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Intravenous carbetocin versus intravenous oxytocin for preventing atonic postpartum hemorrhage after normal vaginal delivery in high-risk singleton pregnancies: a triple-blind randomized controlled trial

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Abstract

Purpose To compare the effectiveness of intravenous carbetocin to that of intravenous oxytocin for prevention of atonic postpartum hemorrhage (PPH) after vaginal delivery in high-risk singleton pregnancies.

Methods This triple-blind randomized controlled trial included singleton pregnant women who delivered at Siriraj Hospital between August 2016 and January 2017 and who were 20 years or older, had a gestational age of at least 34 weeks, had a vaginal delivery, and had at least one risk factor for atonic postpartum hemorrhage. Immediately after vaginal delivery, participants were randomly assigned to receive either 5 U of oxytocin or 100 mcg of carbetocin intravenously. Postpartum blood loss was measured objectively in mL using a postpartum drape with a calibrated bag.

Results A total of 174 and 176 participants constituted the oxytocin and carbetocin groups, respectively. The baseline characteristics were comparable between the groups. The carbetocin group had less postpartum blood loss (146.7 ± 90.4 vs. 195.1 ± 146.2 mL; $p < 0.01$), a lower incidence of atonic PPH (0 vs. 6.3%; $p < 0.01$), less usage of additional uterotonic drugs (9.1 vs. 27.6%; $p < 0.01$), and a lower incidence of postpartum anemia (Hb $\leq$ 10 g/dL) (9.1 vs. 18.4%; $p < 0.05$) than the oxytocin group. No significant differences regarding side effects were evident between the groups.

Conclusions Intravenous carbetocin is more effective than intravenous oxytocin for the prevention of atonic PPH among singleton pregnancies with at least one risk factor for PPH.

Clinical trial registration TCTR20160715004.

Keywords Carbetocin · High-risk pregnancy · Obstetric delivery · Oxytocin · Postpartum hemorrhage

Introduction

Postpartum hemorrhage (PPH) is responsible for one-fourth of maternal deaths worldwide [1]. PPH is defined as postpartum blood loss $\geq$ 500 mL after vaginal delivery and blood loss > 1000 mL after cesarean delivery [2]. Uterine atony is the most common cause of PPH [2]. Active management of the third stage of labor (AMTSL) is recommended for prevention of PPH [2]. Administration of uterotonic agents is an essential component of AMTSL, as this prophylactic strategy has decreased the incidence of PPH by nearly half [3]. Oxytocin is the drug of choice for prevention of PPH [4]. Oxytocin stimulates uterine contraction by binding directly to oxytocin receptors and increasing the intracellular calcium concentration within uterine smooth muscle [3]. Given that oxytocin has a short half-life (4–10 min) and duration of action, continuous intravenous infusion of oxytocin is recommended in routine postpartum practice. Common side effects of oxytocin include decreased blood pressure, nausea, vomiting, cardiac arrhythmia, pulmonary edema, water intoxication, and seizure [3, 5]. To minimize these effects, slow intravenous injection or infusion is recommended, as opposed to rapid bolus intravenous injection [3, 5].

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Carbetocin (1-deamino-1-carba-2-tyrosine(*O*-methyl)-oxytocin) is a long-acting synthetic oxytocin agonist. The half-life of carbetocin is 40 min, which is 4- to 10-fold longer than the half-life of oxytocin. The onset of action occurs within 2 min, and the duration of action is 1 and 2 h after intravenous and intramuscular injection, respectively [3, 5]. A dose of 100 mcg of carbetocin is generally considered to be equivalent to 5 U of oxytocin [3]. The side effects of carbetocin include flushing, decreased blood pressure, transient tachycardia, headache, abdominal pain, and bitter tongue [5, 6]. Although some case reports have described adverse cardiovascular effects (e.g., a prolonged QT interval and acute coronary syndrome), most of these studies reported no serious adverse events after carbetocin administration while reporting side effects that were comparable to those caused by oxytocin [5, 7, 8]. To avoid side effects, the recommendation is for carbetocin to be administered as an intramuscular or intravascular injection over a 1-min period after fetal or placental delivery [3].

