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Original Article

Uterotonics in elective caesarean delivery: a randomised non-inferiority study comparing carbetocin 20 μg and 100 μg

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Summary

Postpartum haemorrhage is the leading cause of maternal mortality worldwide and prophylactic uterotonic drug administration after the delivery of the infant is advised. Carbetocin is recommended as an uterotonic, but the minimum effective dose has not been verified. We compared the efficacy of two doses of intravenous carbetocin (20 μg and 100 μg) in women undergoing elective caesarean delivery. This was a randomised, double-blind, non-inferiority study in women at low risk of postpartum haemorrhage. Carbetocin was administered on delivery of the anterior shoulder of the neonate. Uterine tone was assessed by the obstetrician 2 min and 5 min after carbetocin administration according to an 11-point numerical rating scale (0 = atonic uterus and 10 = firm uterus). The primary outcome was uterine tone 2 min after carbetocin administration. The pre-specified non-inferiority margin was 1 point on the 11-point scale. Secondary outcomes included: uterine tone at 5 min; use of additional uterotonics within 24 h; blood loss; and adverse effects. Data were available for 53 women in the carbetocin-20 group and for 55 women in the carbetocin-100 group. The mean (SD) uterine tone at 2 min was 7.5 (1.9) in the carbetocin-20 group and 8.0 (1.5) in the carbetocin-100 group. The lower limit of the one-sided 95%CI for the mean difference was outside the non-inferiority margin (at −1.1; p = 0.11) meaning non-inferiority of carbetocin 20 μg compared with carbetocin 100 μg could not be confirmed. However, the secondary outcome measures of uterine tone at 5 min, blood loss and use of additional uterotonics were similar in both groups.

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Introduction

Approximately 14 million women around the world suffer from postpartum haemorrhage (PPH) every year and this is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths worldwide [1]. Furthermore, a review of data from the Discharge Abstract Database of the Canadian Institute of Health Information between 2002/2003 and 2010/2011 attributed 1.6 deaths per 100,000 deliveries to PPH [2]. Accordingly, the World Health Organization recommends active management of the third stage of labour, even in women at low risk of PPH. Prophylactic uterotonic drug administration after the delivery of the infant is the main intervention of active management of

the third stage, and has been demonstrated to reduce the incidence of PPH by up to 40% [3].

Oxytocin and carbetocin are common uterotonic drugs used in the active management of the third stage of labour in many countries. Carbetocin is a synthetic oxytocin analogue that binds to oxytocin receptors in the myometrium with similar affinity to oxytocin. The duration of action of carbetocin is four to seven times that of oxytocin due to an increased biological half-life in plasma and at the uterine oxytocin receptors. The onset of action of carbetocin is 2 min after intravenous (i.v.) or intramuscular (i.m.) administration. Despite its longer duration of action, carbetocin is less potent than oxytocin, which may be due to structural molecular differences [4–8].

The 2009 guidelines from the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommended a single 100 μg i.v. bolus dose of carbetocin over 1 min (in lieu of an oxytocin infusion) as the uterotonic agent of choice to prevent PPH after elective caesarean delivery (level 1B evidence) [3]. The justification for 100 μg carbetocin as the effective dose was based on the manufacturer's recommendation and some clinical trials [9–12].

More recently, studies conducted at our institution have attempted to determine the minimum effective dose of carbetocin in order to limit its adverse effects: Cordovani et al. showed no difference in the efficacy of doses ranging from 80 to 120 μg [13]; Anandakrishnan et al. showed no difference in the efficacy of doses ranging from 20 to 100 μg [14]; and Khan et al. demonstrated the effective dose 90% (ED90) of carbetocin to be 14.8 μg [15]. Although it is evident from these studies that doses as low as 15 μg may be effective at elective caesarean delivery, a larger trial comparing the minimum effective dose with the standard 100 μg dose is warranted to confirm these findings.

The purpose of this study was to compare the intensity of uterine tone produced by 20 μg carbetocin and 100 μg carbetocin in women at low risk of PPH undergoing elective caesarean delivery under spinal anaesthesia. We hypothesised that a carbetocin dose of 20 μg would provide uterine tone that was not inferior to a 100 μg dose 2 min after administration.

