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Original Research

Carbetocin versus oxytocin for the prevention of postpartum hemorrhage after elective caesarean section in high risk women: a prospective, randomized, open-label, controlled trial in China

Suya Kang[1,†], Liping Zhou[1,†], Liping Zhu[1,*], Yun Wang[1,*], Yongfei Yue[1], Li Yan[1]

[1]Department of Obstetrics, Suzhou Affiliated Hospital of Nanjing Medical University, Suzhou Municipal Hospital, 215000 Suzhou, Jiangsu, China
*Correspondence: lpzhu3450@163.com (Liping Zhu); wangyuny1234@163.com (Yun Wang)
[†]These authors contributed equally.

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Abstract

Background: To evaluate the efficacy and safety of carbetocin compared with oxytocin for prevention of postpartum hemorrhage (PPH) after elective cesarean section in Chinese high risk women. **Methods**: This was a single-center, prospective, randomized, open-label, controlled trial recruiting 852 pregnant women with one or more PPH risk factors between April 2017 and August 2019. Pregnant woman who was scheduled for an elective cesarean section were randomly assigned to receive carbetocin or oxytocin for prevention of PPH. The primary efficacy endpoint was the proportion of additional uterotonics. **Results**: A total of 852 pregnant women were randomly assigned to receive carbetocin (n = 442) or oxytocin (n = 410). The baseline characteristics were comparable between the two groups. The carbetocin group had lower proportion of requiring additional uterotonics (18.4% vs. 24.4%, $p = 0.03$ in full analysis set [FAS] analysis) to the oxytocin group. The amount of blood loss (intrapartum or postpartum) was no statistically significant difference (all $p > 0.05$). There were no significant differences in the postpartum hemoglobin, rate of hemostatics, blood transfusion, additional surgical interventions or uterine massage between the two groups. The rates of mild asphyxia in carbetocin and oxytocin groups were 2.1% and 1.3%, respectively. No other poor maternal and neonatal outcomes were observed in two groups. **Conclusions**: Carbetocin required lower rate of additional uterotonics than oxytocin for prevention of PPH after elective cesarean section in Chinese high risk women. Carbetocin was comparable to oxytocin in postpartum blood loss, postpartum hemoglobin, hemostatics, blood transfusion, additional surgical interventions or uterine massage.

Keywords: Carbetocin; Cesarean section; Postpartum hemorrhage; Oxytocin

1. Introduction

Postpartum hemorrhage (PPH) constitutes a major cause of maternal mortality and postpartum hysterectomy [1]. It is estimated that 140,000 women worldwide die of PPH every year [2]. The most frequent cause of PPH is uterine atony, resulting in up to 80% of PPH [3]. It is recommended to systematically use uterotonics immediately after delivering the newborn for prevention of PPH [4].

Oxytocin is the most widely used uterotonic agent with a rapid onset of action and a good safety profile [5]. However, due to its short half-life (4–10 minutes), continuous or frequent repeated administration is required [6]. Carbetocin, a long-acting synthetic oxytocin analogue, has a longer duration of action than oxytocin (half-life 85–100 minutes) [7]. The structural difference with oxytocin makes carbetocin more stable, thereby avoiding the cleavage of aminopeptidase and disulfide compounds [8]. Compared with oxytocin, carbetocin has been shown to reduce blood loss and the need for additional uterotonics, and decrease the risk of PPH in cesarean section [9–11]. Cesarean section is a well-known risk factor for PPH [6]. The caesarean section rate in China is about 36.7% in 2018, which is higher than the World Health Organization recommended proportion of 15% [12]. In our clinical practice, we usually encounter the PPH risk maternal population (such as scarred uterus, breech position, uterine fibroid or $\geq$35 years) who may be additionally benefited from carbetocin treatment after caesarean section. However, randomized controlled trials of carbetocin and oxytocin in the prevention of PPH have not been conducted in Chinese population undergoing elective cesarean section. Therefore, pregnant women with one or more PPH risk factors scheduled for an elective cesarean section were recruited in this study. The efficacy and safety of carbetocin compared with oxytocin in prevention of PPH after elective cesarean section was evaluated.

