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Carbetocin compared to oxytocin in emergency cesarean section: a randomized trial☆,☆☆

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ABSTRACT

Objective: To evaluate the uterotonic effect of carbetocin compared with oxytocin in emergency cesarean delivery.

Study design: Participants were randomized to intravenous bolus injection of 100 mcg carbetocin or 10 IU oxytocin after cesarean delivery of the baby. The primary outcome is any additional uterotonic which may be administered by the blinded provider for perceived inadequate uterine tone with or without hemorrhage in the first 24 hours after delivery. Secondary outcomes include operating time, perioperative blood loss, change in hemoglobin and hematocrit levels, blood transfusion and reoperation for postpartum hemorrhage.

Results: Additional uterotonic rates were 107/276 (38.8%) vs. 155/271 (57.2%) [RR 0.68 95% CI 0.57–0.81 $p < 0.001$; NNT_b 6 95% CI 3.8–9.8], mean operating time 45.9 ± 16.0 vs. 44.5 ± 13.1 minutes $p = 0.26$, mean blood loss 458 ± 258 vs. 446 ± 281 ml $p = 0.6$, severe postpartum hemorrhage (≥1000 ml) rates 15/276 (5.4%) vs. 10/271 (3.7%) $p = 0.33$ and blood transfusion rates 6/276 (2.2%) vs. 10/271 (3.7%); $p = 0.30$ for carbetocin and oxytocin arms respectively. There was only one case of re-operation (oxytocin arm). In the cases that needed additional uterotonic 98% (257/262) was started intraoperatively and in 89% (234/262) the only additional uterotonic administered was an oxytocin infusion over 6 hours.

Conclusion: Fewer women in the carbetocin arm needed additional uterotonics but perioperative blood loss, severe postpartum hemorrhage, blood transfusion and operating time were not different.

Introduction

Postpartum hemorrhage (PPH) is a leading cause of maternal mortality worldwide; in Asia and Africa more than 30% of maternal deaths are attributed to PPH [1]. A USA report states that PPH increased 26% between 1994 and 2006 from 2.3% to 2.9%, primarily due to an increase in uterine atony from 1.6% to 2.4% [2]. Severe PPH (>1500 ml) is higher (3.2% vs. 1.9%) in emergency than in planned cesarean section [3]. UK NHS Maternity Statistics 2012–2013 reveal a cesarean rate of 25.5% of which 58% are emergencies [4]. Emergency cesarean deliveries are thus a common scenario that may allow for the confluence of uterine atony and hemorrhage to increase risk of severe maternal morbidity.

According to a 2013 Cochrane review, prophylactic oxytocin can prevent PPH and an intravenous bolus dose of 10 IU is recommended as part of active management of third stage of labor [5]. WHO PPH prevention guideline recommends the use of 10 units oxytocin (intramuscular or intravenous) for the prevention of PPH in all births [6]. A 2012 Cochrane meta-analysis concludes that in cesarean section, prophylactic carbetocin compared to oxytocin resulted in less need for therapeutic uterotonics but not incidence of PPH [7].

Oxytocin has a half-life of 4–10 minutes. Continuous intravenous infusion is often required to maintain postpartum uterine tone [8]. Carbetocin, a synthetic analog of oxytocin has a half-life of 40 minutes but one tenth oxytocin's potency [9].

We hypothesize that in emergency cesarean section during labor, carbetocin is superior to oxytocin leading to a reduction in additional uterotonics and PPH.

☆ The study was conducted in the Department of Obstetrics and Gynaecology, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

☆☆ *Trial Registration*: The trial is registered with ISRCTN trial registry as ISRCTN18976822 (www.controlled-trials.com/isrctn).

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Materials and methods

This was a double-blind, randomized single center study, conducted from December 2008 to September 2012 in a university hospital which has approximately 5000 deliveries per year and a cesarean delivery rate of about 30%. The study was approved by the University of Malaya Medical Center Medical Ethics Committee (reference number 687.18: 17 September 2008). The trial is registered as ISRCTN18976822.

