Update in
Anaesthesia

Oxytocics

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Summary

Postpartum hemorrhage remains the leading cause of maternal mortality and morbidity.

Oxytocic drugs are the main stay in prevention as well as treatment. Oxytocin remains the drug of choice. The use of 5 IU bolus dose has been questioned in recent times. Current evidence suggests infusion to be a preferred choice than bolus dosage. Carbetocin is a newer alternative to oxytocin. Second line drugs include ergot alkaloids (Methyl ergometrine) and prostaglandins (carboprost and misoprostol) which are used as adjuvants to oxytocin in hemorrhage.

INTRODUCTION

Postpartum Haemorrhage (PPH) remains a major cause of both maternal mortality and morbidity with an estimated mortality rate of 140,000 per year or one maternal death every four minutes.[1] In the developing world, death from PPH occurs in approximately 1 out of 1,000 deliveries. Uterine atony is the commonest cause for postpartum hemorrhage accounting to 80% leading to blood transfusion and post partum hysterectomy.

Administration of Oxytocic drugs help in both prevention and treatment of postpartum haemorrhage. The American College of Obstetricians and Gynaecologists (ACOG) recommends prophylactic administration of uterotonic agents to prevent uterine atony. Active management of the third stage of labor includes oxytocin administration. ACOG recommends using Uterotonic agents as first-line treatment for postpartum hemorrhage caused by uterine atony.[2] Three classes of drugs are in use and include oxytocin, ergot alkaloids, and prostaglandins.

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Oxytocin

Oxytocin is a nonapeptide hormone produced in the hypothalamus and later secreted into circulation by posterior pituitary gland. The word oxytocin was coined from the term oxytocic, Greek oxys, and toketos, meaning "quick birth". It was first discovered by Sir Henry Dale in 1909 as extract from pituitary gland that caused uterine contractions in pregnant cat.[3] Oxytocin became the first hormone to be synthesized in 1953 by the American biochemist, Vincent Du Vigneaud for which he received the Nobel Prize.[4] It remains the first-line agent in the management and prevention of uterine atony after vaginal or caesarean delivery. Not only does oxytocin play a role in uterine contraction, but this hormone is also involved in haemodynamic regulation. It can precipitate hypotension especially when given as a bolus, in addition to causing a release of atrial and brain natriuretic peptides. Due to its structural similarity to vasopressin/antidiuretic hormone (ADH), oxytocin may also cause water retention and hyponatremia. Several empirical regimens have been proposed for oxytocin administration during caesarean delivery and this has led to many different practices in its administration worldwide. Carvalho et al. in a report in 2004 stated the minimum effective initial dose of oxytocin in elective caesarean deliveries to be 0.35 IU, which was far less than the previous conventional dosages ranging from 5 to 10 IU.[5] This sparked further research into the administration of oxytocics in rational and judicious manner to minimise the side effects while maintaining efficacy.

Conventionally oxytocin has been used either as bolus administration or continuous infusion. The optimal dose, timing, and rate of administration for oxytocin during caesarean delivery remain ambiguous. Royal College of Obstetricians and Gynaecologists (UK) recommends slow intravenous bolus dose of 5 IU[6], while the American College of Obstetricians and Gynaecologists (ACOG) recommends continuous infusion.[2] WHO recommends 20 IU oxytocin in 1 litre crystalloid infusion at 60 drops per minute and to continue 20 IU in 1 litre crystalloid at 40 drops per hour if bleeding continues to not more than 3 litres of oxytocin containing IV fluid.[7] WHO also recommends to avoid bolus IV dose oxytocin. The use of 5 IU of oxytocin as bolus dose has been questioned

Table 1: Oxytocin protocol for cesarean delivery: "Rule of threes"

3 IU oxytocin intravenous loading dose (administered no faster than 15 seconds[12])
3 min assessment intervals. If inadequate uterine tone, give 3-IU oxytocin intravenous rescue dose
3 total doses of oxytocin (Initial Load + 2 Rescue Doses)
3 IU oxytocin intravenous maintenance dose (3 IU/L at 100mL/h)
3 Pharmacologic options (e.g. ergometrine, carboprost and misoprostol) if inadequate uterine tone persists

in recent times. Oxytocin given prophylactically has known to cause haemodynamic instability including hypotension, tachycardia, arrhythmias and even myocardial ischemia.[8] Other effects include headache, nausea, vomiting and flushing. Bolus dosages of 3 to 5 IU given rapidly have caused cardiovascular collapse and even death.[9] Tsen and Balki[10] in 2010 proposed a new protocol for safe oxytocin administration called "Rule of threes" (Table 1) which is evidence-based as well as easy to remember.

