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ORIGINAL ARTICLE

# Clinical and financial evaluation of carbetocin as postpartum haemorrhage prophylaxis at caesarean section: A retrospective cohort study

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**Background:** The long-acting oxytocic agent; carbetocin, has been consistently shown to reduce the need for additional uterotonics at caesarean section, but not postpartum haemorrhage (PPH). While promising, current evidence is limited by heterogenicity in study design and findings.

**Aims:** To examine whether carbetocin confers clinical or economic benefit compared to oxytocin at caesarean section in an all-risk Australian population.

**Materials and Methods:** A retrospective cohort study was undertaken of all singleton caesarean sections at a public tertiary hospital from 2008 to 2010 (*n* = 2499). From 1 January 2008 to 24 March 2009 all women received prophylactic oxytocin 5–10 units slow push intravenously at delivery, after which all patients received 100 μg intravenous carbetocin. Outcomes were PPH (≥1000 mL) and the requirement of secondary uterotonics. A post hoc cost analysis was also performed.

**Results:** A total of 1467 and 1024 patients received carbetocin and oxytocin, respectively. Incidence of PPH ≥1000 mL was 7.8% for carbetocin compared to and 9.7% for oxytocin (odds ratio (OR) 0.79, 95% CI 0.59–1.05). Moderate blood loss >500 mL was significantly reduced with carbetocin; occurring in 27.3% versus 39.4% (OR 0.57, 95% CI 0.49–0.68). There was a 20.0% reduction in secondary uterotonic treatment with carbetocin (OR 0.42, 95% CI 0.35–0.49). Average drug costs were lower with oxytocin at $4.74 versus $36.42/patient. However, the 1.9% reduction in PPH with carbetocin resulted in a $63.46 reduction in cost per patient, with a cost-effectiveness ratio of $1667 to prevent one case of PPH ≥1000 mL.

**Conclusions:** Carbetocin reduced moderate blood loss >500 mL, but not PPH ≥1000 mL. Carbetocin conferred a 20% reduction in secondary uterotonic treatment, as well as lowering direct medical costs.

KEYWORDS
caesarean section, carbetocin, oxytocin, postpartum haemorrhage, prophylaxis

## INTRODUCTION

Postpartum haemorrhage (PPH) is the leading direct cause of maternal death worldwide, accounting for 27% of maternal deaths,[1] with rates currently increasing in the developed world.[2–4] Uterine atony is the most common cause of PPH, and haemorrhage is significantly reduced by active pharmacological management of PPH with uterotonic agents.[5] The traditional choice of prophylaxis is oxytocin, although in recent years a number of studies have examined carbetocin as an alternative for PPH prophylaxis, particularly at caesarean section (CS). Carbetocin is a long-acting oxytocin receptor agonist, with a half-life of 40 minutes compared to 4–10 minutes for oxytocin.[6] In comparison to oxytocin, carbetocin is also heat- and light-stable; which has clear benefits in a low-resource setting.[7] However, the evidence for carbetocin is heterogenous and insufficient to alter practice widely; to date only the Society for Obstetricians and Gynaecologists of Canada (SOGC) recommend carbetocin as the preferred uterotonic prophylaxis at elective CS.[8]

A 2012 Cochrane review of 11 randomised control trials (RCT) ($n$ = 2635) found patients who received carbetocin had a lower risk of PPH, and a reduction in the need for additional uterotonic therapies or uterine massage.[9] However, only eight trials ($n$ = 820) compared carbetocin to oxytocin, and four ($n$ = 1173) were specific to caesarean section. The authors noted a high risk of bias in this analysis, and were overall reluctant to draw conclusions regarding PPH rates without further high-quality evidence. A more recent meta-analysis of $n$ = 2975 patients consistently demonstrated carbetocin to reduce the need for further uterotonics, but in contrast to Su *et al.* they found no significant difference for reduction of haemoglobin drop, total blood loss, or incidence of PPH.[10] The most recent trial by Razali *et al.* (2016) also echoes these findings.[11]