The inclusion criteria were age ≥18 years, singleton pregnancy, term gestation and decision made for a cesarean section in labor. We excluded women with known coagulopathy, study drug hypersensitivity, cardiac disease (including dysrhythmia), hypertension, liver, renal or endocrine disease (except gestational diabetes), uterine fibroids or suspicion of placental pathology (accreta, previa or abruptio), cases performed under general anesthesia or where a transverse lower segment uterine incision was not used. We define an emergency cesarean section as an unplanned procedure performed after the start of labor and labor as regular contractions at least every 10 minutes and cervical dilatation ≥3 cm.

The trial's patient information sheet was distributed to women admitted for labor to our delivery suite. Written consent was taken after the decision for emergency cesarean delivery.

Sample size calculation

The primary outcome is the requirement for additional uterotonic in the 24 hours after cesarean delivery. In a 1999 trial report that compared carbetocin to oxytocin in elective cesarean delivery, additional uterotonic was required in 4.7% vs. 10.1% respectively [10]. For our higher risk emergency cesarean section cases, we assumed a doubling in the additional uterotonic rates to 9.4% and 20.2%. Taking alpha of 0.05, 90% power, 1 to 1 recruitment ratio and applying the Fisher Exact test, 243 subjects were required in each arm. We increased the recruitment target by 20% to cater for post-randomization drop-outs then rounded up the target recruitment to 300 in each arm.

The randomization sequence was generated by computer in a 1:1 ratio, blocks of 4, and no stratification (by co-author IL). Numbered opaque packets containing the allocated study drug were also prepared by IL who was not involved in trial recruitment. The packets contained either carbetocin 100 mcg (1 ml clear solution in a glass ampoule) or oxytocin 10 IU (1 ml clear solution in a glass ampoule). The original drug ampoules had their labeling covered with an opaque white sticker to sustain blinding to both surgeon and anesthesiologist. The numbered packets were kept in the operating theater and assigned in sequence to participants.

One ml of the allocated drug was administered as a bolus intravenous injection by the anesthesiologist after delivery of the baby. In our unit, the placenta at cesarean section is removed by cord traction. The provider assessed uterine tone and bleeding intra-operatively and had full discretion on whether additional uterotonic is needed and its mode of administration, dose and duration. This is a subjective decision, based on the surgeon's clinical assessment of uterine tone and blood loss as noted in the operative field. In our setting, the rescue uterotonic regimen for uterine atony is an oxytocin (40–80 IU in 500 ml isotonic crystalloid solution) intravenous infusion over 6 hours.

The participants' blood pressure and pulse rate were recorded at 0, 5, 10, 20, 30 and 60 minutes after study drug injection. After skin closure, the provider with the anesthesiologist estimated the operative blood loss by summing up aspirated losses, surgical field spillage and uptake in surgical gauzes. The duration of surgery (skin incised to completed skin closure) was recorded. Standard post cesarean section monitoring was instituted in the recovery area and ward. An intravenous normal saline infusion at a typical rate of 500 ml every 4 hours was routinely maintained post operatively until full oral intake is established. We recorded the need and indication for additional uterotonic in the 24 hours after cesarean section, further surgery for PPH and blood transfusion before hospital discharge. Hemoglobin and hematocrit levels were routinely assessed before and the day after cesarean section.

Data were entered into SPSS 22 (SPSS Inc., Chicago, IL). Independent sample *T*-test was applied to compare mean values. Pearson Chi square test was used for analysis of categorical variables; Fisher's exact test is used when a cell size is less than 5. Repeated measures analysis of variance analysis was applied to compare the series of blood pressure and pulse readings. All tests were 2-sided. Significance level was set at $P < 0.05$.