2. Materials and methods

2.1 Study design and patients

This study was a single-center, prospective, randomized, controlled trial comparing Carbetocin and Oxytocin in prevention of PPH after elective cesarean section. A total of 852 pregnant women with one or more PPH risk factors scheduled for an elective cesarean section were recruited between April 2017 and August 2019. This

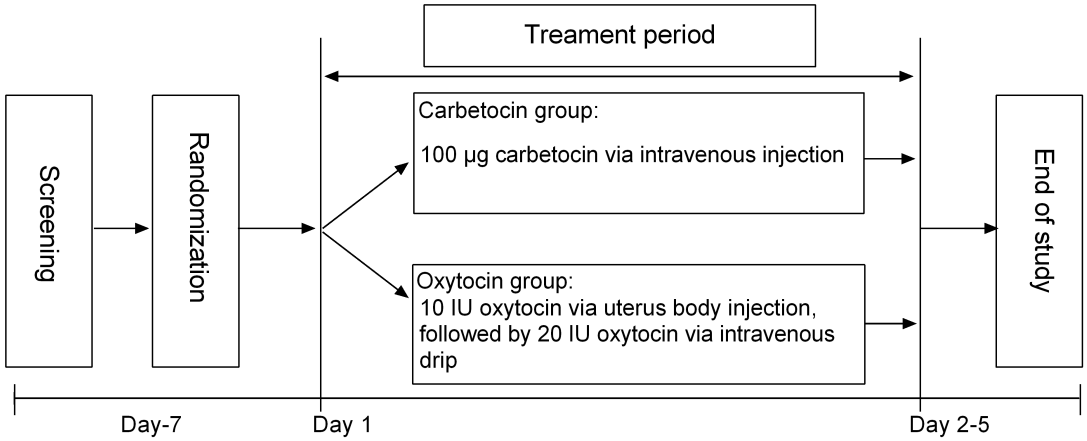

Fig. 1. Study design.

trial was registered with Chinese Clinical Trial Registry (ChiCTR1800015613), and conducted in accordance with Declaration of Helsinki and Good Clinical Practice Guidelines. The protocol had been approved by ethics committee institutional review board of participating center (K2016062), and written informed consent was obtained from each participant.

Women with one or more PPH risk factors, scheduled for cesarean section on term pregnancy were eligible to enter this study. The indications for elective cesarean section and PPH risk factors included scarred uterus (the uterus of a woman that had undergone myomectomy or previous cesarean section), uterine fibroid, breech position, and age $\geq$35 years. The exclusion criteria included age $<$18 years, multiple pregnancy, placenta praevia, suspected placenta accreta, systematic disease (such as liver dysfunction, kidney dysfunction, heart disease or hypertension need to be treated, endocrine disease except diabetes during pregnancy), abnormal coagulation, or hypersensitivity to carbetocin or oxytocin.

2.2 Intervention

All eligible subjects were randomly assigned to carbetocin group or oxytocin group by a computer-generated coding system (Fig. 1). All women underwent low transverse cesarean section under spinal anesthesia, which performed by an obstetrician team including senior physicians and anesthesiologists led by a department chief to ensure the quality and safety. All doctors in our hospital had undergone strict training and assessment which were similar in the level of expertise. The anesthetic drugs included butorphanol (1 mg, intraspinal injection; H20143106, Jiangsu Hengrui Pharmaceutical Co., Ltd., Lianyungang, China), esmolol (1 g, intravenous injection; H19991058, Qilu Pharmaceutical Co., Ltd., Jinan, China), ropivacaine (20 mg, intravenous injection; H20100103, Naropin, AstraZeneca Pharmaceuticals Ltd., Shanghai, China), flurbiprofen axetil (50 mg, intravenous injection; H20041508, Beijing Taide Pharmaceutical Co. Ltd., Beijing, China) and granisetron hydrochloride (20 mg, intravenous injection; H10970243, Ningbo Tianheng Pharmaceutical Co., Ltd., Ningbo, China). In addition, cefoxitin sodium (2.0 g, intravenous drip; H20057973, Yangzijiang Pharmaceutical Group Co., Ltd., Taizhou, China) was used for infection prophylaxis.

After delivering the newborn, women in the carbetocin group received 100 μg carbetocin (H20070013, Ferring Pharmaceutical Co. Ltd., St-Prex, Switzerland) via intravenous injection over one minute. Women in the oxytocin group received 10 IU oxytocin (H31020850, Hefeng Pharmaceutical, Shanghai, China) via uterus body injection, followed by 20 IU oxytocin in 500 mL 5% glucose solution (H11020060, China Resources Zizhu Pharmaceutical Co., Ltd., Beijing, China) via intravenous drip over 1 hour. Uterine atony was evaluated by manual palpation. Decisions relating to administration of additional uterotonics followed the hospital's protocol. According to the hospital's protocol, women who had postpartum bleeding more than 800 mL were predicted to develop PPH. Thus, the management of the prevention of PPH was the use of additional uterotonics. The additional uterotonics included oxytocin (H31020850, Hefeng Pharmaceutical, Shanghai, China), misoprostol (H20000668, China Resources Zizhu Pharmaceutical Co., Ltd., Beijing, China), hemabate (H20170146, Pharmacia and Upjohn Co., New York, USA) and ergometrine (H32024525, Chengdu Beite Pharmaceutical Co., Ltd., Chengdu, China).