Recent clinical studies of carbetocin for PPH prevention have focused mainly on cesarean delivery, with the value of carbetocin in routine obstetric practice being widely acknowledged. A recent Cochrane review has reported that carbetocin is more effective than oxytocin for reducing the need for additional uterotonic drugs following cesarean delivery and the need for uterine massage following both cesarean and vaginal delivery [9]. The Society of Obstetricians and Gynaecologists of Canada (SOGC; 2009) recommends carbetocin as a first-line drug for the prevention of PPH after elective cesarean delivery and after normal vaginal delivery in pregnant woman with one risk factor for PPH [10]. Carbetocin studies that focus on vaginal delivery, especially studies of carbetocin administration via the intravenous route, remain limited. Accordingly, the aim of this study was to compare the effectiveness of intravenous carbetocin with that of intravenous oxytocin for prevention of atonic PPH after vaginal delivery in high-risk singleton pregnancies.

Methods

This triple-blind randomized controlled trial included singleton pregnant women who delivered vaginally at Siriraj Hospital, Thailand's largest, university-based national tertiary referral center, which has around 5000 vaginal births per year, from August 2016 to January 2017 and who were 20 years or older, had a gestational age of at least 34 weeks, had a vaginal delivery, and had at least one risk factor for atonic PPH. The study participants, healthcare providers who administered uterotonic agents, and statistician who analyzed the final data were blinded to the agent administered and to the group allocation. All participants were counseled after admission regarding the study protocol and objectives, after which written informed consent was obtained authorizing their participation in the study. Informed consent was obtained from all individual participants included in the study. The protocol of this triple-blind randomized controlled trial was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (EC241/2559). This study was conducted after being registered and approved by the Thai Clinical Trials Registry (TCTR20160715004).

Risk factors of atonic PPH of which only one was needed for inclusion in this study were as follows: (1) a previous history of PPH; (2) induction or augmentation of labor > 4 h; (3) exposure to tocolytic agents within 4 h prior to delivery; (4) a prolonged active phase of labor > 12 h; (5) precipitated labor; (6) grand multipara (parity > 4); (7) polyhydramnios; and (8) presence of uterine leiomyoma. Patients with one or more of following were excluded: (1) active labor upon admission; (2) underlying medical disease, including bleeding disorders, thrombocytopenia, cardiovascular diseases, liver and renal diseases, asthma, epilepsy, and migraine; (3) history of oxytocin or carbetocin allergy; and (4) obstetric complications, such as preeclampsia and abnormal placentation. Patients who required emergency cesarean delivery or had non-atonic PPH were withdrawn from the study.

After enrollment into the study, 2 mL of blood was collected for a complete blood count. After exclusion or withdrawal of women with abnormal blood tests or who required emergency cesarean delivery, participants were randomized and allocated into either the control group (oxytocin) or the study group (carbetocin) (Fig. 1). Patient randomization in this study was performed by our center's central computer system. Patients in the control group received 5 U of oxytocin via slow intravenous injection over a 1-min period. Patients in the study group received 100 mcg of carbetocin via slow intravenous injection over a 1-min period. Because both drugs required storage at 2–8 °C, each drug was pre-prepared in an unlabeled syringe before injection by our research assistant. After preparation, both drugs were visibly identical and colorless. During the intrapartum period, all patients were cared for according to the standard institutional protocol of our center. Immediately after childbirth but before placental delivery, a pre-prepared unlabeled syringe of oxytocin or carbetocin, according to the randomization, was transferred to both the patient and another healthcare provider who performed the intravenous injection and who was blinded to which patient received which preparation.

The hemodynamic status, pulse rate, and blood pressure were monitored before administration of the assigned drug, every 5 min during the first 30 min postpartum, every 30 min until 1 h postpartum, and at 2 h postpartum. Postpartum blood loss was objectively measured in mL using a postpartum drape with a calibrated bag (Fig. 2).

