REVIEW ARTICLE

The use of uterotonic drugs during caesarean section

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ABSTRACT
The administration of oxytocic drugs during caesarean section is an important intervention to prevent uterine atony or treat established postpartum haemorrhage. Considerable past and current research has shown that these agents have a narrow therapeutic range. A detailed knowledge by anaesthetists of optimal doses and side effects is therefore required. Oxytocin remains the first line agent. In view of receptor desensitisation, second line agents may be required, namely ergot alkaloids and prostaglandins. This review examines the adverse haemodynamic and side effects, and methods for their limitation. An approach to dosing and choices of agent for the limitation of postpartum haemorrhage is suggested.

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“It did not take her very long to die”
Ernest Hemingway, A Farewell to Arms, 1929*

Introduction

Every year 166 000 women die of obstetric haemorrhage, and more than 50% of these deaths occur in sub-Saharan Africa.1 Uterine atony is the commonest cause of severe postpartum haemorrhage (PPH), as tragically described by Hemingway.* Consequently the administration of uterotonic drugs during caesarean section (CS) has become essential to diminish the risk of PPH and improve maternal safety. These agents have a narrow therapeutic range in terms of maternal morbidity. The exact dose, route and rate of administration are therefore important, as well as a detailed knowledge of their pharmacology.

Central to the mechanism of the contraction of uterine smooth muscle during labour, which is enhanced by the action of oxytocin, is the enzyme myosin light chain kinase (MLCK). Intracellular calcium, the levels of which are controlled by voltage and receptor operated channels and by release from the sarcoplasmic reticulum, is bound to calmodulin and stimulates conversion of MLCK-P to MLCK, which in turn phosphorylates myosin and initiates smooth muscle contraction.2

Oxytocin

The nonapeptide oxytocin was discovered by Sir Henry Dale and was the first polypeptide hormone synthesised, by Du Vigneaud, in 1953. The peptide binds to a G-protein on the surface of the uterine myocyte, resulting in the generation of diacylglycerol (DAG) and inositol tri-phosphate (IP3) via the action of phospholipase C on phosphatidyl-inositol bisphosphate (Fig. 1). DAG stimulates prostaglandin synthesis, and IP3 stimulates the release of calcium from the sarcoplasmic reticulum. Oxytocin also activates COX-2 via a further G-protein interaction, and in so doing stimulates prostaglandin synthesis.2 The concentration of myometrial receptors and myometrial gap junctions increase as gestation advances, increasing sensitivity to oxytocin.3

Oxytocin has numerous physiological effects. Most importantly, it causes contraction, followed by relaxation of the uterus, and at pharmacological doses can cause an increased frequency and incomplete relaxation of uterine musculature. It also has a role in cardiovascular regulation, in sexual and maternal behaviour, and in memory and the regulation of food and drink intake. It is the first choice of uterotonic during CS.

Major maternal adverse effects are cardiovascular (hypotension, myocardial ischaemia and arrhythmias), nausea, vomiting, headache and flushing. Cardiovascular effects are complex. Hypotension is predominantly caused by transient relaxation of vascular smooth muscle cells, probably via calcium-dependent stimulation of the nitric oxide pathway. Oxytocin also causes release of atrial and brain natriuretic peptide.4,5 In animal studies, it may have negative inotropic effects,6 but in human tissue, this effect appears to be restricted to the influence of

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its commercial preservative chlorbutanol on atrial myocytes in vitro. Due to structural similarities with vasopressin, overdose of oxytocin may cause water retention, hyponatraemia, seizures and coma.