Despite encouraging evidence to support the use of carbetocin in PPH prophylaxis, particularly at elective CS, there are significant gaps in the research. Van der Nelson *et al.*, (2017) concluded that while there was promising evidence of numerical advantage for carbetocin in reducing rates of PPH, this did not reach statistical significance.[12] Additionally, existing randomised trials are limited by small sample sizes, as well as inconsistency between studies in the dose and mode of administration for the comparative oxytocin arm.[13] There is also no clear consensus on the definition for PPH at caesarean delivery. Of the four major governing bodies, all use slightly different criteria for classifying PPH.[14]Current guidelines for The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) state that blood loss >500 mL be termed 'PPH' and >1000 mL is further subdivided as 'severe PPH', without specifying mode of delivery.[15]

Several studies have also examined the financial aspects of prophylactic uterotonic agents, as carbetocin has a higher index cost compared to oxytocin. With the exception of Higgins *et al.*,[16] multiple small studies have actually demonstrated a cost-benefit in favour of carbetocin, based on reduced need for secondary management of haemorrhage, and observed reduction in time spent in postoperative recovery.[17–19] Subsequent cost extrapolations specific to the UK and Australia using rates observed in the 2012 Cochrane review have also found carbetocin to be, at least, cost neutral compared to oxytocin, if not beneficial when retreatment costs are taken into consideration.[12,17–19] However, it should be noted that the Australian analysis[20] was produced by the Duratocin® manufacturer, Ferring, and needs confirmation by independent assessment.

Overall, despite multiple small RCTs comparing carbetocin to oxytocin use at CS, no single study has included a larger patient population. Pooled data analysis is further limited by the heterogenous nature of these studies, particularly for the comparative oxytocin arms. We undertook a retrospective analysis of all CS ($n$ = 2499) performed at an Australian Level 5 Birthing Unit from 2008 to 2010. Our aim was to identify whether carbetocin confers clinical and/or financial benefit when used as primary PPH prophylaxis at CS. Clinical performance will be assessed by the rate of PPH, blood transfusion, and secondary uterotonic treatment.

## MATERIALS AND METHODS

We conducted a retrospective cohort study at a tertiary public teaching hospital, from 2008 to 2010. Of note, this catchment area services one of the most underprivileged urban regions statewide. Over this time period, the maternity unit averaged 3200 births per annum, of which 25%–30% were caesarean deliveries. All patients with singleton pregnancies undergoing CS during this time period were included, encompassing both elective and emergency clinical indications. Approval for this audit was given by the Director of the Women's and Children's Division at Lyell McEwin Hospital.

Between 1 January 2008 and 31 March 2009 all women undergoing CS received prophylactic oxytocin 5–10 units intravenous (IV) slow push at time of infant delivery. In accordance with a change in the site protocol, all women undergoing CS between 1 April 2009 and 31 December 2010 were treated with 100 μg carbetocin (Duratocin® Ferring) IV.

Data were then collected from operation records and electronic records. Where data were not available via these resources, case notes were reviewed. The primary outcome was PPH (blood loss ≥1000 mL); measured by operating theatre staff at the end of procedure based on suction volumes and number of soaked packs. Analysis was also performed for estimated blood loss >500 mL given current RANZCOG guidelines cite this threshold as 'PPH'. Rates of blood transfusion were also collected via electronic records. Attempts were made to examine postoperative haemoglobin levels as a more objective means of quantifying significant blood loss but this was unable to be performed due to missing data.

Another endpoint was the requirement of secondary uterotonic administration to treat ongoing bleeding and resultant cost effects. As this was an observational study, the administration of

additional uterotonic treatment was at the discretion of the individual surgeon. Drug costs per use for uterotonic agents were obtained through the hospital pharmacy department. Cost per episode of care was assessed according to the Australian Refined Diagnosis Related Groups (ARD-RG) classification system. The ARD-RG divides CS into O01A 'caesarean delivery- minor complexity', O01B 'caesarean delivery- intermediate complexity' and O01B 'caesarean delivery- major complexity'. When performing the cost analysis; we assigned estimated blood loss <1000 mL as 'minor complexity', PPH ≥1000 mL 'intermediate complexity' and PPH ≥1500 mL 'major complexity'. The cost per episode of care assigned to each of these diagnostic codes was obtained from our hospital's coding department.

Data analyses were conducted using Statistical Package for the Social Sciences (SPSS) and InStat statistical software. Multivariate analysis was applied; correcting for age, body mass index (BMI), parity, previous CS, gestational age and birthweight. Chi-square tests were also performed. Variables were considered significant at $P < 0.05$.

