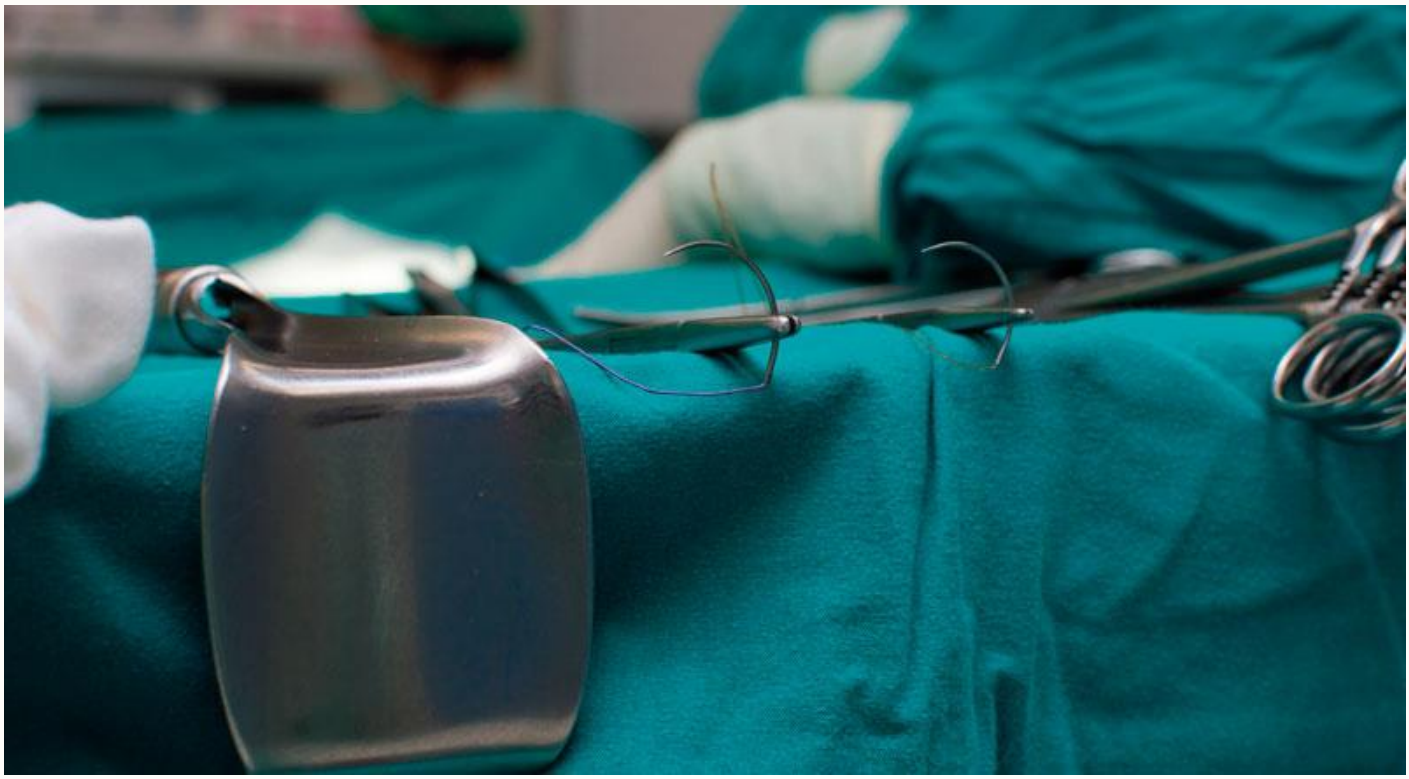
Carbetocin in the Prevention of Postpartum Haemorrhage: An Asian Perspective

Shilla Mariah Yussof, MB BCh BAO (Hons) (Dublin);Horng Yen Wee, MB BCh BAO (Dublin), BA (Dublin), FAMS (Singapore), MRCOG (UK)

01 Oct 2013



INTRODUCTION

Postpartum haemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality. While the rate of PPH varies widely among different countries, it accounts for approximately 30% of maternal deaths in Asia.[1] The prevalence of PPH in South-eastern Asia was estimated to be 4.88%, the highest within Asia, which has an average PPH rate of 2.55%.[2]

The main cause of PPH is uterine atony. Active management of the third stage of labour, which consists of early cord clamping, controlled cord traction, and the prophylactic administration of a uterotonic agent, has been widely used worldwide to reduce PPH.

Of these measures, uterotonic agent is the only one supported by extensive evidence.[3]

The World Health Organization currently recommends active management of the third stage of labour with oxytocin to prevent PPH.[4] However, the half-life of this drug is rather short (4–10 minutes), and it has to be administered continuously via intravenous infusion to achieve sustained uterotonic activity.[5–7] Its dose and duration vary widely across institutions.[8–11]

to oxytocin in risk reduction of mild PPH (500–1,000 mL).[12]

However, syntometrine is limited by its gastrointestinal and cardiovascular side effects, which include maternal vomiting, hypertension, and pain requiring analgesia owing to its ergot alkaloid component.[13] The use of ergot alkaloids is also contraindicated in women with pre-existing hypertension, pre-eclampsia, and cardiac conditions, and in those with a history of migraine or Raynaud phenomenon. Ergometrine is also very unstable and has to be kept refrigerated and shielded from light, which limits its use in rural areas.