Several papers have described the haemodynamic effects of oxytocin in the non-pregnant population and in the pregnant population during CS. Early studies used transthoracic bioimpedance and thermodilution technology. More recently, beat by beat pulse wave form monitors, and additional studies using transthoracic bioimpedance, have provided a clinical picture of peripheral vasodilatation, hypotension, and increased cardiac output mediated by an increase in heart rate and stroke volume. Pulmonary artery pressures are markedly increased and stay so for at least 10 min after a bolus of 10 IU during general anaesthesia. One observational study has demonstrated similar effects of 2.5 IU on the systemic vasculature in patients with severe preeclampsia. These effects are sometimes poorly tolerated when ventricular function is abnormal, and in the presence of mitral or aortic stenosis, or hypovolaemia. A fatality was recorded in the Confidential Enquiry into Maternal Deaths of the United Kingdom in the triennium 1997–1999, when oxytocin 10 IU was administered during the resuscitation of a hypovolaemic patient during spinal anaesthesia for CS. In the most recent Report on Confidential Enquiries into Maternal Deaths in South Africa for the triennium 2005–2007, there were two deaths in which oxytocin was contributory. In one case the cardiovascular effects of a high dose compounded those of spinal hypotension. In the other, a poorly resuscitated patient undergoing emergency CS received 10 IU of oxytocin and a fatal cardiac arrest ensued.

In contrast to the effects on the systemic vasculature, oxytocin injected into the circumflex artery has been shown to cause coronary vasoconstriction in anaesthetised dogs. A recent investigation using the technique of vector-cardiography, showed that there were considerable ST segment changes following 10 IU oxytocin during spinal anaesthesia for CS and in volunteers. These changes were more marked than those following intravenous ergometrine 0.2 mg. One study employing Holter monitoring did not demonstrate clinically significant changes or elevations in markers of ischaemia during spinal or general anaesthesia for CS. Another recent Holter investigation demonstrated significantly more frequent ST segment depression in healthy women during elective CS under spinal anaesthesia following a 10 rather than 5 IU bolus of oxytocin. However, a dose of 10 IU is no longer the standard of care. Although the sensitivity and specificity of vector-cardiography and Holter monitoring as used in these studies for the detection of clinically significant myocardial ischaemia is uncertain, the findings cannot be ignored.

How can the cardiovascular effects of oxytocin be obtnuted? A comparison of intravenous boluses of either 2 or 5 IU showed less marked heart rate and blood pressure changes after 2 IU, with no difference in requests for additional uterotonics. The administration of 5 IU of oxytocin by slow infusion has been shown to produce less cardiovascular instability than a bolus of 5 IU. The efficacy of slow infusions in terms of uterine contraction is difficult to assess other than by objective means, but probably suffices in most cases. In an observational study, oxytocin was used in incremental doses of 0.1–0.5 IU during CS in parturients with advanced cardiac disease that included cardiomyopathy, congenital and valvular heart disease. There was acceptable haemodynamic stability, although even these small doses were associated with transient changes in blood pressure and cardiac output. Co-administration of phenylephrine with oxytocin has been shown to obtnund the peripheral vascular effects, but there was some overshoot of the effects of phenylephrine, suggesting that administration of phenylephrine immediately before oxytocin may be more effective.

In view of the multiple side effects of oxytocin, it is desirable to administer the lowest possible effective dose in the most stable manner. The dose and rate of intravenous infusion of oxytocin after delivery during CS remain controversial. There have been only three dose-finding studies. The first study in healthy uncomplicated pregnancies at low risk for uterine atony found the ED90 to be 0.35 IU. The up-down sequential method of establishing the median effective dose was used. The second study in low-risk patients compared the effects of 0.5, 1.0, 3, and 5 IU boluses and included a placebo group in whom no oxytocin was administered for 2 min post-delivery. The authors concluded that an
Oxytocin is a hormone that induces uterine contractions during childbirth. Its in vivo half-life is only 10–15 min. In 73% of cases in the placebo group, no oxytocin was required 2 min post-delivery. Finally, in a case series of women with arrested labour, the ED90 was found to be 3.0 IU.

There is little definitive evidence for the optimal rate of infusion following the initial bolus or slow intravenous administration of oxytocin. An early investigation showed that when compared with vasopressin, oxytocin is much less active as an antidiuretic when the infusion rate is less than 45 milliunits/min. This suggests that, optimally, the rate of infusion for prophylaxis of PPH should be restricted to a lower infusion rate than this, particularly in patients with preeclampsia, who are at higher risk of pulmonary oedema. However, a recent investigation employing continuous infusion alone of oxytocin after delivery during elective CS, showed that the ED90 of oxytocin infusions is 0.29 IU/min (95% CI 0.15–0.43). Further work is required to establish optimal infusion rates of oxytocin to maintain uterine tone after the initial dose. In patients in whom uterine atony is perceived to be the cause of PPH, the Royal College of Obstetricians and Gynaecologists (RCOG) recommend a rapid infusion oxytocin 40 IU/500 mL crystalloid at 125 mL/h, until haemorrhage is controlled.

