Preventing and Treating Postpartum Haemorrhage: Uterotonics and Tranexamic Acid

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KEY POINTS

- Oxytotics such as oxytocin and its longer-acting analogue carbetocin are the first-line agents to prevent and treat postpartum haemorrhage due to excellent efficacy and a well-tolerated side effect profile.
- Second-line agents such as ergot alkaloids or prostaglandins act via different receptors and have a range of side effects.
- Tranexamic Acid (TXA) is an antifibrinolytic agent that reduces mortality in postpartum haemorrhage without increasing the risk of thrombosis.
- Optimal dosing and timing of uterotonics and TXA are important and require adaptation to individual clinical scenarios.
- Monitoring for side effects, such as cardiovascular changes, is necessary when administering these agents.

INTRODUCTION

Postpartum haemorrhage (PPH) is a leading cause of maternal mortality worldwide, accounting for approximately one-third of all maternal deaths. PPH is commonly defined as ≥1000 mL blood loss after caesarean delivery and ≥ 500-1000 mL after vaginal delivery. Within 24 hours of delivery constitutes primary PPH, or up to 12 weeks after delivery is secondary PPH. Uterine atony accounts for nearly 80% of primary PPH cases, with tissue injury, retained placenta, and coagulopathy as other common causes. Despite global measures to combat mortality, PPH remains a significant public health concern worldwide, particularly in underdeveloped and developing nations. The World Health Organization (WHO) has developed a roadmap to combat PPH between 2023 and 2030, aiming to reduce the global maternal mortality ratio and morbidity associated with PPH.[1]

Tranexamic acid, an antifibrinolytic agent, prevents the breakdown of blood clots. It can significantly reduce PPH and the risk of related morbidity and mortality.[2,3] The International Confederation of Midwives and the International Federation of Gynaecology and Obstetrics have issued a joint statement recommending the use of uterotonics and tranexamic acid (TXA) in the prevention and treatment of PPH.[4]

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Although there is still significant variability in the way in which these medications are utilized, there has been ongoing research and data on the dosage, timing, and adverse effects that may help guide one's practice based on the resources available and the clinical situation.

OVERVIEW OF UTEROTONICS

Oxytocin

Mechanism of Action

Oxytocin, a natural peptide hormone produced by the hypothalamus and secreted by the posterior pituitary gland, plays a crucial role during labour and postpartum by inducing uterine contractions. Exogenous oxytocin may be synthetized for administration. It achieves its effects through the specific binding to oxytocin receptors located on the myometrium, leading to an influx of intracellular calcium and the subsequent activation of myosin light chain kinase. This activation results in the phosphorylation of myosin and the enhancement of uterine contractions. The hormone further increases the sensitivity of uterine smooth muscle cells to calcium, which elevates the frequency and amplitude of contractions.

Pharmacokinetics

When administered intravascularly, oxytocin acts swiftly with an onset of action of approximately 1 minute and a duration of approximately 1 hour. Oxytocin has a notably short half-life, ranging from 1 to 6 minutes. This pharmacokinetic profile requires close monitoring and dose adjustment to ensure efficacy and safety. In contrast, intramuscular administration takes between 3 and 7 minutes for onset but offers a more prolonged effect, lasting about 2–3 hours, which can be beneficial for maintaining uterine tone.

Dosing

Studies have evaluated the optimal timing and dosing (bolus ± infusion) of oxytocin, concluding that lower doses are effective and minimize adverse effects. The variability that remains is often multifactorial depending on the mode of delivery, whether the patient has been exposed and desensitized to oxytocin peripartum, and taking into consideration the patient's comorbidities, haemodynamics, and response. Repeated activation of the oxytocin receptor by oxytocin leads to oxytocin receptor desensitization, with the clinical consequence that women who have been previously exposed to oxytocin (either endogenous in labour or exogenous through labour induction or augmentation) will require much larger doses to achieve a satisfactory contractile effect. For the purposes of this article, dosing specifically to prevent PPH in caesarean delivery is described.