OBSTETRICS I Peer Reviewed

CARBETOCIN – PHARMACOLOGIC PROPERTIES

Carbetocin is an oxytocin agonist. With pharmacologic properties similar to natural oxytocin, the drug binds to the smooth muscle receptors of the uterus, causing rhythmic contractions and increasing the frequency of contractions as well as uterine tone.[14,15] Administered either intravenously or intramuscularly as a single dose of 100 µg, carbetocin has a half-life of about 40 minutes; 4–10 times longer than that of oxytocin.[16] Contraction of the uterus can be achieved within 2 minutes following injection, persisting for an average of 120 minutes following intramuscular injection and an average of 60 minutes with intravenous injection.[17] The main advantage of carbetocin over oxytocin is its longer duration of action, allowing a single intramuscular injection instead of an intravenous infusion. As such, carbetocin is a promising alternative uterotonic agent for the prevention of PPH.

	Carbetocin (Duratocin)	Oxytocin (Syntocinon)	Oxytocin/ergometrine (Syntometrine)
Active ingredient	Carbetocin 100 µg in 1-mL ampoule	Oxytocin 5 IU or 10 IU in 1-mL ampoule	Oxytocin 5 IU + 0.5 mg ergometrine maleate in 1-mL ampoule
Dosage	IV bolus: 100 µg	IV infusion: 5 IU IM: 5–10 IU	IM: maximum three ampoules within 24 h (interval of 2 h)
Onset of action	Within 2 min	IV: < 1 min IM: 2–4 min	~2.5 min
Duration of action	~1 h	IV: less than IM IM: 30–60 min	~3 h
Adverse reaction	Nausea and vomiting, abdominal pain, hypotension	Headache, hypotension, tachycardia/bradycardia	Nausea and vomiting, hypertension, cardiac arrhythmias

IM = intramuscular; IV = intravenous.

CARBETOCIN IN VAGINAL DELIVERIES

A number of studies have evaluated the efficacy of carbetocin in vaginal deliveries. Asian data from a study by Leung *et al* in Hong Kong compared carbetocin and syntometrine in the management of the third stage of labour in 300 women undergoing vaginal delivery.[18] The authors found that intramuscular carbetocin was as effective as intramuscular syntometrine in preventing primary PPH but was less likely to induce hypertension after delivery.[18]

There was no difference in the drop of haemoglobin concentration within the first 48 hours between the two groups.[18] The incidence of additional oxytocic injections, PPH, and retained placenta were also similar.[18] However, the use of carbetocin was associated with a significantly lower incidence of nausea, vomiting, and hypertension after delivery.[18]

Another study by Ngan *et al* in Macau compared 100 µg carbetocin and a combination of 5 IU of oxytocin and

drop, and a statistically significant reduction in the risk of PPH.[19]

Nirmala *et al* in Malaysia compared the use of carbetocin and syntometrine following vaginal delivery in 120 women with risk factors for PPH.[20]

No significant differences in terms of requirement for additional oxytocic agents, time interval to wellcontracted uterus, blood transfusion requirements, adverse events, or complications were noted.[20]

Carbetocin, however, was associated with a significantly lower mean estimated blood loss.[20] The haemoglobin showed a significantly reduced drop in the carbetocin group compared with that in the syntometrine group.[20]

Su *et al* in Singapore conducted a doubleblind, randomized, controlled trial of 370 women comparing the use of carbetocin and syntometrine for the third stage of labour following vaginal delivery.[21] Carbetocin was shown to be as effective as syntometrine in the prevention of PPH but had fewer adverse events.[21] Women given syntometrine were four times more likely to experience nausea and vomiting compared with those who had carbetocin.

Tremor, sweating, retching, and uterine pain were also more likely in the syntometrine group compared with the carbetocin group.[21]

CARBETOCIN IN CAESAREAN SECTIONS

There are currently no Asian studies evaluating the efficacy and safety of carbetocin in caesarean sections.