Methods

Following approval by a research ethics board, this prospective randomised, double-blind, non-inferiority study was conducted from October 2014 to April 2015 at Mount Sinai Hospital, Toronto, Canada. Written informed consent was obtained from all subjects included in the study.

All women judged to be at low risk for PPH undergoing elective caesarean delivery under spinal anaesthesia were considered for inclusion in the study. We did not study patients meeting the following criteria: refusal to give written informed consent; allergy or hypersensitivity to carbetocin or oxytocin; and conditions predisposing to PPH (placenta previa; multiple gestation; pre-eclampsia; eclampsia; macrosomia; polyhydramnios; uterine fibroids; previous history of uterine PPH; bleeding diathesis; and hepatic, renal and/or vascular disease).

Baseline arterial blood pressure and heart rate were obtained in the pre-operative holding area using an automated non-invasive device; three readings were taken at least 1 min apart with the average reading considered the baseline value. On arrival in the operating room, routine monitoring was applied. Immediately preceding spinal anaesthesia, lactated Ringer's solution (10 $ml.kg^{-1}$) was administered via an 18-gauge i.v. cannula. Spinal anaesthesia was performed in the sitting position using a 27-gauge Whitacre needle and a combination of hyperbaric bupivacaine 13.5 mg, fentanyl 10 μg and morphine 100 μg was injected into the intrathecal space over 30 s. The patient was then positioned supine with left uterine displacement using a wedge under the right buttock. After the initial fluid loading dose, minimal additional i.v. fluids were administered. Blood pressure and heart rate were recorded at 1-min intervals until the achievement of adequate uterine tone after delivery and every 5 min thereafter. Systolic arterial blood pressure was targeted to be maintained within 10% of baseline using i.v. phenylephrine 0.1 mg boluses. Any phenylephrine used postdelivery was recorded as a secondary measure of haemodynamic compromise.

Patients were randomly allocated to receive i.v. 20 μg (carbetocin-20 group) or 100 μg (carbetocin-100 group) carbetocin (Ferring Pharmaceutical, Toronto, Canada). Computer-generated randomisation was done in blocks of 10. Group assignment and dilution instructions were kept in sealed, opaque envelopes. Carbetocin was diluted in 10 ml saline and given i.v. over 1 min immediately upon delivery of the anterior shoulder of the baby. The solution was prepared by an anaesthetist or research assistant not involved in patient care. The patient, anaesthetist and obstetrician were blinded to the carbetocin dose. The obstetricians were instructed to perform uterine massage and to allow assisted spontaneous delivery of the placenta rather than active manual extraction. Furthermore, they were asked to keep the uterus inside the abdominal cavity until the placenta was delivered by cord traction. However, the decision to exteriorise the uterus for repair after the

delivery of the placenta was at the discretion of the obstetrician.

The obstetricians were asked to assess the uterine tone at 2 min and 5 min following the completion of the administration of carbetocin. The uterine tone was graded according to an 11-point verbal numerical rating scale (NRS) [16]: if the obstetrician could not depress the uterus with a finger, or if it could only be slightly depressed but it sprung back, the uterus was considered firm (satisfactory tone or 10 score); a uterus that was soft and easily depressible was considered boggy (unsatisfactory tone or 0 score). If the uterine tone was unsatisfactory and at the obstetrician's request, the institutional routine for uterotonic use in caesarean delivery was immediately initiated. This constituted oxytocin 0.5 IU as a bolus followed by infusion (40 milliunits.min^{-1} oxytocin). Additional oxytocin and other uterotonics (e.g. ergometrine, carboprost or misoprostol) were administered if required to optimise uterine tone.

During surgery, any patient complaints of nausea, vomiting, headache, shortness of breath, chest discomfort and palpitations were recorded and treated. As an adjunct to postoperative analgesia, patients received ketorolac 30 mg i.v and paracetamol 1300 mg per rectum at the end of the surgery. Patients were observed for 2 h in the recovery area for bleeding, need for additional uterotonics and the occurrence of adverse effects. Haemoglobin and haematocrit values were recorded before surgery and 48 h after delivery. Administration of any other uterotonic agents in the first 24 h postpartum was recorded.