## RESULTS

In total, $n = 2499$ patients were identified, of which eight patients were excluded due to incomplete records of uterotonic agents given as PPH prophylaxis. The samples were equally distributed, with 1467 and 1024 patients having received carbetocin and oxytocin, respectively. As demonstrated in Table 1, patient demographics were comparable in each treatment arm, with no significant differences in age, parity, BMI, gestational age at delivery or birthweight. Overall, 59.7% of women were multiparous. The mean BMI was 29, just above the average for Australian women of 27.4.[21] There was also no significant difference between the two arms regarding indication for CS; with an overall proportion of 58.6% emergency CS and 41.4% elective CS.

Average estimated blood loss (EBL) was 503 versus 573 mL for the carbetocin and oxytocin groups, respectively; which was not significant. The incidence of PPH ≥1000 mL was marginally reduced with carbetocin compared to oxytocin; with an incidence of 7.8% and 9.7%, respectively, but this was not significant (odds ratio (OR) 0.79, 95% CI 0.59–1.05). However, a highly significant difference in the incidence of moderate blood loss >500 mL was observed, with lower rates of 27.3% for carbetocin compared to 39.4% in the oxytocin group (OR 0.57, 95% CI 0.49–0.68, $P < 0.0001$). There was no significant difference in blood transfusion rates, occurring in 1.2% versus 1.6% for carbetocin and oxytocin, respectively. Sub-group analysis of elective versus emergency indications for CS did not change these findings, as depicted in Table 2.

There was also a highly significant difference in the need for secondary treatment of PPH between the groups. Secondary treatment was required 20.0% less for carbetocin compared to oxytocin, with rates of 26.9% and 46.9%, respectively (OR 0.42, 95% CI 0.35–0.49). In the oxytocin arm, a 40 IU oxytocin infusion over four hours was by far the most common second-line treatment. In this group, 480 (46.9%) patients received secondary uterotonics, of which the majority received oxytocin infusion (see Table 3). Comparatively, of the patients requiring secondary uterotonics in the carbetocin group, only 132 were given oxytocin infusions. Instead, alternative agents misoprostol and ergometrine were used in 277 and 85 patients, respectively. Overall, the use of carbetocin led to a 79% relative reduction in the requirement for an oxytocin infusion. The average number of secondary agents required was not different between treatment arms. We also performed a post hoc cost analysis examining uterotonic drug costs and cost per episode of care according to the observed rate of PPH. Based on uterotonic drug cost alone, carbetocin was still more expensive despite the reduction in use of secondary agents, with an average uterotonic drug cost of $36.42 AUD compared to $4.74 AUD for oxytocin (see Table 3). However, the average cost/patient was reduced by $63.46 with carbetocin based on ARD-RG (see Table 4). This translates to a cost-effectiveness ratio of $1667 to prevent one case of PPH ≥1000 mL.

## DISCUSSION

In this large cohort study, the findings clearly demonstrate the advantages of carbetocin over standard oxytocin for primary PPH prophylaxis at CS. The use of carbetocin was associated with a highly significant reduction in the rate of moderate blood loss, and importantly a 20.0% absolute decrease in the need for secondary uterotonic treatment for PPH. Despite the non-randomised study design, the large sample size and comparable demographics add substantially to the validity and clinical significance of these results. In keeping with the current literature,[10] there was no significant difference in severe PPH (EBL ≥1000 mL) between treatment arms. However, there was a notable reduction in the incidence of moderate blood loss >500 mL in the carbetocin group. We found no difference in rates of blood transfusion for patients categorised as PPH, which is consistent with previous pooled data analysis.[10]

Additionally, while carbetocin did not demonstrate a reduction in PPH ≥1000 mL, there was a highly significant reduction in requirement for secondary treatment of PPH in the carbetocin arm, with a 20.0% difference between the two groups. Pharmacologically, this relates to the longer half-life of carbetocin. The similar PPH rate likely reflects clinician's appropriate use of a secondary uterotonic in the oxytocin group when ongoing bleeding was observed. This result is supportive of our hypothesis that carbetocin confers clinical benefit at CS.