Results

600 women were enrolled as planned: 300 women each were randomized to carbetocin and oxytocin. 53 women (24 in carbetocin arm and 29 in oxytocin arm) were excluded as the allocated drug was not used; the reasons for omission were as listed in Fig. 1. 38 ampoules were not given by the anesthetist

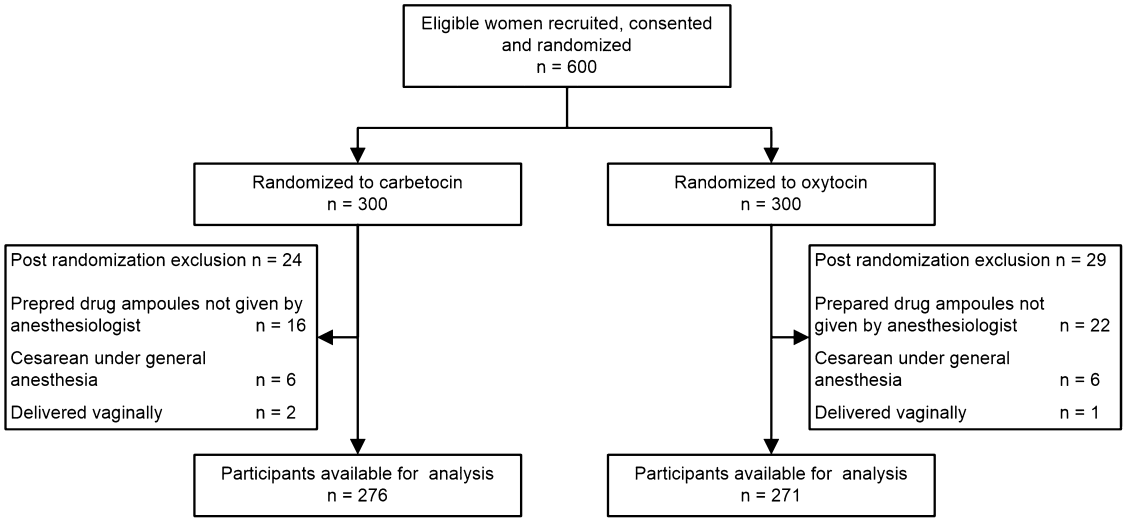

Fig. 1. Recruitment flow chart for a randomized trial of intravenous bolus carbetocin compared to intravenous bolus oxytocin in emergency cesarean section.

Table 1
Demographic with other baseline data according to study groups.

	Carbetocin (n = 276)	Oxytocin (n = 271)
Age (years)	29.5 (4.60)	29.7 (4.30)
BMI (kg/m^2)	29.2 (4.30)	29.3 (5.00)
Parity, median (range)	0 (0–4)	0 (0–5)
Previous cesarean section (%)	26 (9.4%)	33 (12.2%)
No previous cesarean section (%)	250 (90.6%)	238 (87.8%)
Risk factors for PPH (%)	143 (51.8%)	132 (48.7%)
Labor induction/augmentation	120 (43.5%)	117 (43.2%)
Prolonged labor	7 (2.5%)	3 (1.1%)
Grand multiparity	6 (0.9%)	2 (0.7%)
Fetal macrosomia	2 (0.7%)	5 (1.8%)
Others	8 (2.9%)	5 (1.8%)
Indications for cesarean section (%)		
Non reassuring fetal status	136 (49.5%)	131 (48.2%)
Failure to progress in labor	97 (35.2%)	92 (33.9%)
Malpresentation	16 (5.9%)	18 (6.7%)
Prolonged second stage	7 (2.3%)	8 (2.7%)
Others	20 (7.3%)	22 (8.5%)

Data expressed as mean ± standard deviation, median [interquartile range] or number (%).
NS: not significant.

(16 in the carbetocin arm and 22 in the oxytocin arm) for reasons such as the drug was not passed to them or not given by them in the hastiness of the situation. 547 participants (276 in the carbetocin arm and 271 in the oxytocin arm) were available for analysis. The characteristics of the participants in both the trial arms were similar (Table 1).

On the primary outcome of additional uterotonic, the rates were 107/276 (38.8%) vs. 155/271 (57.2%) [RR 0.68; 95% CI 0.57–0.81; $P < 0.001$; NNT_b 6; 95% CI 3.8–9.8] for carbetocin and oxytocin arms respectively (Table 2).

Overall, 98% (257/262) of the additional uterotonics were given in the intraoperative period [98% vs. 98%. P = 1.00]. Two women in the oxytocin group needed additional uterotonic agent immediately after skin closure and another while in the recovery area; two women from the carbetocin group needed their additional uterotonic in the postnatal ward within 24 hours of their cesarean section.