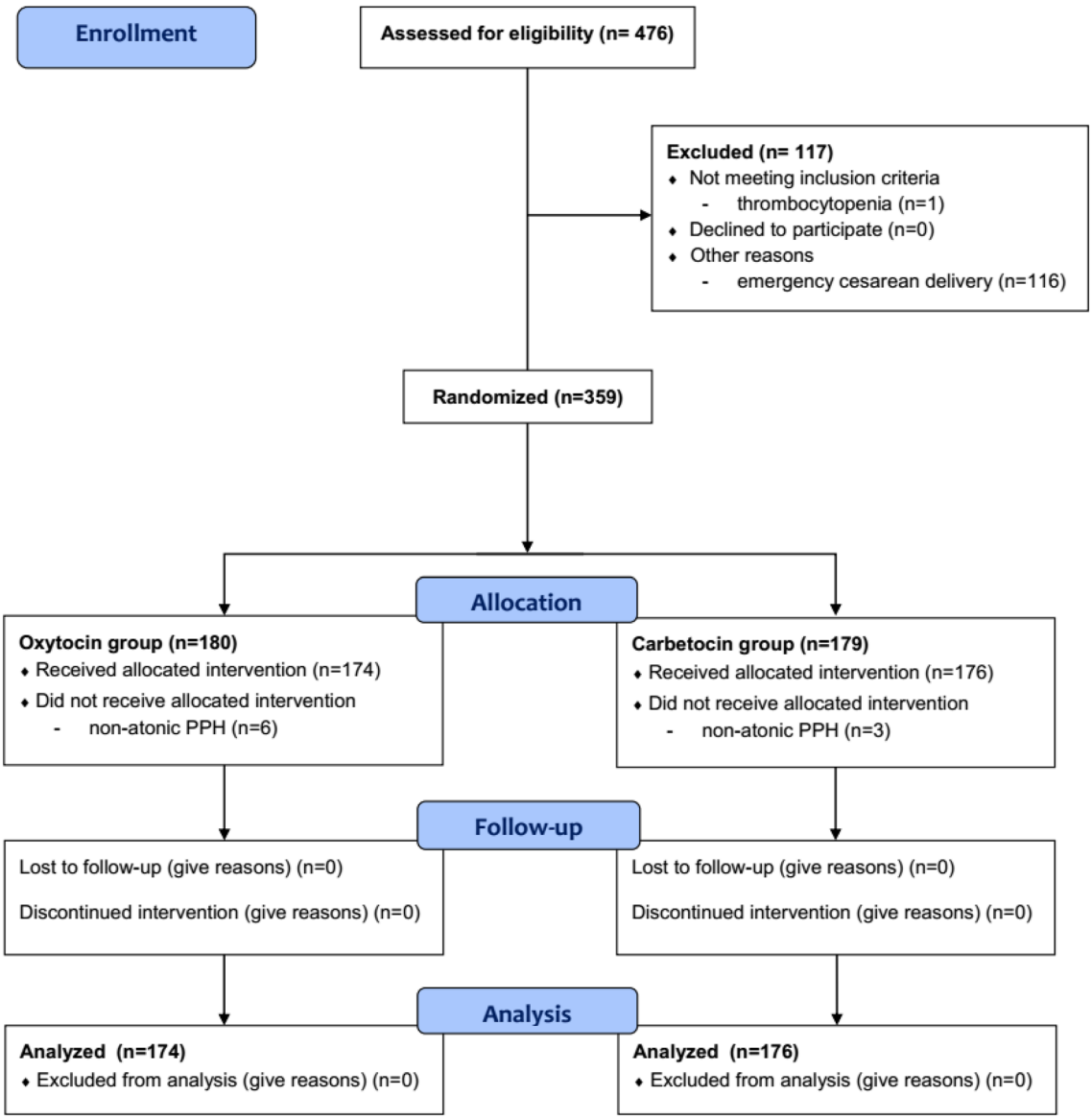

Fig. 1 Flow diagram of the study protocol

Uterine atony was evaluated by manual palpation. Decisions relating to administration of additional uterotonic agents depended on the decision of the doctor on duty, and PPH management was performed according to the standard institutional protocol of our center. At 24 h after delivery, 2 mL of blood was collected for repeated complete blood counts. The patient baseline characteristics, pregnancy outcomes, hemodynamic changes, additional uterotonic agent usage, side effects, and pre- and post-delivery hemoglobin and hematocrit were recorded and analyzed. This study was carefully monitored by our Institutional Data Safety Monitoring Board and included an interim analysis when data from half of the minimum number of participants became available.

Sample size calculation and statistical analysis

The sample size for this study was based on data reported from a 2016 study by Maged et al. [11]. The authors reported a fourfold decrease in the incidence of PPH when using carbetocin, compared to the incidence of PPH when using oxytocin (4 vs. 16%, respectively). A sample size of at least 163 women per group was calculated based on a power of 80%, a significance level of 0.05, and an expected 10% prevalence of PPH.

PASW Statistics version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Descriptive data are presented as the number and percentage or the mean ± standard deviation. Comparisons between the groups

Fig. 2 The three images show the method of postpartum blood collection at Siriraj Hospital used in this study. A postpartum drape with a calibrated bag was used to collect postpartum blood and measure blood loss immediately after vaginal delivery and before placental delivery

were performed using independent *t* test for continuous data, and the Chi-square test or Fisher's exact test for categorical data. A p value < 0.05 was considered to be statistically significant.