In 2019, an international consensus statement reviewed the available literature and offered guidance on the use of uterotonics at elective and intrapartum caesarean delivery. It recommended a bolus of 1 IU oxytocin for elective caesarean delivery, followed by an infusion of 2.5–7.5 IU per hour (0.04–0.125 IU per minute). The administration should commence after the delivery of the baby and clamping of the umbilical cord. In the case of intrapartum caesarean delivery, 3 IU of oxytocin should be administered over at least 30 seconds, followed by an infusion at 7.5–15 IU per hour (0.125–0.25 IU per minute). In both cases, a second bolus of 3 IU over 30 seconds may be delivered if required after reassessment at 2–3 minutes. A second-line agent (ergot alkaloids or a prostaglandin) should be considered promptly if this regimen fails to maintain sustained uterine tone. A review of the patient's clinical condition is essential before discontinuing the infusion, which typically occurs between 2 and 4 hours after initiation.[5]

Oxytocin-Related Cardiovascular Effects and Other Adverse Reactions

Cardiovascular Responses to Oxytocin

The cardiovascular effects of oxytocin are multifactorial, depending on the dose, administration rate, pre-existing conditions, fluid status, and dose frequency. Studies using pulse wave and transthoracic bioimpedance technologies have reported that oxytocin administration during caesarean delivery can lead to peripheral vasodilation, hypotension, tachycardia, and increased stroke volume and cardiac output.[6] A 10-unit oxytocin bolus has been shown to significantly decrease femoral artery pressure and vascular resistances while markedly increasing heart rate and stroke volume under general anaesthesia.[7] Slower infusion rates yield a more muted cardiovascular response, suggesting that oxytocin's effects are modulated by the rate of administration and oxytocin receptor desensitization with repeated doses.[6]

Electrocardiographic Changes and Myocardial Considerations

Electrocardiographic ST segment changes, a potential sign of myocardial injury, occur in a significant fraction of women (25%–60%) during caesarean delivery, with various factors, including oxytocin administration, being implicated.[8–10] One study further investigated the incidence of chest pain and concurrent elevated levels of troponin with these ST-segment changes, which was much less common but suggested possible myocardial ischemia.[11]

Additional Adverse Effects of Oxytocin

Beyond its haemodynamic impact, oxytocin is importantly associated with water retention and hyponatremia due to its similarity to antidiuretic hormone (ADH), which leads to ADH receptor activation.[12,13] Nausea and vomiting were also reported in 15% of women receiving oxytocin in one study.[14] Other side effects include warmth, palpitations, skin flushing, nasal congestion, dry mouth, metallic taste, and headaches.[15]

Carbetocin

Mechanism of Action

Carbetocin is a synthetic analogue of oxytocin. It functions mechanistically like oxytocin binding to oxytocin receptors on the myometrium, triggering an influx of intracellular calcium, which activates myosin light chain kinase. The downstream effect is the phosphorylation of myosin, leading to uterine contractions. Carbetocin also increases uterine smooth muscle cells' sensitivity to calcium, enhancing the frequency and amplitude of the contractions.[5]

Dosing and Pharmacokinetics

Carbetocin is usually administered intravenously (or intramuscularly, especially in the case of vaginal delivery), with a recommended dose of 100 mcg, producing equivalent effects to 10 mcg (5 IU) of oxytocin. Dose-finding studies indicate that the effective dose (ED90) for elective caesarean delivery in low-risk women could be as low as 14.8 mcg, significantly lower than the standard dose.[16] After injection, time to onset can be within 2 minutes, and duration of action is 60 minutes if given IV and 2–3 hours if administered IM. However, with a plasma half-life of approximately 40–80 minutes, carbetocin has a longer clinical effect compared to oxytocin, whose half-life is around 2–3 minutes.[17] The drug's structural modifications, namely 1-de-amino-1-carba-2-tyrosine (0-methyl) oxytocin, confer increased stability and reduced susceptibility to enzymatic breakdown, leading to a longer receptor half-life.[18] Thus, unlike oxytocin, carbetocin is given as a single bolus dose without subsequent infusion.