Great care should be exercised in the hypovolaemic patient, when effective resuscitation and vasopressor therapy should accompany oxytocin administration. In keeping with the mechanism of action of oxytocin, involving G-protein receptor interactions, the phenomenon of receptor desensitisation may influence the effectiveness of the dose given by the anaesthetist at delivery. A recent publication in which a second dose of oxytocin was administered in the same patient, suggested that the cardiovascular response to a second dose was diminished. This could be explained by receptor down-regulation. More definitive laboratory work has shown that there is loss of oxytocin receptors during oxytocin-induced and oxytocin-augmented labour. The concentration of oxytocin receptors decreased more than 3-fold, and oxytocin receptor mRNA concentrations decreased 60-fold and 300-fold during oxytocin-augmented and oxytocin-induced labour respectively. Prior exposure of rat myometrium to oxytocin suggests that efficacy falls as concentration increases, and this is independent of time. By contrast, the tonic effects of ergometrine and prostaglandin F2α do not appear to be affected by the phenomenon of receptor desensitisation in rat myometrial strips. In view of the fact that repeated doses of oxytocin may become increasingly ineffective, second line uterotonic agents are still required.

**Carbetocin**

The in vivo half-life of oxytocin is only 10–15 min. The newly developed synthetic analogue of oxytocin, carbetocin (1-desamino-1-monocarboxy-[2-O-methyltyrosine]-oxytocin), has a half-life 4–10 times the duration of oxytocin. A tetanic uterine contraction is produced 2 min after an intravenous injection of 8–30 μg or intramuscular injection of 10–70 μg, which persists for approximately 11 min. Rhythmic uterine contractions persist for 60 and 120 min after intravenous and intramuscular injection respectively. There remains no clear-cut dosage recommendation; a suggested dose of 100 μg intramuscularly is based on a randomised trial of carbetocin versus oxytocin during CS, and an ascending dose tolerance study in only 45 healthy parturients undergoing vaginal delivery, which found a maximum tolerated dose of 200 μg.

A recent review assessing comparative efficacy of carbetocin and conventional uterotonic agents, included vaginal and caesarean deliveries. A statistically significant reduction in the need for therapeutic uterotonic drugs was found in patients undergoing CS who received carbetocin rather than oxytocin at delivery. The side effect profile of carbetocin is similar to that of oxytocin. Preeclampsia remains a contraindication to its use, for reasons which are unclear. The issue of receptor desensitisation is as yet unstudied, and further work on the efficacy of carbetocin is awaited.

**Ergot alkaloids**

Ergot, derived from the fungus *Claviceps purpurea*, was the first effective oxytocic drug. Since 600 BC the fungus has been known as “the noxious pustule in the ear of grain”, owing to epidemics of ergotism, characterised by either central nervous complications or peripheral gangrene. These agents were used in obstetrics from 1582 to 1822, when the view on their role changed from “pulvis ad partum” (the powder of birth), to “pulvis ad mortem” (the powder of death), due to the associated tetricic uterine contractions, leading to fetal asphyxia, stillbirth and uterine rupture.

Ergometrine is a naturally occurring alkaloid, first isolated in 1932 by Dudley and Moir. Currently this agent, although appropriately banned from intrapartum use, remains the second line intervention in the absence of contraindications, if uterine atony persists after oxytocin administration during caesarean delivery. Ergometrine maleate or methylergometrine cause a rapid and sustained contraction of the pregnant and non-pregnant uterus. The half-life of ergometrine is 120 min. Little is known about the mechanism of action, which may be via a calcium channel, or an α-receptor in the inner myometrial layer. Ergometrine is also a partial agonist at α-adrenergic, 5HT-1, and dopamine receptors. Although ergometrine and methylergometrine have the least vasoconstrictor effects of all the ergot alkaloids, the use of ergometrine has been associated with a mean arterial pressure increase of 11% after intravenous injection of
0.2 mg, and pulmonary wedge and pulmonary artery pressures increase by 30%. There are also reported cases of renal and coronary artery spasm, and there are eight reported cases of myocardial infarction associated with their use. In several of these cases the use of ergot alkaloids was inappropriate. One patient had familial hypercholesterolaemia and ergometrine precipitated a requirement for stenting of the left anterior descending coronary artery. In another case a fatal myocardial infarction followed the administration of ergometrine to a hypertensive patient with preeclampsia.