Results

Of the 476 pregnant women enrolled in this study during the study period from August 2016 to January 2017, 116 were withdrawn due to a need for emergency cesarean delivery, and 1 were excluded because of thrombocytopenia that was discovered from the complete blood count analysis. The remaining 359 participants were randomized and allocated into one or the other of the two study groups. Of these patients, six from the oxytocin group and three from the carbetocin group were withdrawn from the study because they had non-atonic PPH. As a result, 350 participants were included in the final analysis, with 174 and 176 participants in oxytocin and carbetocin groups, respectively.

Demographic characteristics, clinical characteristics, and pregnancy outcomes were comparable between the groups (Table 1). The hemodynamic changes before and after drug administration between the groups are shown in Table 2. The diastolic blood pressure at 60 and 90 min postpartum was significantly higher in the carbetocin group than that in the oxytocin group ($p < 0.05$). The pulse rate at 90 and 120 min postpartum was also significantly lower in the carbetocin group than that in the oxytocin group ($p < 0.05$). No patients in either group developed clinical hypotension.

The pregnancy outcomes related to PPH are presented in Table 3. The carbetocin group had less postpartum blood loss (146.7 ± 90.4 vs. 195.1 ± 146.2 mL; $p < 0.01$), a lower incidence of atonic PPH (0 vs. 6.3%; $p < 0.01$) and less usage of additional uterotonic drugs (9.1 vs. 27.6%; $p < 0.01$) than the oxytocin group. Compared to the predelivery period, the 24-h postpartum levels of hemoglobin and hematocrit were significantly higher in the carbetocin group than those in the oxytocin group (11.6 ± 1.3 vs. 11.2 ± 1.4 g/dL; $p < 0.01$ and 35.7 ± 3.8 vs. 34.6 ± 4.0%; $p < 0.01$, respectively). The incidence of postpartum anemia (Hb $\leq$ 10 g/dL) was lower in the carbetocin group than that in the oxytocin group (9.1 vs. 18.4%; $p < 0.05$). The proportion of patients with anemia increased by approximately threefold in both groups (13–38 patients in the oxytocin group vs. 6–17 patients in the carbetocin group). Although no significant difference regarding severe anemia (Hb $\leq$ 8 g/dL) was apparent between the groups (0.6 vs. 3.4%; $p > 0.05$), the number of patients with severe anemia remained stable in the carbetocin group, whereas the number of patients with severe anemia in the oxytocin group showed a sixfold increase (from 1 to 6 patients). Regarding side effects, no significant differences were evident between the groups. No patient in either group had a massive hemorrhage (EBL > 1000 mL), received a blood transfusion or underwent peripartum hysterectomy.

Table 1 Demographic characteristics, clinical characteristics, and pregnancy outcomes of the study population ($N=350$)

	Reported values[a]	
	Oxytocin ($n=174$)	Carbetocin ($n=176$)
Age ≥ 35 years	19 (10.9%)	26 (14.8%)
Nulliparity	68 (39.1%)	59 (33.5%)
Gestational age (weeks)	38.4 ± 1.2	38.5 ± 1.3
Antepartum hematocrit (%)	37.7 (3.7)	37.8 (3.6)
Antepartum hemoglobin (g/dL)	12.3 ± 1.4	12.3 ± 1.3
≤ 10 g/dL	12 (6.9%)	5 (2.8%)
≤ 8 g/dL	1 (0.6%)	1 (0.6%)
Antepartum anemia (hemoglobin < 11 g/dL)	26 (14.9%)	23 (13.1%)
Third stage of labor (min)	8.0 ± 5.3	8.4 ± 8.8
Mode of delivery		
Normal vaginal delivery	163 (93.7%)	171 (97.2%)
Instrumental vaginal delivery	11 (6.3%)	5 (2.8%)
Infant birth weight (g)	3055.3 ± 397.1	3054.9 ± 412.3
Perinatal asphyxia (1-min Apgar score < 7)	3 (1.7%)	6 (3.4%)

[a]Data are reported as the number and percentage or the mean ± standard deviation