The primary outcome was uterine tone, as evaluated by the obstetrician using the NRS, 2 min after the completion of carbetocin injection. Secondary outcomes were: uterine tone 5 min after completion of carbetocin injection; use of additional uterotonics administered up to 24 h postpartum; uterine exteriorisation and massage; and estimated blood loss (EBL). Estimated blood loss was calculated by the difference in haematocrit values assessed before and at 48 h after delivery according to the following formula [17]:

$$\text{EBL} = \text{EBV} \times [(\text{pre-operative Hct} - \text{postoperative Hct})/\text{pre-operative Hct}]$$

where EBL = estimated blood loss (ml); EBV = estimated blood volume (ml) based on patient's weight in kg × 85; and Hct = haematocrit.

The following adverse effects were also recorded: hypotension (systolic blood pressure < 20% of baseline despite the prophylactic use of phenylephrine); hypertension (systolic blood pressure > 20% of baseline); bradycardia (heart rate < 30% of baseline); tachycardia (heart rate > 30% of baseline); nausea (reported by patient); vomiting; chest pain; shortness of breath; headache; and flushing.

Sample size was calculated for non-inferiority analysis using a two-sample t-test, with a non-inferiority margin of 1 point on the 11-point scale in mean uterine tone NRS for the difference between groups. The assumed between subject standard deviation was 2 points. To demonstrate non-inferiority of the 20 μg carbetocin dose, 51 patients per group were required (one-sided alpha 0.05, power 80%). To account for potential protocol violations and losses to follow-up, we aimed to recruit 110 patients.

The pre-specified analyses for the NRS of uterine tone at 2 min (primary outcome) and 5 min (secondary outcome) compared the difference in mean scores in the groups (carbetocin-20 group − carbetocin-100 group) to the non-inferiority margin of −1.0, using a one-sided t-test. The results are reported as mean difference and lower one-sided 95%CI, along with a one-sided p value. Other outcomes were compared using two-sided testing of the hypothesis that means, rates or proportions were the same in the two groups and are presented with two-sided CIs. Student's t-test was used for comparing estimated blood loss and Wilcoxon rank sum test for comparing postpartum phenylephrine doses. Chi-squared tests were used to compare proportions using other uterotonics unless expected cell counts were small, when Fisher's exact test was used. Adverse effects were compared using logistic regression using pre-treatment occurrence of the adverse effect as a covariate. To ensure that the NRS score was able to identify important differences in uterine tone, we compared the NRS scores between women who did and did not require additional uterotonics. Statistical analysis was performed using R 3.4 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Two-hundred and six patients were approached to participate in the study, with 110 patients recruited. In two patients, macrosomia (an exclusion criterion) was part of the indication of the caesarean delivery; however, this information was overlooked at recruitment and these patients were not analysed. Data analyses were completed for 108 patients; 53 in the carbetocin-20 group and 55 in the carbetocin-100 group (Fig. 1). Baseline characteristics of patients in the two groups are shown in Table 1.

The NRS rating of uterine tone 2 min after carbetocin administration was similar in the carbetocin-20 and carbetocin-100 groups (mean (SD) 7.5 (1.9) vs. 8.0 (1.5), respectively). The lower 95%CI for the difference in mean

score was −1.1, which was outside the non-inferiority margin of −1; therefore, we could not reject inferiority of the carbetocin 20 μg dose (p = 0.11) (Table 2). The secondary outcome measure of uterine tone 5 min after carbetocin administration was also similar in the carbetocin-20 and carbetocin-100 groups (mean (SD) 7.9 (1.4) vs. 8.3 (1.4), respectively). Here, however, the lower limit of the 95%CI was − 0.8, which indicated non-inferiority of the carbetocin 20 μg dose at 5 min (p = 0.009) (Table 2).

Nine patients needed additional uterotonics in the operating theatre in the carbetocin-20 group compared with seven patients in the carbetocin-100 group (p = 0.73) (Table 2). All of these patients received additional oxytocin. One patient in the carbetocin-100 group received ergometrine and misoprostol, and one patient in each group received carboprost. Blood loss was similar in both groups (Table 2).