Despite these rare complications, ergot alkaloids still have an important role as a second-line agent at CS when administered with due care, but are contraindicated in preeclampsia. The RCOG guideline recommends an intravenous injection of 0.5 mg slowly for the management of uterine atony, while the World Health Organisation (WHO) stipulates 0.2 mg intravenously or intramuscularly, to be repeated as necessary every 15 min to a maximum of 1 mg. The high incidence of nausea and vomiting after the recommended 0.5 mg dose has discouraged its use as a first-line agent at CS. There are no published dose response curves for its use during CS, and it may be that doses smaller than those currently recommended work well enough, as in the case of oxytocin. One early publication described a dose-response curve during the first 4 days postpartum, employing a strain gauge tocograph positioned upon the abdomen. This study, employing 15, 30 and 60 μg intravenous boluses of ergometrine, showed dose-related increases in uterine contraction.

**Syntometrine**

Syntometrine is a combination preparation, seldom used during CS, containing 5 IU oxytocin and 0.5 mg ergometrine. Following intramuscular administration, the time to onset of the uterine response is considerably shorter than after ergometrine alone, and the duration of action is several hours.

**Prostaglandins**

Like oxytocin, prostaglandins increase intramyometrial calcium concentrations and enhance uterine contraction. Their effects are mediated via G-proteins and the activation of calcium channels. Side effects after pharmacological administration include fever, diarrhoea, nausea and vomiting.

The use of intramyometrial prostaglandin F2α (dinoprost) for atonic PPH was first described by Takagi in 1976. Subsequently, 15-methyl prostaglandin F2α (carboprost) was shown to have an extended half-life, fewer gastrointestinal and vasopressor side effects, and good uterotonic activity. Since 15-methyl prostaglandin F2α may be associated with bronchospasm, ventilation–perfusion mismatch and hypoxaemia, it is best used not as a first-line agent and not as prophylaxis. There is very limited experience with intravenous administration. Infusion at 100 μg/min during early pregnancy has been shown to cause systemic and pulmonary hypertension, and administration via the intravenous route is contraindicated. By contrast, prostaglandin E2 is associated with a marked decrease in systemic vascular resistance and hypotension. The recommended dose is 250 μg intramuscularly, repeated every 15 min to a maximum of eight doses. Carboprost 500 μg may be administered intramyometrically, but this remains the responsibility of the clinician.

Prostaglandin E1 (misoprostol) is a cheap and widely available oxytocin, which has been little studied during CS. It is less effective than oxytocin and ergometrine, but has a role as a first line agent where the former are unavailable, and is under extensive investigation as a second-line agent (www.misoprostol.org). The sublingual route is probably the most reliable, since misoprostol is a methyl ester and undergoes first pass elimination. Misoprostol is frequently used off-label via the sublingual or rectal route for the management of uterine atony. Studies of its use during CS are few. One concluded that buccal misoprostol may reduce the need for additional uterotonic agents at CS. In a further small randomised comparison, oral misoprostol was concluded to be as effective as intravenous oxytocin in reducing intra-operative blood loss during elective CS under regional anesthesia. Importantly, 600 μg misoprostol via the vaginal route in the midtrimester did not alter maternal haemodynamics as assessed by trans-thoracic bioimpedance measurements. The known benefits and risks (in particular maternal hyperpyrexia) of various doses and routes of administration of misoprostol in the prevention and treatment of PPH following vaginal and caesarean delivery, are summarised in excellent recent reviews and guidelines. Following vaginal delivery and prophylactic oxytocin, sublingual misoprostol 800 μg has been found to be clinically equivalent to the rapid intravenous administration of a high dose of oxytocin (40 IU) in the management of PPH. There was a higher incidence of shivering and fever in the misoprostol group. A recent editorial highlighted the dose dependent nature of side effects, and cautions that the administration of a therapeutic dose of misoprostol after an initial prophylactic dose may be harmful. A recent systematic review reports 11 maternal deaths during five trials. Eight of these women received 600 μg or more of misoprostol and three were controls. Further research will elucidate whether a dose of 400 μg is safer than 600 μg as prophylaxis, and whether doses as high as 800 μg are required for treatment of PPH. Unlike most other uterotonics misoprostol does not need to be kept refrigerated to maintain its pharmacological activity.
Nausea and vomiting