Discussion

Use of a uterotonic agent is key to preventing PPH, making the agent the most important component of AMTSL [2, 12]. Given the short duration of action of oxytocin, carbetocin, a long-acting oxytocin agonist, was developed in the 1970s [5]. The pharmacodynamic activity of oxytocin and carbetocin is similar in that they both bind to oxytocin receptors within the myometrium and effectuate rhythmic uterine contractions. Carbetocin also increases the amplitude of uterine tone and the frequency of existing uterine contractions [13, 14]. Carbetocin was determined to be safe for breast feeding because only a small amount of carbetocin passes into the breast milk after a single intravenous injection and because the carbetocin injection does not provoke adverse effects or clinical changes in the baby [15]. In the present study, we found that intravenous carbetocin had a higher efficacy than oxytocin regarding postpartum blood loss, the need for uterotonic agents, and postpartum anemia after vaginal delivery among high-risk patients. Although we observed some changes in the postpartum hemodynamic status between the groups at 60, 90, and 120 min, the changes had no clinical significance because no patient in either group demonstrated hemodynamic instability during the 2-h postpartum period that we evaluated. Rosselland et al. reported changes in hemodynamic status during cesarean delivery among carbetocin-, oxytocin-, and placebo-treated patients [16]. The authors reported similar hypotensive effects between the carbetocin injection and oxytocin injection, and the effects occurred less than 2.5 min after administration, with no resulting hemodynamic instability and with similarly minor side effects between the agents.

Very few studies have focused on the use of carbetocin after vaginal delivery, and the data are inconclusive. Most previous studies have compared carbetocin to either oxytocin or syntometrine (a combination of 500 mcg of ergometrine maleate and 5 IU of oxytocin), and most of these studies reported a preference for the intramuscular route of administration. In 2004, Boucher et al. compared the effectiveness of 100 mcg of intramuscular carbetocin to 2 h of 10 U of intravenous oxytocin infusion among 320 high-risk pregnancies after vaginal delivery [17]. The authors reported that the benefit of carbetocin was the need for significantly less uterine massage than oxytocin, with no significant difference between the agents regarding the need for additional uterotonic drugs. In 2011, Askar et al. compared the effect of 100 mcg of intramuscular carbetocin to syntometrine following vaginal delivery among 240 term low-risk pregnant women in a double-blind randomized controlled trial [18]. The authors concluded that intramuscular carbetocin was superior to syntometrine, as carbetocin caused less blood loss, less postpartum anemia, and fewer side effects than syntometrine; however, the authors found the two agents to be comparable in terms of the need for additional uterotonic drugs. In 2016, Maged et al. compared the effectiveness of 100 mcg of intramuscular carbetocin to that of 5 U of intramuscular oxytocin for prevention of PPH among 200 term pregnant women who had at least 2 risk factors for PPH [11]. The authors found that the two agents to be similar regarding hemodynamic effects and safety but carbetocin was superior to oxytocin regarding postpartum blood loss, the need of additional uterotonic drugs, the need for uterine massage, and the change in hemoglobin level. A recent meta-analysis in 2016 by Jin et al. concluded that only fewer risk of adverse effects were present after the use of carbetocin

Table 2 Hemodynamic changes between the oxytocin and carbetocin groups ($N=350$)