2.3 Observation indicators

The baseline characteristics, additional uterotonics usage, blood loss during surgery, PPH, antepartum hemoglobin and postpartum hemoglobin, maternal and neonatal outcomes of patients were recorded and analyzed. Blood loss was calculated by measuring the volume in the suction bottle and the absorption in the surgical drapes, gauzes, and pads.

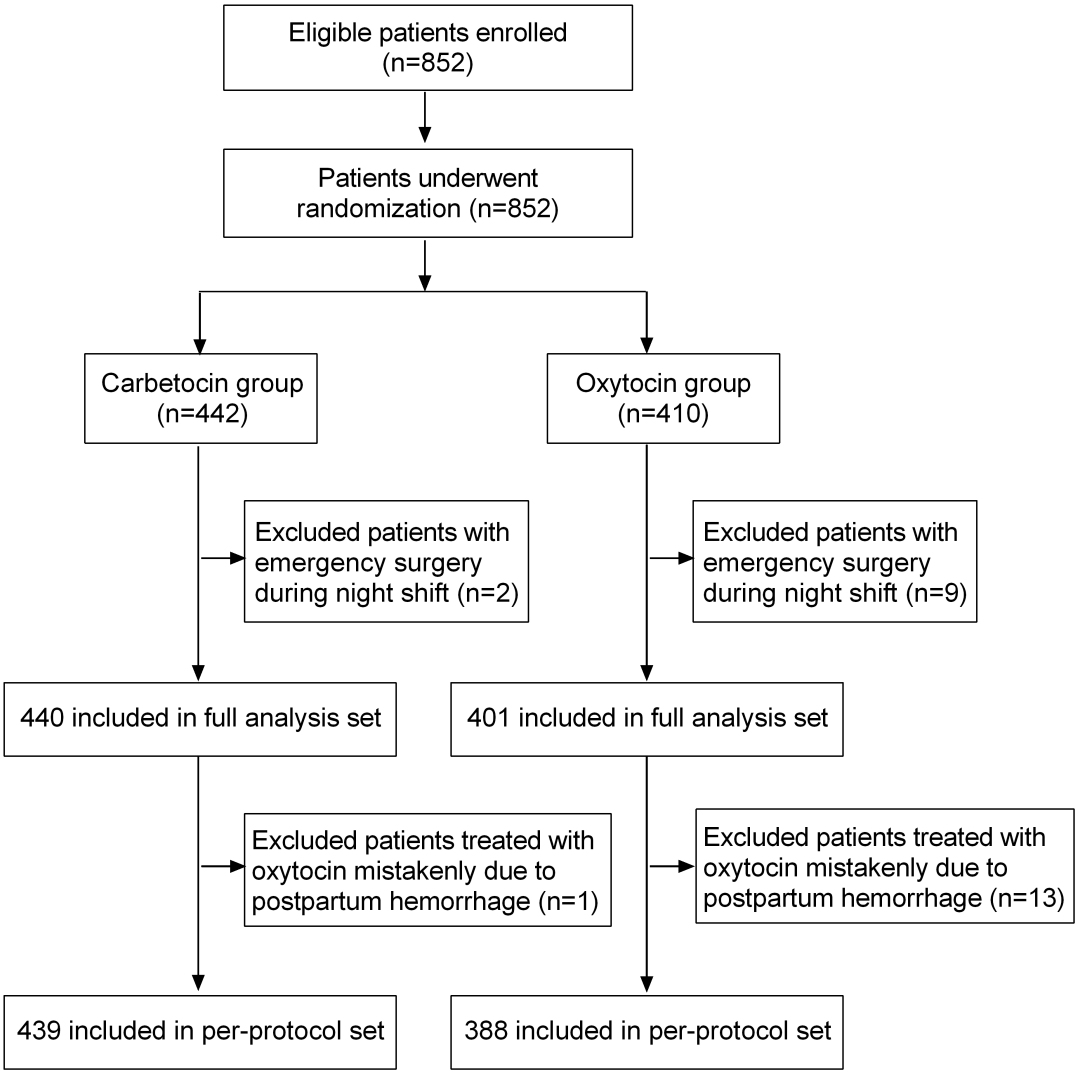

Fig. 2. Patients flowchart.

