Original Article

Prophylaxis Post-Cesarean Hemorrhage Using Carbetocin versus Oxytocin in High-Risk Women: A Double-Blind Randomized Controlled Trial

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Objective: To compare the effectiveness of carbetocin and oxytocin in the prevention of postpartum hemorrhage (PPH) in terms of additional drug use after Cesarean sections in high-risk women.

Materials and Methods: A double-blind randomized controlled trial (1:1 ratio) conducted between October 2018 and April 2019 at Rajavithi Hospital in 120 singleton pregnant women that undergone elective or emergency Cesarean sections after 34 weeks of gestation with viable fetuses and presenting at least one of the high-risk factors for PPH. The participants were randomized to receive either intravenous carbetocin 100 µg (60 cases) or oxytocin 20 IU in 1,000 mL of lactate ringer solution as infusion 120 mL/hour (60 cases) after birth of the baby or delivery of the placenta.

Results: The mean maternal age, BMI, gestational age at delivery, and risk factors for PPH were not significantly different between the carbetocin and the oxytocin group. A previous Cesarean section was the most common risk factor in both groups. Most of the participants in both groups were multiparity. There was a significant difference between the carbetocin and oxytocin groups in terms of additional uterotonic drug usage at 20.0% versus 36.7% (p=0.04), while the type of uterotonic agents and time from post-delivery until the administration additional drugs were not different. The estimated blood loss, rate of PPH, operative time, or adverse drug effect were comparable between the two groups.

Conclusion: The carbetocin group requires less additional uterotonic drugs than the oxytocin group with equal safety profiles. However, its effectiveness in the prevention of PPH is debatable since the incidence of PPH observed was not significantly different. Further studies including the efficacy of the drug in preventing PPH and cost-effectiveness analysis with a larger sample size should be performed.

Keywords: Cesarean section; Carbetocin; Oxytocin; Postpartum hemorrhage

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Postpartum hemorrhage (PPH) is defined as cumulative blood loss equal to or greater than 1,000 mL or an accumulated blood loss within 24 hours after the birth process, including intrapartum loss, regardless of the route of delivery, which causes signs and symptoms of hypovolemia[1]. Recent studies have indicated that PPH causes 30.8% of all maternal deaths in developing countries[2]. The most common causes of PPH are uterine atony, over-distension of the uterus as in polyhydramnios/macrosomia, and multiple uterine fibroids[1,2]. Nowadays, protocols have been developed for improving the outcomes of PPH[3].

Oxytocin, a peptide hormone, and a neuropeptide is the uterotonic drug of choice for the prevention of PPH and offers advantages of abrupt onset, low cost, and wide availability[3]. A short half-life and high risk for water intoxication after prolonged use are its limitations[4]. Therefore, carbetocin, a newer analog of oxytocin, has been generated. It has a longer half-life, lower risk of water intoxication, and high efficacy[5-9]. Experimental studies on high-risk pregnant women that underwent Cesarean sections have reported that carbetocin is more effective than oxytocin in the prevention of PPH in terms of its reduction of the need for additional uterotonic drugs use with minimal side effects[5,6,10,11]. Contrarily, other studies have shown no benefits of carbetocin over oxytocin[12,13].

At Rajavithi Hospital, between 2015 and 2017, the incidence of PPH was annually 8.5%, 5.95%, and 5.25% respectively. To reduce PPH, carbetocin is considered as an alternative uterotonic drug in high-

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risk pregnant women. The aim of the present study was to evaluate the efficacy of single-dose carbetocin intravenous administered intraoperatively compared to 8-hour oxytocin infusion in terms of the need for additional uterotonic drug use, estimated blood loss, and adverse events.

Materials and Methods

The present study was a double-blind randomized controlled trial (1:1 ratio) conducted at Rajavithi Hospital between October 2018 and April 2019. The study was approved by the Ethics Committee Rajavithi Hospital (reference: 61119, 128/2561) and registered on the website Clinical Trials (ID: NCT04089176). Inclusion criteria were singleton pregnant women aged 18 years or older that undergone elective or emergency Cesarean sections after 34 weeks of gestation, presented with at least one of the high-risk factors for PPH including previous PPH, polyhydramnios as AFI greater than 25 cm or DVP greater than 8 cm, fetal macrosomia as EFW greater than 4,000 g, previous Cesarean sections, grand-multiparity or history of giving birth five times or more at GA of 20 weeks or more, intramural myoma, augmentation by oxytocin, chorioamnionitis, prolonged premature rupture of the membrane as rupture of membrane for 18 hours or more, or previous surgery that involved uterine cavity[1,5-8,14,15]. Patients with multiple gestations, placenta previa, placenta adherens, placental abruption, chronic hypertension, preeclampsia, receiving anticoagulants, underlying coagulopathy, heart diseases, or kidney disease were excluded. Additionally, participants with unpredictable exclusion criteria after recruitment or exhibiting anaphylaxis to medications were excluded.

