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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

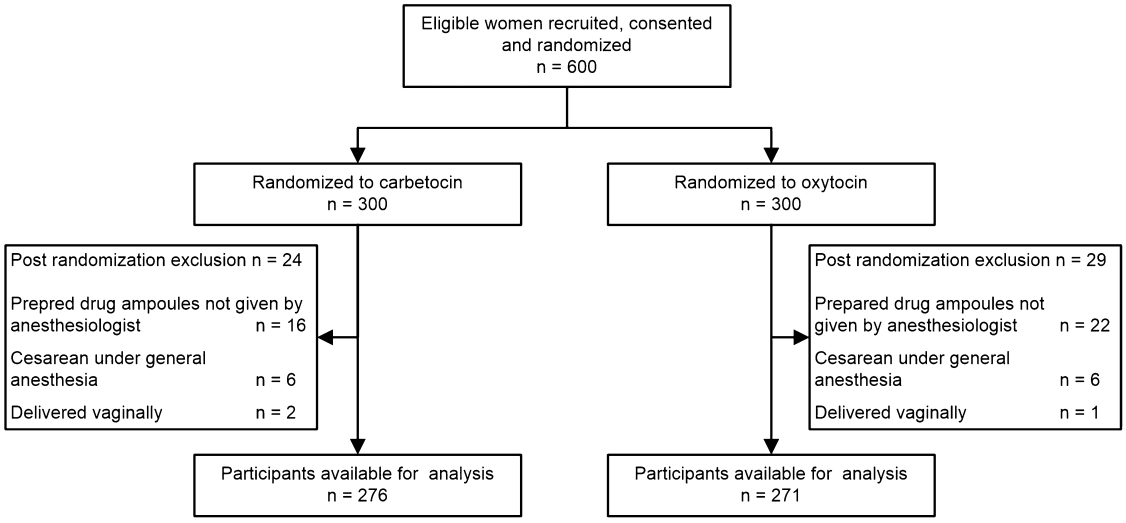

Fig. 1. Recruitment flow chart for a randomized trial of intravenous bolus carbetocin compared to intravenous bolus oxytocin in emergency cesarean section.