Nevertheless, according to a recent Cochrane review, the risk of PPH in caesarean deliveries was similar in women treated with carbetocin and oxytocin (relative risk [RR], 0.91; 95% CI, 0.39–2.15; two trials, 432 women).[22] In addition, compared with the oxytocin group, the need for subsequent additional uterotonics was lower in the carbetocin group (RR, 0.62; 95% CI, 0.44–0.88; four trials, 1,173 women).[22] There was no statistically significant difference in the need for blood transfusion between the carbetocin and syntometrine group.[22] Similar to vaginal deliveries, there was also a reduced need for uterine massage when comparing carbetocin and oxytocin (RR, 0.54; 95% CI, 0.37–0.79; two trials, 739 women).[22]

CARBETOCIN SAFETY AND TOLERABILITY

The recent Cochrane review by Su *et al* also compared the adverse effects of different uterotonic agents.[22] The risk of experiencing headache, chills, abdominal pain, dizziness, tremor, nausea, vomiting, back pain, pruritus, feeling of warmth, metallic taste, flushing, sweating, shortness of breath, and premature ventricular contractions were similar between the carbetocin and oxytocin groups for both vaginal and caesarean deliveries. Although women who underwent vaginal deliveries experienced fewer headaches, nausea, and vomiting when treated with carbetocin compared with oxytocin, the difference was not statistically significant. When compared with syntometrine in vaginal delivery, the risk of nausea (RR, 0.24; 95% CI, 0.15–0.40) and vomiting (RR, 0.21; 95% CI, 0.11–0.39) was significantly lower in the women treated with carbetocin.[22]

vaginal delivery.[22] See Table 1 for a summary of oxytocic drugs currently available.

COST-EFFECTIVENESS OF CARBETOCIN

Many factors, such as cultural differences, government policy, availability of trained medical staff, storage space, and cost-effectiveness, may contribute to differences in the management of PPH and, ultimately, the choice of uterotonic agents. Although there is currently limited data on the costeffectiveness of individual uterotonic agents, one study from Mexico compared the cost-effectiveness of prophylactic carbetocin with oxytocin following caesarean delivery.[23] The authors compared the incidence of uterine atony in patients receiving carbetocin vs oxytocin (8% vs 19%; $P < 0.0001$) and, with additional financial data from the Mexican Institute of Social Security, were able to calculate the mean cost-effectiveness ratio using incremental cost-effectiveness ratio analysis.[23] The mean cost per patient treated was lower for the carbetocin group (US$3,525 vs US$4,054; $P < 0.0001$), suggesting that carbetocin was more cost-effective.[23]

CURRENT USE OF CARBETOCIN

Carbetocin has been approved for use in the prevention of uterine atony after delivery by caesarean section with spinal or epidural anaesthesia in 23 countries, including China, Hong Kong, Malaysia, and Singapore. The Royal College of Obstetricians and Gynaecologists states that carbetocin is as effective as oxytocin infusion for the prevention of PPH in caesarean section and syntometrine in vaginal delivery.[24] However, the drug is currently not recommended for routine use owing to the limited data to support its cost-effectiveness. The Society of Obstetricians and Gynaecologists of Canada recommends the use of carbetocin for the prevention of PPH instead of continuous oxytocin infusion in elective caesarean section and for women delivering vaginally with one risk factor for PPH.[25]

CONCLUSION

Postpartum haemorrhage is one of the most common causes of maternal morbidity and mortality worldwide. Prophylactic administration of a uterotonic agent plays an important role in the prevention of PPH. While there are already numerous effective agents available on the market, each agent has its own advantages and drawbacks. While both oxytocin and ergometrine are effective in preventing PPH, oxytocin is limited by its short duration of action, whereas syntometrine is associated with multiple side effects. Carbetocin is a long-acting oxytocin analogue that combines the safety and tolerability of oxytocin with sustained uterotonic activity. So far, data from several studies, including meta-analyses, have shown that carbetocin is effective and safe in both caesarean and vaginal delivery, with a better side effect profile. These promising findings suggest that carbetocin may be suitable as the drug of choice for primary prevention of PPH.

Further studies on the cost effectiveness of carbetocin, compared with other uterotonic agents, and the use of carbetocin as a therapeutic agent for PPH are useful areas to be explored.

About the Authors

Dr Yussof is Medical Officer in the Department of Obstetrics and Gynaecology at KK Women's and Children's Hospital. Dr Wee is Senior Consultant, and Obstetrician and Gynaecologist at Novena Medical Centre; and Visiting Consultant in the Department of Obstetrics and Gynaecology at KK Women's and Children's Hospital, Singapore.

and the *Journal of Paediatrics, Obstetrics and Gynaecology*. KKH is the largest medical facility in Singapore which provides specialized care for women, babies and children.

REFERENCES

1. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066–1074.

2. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol 2008;22:999–1012.

3. Aflaifel N, Weeks AD. Active management of the third stage of labour. BMJ 2012;345:e4546.

4. World Health Organization. WHO guidelines for the management of postpartum haemorrhage and retained placenta. Available at: http://whqlibdoc.who.int/publications /2009/9789241598514_eng.pdf. Accessed November 23, 2012.

5. Ryden G, Sjoholm I. Half-life of oxytocin in blood of pregnant and non-pregnant women. Acta Endocrinol (Copenh) 1969;61:425–431.

6. Fabian M, Forsling M, Jones J. The clearance and antidiuretic potency of neurohypophysial hormones in man, and their plasma binding and stability. J Physiol 1969;204:653–668.

A complete list of references can be obtained upon request to the editor.

Related MIMS Drugs

DURATOCIN