Adverse Effects

Carbetocin is generally well-tolerated and has a favourable safety profile compared to oxytocin. However, it may also cause cardiovascular effects, such as hypotension and tachycardia. Comparative studies of 100 mcg carbetocin and 5IU oxytocin during spinal anaesthesia for caesarean sections have shown similar hemodynamic effects.[15]

Drug Storage

Carbetocin's stability in high temperatures is notable. The manufacturer states that it remains stable for 1 month at 60°C, 3 months at 50°C, 6 months at 40°C, and up to 3 years at 30°C.[19] This is crucial for maintaining the drug's efficacy in low-resource settings where cold chain storage is compromised.

Ergot Alkaloids (Ergometrine and Methylergometrine)

Mechanism of Action

Ergometrine and its derivative methylergometrine (also known as ergonovine and methylergonovine, respectively) are ergot alkaloids that induce sustained contraction of the uterus. They work by nonspecifically activating various receptors on the uterine smooth muscle, including adrenergic, dopaminergic, and serotonin (5-HT) receptors, which increase uterine muscle tone.

Dosing and Pharmacokinetics

These medications are usually given intramuscularly. In the UK, the licensed dose of ergometrine can reach up to 500 mcg. However, it is recommended to administer lower doses, typically 200–250 mcg, repeated every 2–4 hours, to achieve effective uterine contraction while reducing the risk of adverse effects. The time to onset is about 5 minutes.

Adverse Effects

Vascular Effects

Ergometrine acts as an α-adrenergic receptor agonist, which may cause peripheral vasoconstriction. This action can result in increased systemic arterial and central venous pressures, making hypertension a notable adverse effect. Women with pre-existing conditions like preeclampsia or hypertension may have an increased risk of significant hypertensive responses due to ergometrine's vasoconstrictive properties and, thus, a relative contraindication. It can result in myocardial ischemia and coronary vasospasm; however, these effects are infrequently reported in the literature.

Gastrointestinal Effects

Activation of 5-HT receptors by ergometrine frequently causes nausea and vomiting.

Neurologic Effects

Ergometrine can induce headaches due to hypertension and may increase the risk of seizures.

Drug Storage

To maintain the stability and effectiveness of ergometrine, it is recommended to store in a cool and dry place, protected from light. Ideally, the temperature should be between 2°C and 8°C (36°F and 46°F). If stored outside of the refrigerator, the maximum temperature should not exceed 25°C (77°F) for a period of 12 weeks. After this period, the medication should be discarded.[20,21]

Prostaglandins (Misoprostol, Carboprost, and Sulprostone)

Mechanism of Action

Prostaglandins are potent bioactive lipids, synthesized from arachidonic acid, which function as paracrine or autocrine signaling molecules, interacting with various G protein-coupled receptors. Specific prostaglandins instigate the contraction of myometrial muscle fibres by activating FP, EP1, EP3, and TP receptors.

Dosing and Pharmacokinetics

Misoprostol, a prostaglandin-E1 analogue, is rapidly absorbed within 9–5 minutes when administered sublingually, orally, vaginally, or rectally, with a half-life ranging from 20 to 40 minutes.[22,23] The typical dose is 400–800 mcg in divided doses after 15 minutes or as a single dose, up to 800 mcg total max dose.

Carboprost, a PGF2α synthetic analogue, and sulprostone, a synthetic PGE2 analogue, are used as treatments for postpartum haemorrhage, but their adverse effect profiles deter their prophylactic use during caesarean delivery.[24–27] Typical dose for carboprost is 250 mcg intramuscular or intrauterine every 15–90 minutes, not to exceed 2000 mcg in 24 hours. Sulprostone can be given 500 mcg IV followed by an infusion at 100 mcg/hr with a max dose of 1500 mcg. After injection, the time to peak is about 15–60 minutes, and the half-life is about 8 minutes.