According to the study by Hassan et al[5], 18% of the pregnant women at high risk for PPH that underwent Cesarean sections and received carbetocin exhibited a need for additional uterotonic drugs while 43% of the oxytocin group needed additional uterotonic drugs. Therefore, the average percentage of patients suffering from complications even after being administered both medications was 31%. Resultantly, the participants in the present study were calculated to be 106 women or 53 per group, to detect this difference using 43% versus 18%, with a power of 80% and α=0.05. Considering an approximately 20% drop-out rate per group, the number of participants was increased to 120. Hence, 60 participants in each group were recruited in the present study. Informed consents were obtained from all participants before the study commenced.

The randomization sequence (1:1 ratio; computer-generated number) was generated by the researcher. Participants were randomized to receive either 20 IU of oxytocin (Oxytocin; F.C.P., Chachoengsao, Thailand) or 100 mcg carbetocin (Duratocin; Ferring, Langley, UK). Each ampule of the drug contains 1 mL of either oxytocin or carbetocin according to the randomization order. All boxes and ampules were identically labeled with the study number (1 to 120) being the only differentiating feature between the different drug packs. Because of the non-heat-stable carbetocin used in the present study, both the carbetocin and the oxytocin boxes and ampules were stored in the refrigerator. The random allocation sequence was not known to the investigators until the study was completed and the analysis was initiated. The recruited women were randomized into the study immediately before transferring them to the operating theatre, and the drug pack boxes with labeled numbers were taken to the theatre with the patients.

The study medications were divided into the following two protocols:

- Protocol A/Group A (carbetocin + placebo): Carbetocin 100 microgram + ringer lactate solution (RLS) 10 mL in syringe 20 mL intravenous slowly pushed over 30 to 60 seconds and followed with RLS 1,000 mL plus RLS 4 mL intravenously administered at a rate of 120 mL/hour for 8 hours.
- Protocol B/Group B (oxytocin + placebo): RLS 11 mL in syringe 20 mL intravenous slowly pushed over 30 to 60 seconds and followed with RLS 1,000 mL plus oxytocin 20 IU intravenously administered at a rate of 120 mL/hour for 8 hours.

On admission, the complete personal, maternal, and obstetric history of the enrolled patients were collected. Full general examination was performed with a special focus on vital signs as blood pressure, pulse, and body temperature. Routine laboratory investigations were conducted at the antenatal clinic. Cross matching and packed red cells were prepared. Complete blood count (CBC) with platelet counts was recorded on admission and at 24 hours post Cesarean section. Continuous pulse oximetry was performed, and Foley's catheter was inserted in the operation room. Vital signs were noted at three readings, pre, peri, and post-operative. Indication for Cesarean section was followed by obstetrics indications. The Cesarean section procedure was performed step by step. The anesthesiologist recorded the estimated blood loss. The study medications were administered intravenously by the anesthetist after the birth of

Table 1. Clinical characteristics and risk factors of the two study groups

	Carbetocin (n=60)	Oxytocin (n=60)	p-value
Clinical characteristics			
Age (year); mean±SD	30.83±5.126	29.43±5.469	0.151
BMI (kg/m^2); mean±SD	29.25±5.025	28.54±3.91	0.113
Parity; n (%)			0.03*
• Nulliparous	20 (33.3)	10 (16.7)	
• Multiparous	40 (66.7)	50 (83.3)	
Gestation age at delivery (weeks); mean±SD	38.38±1.27	38.52±1.21	0.058
Nationality; n (%)			0.578
• Thai	44 (73.3)	45 (75.0)	
• Myanmar	10 (16.7)	7 (11.7)	
• Cambodia	4 (6.7)	3 (5.0)	
• Laos	2 (3.3)	3 (5.0)	
• Other (Pakistan, homeless)	0 (0.0)	2 (3.3)	
Risk factors[a]; n (%)			
Previous Cesarean section (elective)	25 (41.7)	31 (51.7)	0.27
Previous Cesarean section (emergency)	13 (21.7)	16 (26.7)	0.52
Previous postpartum hemorrhage	1 (1.7)	0 (0.0)	0.31
Polyhydramnios (AFI >25 cm or DVP >8 cm)	1 (1.7)	1 (1.7)	1.0
Fetal macrosomia (EFW ≥4,000 g)	2 (3.3)	5 (8.3)	0.24
Grand multiparity (history of gave birth ≥5 times at GA ≥20 weeks)	1 (1.7)	0 (0.0)	0.31
Prolonged premature ruptured of membrane (rupture of membrane ≥18 hours)	5 (8.3)	3 (5.0)	0.46
Chorioamnionitis	2 (3.3)	0 (0.0)	0.15
Myoma uteri	1 (1.7)	1 (1.7)	1.0
Induction or augmentation by oxytocin >6 hours	12 (20.0)	6 (10.0)	0.12