In 89% (234/262) of participants who were administered additional uterotonics, only a standard 40–80 IU oxytocin infusion over 6 hours was needed. Third line uterotonics [which includes carboprost (intramuscular or intramyometrial), gameprost (rectal)] rates were 5.8% (16/276) vs. 4.4% (12/271) RR 1.3 95% CI 0.63–2.71 P = 0.47 (carbetocin vs. oxytocin). Post hoc, considering only participants who required a rescue uterotonic, interestingly a larger proportion of the carbetocin exposed participants needed a third uterotonic [15.0% (16/107) vs. 7.7% (12/155) RR 1.9 95% CI 0.95–3.92 P = 0.06]. Third line agents were usually given to recalcitrant cases of uterine atony.

The mean ± standard deviation blood loss were 458 ± 258 vs. 446 ± 281 ml P = 0.6, PPH (>500 ml) 39% (107/276) vs. 36% (97/271) P = 0.47 [RR 1.1 95% CI 0.9–1.3], severe PPH (>1000 ml) 5.4% (15/276) vs. 3.7% (10/271) [RR 1.5 95% CI 0.7–3.2 P = 0.33], blood transfusion 2.2% (6/276) vs. 3.7% (10/271) [RR 0.6 95% CI 0.2–1.6 P = 0.30] and mean operating times (minutes) 45.9 ± 16.0 vs. 44.5 ± 13.1 P = 0.26 for carbetocin and oxytocin arms respectively; all these outcomes were not significantly different.

One woman in the oxytocin arm had a hysterectomy due to massive PPH secondary to uterine atony with blood loss of 2500 ml. One woman who received carbetocin had a self-limited intraoperative episode of ventricular tachycardia which lasted for

Table 2
Trial outcomes and reported adverse outcome according to randomization to Carbetocin or Oxytocin.

	Carbetocin n = 276	Oxytocin n = 271	P value	RR (95% confidence interval)	NNTb[a] (95% CI)
Primary outcome					
Additional uterotonic	107 (38.8)	155 (57.2)	$P < 0.001$	0.68 (0.57–0.81)	6 (3.8–9.8)
Secondary outcome					
Type of additional uterotonics					
Oxytocin infusion only	91 (33.0)	143 (52.8)	$P < 0.001$	0.6 (0.51–0.76)	
Other uterotonics[b]	16 (5.8)	12 (4.4)	P = 0.47	1.3 (0.63–2.71)	
Timing of additional uterotonics					
Intraoperatively	105 (98.1)	152 (98.1)	P = 1.0		
After skin closure	0 (0.0)	2 (1.3)			
In recovery room	0 (0.0)	1 (0.6)			
In postnatal ward	2 (1.9)	0 (0.0)			
Estimated blood loss (ml)					
Mean (SD)	458 (258)	446 (281)	P = 0.6		
Blood loss ≥500 ml	107 (39)	12 (36)	P = 0.47	1.1 (0.9–1.3)	
Blood loss ≥1000 ml	15 (5.4)	10 (3.7)	P = 0.33	1.5 (0.7–3.2)	
Total operating time (min)					
Mean (SD)	45.9 (16)	44.5 (13)	P = 0.26		
Hemoglobin (g/dL)					
Mean fall (SD)	1.2 (0.98)	1.3 (1.07)	P = 0.18		
Hematocrit					
Mean Fall (SD)	0.03 (0.03)	0.03 (0.02)	P = 0.61		
Adverse outcome					
Blood transfusion	6 (2.2)	10 (3.7)	P = 0.30	0.6 (0.22–1.6)	
Additional surgical intervention	0 (0.0)	1 (0.4)			
Cardiac arrhythmias	1 (0.4)	0 (0.0)			

Data expressed as mean ± standard deviation, median [interquartile range] or number (%).
[a] Number need to treat to benefit with carbetocin compared with oxytocin.
[b] Includes carboprost (intramuscular or intramyometrial), gameprost (rectal).