This reduction in secondary uterotonic administration is highly relevant when considering the financial burden of treatment. This aspect of comparison is currently an area of great interest when assessing the use of carbetocin. Our analysis

**TABLE 1** Comparison of patient demographics

| Characteristic | Carbetocin *N* = 1467 | Oxytocin bolus *N* = 1024 | *P*-value |
|---|---|---|---|
| Maternal age, years | 29.2 ± 5.8 | 29.0 ± 5.9 | 0.835 |
| BMI | 29.2 ± 7.6 | 29.3 ± 7.7 | 0.507 |
| Gravida | | | |
| 1 | 399 (27.2%) | 296(29.0%) | 0.319 |
| >1 | 1068(72.8%) | 724(71.0%) | |
| Parity | | | |
| Primiparous (0) | 578 (39.4%) | 442 (41.4%) | 0.324 |
| Multiparous (>0) | 889(60.6) | 598 (58.6) | |
| Previous CS | | | |
| No | 819 (55.8%) | 591(57.9%) | 0.296 |
| Yes | 648(44.2%) | 429(42.1%) | |
| Method of delivery | | | |
| Elective CS | 629 (42.9%) | 402 (39.4%) | 0.084 |
| Emergency CS | 838 (57.1%) | 618 (60.6%) | |
| Gestational age, weeks | 38.7 ± 1.7 | 38.6 ± 1.8 | 0.407 |
| Birthweight, grams | 3408 ± 601 | 3385 ± 589 | 0.841 |

BMI, body mass index; CS, caesarean section.

**TABLE 2** Comparison of blood loss at caesarean section for patients receiving oxytocin versus carbetocin as PPH prophylaxis

| Outcome | Carbetocin *N* = 1467 | Oxytocin bolus *N* = 1024 | Odds ratio (95% CI) |
|---|---|---|---|
| PPH | | | |
| >500 mL | 401 (27.3%) | 404 (39.4%) | 0.57 (95% CI 0.49–0.68)*** |
| ≥1000 mL | 115 (7.8%) | 99 (9.7%) | 0.79 (95% CI 0.59–1.05) |
| EBL | 503 ± 312 | 573 ± 315 | −70 (95% CI −95 to −45) |
| Secondary uterotonic treatment | | | |
| Secondary uterotonic required | 394 (26.9%) | 480 (46.9%) | 0.42 (95% CI 0.35–0.49)*** |
| Blood transfusion | | | |
| Blood transfusion required | 19 (1.2%) | 17 (1.6%) | 0.78 (95% CI 0.40–1.5) |
| **Elective caesarean sections** | ***N* = 629** | ***N* = 403** | |
| PPH | | | |
| >500 mL | 136 (21.6%) | 134 (33.3%) | OR 0.55 (CI 0.42–0.73)*** |
| ≥1000 mL | 39 (6.2%) | 28 (6.9%) | OR 0.88 (CI 0.54–1.46) |
| Secondary uterotonic treatment | | | |
| Required | 114 (18.1%) | 140 (34.7%) | OR 0.42 (CI 0.31–0.56)*** |
| **Emergency caesarean sections** | ***N* = 838** | ***N* = 621** | |
| PPH | | | |
| >500 mL | 272 (32.5%) | 274 (44.1%) | OR 0.61 (CI 0.49–0.75)*** |
| ≥1000 mL | 80 (9.6%) | 74 (11.9%) | OR 0.78 (CI 0.59–1.1) |
| Secondary treatment | | | |
| Required | 280 (33.4%) | 340 (54.8%) | OR 0.41 (CI 0.34–0.51)*** |

***Highly significant ($P < 0.0001$).
EBL, estimated blood loss; PPH, postpartum haemorrhage.

**TABLE 3** Average uterotonic drug cost for patients receiving oxytocin versus carbetocin

| Outcomes | Cost per dose† | Number of doses administered | Total cost† |
|---|---|---|---|
| Carbetocin | | | |
| Carbetocin | 33.66 | 1467 | 49 379.22 |
| Oxytocin IV bolus | 1.05 | 37 | 155.4 |
| Oxytocin infusion | 4.2 | 132 | 554.4 |
| Ergometrine | 21.49 | 85 | 1826.65 |
| Misoprostol | 1.87 | 277 | 517.99 |
| Prostaglandin F2α | 71.45 | 14 | 1000.3 |
| Average cost/patient | | | $36.42 |
| Oxytocin | | | |
| Oxytocin (primary) | 1.05 | 1024 | 1075.2 |
| Oxytocin IV bolus | 1.05 | 18 | 18.9 |
| Oxytocin Infusion | 4.2 | 430 | 1806 |
| Ergometrine | 21.49 | 35 | 752.15 |
| Misoprostol | 1.87 | 151 | 282.37 |
| Prostaglandin F2α | 71.45 | 13 | 928.85 |
| Average cost/patient | | | $4.74 |