SD=standard deviation

* Significance at p-value less than 0.05, [a] 6 participants had 2 risk factors and 1 participant had 3 risk factors

the infant or after the expulsion of the placenta. Uterine contraction and intraoperative bleeding were observed. In cases of poor uterine contraction or continuous uterine bleeding, one or more types of additional uterotonic drugs were administered to prevent further bleeding. Additionally, standard guideline management for PPH was applied in case PPH was encountered. In the case of adverse drug effects such as nausea/vomiting or hypotension, the participants are considered for administering ondansetron or adrenaline.

Estimated blood loss was recorded by the anesthesiologist, who calculated the total blood loss from the blood measuring container and the swabs and gauzes. A 4×4 gauze collected 10 mL blood, a 6×6 swabs collected 50 mL blood, and a 6×12 swabs collected 100 mL blood.

In the case of uterine atony with or without bleeding, additional uterotonic drugs including ergonovine (Methergine®), misoprostol (Cytotec®), and sulprostone (Nalador®) were administered according to the surgeon's consideration.

The primary outcome was the effectiveness of the intervention drugs assessed in terms of the need for additional uterotonic drugs including timing from intervention drugs to additional drug use and the type of additional uterotonic drugs use. Secondary outcomes were estimated blood loss, pre-operative and post-operative hemoglobin count, operative time, postoperative length of stay at hospital, and adverse effects of the test drugs.

Statistical analysis

The data were analyzed by IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Concerning the descriptive statistics range, mean and standard deviation (SD) were used. In inferential statistic, Student t-test and Mann-Whitney U test were used for analyzing quantitative data. The confounder was adjusted by logistic regression analysis. Chi-square or Fisher's exact test was used for analyzing qualitative data and ANCOVA was employed for adjusting the confounder. A p-value of less than 0.05 was considered statistically significant.

Table 2. Additional uterotonic drugs use, estimated blood loss, hemoglobin level, and mode of delivery of the two study groups

	Carbetocin (n=60)	Oxytocin (n=60)	p-value
Additional uterotonic drugs use; n (%)			0.04*
Not use additional uterotonic drugs	48 (80.0)	38 (63.3)	
Use additional uterotonic drugs	12 (20.0)	22 (36.7)	
Time to additional uterotonic drugs use (minute); mean±SD	2.90±8.73	5.15±11.90	0.24
Type of additional uterotonic drugs use; n (%)			0.15
Methyl ergonovine	10 (16.6)	18 (30.0)	
Methyl ergonovine + misoprostol	1 (1.7)	2 (3.3)	
Methyl ergonovine + sulprostone	0 (0.0)	1 (1.7)	
Methyl ergonovine + oxytocin	1 (1.7)	0 (0.0)	
Methyl ergonovine + misoprostol + sulprostone	0 (0.0)	1 (1.7)	
Estimated blood loss; n (%)			0.86
<500 mL	43 (71.7)	39 (65.0)	
500 to 1,000 mL	17 (28.3)	20 (33.3)	
>1,000 mL	0 (0.0)	1 (1.7)	
Mean±SD (mL)	348±141	400±252	0.66
Hemoglobin level (g/dL); mean±SD			
Pre-operative hemoglobin levels	11.8±1.22	11.9±1.15	0.95
Post-operative hemoglobin levels	11.5±1.31	11.7±1.25	0.57
Post-operative hemoglobin change	0.32±1.00	0.22±1.13	0.28
Operative time (minute); mean±SD	69.10±21.56	72.02±26.08	0.50
Mode of delivery; n (%)			0.10
Elective Cesarean section	27 (45.0)	36 (60.0)	
Emergency Cesarean section	33 (55.0)	24 (40.0)	
Operator; n (%)			0.16
Resident 1	4 (6.7)	11 (18.3)	
Resident 2	29 (48.3)	31 (51.7)	
Resident 3	11 (18.3)	7 (11.7)	
Staff	16 (26.7)	11 (18.3)	