The primary efficacy endpoint was the proportion of women requiring additional uterotonics after administration of the investigative drug (carbetocin or oxytocin). The primary efficacy endpoint was chosen instead of the occurrence of PPH for the following reasons: firstly, the amount of bleeding was known to be underestimated [13]; secondly, continuous and slow bleeding from the surgical incision contributed to the incidence and severity of PPH [14]; lastly, the administration of several additional uterotonics may be used to successfully avoid bleeding in some cases. Secondary efficacy endpoints included the following: (1) the amount of intrapartum blood loss; (2) the incidence of blood loss $\geq$800 mL intrapartum; (3) blood loss within 2 hours after delivery; (4) blood loss within 24 hours after delivery; (5) the incidence of blood loss $\geq$1000 mL postpartum; (6) the incidence of blood loss $<$1000 mL within 2 hours and $\geq$1000 mL within 24 hours postpartum; (7) postpartum hemoglobin; (8) rate of hemostatics, defined as the proportion of women requiring hemostatics after delivery; (9) rate of blood transfusion, defined as the proportion of women requiring blood transfusion; (10) rate of additional surgical interventions, defined as the proportion of women requiring additional surgical interventions; (11) rate of uterine massage, defined as the proportion of women requiring additional uterine massage.

The safety was evaluated by the maternal and neonatal outcomes. The organ damage (heart, lung, brain, liver or kidney), need for respirator support and hemofiltration or plasmapheresis were used to evaluate the maternal outcomes. Meanwhile, Apgar score and neonatal intensive care unit (NICU) admission were selected to evaluate the neonatal outcomes.

2.4 Statistical analysis

The sample size calculation for this trial was based on primary endpoint according to the parameter of previous study [15]. The investigator anticipated a better performance of carbetocin on the efficacy at a significant level of

Table 1. Baseline characteristics of the patients.

Characteristic	FAS analysis			PPS analysis		
	Carbetocin group (n = 440)	Oxytocin group (n = 401)	*p* value	Carbetocin group (n = 439)	Oxytocin group (n = 388)	*p* value
Maternal age (year, Mean ± SD)	31.6 ± 4.1	31.7 ± 3.8	0.08	31.6 ± 4.1	31.7 ± 3.8	0.06
BMI (kg/m^2, Mean ± SD)	27.6 ± 3.2	27.8 ± 3.1	0.4	27.6 ± 3.1	27.8 ± 3.2	0.4
Gestational age (weeks, Mean ± SD)	39.1 ± 0.6	39.2 ± 0.6	0.9	39.1 ± 0.6	39.2 ± 0.6	0.9
Parity (n, %)			0.8			0.6
Nulliparous	107 (24.3)	94 (23.4)		107 (24.4)	88 (22.7)	
Multiparous	333 (75.7)	307 (76.6)		332 (75.6)	300 (77.3)	
Antepartum hemoglobin (g/L, Mean ± SD)	116.6 ± 12.0	117.4 ± 11.4	0.3	116.6 ± 12.0	117.2 ± 11.1	0.3
Normal (≥110 g/L, n/%)	324 (73.6)	301 (75.1)		323 (73.6)	290 (74.7)	
Mild anemia (100–110 g/L, n/%)	80 (18.2)	78 (19.5)		80 (18.2)	76 (19.6)	
Moderate anemia (70–100 g/L, n/%)	36 (8.2)	22 (5.5)		36 (8.2)	22 (5.7)	
Severe anemia (±70 g/L, n/%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Antepartum hematocrit (Mean ± SD)	0.3 ± 0.03	0.4 ± 0.03	0.1	0.3 ± 0.03	0.4 ± 0.03	0.1
Hypertension (n, %)	6 (1.4)	1 (0.2)	0.2	6 (1.4)	1 (0.3)	0.2
Uterine fibroids (n, %)	6 (1.4)	13 (3.2)	0.1	6 (1.4)	13 (3.4)	0.1
Diabetes (n, %)	94 (21.4)	81 (20.2)	0.7	94 (21.4)	79 (20.4)	0.7
Birth weight (g, Mean ± SD)	3432.6 ± 419.4	3400.4 ± 395. 8	0.25	3431.4 ± 419.2	3999.9 ± 395.3	0.7
PPH risk factors (n, %)			0.2			0.8
Scarred uterus	319 (72.7)	294 (78.6)		318 (72.6)	287 (74.0)	
Uterine fibroid	2 (0.5)	1 (0.2)		2 (0.5)	1 (0.3)	
Breech position	85 (19.4)	70 (14.0)		85 (19.4)	67 (17.3)	
Age ≥35 years	19 (4.3)	17 (4.2)		19 (4.3)	16 (4.1)	

FAS, full analysis set; PPS, per-protocol set; BMI, body mass index; SD, standard deviations; PPH, postpartum hemorrhage.