Nausea and vomiting can make caesarean delivery under spinal anaesthesia unpleasant. Contributing factors have been well summarised in a recent review, and uterotonic drugs are frequently the cause. The incidence of nausea has been reported as 29%, and vomiting 9% after a bolus of 5 IU of oxytocin, and 10% after 250 μg of intramyometrial 15-methyl prostaglandin F2α during elective caesarean delivery under spinal anaesthesia. A high incidence of 46% of nausea or vomiting has been reported after 0.5 mg intravenous ergometrine. A recent Cochrane review of the obstetric literature suggested that for the prevention of PPH >1000 mL, syntometrine had a similar efficacy to oxytocin, but was associated with a 5-fold increase in nausea, vomiting and hypertensio.

Recommendations

Uterotonic drugs remain an important intervention in the prevention of uterine atony. In addition, these agents are essential adjuncts to aggressive resuscitation and surgical management of PPH during CS. Current evidence is that oxytocin remains the uterotonic of first choice. There are few definitive studies upon which to base a protocol for recommendations for dosing of oxytocin and second-line uterotonics. Recommendations vary considerably from country to country. The following is a reasonable protocol, based upon current evidence:

Prophylaxis against uterine atony

In healthy parturients at low risk for uterine atony, an infusion of oxytocin of no more than 3 IU over 3–5 min, or a bolus dose of up to 3 IU intravenously over 30 s in combination with phenylephrine, is recommended. This dose of oxytocin may be repeated after 3-5 min should the initial response be inadequate. Optimal subsequent infusion rates require further investigation. Carbetocin requires further investigation; current evidence suggests an intravenous or intramuscular dose of 100 μg. In patients with preeclampsia, the slow administration of up to 3 IU oxytocin is a reasonable first-line intervention, followed by infusion at the lowest required rate, to avoid fluid retention. Administration of oxytocin in advanced cardiac disease requires further investigation. Slow infusion of small doses would seem prudent, with special care in patients with pulmonary hypertension.

Management of established uterine atony

The anaesthetist should at all times base the risk-assessment of uterine atony upon the clinical presentation before CS, and plan pharmacological interventions appropriately. In uncomplicated cases of labour arrest, at least 3 IU of oxytocin are required. During established PPH, the infusion of oxytocin 40 IU/500 mL at 125 mL/h has been recommended, accompanied by effective resuscitation and the co-administration of second-line agents as described. Extreme care is required in the use of oxytocin in haemodynamically unstable patients.

In view of down-regulation of oxytocin receptors following prior exposure to oxytocin, there should be a low threshold for the use of uterotonic agents with a different mechanism of action, such as ergometrine, and prostaglandins F2α and E1, in cases of established uterine atony. Intravenous ergometrine 0.2–0.5 mg given slowly or by intramuscular injection, in the absence of contraindications, is the currently recommended second-line therapy, but many practitioners use doses as low as 0.05 mg intravenously at CS, and a dose response curve would be useful. Many clinicians use 15-methyl prostaglandin F2α, 250–500 μg intramyometrially, but this agent is not licensed for administration via this route. Current guidelines stipulate that 250 μg should be given intramuscularly, repeated every 15 min to a maximum of eight doses, as the last resort. In preeclampsia, the best second-line agent is misoprostol, since ergot alkaloids are contraindicated, and prostaglandin F2α may be hazardous. The optimal dose and route of administration of misoprostol for the prophylaxis and management of PPH, remain to be established.

Ongoing anaesthesia and obstetric audits and research into these drugs with their narrow therapeutic range, should improve the anaesthetist’s ability to limit obstetric haemorrhage during caesarean section, while at the same time reducing unpleasant or dangerous maternal side effects.

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References

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