Lower uterine tone NRS score was related to the need for additional uterotonics in both groups. In the carbetocin-20 group at 2 min, mean (SD) uterine tone was 5.8 (2.1) in the patients that needed additional uterotonics vs. 7.8 (1.7) in those that did not (p = 0.004). At 5 min, mean (SD) uterine tone in the carbetocin-20 group was 6.6 (1.4) in the patients that needed additional uterotonics vs. 8.2 (1.2) in those who did not (p = 0.001). In the carbetocin-100 group, the corresponding mean (SD) uterine tone scores were 6.0 (2.5) vs. 8.3 (1.1) at 2 min (p = 0.049) and 5.4 (1.5) vs. 8.7 (0.8) at 5 min (p = 0.001). The frequency distribution of NRS scores in women requiring and not requiring additional uterotonics at 2 min and 5 min are shown in Fig. 2a and b,

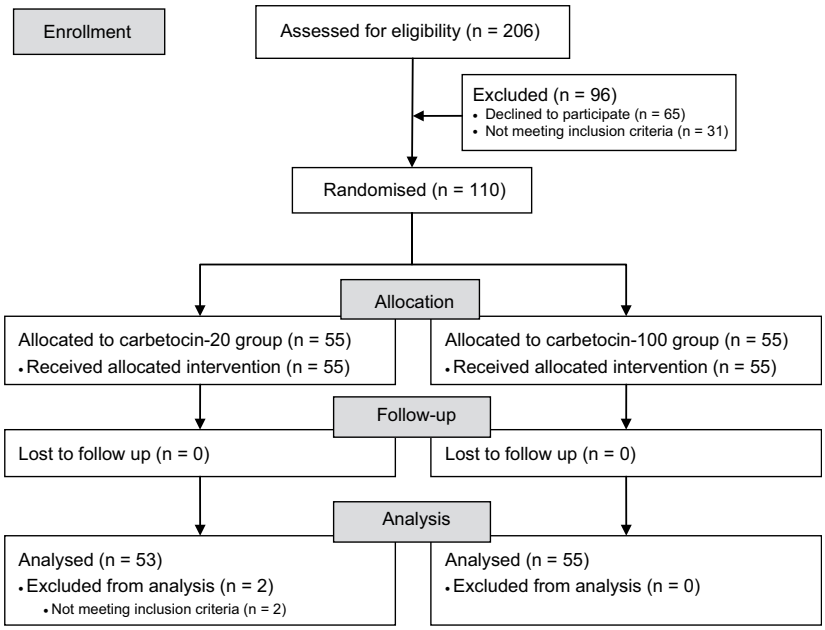

Figure 1 CONSORT flow diagram.

Table 1 Characteristics of patients receiving carbetocin 20 μg (carbetocin-20 group) or carbetocin 100 μg (carbetocin-100 group) as a uterotonic during elective caesarean delivery. Values are mean (SD) or number.

	Carbetocin-20 group n = 53	**Carbetocin-100 group n = 55**
Age; years	34 (3.9)	35 (3.4)
Height; cm	161 (9.0)	162 (7.0)
Weight; kg	78 (17.0)	78 (13.0)
BMI; $kg.m^{-2}$	30 (6.7)	30 (4.2)
Gestational age; weeks	39 (0.6)	39 (0.5)
Repeat caesarean delivery	38	43

BMI, body mass index.

Table 2 Intra-operative uterine tone, additional uterotonic usage and blood loss in patients receiving carbetocin 20 μg (carbetocin-20 group) or carbetocin 100 μg (carbetocin-100 group) as a uterotonic during elective caesarean delivery. Values are mean (SD) or number.

	Carbetocin-20 group n = 53	Carbetocin-100 group n = 55	p value[a]
Uterine tone at 2 min assessed by NRS	7.5 (1.9)	8.0 (1.5)	0.109
Uterine tone at 5 min assessed by NRS	7.9 (1.4)	8.3 (1.4)	0.009
Uterine exteriorisation	38	32	0.200
Uterine massage	39	43	0.740
Additional uterotonic(s)			
In the operating theatre	9	7	0.730
In the first 24 h postoperatively	3	0	0.110
Time to request of additional uterotonic(s); min			
In the operating theatre	7.7 (4.9)	8.0 (2.6)	0.870
In the first 24 h postoperatively	175.3 (101.0)	–	–
Blood loss; ml	890 (531)	805 (430)	0.380

NRS, numerical rating scale.
[a]Non-inferiority outcomes compare the difference in mean uterine tone in the two groups to the non-inferiority margin of −1 using a one-sided test. Other outcomes tested use two-sided tests.

respectively. In all except two cases, additional uterotonics were administered after the 5-min assessment; both these patients were in the carbetocin-20 group and received additional uterotonics at 3 min and 4 min.