SD=standard deviation

* Significance at p-value less than 0.05

Methyl ergonovine (Methergine®), misoprostol (Cytotec®), sulprostone (Nalador®)

Results

All the participants, who were 60 participants in each group, were analyzed. There was no statistical difference in the clinical characteristics and risk factors for PPH between the two groups, except in parity. The mean gestational age at the time of the Cesarean section was 38 weeks in both groups. The average age of the patients was 30 years in the carbetocin group and 29 years in the oxytocin group. The most frequent risk factor was a previous Cesarean section (Table 1).

There were statistically different of additional uterotonic drugs used between the two groups (Table 2). Twelve pregnancies in the carbetocin group required additional uterotonic drugs compared to the 22 women in the oxytocin group as 20.0% versus 36.7% (p=0.04). Methylergonovine was the most frequently used additional uterotonic drug. The duration of the drug administration to additional uterotonic drug use was similar in both groups. No significant difference was observed between the estimated blood loss at 348 mL versus 400 mL (p=0.66) and the change of post-operative hemoglobin levels between the two groups. Almost all the participants in both groups had an estimated blood loss lower than 500 mL. The operative time were similar in both groups. Most of the participating surgeon were second year obstetrics residents and no difference between groups.

Table 3 shows the comparison of the outcomes after adjusting the confounding factors of parity. Additional uterotonic drugs use was still statistically different between the two groups, while there was no significant difference in estimated blood loss.

Table 3. Comparison of outcomes after adjusted confounding factors of parity

Outcomes	Carbetocin (n=60)	Oxytocin (n=60)	Effect size	95% CI	p-value
Additional uterotonic drugs use; n (%)	12 (20.0)	22 (36.7)	Odd ratio 0.42	0.18 to 0.96	0.040*
Estimated blood loss (mL), mean±SD	348±141	400±252	Mean difference –53.13	–127.35 to 21.08	0.159

CI=confidence interval; SD=standard deviation

* Significance at p-value less than 0.05 after adjusted confounding factors of parity

Table 4. Peri-operative and post-operative side effects of the test drugs

	Carbetocin (n=60); n (%)	Oxytocin (n=60); n (%)	p-value
Peri-operative			
No side effect	26 (43.3)	27 (45.0)	0.50
Abdominal pain	0 (0.0)	1 (1.7)	0.31
Nausea/vomiting	36 (60.0)	33 (55.0)	0.58
Hypotension	5 (8.3)	1 (1.7)	0.09
Post-operative			0.31
No side effect	60 (100)	59 (98.3)	
Abdominal pain	0 (0.0)	1 (1.7)	
Nausea/vomiting	0 (0.0)	0 (0.0)	
Hypotension	0 (0.0)	0 (0.0)	

Table 4 shows no difference in the frequency of signs and symptoms peri-operative and post-operative in the two groups. Five participants in the carbetocin group and one participant in the oxytocin group had hypotension or BP of less than 90/60 mmHg. They received intravenous fluid and hypotension improved. A need for blood component transfusion or inotropic drugs was not recorded.

Discussion

Studies have compared the effectiveness of carbetocin and oxytocin in the prevention of PPH in vaginal delivery or Cesarean section in low-risk and high-risk pregnant women[5-14]. Studies demonstrated that carbetocin is more effective than oxytocin in reducing PPH in terms of the need for additional uterotonic drugs. For example, Attilakos et al[6] conducted a double-blind randomized study to compare the effectiveness of carbetocin with oxytocin in low-risk patients following Cesarean section. The study found carbetocin significantly reduced the use of additional uterotonic agent (p=0.023) with similar adverse effects between the two groups. Hassan et al[5] conducted a prospective case-controlled study to compare the effectiveness of carbetocin with oxytocin for the prevention of PPH in high-risk patients following Cesarean section. They observed that the amount of blood loss and the need for additional uterotonic agents is significantly lower in the carbetocin group than in the oxytocin group (p<0.001), while adverse effects were similar between the two groups. Comparable results were found in the studies by Taheripanah et al and Khalafalah as well[10,11]. However, studies show conflicting results. Higgins et al[12] found no clinically significant benefit with the use of carbetocin instead of oxytocin.