Table 3
Systolic, diastolic blood pressure and pulse rate changes over time following study drug administration.

		Time (min)					
		0	5	10	20	30	60
Carbetocin	Systolic BP	112.4 (15.1)	111.2 (15.7)	109.7 (14.8)	110.42 (14.9)	109.7 (16.3)	114.1 (17.0)
	Diastolic BP	66.0 (13.6)	63.23 (12.4)	62.4 (12.3)	61.9 (11.9)	62.7 (12.2)	65.8 (11.5)
	Pulse	92.1 (16.7)	92.8 (15.8)	92.4 (16.8)	91.6 (16.3)	90.2 (17.2)	85.3 (17.7)
Oxytocin	Systolic BP	116.0 (16.6)	113.9 (16.6)	113.1 (16.5)	111.3 (14.7)	112.3 (15.5)	113.7 (16.5)
	Diastolic BP	67.2 (13.4)	64.4 (12.3)	63.7 (12.4)	63.0 (12.0)	64.2 (11.4)	66.8 (12.4)
	Pulse	94.2 (17.1)	92.5 (18.5)	91.9 (18.1)	92.2 (16.8)	90.0 (16.3)	88.0 (40.30)

Data expressed as mean ± standard deviation.

less than one minute. Hypotension was noted 30 minutes after carbetocin and intravenous ephedrine was given as part of the management to correct her hypotension. This participant had an uneventful post cesarean recovery.

Participants' mean ± standard deviation blood pressure and pulse at 0, 5, 10, 20, 30 and 60 minutes are shown in Table 3. Systolic blood pressure over time was marginally lower in the carbetocin arm but the difference was statistically significant $P = 0.03$ (after repeated measures analysis of the variance). The diastolic blood pressure and pulse rate over time between the two arms were not different.

Comments

We performed a PubMed search via http://www.ncbi.nlm.nih.gov/pubmed on September 7, 2014, using the search words "carbetocin randomized trial" without any search limit. The search returned 21 articles, none of which concerned a carbetocin trial exclusively for emergency cesarean delivery. There was one trial that recruited a mix of elective and emergency cesarean section cases [11].

We found a reduction in the need for additional uterotonic to maintain uterine tone in the carbetocin arm compared to oxytocin [NNT_B 6 95% CI 3.8–9.8]. In 89% of those administered an additional uterotonic only a 40–80 IU oxytocin infusion over 6 hours was given and in 98% the oxytocin infusion was started intraoperatively. Interestingly, mean blood loss, incidence of PPH (>500 ml) and severe PPH (>1000 ml), the need for third line uterotonics and the operating time (see Table 2) were all marginally (non-significant) higher in the carbetocin arm. Our operating theater is well-staffed, the oxytocin infusion is typically "piggy-backed" onto the existing intravenous infusion line, postoperatively close nursing surveillance is standard and the postoperative maintenance fluid infusion is rarely stopped at just 6 hours after an emergency cesarean section. Hence in our setting a six hour oxytocin infusion started in the operating theater probably entailed minimal incremental staff cost or inconvenience to the woman. In our current context, a 100 mcg carbetocin ampoule costs RM70 (exchange rate 1 euro = RM4.2) whereas a 10 IU oxytocin ampoule costs RM1. Routine carbetocin in emergency cesarean section is likely to cost more in our setting.

Our data specific to women who underwent emergency cesarean delivery in labor is consistent with the 2012 Cochrane meta-analysis finding that "for women who undergo Cesarean section, carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotonics compared to oxytocin, but there is no difference in the incidence of postpartum haemorrhage" [7]. Our data support the WHO (2012) PPH prevention guideline assertion that "the use of carbetocin is considerably more expensive than oxytocin" in cesarean delivery [6].

Since the 2012 Cochrane review on carbetocin [7], a couple of trials have similarly report that carbetocin prophylaxis (vs. oxytocin) at cesarean section do not reduce PPH [12,13]. A recent large scale (2069 women enrolled) double blinded trial that compared intravenous bolus 5 IU oxytocin with intravenous bolus 5 IU oxytocin plus 40 IU oxytocin infusion over 4 hours concluded that "the addition of an oxytocin infusion after cesarean delivery reduces the need for additional uterotonic agents but does not affect the overall occurrence of major obstetric haemorrhage" [14]. These data continue to support the first line use of intravenous bolus oxytocin for PPH prophylaxis at cesarean delivery.