The incidence of adverse effects was similar between the two groups with the exception of tachycardia, which was higher in the carbetocin-20 group (Table 3). The incidence of hypotension in the carbetocin-20 and carbetocin-100 groups was 45% and 35%, respectively (OR (95%CI) 1.4 (0.6–3.2); p = 0.40). Median (IQR [range]) dose of phenylephrine post-delivery was similar in both the carbetocin-20 and carbetocin-100 groups (0.1 (0.0–0.2) [0.0–20.0] mg vs. 0.2 (0.0–0.4) [0.0–3.0] mg, respectively; p = 0.10).

Discussion

We were unable to establish non-inferiority of carbetocin 20 μg compared with carbetocin 100 μg at 2 min after its administration, when judged against a non-inferiority margin of 1 point on an 11-point NRS for intensity of uterine tone. At 5 min after carbetocin administration, the intensity of uterine tone induced by carbetocin 20 μg was not inferior to that induced by carbetocin 100 μg; however, this was not the primary outcome measure of the study. Both carbetocin doses were associated with similar requirement for additional uterotonics and blood loss.

The initial recommendation for carbetocin 100 μg as a bolus dose has been derived from rat uterine studies showing that carbetocin possesses one-tenth the activity of oxytocin [8, 9]. This led Hunter et al. [6] to assume that carbetocin 100 μg would produce the same contraction as 10 μg (equivalent to 5 IU) oxytocin. However, animal data may not be readily transferable to humans, particularly in the case of carbetocin, as it has been suggested that the human myometrium is much more sensitive to carbetocin than the rat myometrium [6, 7]. Furthermore, carbetocin exerts its uterotonic effects by binding with oxytocin receptors [18], which have been shown to increase in concentration progressively throughout pregnancy [19, 20]. We postulate that an increased sensitivity of the pregnant uterus leads to effective uterine contraction even with small doses.

The rationale behind our current study was based on three previous dose-finding studies conducted at our institution. The first randomised double-blind study by Cordovani et al. suggested that the effective dose for carbetocin was lower than that currently recommended [13]. This study involved 80 patients allocated to groups that received carbetocin doses of 80 μg, 90 μg, 100 μg, 110 μg and 120 μg. An overall 87.5% success rate for achieving adequate uterine tone was seen across all groups. In addition, the incidence of hypotension was similar for all doses (approximately 55%). This study, however, could not establish the minimum effective dose 90% (ED90) given that a similar incidence of adequate uterine tone was observed in all groups. Moreover, due to the high incidence of hypotension in all groups, it became necessary to conduct a study that included lower doses. As such, Anandakrishnan et al. reported a second study in women undergoing elective caesarean delivery [14]. A total

of 120 women were randomly allocated to groups receiving carbetocin doses of 20 μg, 40 μg, 60 μg, 80 μg and 100 μg. There was no difference in uterine tone among all dose groups and there still appeared to be an unacceptably high incidence of hypotension. Finally, Khan et al. reported a third study of 40 women undergoing elective caesarean delivery who received i.v carbetocin upon delivery of the fetus in an up–down sequential allocation manner using a biased coin study design [15]. A starting dose of 10 μg was used with subsequent 5-μg increments/decrements. The ED90 for carbetocin to produce adequate uterine tone with no requirement of additional intra-operative uterotonics was found to be 14.8 μg (95%CI 13.7–15.8).