Time	Mean ± SD		*p* value
	Oxytocin ($n=174$)	Carbetocin ($n=176$)	
Before administration			
Pulse rate (per min)	89.5 ± 13.7	89.6 ± 12.2	0.92
SBP (mmHg)	117.9 ± 11.8	118.2 ± 11.8	0.82
DBP (mmHg)	66.6 ± 10.8	68.4 ± 11.7	0.13
After administration			
5 min			
Pulse rate (per min)	90.0 ± 14.6	90.4 ± 13.4	0.78
SBP (mmHg)	115.8 ± 12.8	116.4 ± 12.4	0.66
DBP (mmHg)	65.0 ± 10.9	65.9 ± 10.7	0.45
10 min			
Pulse rate (per min)	88.1 ± 13.8	88.4 ± 12.0	0.83
SBP (mmHg)	117.0 ± 11.1	116.8 ± 11.5	0.83
DBP (mmHg)	68.4 ± 10.4	67.1 ± 10.3	0.24
15 min			
Pulse rate (per min)	86.2 ± 13.0	86.6 ± 11.5	0.79
SBP (mmHg)	116.3 ± 12.0	117.7 ± 10.4	0.24
DBP (mmHg)	68.3 ± 10.2	68.8 ± 9.3	0.65
20 min			
Pulse rate (per min)	86.0 ± 12.6	85.7 ± 10.3	0.81
SBP (mmHg)	116.5 ± 10.1	117.2 ± 10.1	0.55
DBP (mmHg)	68.8 ± 9.5	68.8 ± 8.8	0.99
25 min			
Pulse rate (per min)	86.0 ± 12.4	84.6 ± 10.5	0.27
SBP (mmHg)	116.0 ± 10.6	117.3 ± 9.6	0.25
DBP (mmHg)	68.0 ± 9.7	69.4 ± 8.9	0.17
30 min			
Pulse rate (per min)	85.6 ± 12.9	84.4 ± 10.9	0.31
SBP (mmHg)	115.3 ± 9.7	117.0 ± 9.9	0.11
DBP (mmHg)	68.1 ± 9.2	69.6 ± 8.6	0.11
60 min			
Pulse rate (per min)	85.3 ± 11.7	83.5 ± 11.5	0.14
SBP (mmHg)	114.8 ± 11.0	115.7 ± 10.6	0.43
DBP (mmHg)	67.8 ± 9.3	70.2 ± 8.5	0.01*
90 min			
Pulse rate (per min)	84.7 ± 12.2	82.2 ± 11.2	0.04*
SBP (mmHg)	113.9 ± 10.0	115.3 ± 11.0	0.23
DBP (mmHg)	67.8 ± 9.8	70.2 ± 9.1	0.02*
120 min			
Pulse rate (per min)	84.7 ± 12.1	82.2 ± 10.6	0.04*
SBP (mmHg)	114.6 ± 10.2	115.7 ± 10.5	0.30
DBP (mmHg)	69.5 ± 8.1	70.7 ± 8.5	0.19

*p value <0.05 indicates statistical significance

post-vaginal delivery, but no statistical significance was evident for postpartum hemorrhage, massive postpartum hemorrhage and the need for additional uterotonic agents [19]. As the data of carbetocin showed its tendency to be effective, the World Health Organization (WHO) recently developed a study protocol for a randomized controlled trial to evaluate the effectiveness of room-temperature-stable carbetocin for the prevention of PPH and severe PPH among 30,000 women delivering vaginally in 10 countries, and the process is ongoing [20].

The present study has more inherent strengths than previous studies, and these strengths enhance the value of our

Table 3 Pregnancy outcomes related to postpartum hemorrhage (PPH) ($N = 350$)

	Reported values[a]		*p* value
	Oxytocin ($n = 174$)	Carbetocin ($n = 176$)	
Estimated blood loss (mL)	195.1 ± 146.2	146.7 ± 90.4	< 0.01*
≥ 500 mL	11 (6.3%)	0 (0%)	< 0.01*
Postpartum hematocrit (%)	34.6 ± 4.0	35.7 ± 3.8	0.01*
24-h postpartum hemoglobin (g/dL)	11.2 ± 1.4	11.6 ± 1.3	< 0.01*
≤ 10 g/dL	32 (18.4%)	16 (9.1%)	0.01*
≤ 8 g/dL	6 (3.4%)	1 (0.6%)	0.07
Additional uterotonic agents	48 (27.6%)	16 (9.1%)	< 0.01*
Side effects	9 (5.2%)	12 (6.8%)	0.52
Dizziness	3/9	6/12	
Headache	2/9	0/12	
Flushing	1/9	4/12	
Abdominal cramping	1/9	1/12	
Palpitation	1/9	3/12	
Nausea/vomiting	1/9	1/12	
Fainting	0/9	1/12	

[a]Data are reported as the number and percentage or the mean ± standard deviation

*p value < 0.05 indicates statistical significance

results. Although the accuracy of the postpartum blood loss measurement has been a weakness for most studies, our study measured postpartum blood loss in mL using a postpartum drape with a calibrated bag. This method was recommended as being acceptable for measurements of blood loss after childbirth [21, 22]. A 2009 double-blind randomized controlled trial by Su et al. reported comparable efficacy between intramuscular carbetocin and syntometrine among 370 low-risk pregnancies that were over 34 weeks gestation [23]. However, given that the authors used visual estimations to measure postpartum blood loss, the 1.6% incidence of PPH that they reported may be an underestimation. Similarly, a 2016 retrospective study from Taiwan reported no significant difference in the incidence of PPH between the carbetocin and non-carbetocin groups, with the limitation that the study involved visual estimation of blood loss [24]. Our 2016 study demonstrated that visual estimation was underestimation as it missed 65.4% of PPH and had low correspondence of blood loss measurement (27.6%) when compare with a blood collection bag. We recommended that the use of a blood collection bag was easier and more reliable than visually estimating blood loss [25]. As a result, the reported outcomes from our study regarding PPH are highly reliable. Moreover, the triple-blind design of our study, which included the blinding of study participants, healthcare providers, and our statistician, reduced the likelihood of study bias, which increased the accuracy and reliability of our results.

