studies comparing the results of prophylactic use of

misoprostol for the reduction of blood loss with conventional uterotonics have concluded that misoprostol had a positive effect.¹⁷ Although some studies have found that conventional uterotonics were superior to misoprostol, none has rejected using misoprostol when injectable uterotonics are not available or cannot be properly used.

PHARMACOLOGY OF MISOPROSTOL

Misoprostol is a synthetic PGE₁ analogue which is stable at ambient temperatures and has a long shelf life. Following oral administration, it is absorbed quickly and de-esterified to be converted into its active pharmacological form, misoprostol acid. Primary site of metabolism is the liver and the drug has no known drug interactions.

Mechanism of action

It is a myometrial stimulant, which binds to both E₂ and E₃ prostanoid receptors. Apart from its uterotonic effects, misoprostol has known pharmacologic effects on several organ systems. It inhibits platelet-activating factor and affects metabolic and physiological processes, including thermoregulation.¹⁸

SAFETY PROFILE

Temperature changes

Shivering, chills and/or fever are all commonly associated with misoprostol. Shivering is the most common side effect and is occasionally accompanied by fever. In the large WHO multicentre study using 600 µg oral misoprostol, shivering was experienced by 18% of women, but temperatures of over 38°C or 40°C were found in only 6 and 0.1%, respectively. Similarly, when Derman et al. used 600 µg in rural India, shivering occurred in 52.2% of women, but fever in only 4.2%.¹⁹ The shivering is self-regulating and even if high temperatures occur, they are transient and settle with reassurance and symptomatic treatment.

Gastro-intestinal effects

Transient diarrhoea, nausea and vomiting may occur following misoprostol, but are rare, occurring in less than 1% women.²⁰ An anti-emetic can be used if needed, but in general no action is required except to reassure the woman and her family.

Breast feeding

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

Life-threatening hyperpyrexia has been reported following the use of misoprostol, 800 µg orally, after

childbirth.²¹ However, no mortality has been reported due to use of misoprostol for PPH.

However, overdose has been clinically manifested by sedation, tremor, convulsion, dyspnea, abdominal pain, fever, diarrhea, palpitation, hypotension or bradycardia and should be treated with supportive therapy.²²

RCOG GUIDELINES FOR PREVENTION OF POSTPARTUM HEMORRHAGE

- Risk factors for PPH may present antenatally or intrapartum; care plans must be modified as and when risk factors arise.
- Clinicians must be aware of risk factors for PPH and should take these into account when counselling women about place of delivery.
- Women with known risk factors for PPH should only be delivered in a hospital with a blood bank on site
- Antenatal anaemia should be investigated and treated appropriately as this may reduce the morbidity associated with PPH [New 2016].
- Uterine massage is of no benefit in the prophylaxis of PPH [New 2016].
- Prophylactic uterotonics should be routinely offered in the management of the third stage of labour in all women as they reduce the risk of PPH.
- For women without risk factors for PPH delivering vaginally, oxytocin (10 IU by intramuscular injection) is the agent of choice for prophylaxis in the third stage of labour. A higher dose of oxytocin is unlikely to be beneficial.
- For women delivering by caesarean section, oxytocin (5 IU by slow intravenous injection) should be used to encourage contraction of the uterus and to decrease blood loss.
- Ergometrine–oxytocin may be used in the absence of hypertension in women at increased risk of haemorrhage as it reduces the risk of minor PPH (500–1000 ml).
- For women at increased risk of haemorrhage, it is possible that a combination of preventative measures might be superior to syntocinon alone to prevent PPH [New 2016]
- Clinicians should consider the use of intravenous tranexamic acid (0.5–1.0 g), in addition to oxytocin, at caesarean section to reduce blood loss in women at increased risk of PPH [New 2016].

RECOMMENDATIONS FOR USE OF MISOPROSTOL

- World Health Organization recommendations for the prevention and treatment of postpartum haemorrhage. 2012 recommends Intravenous oxytocin for the treatment of PPH. 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.

- RCOG Green-top guideline. Management of postpartum haemorrhage. 2009 recommends misoprostol 1000 ug per rectally.
- FIGO guidelines for prevention of PPH 2012: Misoprostol was inferior to oxytocin and other uterotonics with regard to any of the third stage of labor outcomes assessed. However, when compared to placebo, misoprostol had a decreased risk of needing additional uterotonics. Thus, in less-developed countries where administration of parenteral uterotonic drugs may be problematic, misoprostol represents a reasonable agent for the management of the third stage of labor.²³
- Guidelines on prevention, 2012: Regimen A single dose of misoprostol 600 µg orally administered immediately after delivery of the newborn after confirming no additional babies in utero.
- Guidelines on treatment, 2012: Regimen One dose of misoprostol 800 µg sublingually. Irrespective of the prophylactic measures, When 40 IU IV oxytocin is not available, Once PPH is diagnosed, the treatment should be immediate.
- Contraindications: History of allergy to misoprostol or other prostaglandin
- *The recommended dose does not change according to the woman's weight
- Repeat or consecutive doses: Repeat doses of misoprostol for PPH treatment (eg first-line treatment with misoprostol followed by another dose to control bleeding) are not recommended
- If oxytocin is already being provided for treatment of PPH, simultaneous use of misoprostol has no added benefit
- Precautions: caution is advised where misoprostol is provided as prophylaxis for PPH, especially if the initial dose was associated with pyrexia or shivering
- FOGSI Guidelines for prevention of PPH, 2012: 600 µg orally, sublingually or per-rectally for prevention of PPH
- Government of India Guidelines, 2013 recommend 600 µg misoprostol orally after delivery for prevention of PPH.

CONCLUSION

In conclusion, misoprostol is a proven, potent uterotonic agent. In situations where oxytocin and or ergometrine are not consistently and appropriately used for active management of the third stage of labor for various reasons (i.e. drug shortage, shortage of staff to administer i.v./i.m., storage and or refrigeration problems, high caseload, etc.), misoprostol should be considered for inclusion in the protocol for active management of third stage of labour.

Evidence has been building for the use of oral misoprostol to be effective and safe in areas with low

access to facilities and skilled healthcare providers and future research on misoprostol use in the community should focus on implementation issues.

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