Carebetocin

Carbetocin is a synthetic analogue of oxytocin with similar pharmacodynamic properties but longer acting. It is an octapeptide while oxytocin is nonapeptide and due to its structural difference carbetocin is more stable and is more resistant to degradation by disulphidase, aminopeptidase and oxidoreductase enzymes.[10] It has a half life of about 40 minutes which is 10 times that of oxytocin. Side effects of carbetocin are similar to oxytocin including hypotension, flushing, headache and abdominal pain. A Cochrane database review in 2012 found lower incidence of PPH after caesarean deliveries with carbetocin compared with oxytocin.[11] The ED90 dose of carbetocin during caesarean delivery to maintain uterine tone ranged from 14.8μg[12] in non labouring women to 121μg[13] in labouring women. The Society of Obstetricians and Gynaecologists of Canada recommends carbetocin 100μg be given as an intravenous bolus over one minute to prevent PPH.[14] The current evidence in use of carbetocin is quite encouraging and further large scale studies are needed to know the effective dose and side effect profile.

Methyl Ergometrine

Ergot, derived from the fungus Claviceps purpurea, was the first effective oxytocic drug to be used in obstetrics. From 1582 to 1822 it was used to speed up delivery, it was no longer used after due to complications including uterine rupture, still birth, and maternal death.[15] Methyl ergometrine is a semisynthetic ergot derivative. It causes sustained contraction of uterus and is the second line agent for treatment of PPH. WHO recommends 0.2mg intravenously or intramuscularly repeated every 15 min up to a maximum dosage of 1mg for PPH7. ACOG recommends 0.2mg intramuscularly every 2 to 4 hours.[2] Side effects include hypertension with headache and even seizures, rarely coronary vasospasm and myocardial ischaemia.[16] It is contraindicated in hypertensive patients and should be avoided in patients taking CYP3A4 inhibitors.

Carboprost

Carboprost is a prostaglandin F2α analogue used as second line agent in uterine atony. Prostaglandins increase intramyometrial calcium concentrations and enhance uterine contraction. Their effects are mediated via G-proteins and the activation of calcium channels.[17] Prostaglandin F2α was first used by Takagi in 1976 as intramyometrial agent for PPH.[18] The recommended dosage of carboprost is 250μg intramuscularly repeated every 15 to 30 minutes up to a maximum of 2mg i.e. 8 times. Butwick et al.[19] in a retrospective study reported carboprost to be less effective than methyl ergometrine in treating PPH. Carboprost is preferred as second line agent in uterine atony when methyl ergometrine is contraindicated or ineffective. Side effects include nausea, vomiting and diarrhoea. Its use should be avoided in patients with bronchial asthma due to its potential to cause bronchospasm[20].

Misoprostol

Another second line drug for treatment of PPH, misoprostol is a Prostaglandin E1 analogue. It can be used in various routes: Oral, sublingual, buccal, vaginal or rectal. WHO recommends sublingual misoprostol 200 - 800μg.[7] Side effects include pyrexia, shivering and GI disturbances. In a meta-analysis misoprostol prevented postpartum hemorrhage by 24% and severe postpartum hemorrhage by 41% compared to placebo.[21] But in other study there was no clear benefit of use of misoprostol as adjuvant to oxytocin in terms of major outcomes such as mortality and blood loss.[22] Misoprostol is best used when all other methods have failed or when oxytocin and methyl ergometrine is unavailable.

Conclusion

1 out of 1000 women die during delivery in developing world due to PPH. Oxytocic drugs remain an important intervention in both prevention and treatment of uterine atony. Oxytocin remains the drug of choice as well as the first line agent. But the dosage and administration remain ambiguous and require standardization. Slow infusion is preferred compared to bolus doses. WHO recommends 20 IU oxytocin in 1 litre crystalloid infusion at 60 drops per minute. Carbetocin is an alternative to oxytocin with similar profile but longer duration of action. Though current evidences are promising further research is needed to delineate proper dosage as well as efficacy. Second line of drugs include ergot alkaloids and prostaglandins with methyl ergometrine being superior than carboprost in terms of treating uterine atony. Prostaglandins are best suited if methyl ergometrine is contraindicated or when bleeding persists.

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