This study had some notable limitations. First, given that we did not interrupt or change our institutional standards and protocols for postpartum care, the decision of whether to prescribe additional uterotonic agents would likely have varied depending on the doctors on duty. Therefore, given our high-risk study population, the possibility exists that patients were overtreated in some instances. However, because the difference in the use of additional uterotonic agents between the carbetocin and oxytocin groups in this study was high (9.1 vs. 27.6%; $p < 0.01$), the argument that carbetocin was superior to oxytocin for reducing the need for additional uterotonic agents is strong. Due to the relatively small size of our study population, we were not able to determine the efficacy of carbetocin regarding a reduction in massive hemorrhage, postpartum blood loss > 1000 mL, major morbidity, a need for a massive blood transfusion, peripartum hysterectomy, ICU admission, or maternal mortality. This study needs to be repeated with a much larger study population or in a multicenter setting to identify the impact of carbetocin on the aforementioned factors and to confirm the findings of this study. Lastly, the cost effectiveness of carbetocin for prevention of PPH has not been conclusively established. Although there were studies approved that carbetocin had cost effectiveness in term of PPH prevention [26, 27], given the differences in healthcare and economic systems between countries and the fact that most previous studies have focused on cesarean deliveries, the overall cost effectiveness of carbetocin in Thailand and other developing countries remains unknown. Thus, further study of the cost effectiveness of carbetocin in Thailand is needed.

In conclusion, intravenous carbetocin is more effective than intravenous oxytocin for reducing postpartum blood

loss, postpartum anemia, the incidence of atonic PPH, and the use of additional uterotonic agents in high-risk pregnancy with at least one risk factor for PPH.

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Author contributions TL: protocol/project development, data analysis and interpretation, manuscript writing/editing, final form of manuscript. PA: data collection and management, manuscript writing, funding management. DB: protocol/project development, data analysis and interpretation. JL: data collection and management. RS: data collection and management. RJ: data collection and management, funding management.

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Compliance with ethical standards

Conflict of interest Assistant professor Tripop Lertbunnaphong has received a speaker honorarium from Ferring Pharmaceutical Ltd., Thailand. Paweena Amornpetchakul, Dittakarn Boriboonhiransarn, Jarunee Leetheeragul, Ratree Sirisomboon and Ratchada Jiraprasertwong declare that they have no conflict of interest.