$\alpha = 0.05$ and $\beta = 0.2$, therefore the test validity was 80%. Accordingly, 374 women per group were sufficient with a level of significance of 95% ($\alpha = 0.05$) and a power of 80% ($\beta = 0.2$). Considering drop-out rate of 10%, a total of 832 samples were needed at least. Therefore, the investigator planned to enroll 416 cases in each group.

Efficacy analysis was performed based on the intention-to-treat population. All results were analyzed in full analysis set (FAS) and per-protocol set (PPS). SPSS version 22.0 (SPSS Institute, Chicago, IL, USA) was used to perform the statistical analyses. Quantitative data were expressed as means ± standard deviations (means ± SD) and were compared using independent samples *t* test. Qualitative data were expressed as number and percentage, and were evaluated using χ^2 test. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Baseline characteristics

852 eligible pregnant women were randomly assigned to receive carbetocin (n = 442) or oxytocin (n = 410). A total of 841 women were included in FAS analysis (carbetocin group: n = 440; oxytocin group: n = 401). The reasons for not including in FAS analysis was a need for emergency surgery during night shift (n = 11). 827 patients were included in the PPS analysis (carbetocin group: n = 439; oxytocin group: n = 388). 14 patients who were treated with oxytocin mistakenly due to PPH were excluded from PPS analysis (Fig. 2). Baseline characteristics of patients were shown in Table 1. The two groups were generally well balanced for the maternal age, body mass index (BMI), gestational age, parity, antepartum hemoglobin, antepartum hematocrit, pregnancy complications, birth weight and PPH risk factors.

3.2 Clinical outcomes

The primary and secondary efficacy endpoints were analyzed in FAS and PPS. When the conclusions of the two were inconsistent, the FAS analysis results were mainly considered.

The primary efficacy endpoint of the use of additional uterotonics (FAS analysis) occurred in 81 (18.4%) cases in the carbetocin group, as compared with 98 (24.4%) in the oxytocin group (Table 2). Compared with oxytocin, carbetocin showed the superiority in terms of the primary efficacy endpoint (FAS analysis, $p = 0.03$, odds ratio = 0.7, 95% CI 0.5–0.9).

The amount of intrapartum blood loss was 370.3 ± 177.4 mL in carbetocin group and 386.6±191.6 mL in oxytocin group (FAS analysis), which was no statistically

Table 2. The primary and secondary efficacy endpoint of each group.

Outcomes	FAS analysis			PPS analysis		
	Carbetocin group (n = 440)	Oxytocin group (n = 401)	*p* value	Carbetocin group (n = 439)	Oxytocin group (n = 388)	*p* value
Primary efficacy endpoint						
The use of additional uterotonics (n, %)	81 (18.4)	98 (24.4)	0.03	80 (18.2)	89 (22.9)	0.1
Secondary efficacy endpoint						
Intrapartum blood loss (mL, Mean ± SD)	370.3 ± 177.4	386.6 ± 191.6	0.2	370.3 ± 177.6	384.7 ± 185.0	0.3
Blood loss ≥800 mL intrapartum (n, %)	16 (3.6)	19 (4.7)	0.4	13 (3.0)	12 (3.1)	0.9
Blood loss within 2 hours after delivery (mL, Mean ± SD)	421.8 ± 190.8	456.1 ± 330.6	0.1	421.8 ± 190.8	456.8 ± 331.7	0.1
Blood loss within 24 hours after delivery (mL, Mean ± SD)	501.7 ± 218.1	513.7 ± 232.5	0.5	501.7 ± 218.1	513.6 ± 232.9	0.5
Blood loss ≥1000 mL postpartum (n, %)	14 (3.2)	21 (5.2)	0.1	14 (3.2)	21 (5.4)	0.1
Blood loss <1000 mL within 2 hours and ≥1000 mL within 24 hours postpartum (n, %)	8 (1.8)	10 (2.5)	0.5	8 (1.8)	10 (2.6)	0.5
Postpartum hemoglobin (g/L, Mean ± SD)	116.7 ± 12.6	116.8 ± 12.6	0.9	116.7 ± 12.6	116.9 ± 12.6	0.8
Normal (≥110 g/L, n/%)	315 (72.1)	285 (71.4)		315 (72.1)	278 (71.7)	
Mild anemia (100–110 g/L, n/%)	77 (17.6)	84 (21.1)		77 (17.6)	80 (20.6)	
Moderate anemia (70–100 g/L, n/%)	45 (10.3)	30 (7.5)		45 (10.3)	30 (7.7)	
Severe anemia (<70 g/L, n/%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Hemostatics (n, %)	1 (0.2)	5 (1.2)	0.2	1 (0.2)	4 (1.0)	0.3
Blood transfusion (n, %)	1 (0.2)	6 (1.5)	0.1	1 (0.2)	6 (1.6)	0.1
Additional surgical interventions (n, %)	26 (5.9)	20 (5.0)	0.6	26 (5.9)	19 (4.9)	0.5
Uterine massage (n, %)	1 (0.2)	4 (1.0)	0.3	1 (0.2)	4 (1.0)	0.3