Adverse Effects

Misoprostol is commonly associated with hyperpyrexia, nausea, vomiting, and diarrhea as predominant side effects.[22,23]

Carboprost has been linked to severe bronchospasm, even in nonasthmatic patients, and can also cause hypertension, diarrhea, nausea, vomiting, flushing, hyperpyrexia, and myalgia.[24,25]

Sulprostone may lead to fever, diarrhea, and painful uterine contractions. There are concerns about cardiac or respiratory complications, including cardiac arrest, particularly when used during haemorrhagic shock, combined with dinoprost, or administered off-label as a continuous intravenous infusion.[26,27]

Comparison of Efficacy Among Different Uterotonics

A Cochrane network meta-analysis, including 196 trials with 135,559 women, evaluated the prophylactic use of these common uterotonic drugs and various combinations to prevent PPH at vaginal and caesarean deliveries. Analysis included oxytocin, carbetocin, ergometrine, misoprostol, prostaglandin, oxytocin + ergometrine, and oxytocin + misoprostol. The analysis found that all agents were effective for preventing PPH >500 mL compared to placebo or no treatment. There was no superiority to using ergometrine, misoprostol, or prostaglandin compared to oxytocin. There was some evidence that carbetocin, oxytocin + ergometrine, and oxytocin + misoprostol may reduce PPH >500 mL more than oxytocin, although this was less apparent when the outcome was defined to be PPH >1000 mL. The two combination regimens produced more side effects than oxytocin alone, mostly in the form of fever and nausea.[20] Carbetocin had equivalent efficacy to the combination drug regimens but with less associated side effects, suggesting the superiority of this drug.

A secondary analysis using registry data examined the difference in morbidity of second-line uterotonics for persistent uterine atony after oxytocin prophylaxis had failed. The data from 1335 women who had received carboprost or methylergometrine during caesarean section revealed an increased risk of haemorrhage-related morbidity in the carboprost group, which was significant even after adjusting for confounding factors.[28]

Emerging evidence suggests that adopting an escalating management strategy for significant bleeding after vaginal delivery may reduce postpartum haemorrhage rates, and this approach might be applicable to caesarean sections as well.[29,30]

Novel Agents

A number of recent studies have evaluated the potential of intravenous calcium chloride to treat postpartum haemorrhage.[36,38] Initial positive findings require further investigation and larger clinical trials. Dexmedetomidine hydrochloride, a highly selective α-2 receptor agonist, is used in anaesthesia and intensive care, primarily as a sedative. There is emerging evidence from *in vitro* studies suggesting it may influence contractility of human myometrium.[39,40]

Tranexamic Acid

Mechanism of Action

TXA functions as an antifibrinolytic agent. It is a synthetic lysine derivative that inhibits plasminogen binding to lysine residues on fibrin. This prevents plasminogen's conversion to plasmin, a molecule that would normally degrade fibrin clots. By blocking this process, TXA stabilizes the fibrin clot and contributes to haemostasis.[31,32]

Dosing and Pharmacokinetics

For the treatment of PPH, TXA is typically administered when blood loss exceeds 500–1000 mL after vaginal delivery or 1000 mL after caesarean section, or if the patient's hemodynamic stability is compromised by blood loss. The initial dose is 1 g of TXA, provided intravenously at a concentration of 100 mg/mL, infused at a rate of 1 mL/min. If bleeding persists after 30 minutes or returns within 24 hours, a second 1g dose may be administered in the same fashion.[33]

Efficacy and Adverse Effects

The WHO recommends early use of TXA within 3 hours of birth in addition to standard care for women with clinically proven PPH after vaginal delivery or caesarean section. TXA is generally well-tolerated. Studies have not shown a significant increase in this risk when used in pregnant women.[34] There is an increased risk of nausea and vomiting with the administration of TXA and a risk of seizures. A number of recent reports have highlighted the risks of accidental neuraxial administration of TXA. Intrathecal tranexamic administration has a fatality rate of about 40%.[41] Accidental administration via epidural route may be less catastrophic; however, it warrants strict adherence to safety norms prior to administration of drugs via all routes.