Research involving human participants and/or animals Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, Gulmezoglu AM, Temmerman M, Alkema L (2014) Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2(6):e323–e333
2. World Health Organization (2012) WHO recommendations for the prevention and treatment of postpartum haemorrhage. WHO Guidelines Approved by the Guidelines Review Committee, Geneva
3. Cordovani D, Carvalho JCA, Boucher M, Farine D (2012) Carbetocin for the prevention of postpartum hemorrhage. In: Arulkumaran S, Karoshi M, Keith LG, Lalonde AB, B-Lynch C (eds) A Comprehensive textbook of postpartum hemorrhage: an essential clinical reference for effective management, 2nd edn. Sapiens Publishing, London, pp 361–368
4. Westhoff G, Cotter AM, Tolosa JE (2013) Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD001808.pub2
5. Meshykhi LS, Nel MR, Lucas DN (2016) The role of carbetocin in the prevention and management of postpartum haemorrhage. Int J Obstet Anesth 28:61–69
6. Samimi M, Imani-Harsini A, Abedzadeh-Kalahroudi M (2013) Carbetocin vs. syntometrine in prevention of postpartum hemorrhage: a double blind randomized control trial. Iran Red Crescent Med J 15(9):817–822
7. Bruyere M, Ait Hamou N, Benhamou D, Chousterman B, Boulard V, Charbit B (2014) QT interval prolongation following carbetocin in prevention of post-cesarean delivery hemorrhage. Int J Obstet Anesth 23(1):88–89
8. Jacquenod P, Cattenoz M, Canu G, Bois E, Lieutaud T (2015) Acute coronary syndrome following a 100 microg carbetocin injection during an emergency Cesarean delivery. Can J Anaesth 62(5):513–517
9. Su LL, Chong YS, Samuel M (2012) Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD005457.pub4
10. Leduc D, Senikas V, Lalonde AB, Ballerman C, Biringer A, Delaney M, Clinical Practice Obstetrics Committee; Society of Obstetricians and Gynaecologists of Canada et al (2009) Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can 31(10):980–993
11. Maged AM, Hassan AM, Shehata NA (2016) Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women. J Matern Fetal Neonatal Med 29(4):532–536
12. Gulmezoglu AM, Lumbiganon P, Landoulsi S, Widmer M, Abdel-Aleem H, Festin M, Carroli G, Qureshi Z, Souza JP, Bergel E, Piaggio G, Goudar SS, Yeh J, Armbruster D, Singata M, Pelaez-Crisologo C, Althabe F, Sekweyama P, Hofmeyr J, Stanton ME, Derman R, Elbourne D (2012) Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. Lancet 379(9827):1721–1727
13. Hunter DJ, Schulz P, Wassenaar W (1992) Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clin Pharmacol Ther 52(1):60–67
14. Amsalem H, Aldrich CJ, Oskamp M, Windrim R, Farine D (2014) Postpartum uterine response to oxytocin and carbetocin. J Reprod Med 59(3–4):167–173
15. Silcox J, Schulz P, Horbay GL, Wassenaar W (1993) Transfer of carbetocin into human breast milk. Obstet Gynecol 82(3):456–459
16. Rosseland LA, Hauge TH, Grindheim G, Stubhaug A, Langesaeter E (2013) Changes in blood pressure and cardiac output during cesarean delivery: the effects of oxytocin and carbetocin compared with placebo. Anesthesiology 119(3):541–551
17. Boucher M, Nimrod CA, Tawagi GF, Meeker TA, Rennicks White RE, Varin J (2004) Comparison of carbetocin and oxytocin for the prevention of postpartum hemorrhage following vaginal delivery: a double-blind randomized trial. J Obstet Gynaecol Can 26(5):481–488
18. Askar AA, Ismail MT, El-Ezz AA, Rabie NH (2011) Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. Arch Gynecol Obstet 284:1359–1365
19. Jin B, Du Y, Zhang F, Zhang K, Wang L, Cui L (2016) Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med 29(3):400–407
20. Widmer M, Piaggio G, Abdel-Aleem H, Carroli G, Chong YS, Coomarasamy A, Fawole B, Goudar S, Hofmeyr GJ, Lumbiganon P, Mugerwa K, Nguyen TM, Qureshi Z, Souza JP, Gulmezoglu

AM (2016) Room temperature stable carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally: study protocol for a randomized controlled trial. Trials 17(1):143
21. (2017) Prevention and management of postpartum haemorrhage: green-top guideline no. 52. BJOG 124(5):e106–e149. https://doi.org/10.1111/1471-0528.14178
22. Snelgrove JW (2009) Postpartum haemorrhage in the developing world a review of clinical management strategies. Mcgill J Med 12(2):61
23. Su LL, Rauff M, Chan YH, Mohamad Suphan N, Lau TP, Biswas A, Chong YS (2009) Carbetocin versus syntometrine for the third stage of labour following vaginal delivery—a double-blind randomised controlled trial. BJOG 116(11):1461–1466
24. Chen CY, Su YN, Lin TH, Chang Y, Horng HC, Wang PH, Yeh CC, Chang WH, Huang HY (2016) Carbetocin in prevention of postpartum hemorrhage: experience in a tertiary medical center of Taiwan. Taiwan J Obstet Gynecol 55(6):804–809
25. Lertbunnaphong T, Lapthanapat N, Leetheeragul J, Hakularb P, Ownon A (2016) Postpartum blood loss: visual estimation versus objective quantification with a novel birthing drape. Singap Med J 57(6):325–328
26. Luni Y, Borakati A, Matah A, Skeats K, Eedarapalli P (2017) A prospective cohort study evaluating the cost-effectiveness of carbetocin for prevention of postpartum haemorrhage in caesarean sections. J Obstet Gynaecol 37(5):601–604
27. van der Nelson HA, Draycott T, Siassakos D, Yau CW, Hatswell AJ (2017) Carbetocin versus oxytocin for prevention of post-partum haemorrhage at caesarean section in the United Kingdom: an economic impact analysis. Eur J Obstet Gynecol Reprod Biol 210:286–291