In the present study, carbetocin was more effective than oxytocin in terms of reducing the need for additional uterotonic agents in pregnant women at high risk of PPH that undergone either elective or emergency Cesarean section. Participants requiring additional uterotonic drugs was 20% in the carbetocin group compared to 36.7% in the oxytocin group (p=0.04). This outcome might in part be explained by the pharmacological properties of the drugs. Carbetocin selectively binds to oxytocin receptors in the smooth muscle of the uterus resulting in rhythmic uterine contractions, increased frequency of uterine contractions and uterine tone. The onset of uterine contraction following intravenous carbetocin administration is rapid, with a tetanic contraction being obtained within two minutes, and lasted about six minutes, followed by rhythmic contractions for a further 60 minutes. The prolonged effect of carbetocin can be attributed to the longer half-life of approximately 40 minutes compared to oxytocin, which having a short half-life of 3 to 5 minutes. This pharmacological effect is related to the modification of the molecular structure that increased lipophilicity and stability against peptidase degradation. Thus, in comparison to oxytocin, carbetocin induces a prolonged uterine response in terms of both amplitude and frequency of contractions and thereby reducing the risk of PPH that accompanies the need of additional uterotonic agents[16,17]. Additionally, multiparity is another factor of PPH due to decreasing of myometrial strength from reduction of collagen fiber, particularly Cesarean section might affect the function of collagen fibers[18]. As in the present study, the incidence of multiparity is significant greater in the oxytocin group than the carbetocin group, therefore, increasing the need for additional uterotonic drugs in

the oxytocin group. However, despite of the higher incidence of PPH at 500 mL or more, or severe PPH at 1,000 mL or more in the oxytocin group, it did not reach a statistically significant difference.

The efficacy of carbetocin in the present study was consistent with the recent meta-analysis of randomized trials, which showed that carbetocin, when compared to oxytocin, reduced the need for additional uterotonic use and postpartum blood transfusion in women at an increased risk of PPH undergoing Cesarean delivery. However, the risk of PPH was similar between carbetocin and other uterotonic agents[15]. Another systematic review and meta-analysis of randomized controlled trials demonstrated that carbetocin is associated with a reduced need for additional uterotonics compared to oxytocin at elective Cesarean delivery but is inconclusive regarding the prevention of PPH[19]. Moreover, a 2018 network meta-analysis of randomized trials found that carbetocin also reduced the use of additional uterotonics and was more effective than oxytocin for preventing PPH. However, when restricting the analysis to only trials at low risk of bias, carbetocin did not appear to be more effective than oxytocin[4].

Considering the adverse effects, previous studies found that the safety profile of carbetocin was comparable with oxytocin[4,5,10,11,20]. The present study also showed that there is no statistical difference in the adverse effects of carbetocin and oxytocin use. Nausea and vomiting have been proposed as the most frequent adverse effects encountered when carbetocin or oxytocin is used[11,20]. Similarly, approximately half of the women in the present study exhibited adverse effects of nausea and vomiting. Hemodynamic variable including hypotension is a concerning adverse event in carbetocin use. The present study found only 8.3% incidence of hypotension in the carbetocin group. It has been reported that carbetocin within the dose range of 80 to 120 mcg in elective Cesarean section in women with a low risk for PPH produced a 55% incidence of hypotension[14].

The strength of the current study is that it is a double-blind randomized controlled trial study and was performed in women with high risk to PPH. However, limitations occurred due to the small sample size, short duration of study, and the indication for additional uterotonics drugs being dependent on surgeon's consideration. Therefore, there was inadequate data to address the PPH rate, especially with respect to severe PPH.

In conclusion, the present study demonstrated that the carbetocin group requires less additional uterotonic drugs than the oxytocin group with equal safety profiles. However, the prevention of PPH is questionable due to the incidence of PPH not being different in the carbetocin group compared to the oxytocin group. Even though a significant amount of study has not been conducted on the cost-effectiveness analysis of carbetocin, the authors suggest that carbetocin should be used in high-risk postpartum cases to reduce hospital cost and hospital length of stay. Further study including on the efficacy for prevention of PPH and cost-effectiveness analysis with an increased sample size should be performed.

What is already known on this topic?

Carbetocin has been considered an alternative uterotonic drug for prevention of PPH in high-risk pregnant women undergoing Cesarean section. However, the efficacy must be confirmed because of conflicted results.

What this study adds?

The high-risk for PPH pregnant women undergoing Cesarean section with carbetocin administration require less additional uterotonic drugs than the pregnant women who receive oxytocin with equal safety profiles. Therefore, the study is supporting the higher efficacy of carbetocin compared with oxytocin for PPH prevention.

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Conflicts of interest

The authors declare no conflict of interest.

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