The WOMAN (World Maternal Antifibrinolytic) trial demonstrated that TXA for treatment of PPH significantly reduces the risk of death due to haemorrhage without an appreciable increase in thrombotic events.[35] The subsequent TRAPP (TRAnexamic Acid for Preventing postpartum haemorrhage) trials determined that while *prophylactic* TXA may reduce PPH at caesarean delivery (by definition, EBL >1000 ml), there was no appreciable clinical difference such as clinically significant blood loss, blood transfusion, or use of additional uterotonic agents.

SUMMARY

Uterotonic Agent	Indication	Dose	Administration Timing	Duration of Action	Repeat Dosing	Max Dose	Notes
Oxytocin	Elective caesarean delivery	Bolus: 1 IU IV Infusion: 2.5–7.5 IU/h (0.04–0.125 IU/min)	After delivery of baby and umbilical cord clamping	Intravascular: <1 h Intramuscular: 2–3 h	Can give 3 IU over 30 sec if needed after 2–3 min ×2	-	Adjust infusion rate as needed
	Intrapartum caesarean delivery	Bolus: 3 IU IV over ≥ 30 s Infusion: 7.5–15 IU/h (0.125–0.25 IU/min)	After delivery of baby and umbilical cord clamping	Intravascular: I hour Intramuscular: 2–3 h	Can repeat 3 IU over 30 sec if needed after 2–3 min ×2 Consider second-line agent early if inadequate uterine tone	-	Review patient before discontinuation, typically 2–4 h after commencement
Carbetocin	Elective caesarean delivery	100 mcg IM or IV over ≥ 30 s	After delivery of baby and umbilical cord clamping	Intravascular: 1 h Intramuscular: 2–3 hours (Single dose duration longer than oxytocin, which may require multiple boluses/ infusion for optimal steady state effect)	Typically not necessary. If smaller dose initially given, repeated doses may be given (e.g., 20 mcg initially and repeated up to total of 100 mcg)	Do not exceed 100 mcg	Do not exceed 100 mcg—if more than 100 mcg is required then it is recommended to move to second-line agent.
	Intrapartum Caesarean delivery	100 mcg IM or IV over ≥ 30 sec	After delivery of baby and umbilical cord clamping	Single dose duration longer than oxytocin	Not recommended to repeat	Do not exceed 100 mcg	Move to second-line drug if needed
Misoprostol	PPH Prophylaxis and delivery	400–800 mcg oral, sublingual, vaginal, or per rectum	After delivery of baby and umbilical cord clamping or when PPH is identified	Oral: 2 h Sublingual: 3 h Vaginal: 4 h Rectal: 4 h	Repeat after 15 min if required	800 mcg	Common side effects include fever, nausea, vomiting, and diarrhea
Sulprostone	PPH Prophylaxis and treatment	500 mcg IV followed by Infusion: 100 mcg /h with max dose of 1500 mcg	After delivery of baby and umbilical cord clamping or when PPH is identified	10–20 mins		1500 mcg	Common side effects include fever, diarrhea, and painful uterine contractions.
Carboprost	PPH treatment	250 mcg intramuscular or intrauterine	After diagnosis of PPH	60–120 mins (IM)	Repeat every 15 min if required	2000 mcg (8 doses)	Side effects include diarrhea, nausea, vomiting, flushing, and bronchoconstriction (relatively contraindicated in patients with asthma)
Ergot Alkaloids (Ergometrine)	PPH treatment	200–500 mcg intramuscular	After diagnosis of PPH	Intramuscular: 3 h or more IV: ~45 min	Can repeat after 2–4 h	-	Would avoid IV or slow IV in exceptional circumstances Side effects include hypertension, headache, seizures, chest tightness, nausea and vomiting. Relatively contraindicated in patients with hypertension.
Tranexamic Acid	PPH treatment	1 gram IV bolus over 10 min	As soon as possible after onset of PPH	Active for the duration of the 8-h infusion	If no infusion, can bolus another 1 g IV over 10 min after 30 min	-	

Dosing and Timing of Uterotonics[5]

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