†Australian Dollars (AUD).
IV, intravenous

**TABLE 4** Average cost per episode of care according to ARD-RG diagnostic classification for carbetocin versus oxytocin

| Outcomes | Cost per episode of care† | Number of patients | Total cost† |
|---|---|---|---|
| Carbetocin | | | |
| Caesarean – Minor Complexity | $8286.26 | 1352 | $11 203 023.52 |
| Caesarean – Intermediate Complexity | $10 007.09 | 83 | $830 588.47 |
| Caesarean – Major Complexity | $14 281.91 | 32 | $457 021.12 |
| Average cost/patient | | | $8514.41 |
| Oxytocin | | | |
| Caesarean – Minor Complexity | $8286.26 | 925 | $7 664 790.50 |
| Caesarean – Intermediate Complexity | $10 007.09 | 69 | $690 489.21 |
| Caesarean – Major Complexity | $14 281.91 | 30 | $428 457.30 |
| Average cost/patient | | | $8577.87 |

†Cost in Australian Dollars (AUD).
ARD-RG, Australian Refined Diagnosis Related Groups

showed that carbetocin was associated with a 79% relative reduction in the use of oxytocin infusions for secondary uterotonic treatment. This practical component can reasonably be applied to our own cohort, as greater requirement of secondary treatment inherently translates to further pharmacological and staffing resources associated with maintaining IV oxytocin infusions. A small British audit[19] has also found that patients receiving oxytocin required a longer time in recovery post-operatively compared to carbetocin, which may confer higher treatment cost.

Additionally, we performed a post hoc cost analysis including uterotonic drug cost, and cost per episode of care based on the ARD-RG coding system. By drug cost alone, carbetocin remains more expensive than oxytocin. However, carbetocin conferred a numerical reduction in rates of PPH ≥1000 mL from 9.7% with oxytocin to 7.8% with carbetocin. While this was not a statistically significant reduction, it did confer a $63.46 reduction in average cost per patient. This translated to a cost-effectiveness ratio of $1667 to prevent one case of PPH ≥1000 mL.

## Strengths and Limitations

There is an increasing body of evidence comparing carbetocin with oxytocin for the use of pharmacological PPH prophylaxis. To date,

only small RCTs have directly compared these agents, but none on a larger scale. Additionally, limitations of sample size are compounded by a lack of standardisation in oxytocin dose and administration when assessing pooled results. In this regard, our study is by far the largest cohort to date examining carbetocin efficacy (*n* = 2499).

Therefore, a key strength of this study is the large sample size. There were also no exclusion criteria, and patient demographics were comparable between treatment arms. Hence, despite the non-randomised study design, there was no selection bias applicable in this 'all risk' model.

A key limitation is that estimated blood loss is inherently difficult to standardise,[22] although possibly more precise at CS compared to vaginal birth.[23] Despite the lack of more precise methods for estimating blood loss, the reliability of clinical estimation was surprisingly reassuring according to an RCT analysis comparing four different methods of blood loss estimation after CS. In this study, the authors found no difference in mean EBL between visual estimation and more precise gravimetric and haemoglobin calculation measures.[24] However, it should be noted that this study was based on routine CS uncomplicated by PPH, limiting the extrapolation in this setting.

Not all patients had postoperative haemoglobin measurements available to complement this estimation, therefore the presence of anaemia or haemoglobin drop could not be reported. Additionally, blood transfusion rate may have been underestimated if electronic records incomplete. Other limitations include lack of standardisation in the treatment with secondary uterotonics, which was ultimately an individual clinical decision. Finally, our cost comparison was limited to diagnostic coding and drug cost estimates, and does not account for time spent in recovery, staffing and equipment associated with maintenance of an IV oxytocin infusion.

## CONCLUSION

In this large cohort study, we demonstrated a statistically significant reduction in moderate blood loss >500 mL and an observed 20% reduction in the requirement of further uterotonics with the use of carbetocin compared with oxytocin bolus. While the reduction in PPH ≥1000 mL with carbetocin was not statistically significant, it did confer an absolute cost reduction with carbetocin. More detailed cost comparison could be undertaken in future, taking into consideration other associated staffing and infusion costs.

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