A 2014 abstract of a large trial of 1210 women with at least one risk factor for PPH reports that comparing 100 mcg carbetocin as an intravenous bolus to oxytocin 20 IU as a 6-hour infusion, PPH (>500 ml), need for additional uterotonic and fluid resuscitation were all reduced in favor of carbetocin but severe PPH (>1000 ml) and blood transfusion rates were similar [15]. The pertinent question is whether this trial compared oxytocic drugs or a high dose bolus regimen of an oxytocic (carbetocin) against a low dose infusion regimen of another oxytocic (oxytocin)? In the first 5 minutes of a 20 IU oxytocin continuous infusion regimen scheduled to run over 6 hours, less than 0.3 IU of oxytocin is administered.

We had a single participant who developed hypotension after carbetocin administration which prompted intravenous ephedrine followed by a short-lived ventricular tachycardia. Our data also demonstrated a clinically small but statistically significant decrease in systolic blood pressure in the hour after study drug administration in the carbetocin arm. Recent studies on the hemodynamic effects of intravenous bolus oxytocics are illuminating. It has been reported that a maximal effect occurred at 30–40 seconds: heart rate increased 18 bpm vs. 14 bpm and systolic blood pressure decreased 27 mmHg vs. 23 mmHg for oxytocin vs. carbetocin respectively. Carbetocin subjects recovered more slowly to baseline [16]. Carbetocin within the dose range of 80–120 mcg at elective cesarean section produced satisfactory uterine tone but a 55% incidence of hypotension [17]. In a follow up study, carbetocin in doses of 20, 40, 60, 80, or 100 mcg intravenously at elective cesarean section produced satisfactory uterine tone and an overall 42.5% incidence of hypotension [18]. In the latest carbetocin dose finding study, the ED90 (dose to produce satisfactory uterine tone at 2 minutes in 90% of women) of carbetocin was 14.8 mcg (95% CI 13.7–15.8) but even at this dose, hypotension occurred in 37.5% [19]. In another study, the mean systolic arterial pressure decrease was 28 mmHg (largest decrease occurred at 80 seconds) after oxytocin and 26 mmHg (largest decrease occurred at 63 seconds) after carbetocin. The differences were nearly undetectable after 2.5 minutes but the effect of carbetocin was significantly larger compared to the placebo arm

[20]. These data consistently show that intravenous boluses of oxytocic agents even at the lowest effective dose impacts on maternal hypotension and tachycardia; the effect is longer lasting with carbetocin.

A 2010 trial report compared intravenous bolus oxytocin (5 IU) vs. carbetocin (100 mcg) in a mixed population of elective and emergency cesarean deliveries shows a 45.5% vs. 33.5% rate for additional oxytocic [11]. Our additional uterotonic rates in emergency cesarean section of 56.8% vs. 38.8% are higher, reflecting a lower threshold to start oxytocin infusion in a higher PPH risk population.

Our trial has strengths and limitations. Our sample size of 600 women is powered to address the primary outcome of additional uterotonics in emergency cesarean section. However, the sample size is not powered to address the PPH rate, blood transfusion requirement or the need for surgical intervention. We believe our blinding of trial interventions to be robust. We did not precisely measure blood loss but pre and post-operative hemoglobin and hematocrit changes were consistent with our estimates. Our findings might not be generalizable to practices where the threshold for the use of an additional uterotonic during emergency cesarean section is higher resulting in delayed intra-operative oxytocin infusion.

Conclusion

Carbetocin compared to oxytocin at emergency cesarean delivery reduces the need for additional uterotonic but did not reduce mean blood loss, drop in hemoglobin or hematocrit levels, postpartum hemorrhage or blood transfusion rates. In our considered view, carbetocin is unlikely to be cost effective in emergency cesarean section.

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Conflict of interest

The authors report no conflict of interest.

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