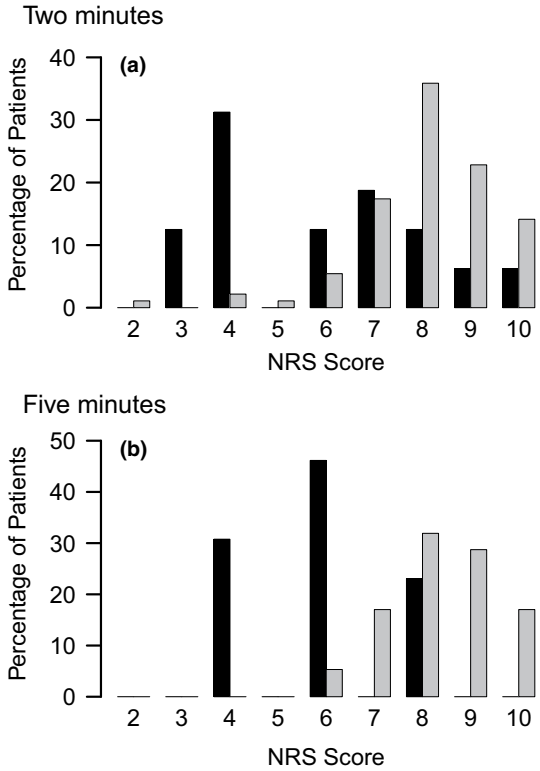

Figure 2 (a) Frequency distribution of the numeric rating scale score of the intensity of uterine contraction at 2 min within those requiring (black) and those not requiring (grey) additional uterotonics at 2 min or later; (b) Frequency distribution of the numeric rating scale score of the degree of uterine contraction at 5 min within those requiring (black) and those not requiring (grey) additional uterotonics at 5 min or later.

The findings of our three previous dose-finding studies were not surprising, as our group and other investigators had previously described similar findings for oxytocin. Carvalho et al. determined the ED90 of oxytocin for elective caesarean delivery to be 0.35 IU (95%CI 0.18–0.52) [21], almost 10 times lower than the routinely recommended 5 IU bolus dose. Butwick et al., in a study aimed at determining the lowest effective bolus dose of oxytocin to produce adequate uterine tone during elective caesarean section, confirmed these results, and concluded that the routine use of 5 IU oxytocin should no longer be recommended, as adequate tone could be achieved with lower doses of oxytocin (0.5–3 IU) [16].

The results of our current study differ somewhat from the findings of our previous studies [14, 15]. However, it is important to highlight that all our previous studies used a different primary outcome. The primary end-point in our current study was the intensity of the uterine tone evaluated by the obstetrician 2 min after completion of carbetocin injection. This differs from our previous studies where the primary outcome was either a binary end-point of satisfactory/unsatisfactory uterine tone or the need for additional uterotonic drugs [13, 14]. In the current study, we used an 11-point NRS for uterine tone assessment. This is a limitation of our study as the NRS is not an independent measure and has potential for inter-individual variation. We

Table 3 Incidence of adverse effects in patients receiving carbetocin 20 μg (carbetocin-20 group) or carbetocin 100 μg (carbetocin-100 group) as a uterotonic during elective caesarean delivery. Values are number and are compared using logistic regression controlling for pre-delivery occurrence of the same adverse effect.

	Carbetocin-20 group (n = 53)	**Carbetocin-100 group (n = 55)**	**OR (95%CI)**	**p value**
Hypotension	24	19	1.4 (0.6–3.2)	0.40
Tachycardia	16	7	2.7 (1.0–7.9)	0.05
Nausea	12	8	1.7 (0.6–4.7)	0.32
Flushing	5	7	0.7 (0.2–2.4)	0.58
Hypertension	4	2	1.6 (0.2–12.7)	0.65
Vomiting	1	4	0.2 (0.0–1.7)	0.21
Headache	1	1	1.0 (0.0–26.7)	0.98
Bradycardia	1	4	0.3 (0.0–1.8)	0.23

believe that our NRS score may be a more specific tool for assessing the intensity of the uterine tone (compared with the satisfactory/unsatisfactory grading) and that it may be sensitive enough to guide the request for additional uterotonic usage by the obstetricians. However, further studies to validate this scoring system are warranted.

The incidence of adverse effects after carbetocin administration was similar in both groups, with the exception of the incidence of tachycardia, which was higher in the carbetocin-20 group; we cannot explain this finding. It was interesting to find that the incidence of hypotension and vasopressor usage was also similar in both groups, in keeping with previous studies. This suggests that even the lower doses of carbetocin we used may still induce significant haemodynamic effects. However, our study was not powered to test for differences in adverse effects between groups. Further strategies such as the slow administration of carbetocin may be useful to reduce the incidence of hypotension.

In summary, we were unable to show that our primary outcome measure of the intensity of the uterine tone induced at elective caesarean delivery by carbetocin 20 μg was non-inferior to that induced by carbetocin 100 μg when the tone was assessed 2 min after administration. However, all other outcome measures such as the intensity of uterine tone at 5 min, the requirement for additional uterotonics and blood loss, were similar for both doses. Further studies are warranted to clarify the clinical implications of these findings.

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