FAS, full analysis set; PPS, per-protocol set; SD, standard deviations.

Table 3. The maternal and neonatal outcomes of included pregnant women.

Outcomes	Carbetocin group (n = 439)	Oxytocin group (n = 388)
Maternal outcomes (n, %)		
Organ damage	0 (0.0)	0 (0.0)
Need for respirator support	0 (0.0)	0 (0.0)
hemofiltration or plasmapheresis	0 (0.0)	0 (0.0)
Neonatal outcomes (n, %)		
Apgar score		
8–10	430 (98.0)	383 (98.7)
4–7	9 (2.1)	5 (1.3)
1–3	0 (0.0)	0 (0.0)
NICU admission	0 (0.0)	0 (0.0)

NICU, neonatal intensive care unit.

significant difference ($p > 0.05$). Either the amount of blood loss within 2 or 24 hours after delivery, the incidence of blood loss $\geq$800 mL intrapartum, the incidence of blood loss $\geq$1000 mL postpartum, or the incidence of blood loss $<$1000 mL within 2 hours and $\geq$1000 mL within 24 hours postpartum were identical between two groups (Table 2, all $p > 0.05$ in FAS and PPS analysis). In addition, there was no difference between the two groups in the postpartum hemoglobin, rate of hemostatics, blood transfusion, additional surgical interventions or uterine massage (Table 2, all $p > 0.05$ in FAS and PPS analysis).

3.3 Maternal and neonatal outcomes

The maternal and neonatal outcomes were listed in Table 3. Regarding maternal outcomes, no poor outcomes such as organ damage (heart, lung, brain, liver or kidney), need for respirator support and hemofiltration or plasmapheresis were observed in carbetocin and oxytocin groups. For neonatal outcomes, mild asphyxia (Apgar score 4–7) was occurred in 9 (2.1%) cases in the carbetocin group, as compared with 5 (1.3%) cases in the oxytocin group. No other poor neonatal outcomes such as severe asphyxia (Apgar score 1–3) or NICU admission were observed in two groups.

4. Discussion

Our study compared the efficacy and safety of initial use of carbetocin or oxytocin for prevention of PPH after elective cesarean section in Chinese high risk women. The present study found that carbetocin significantly reduced the proportion of additional uterotonics after elective cesarean section compared with oxytocin. However, no significant difference was found in the other clinical indicators of blood loss between the two groups, such as postpartum blood loss, postpartum hemoglobin, hemostatics, blood transfusion, additional surgical interventions or uterine massage.

Caesarean section is a risk factor for PPH [16,17]. Preventive use of uterotonics can reduce mean blood loss, thereby reducing maternal morbidity and mortality [6]. Although oxytocin is the first-line agent in the prevention of postpartum hemorrhage, carbetocin has found its place in modern obstetrics [18]. So far, the best products to prevent PPH have yet to be determined. In present study, we found that the carbetocin group had lower proportion of requiring additional uterotonics (18.4% vs. 24.4%, $p = 0.03$ in FAS analysis) to the oxytocin group. Similarly, Attilakos *et al.* [19] found a reduced number of additional uterotonic agents were requried in the carbetocin group compared with oxytocin group. Another study by Dansereau *et al.* [20] also concluded that carbetocin compared with oxytocin resulted in a less use of further uterotonic agents. These results demonstrated that carbetocin required lower rate of additional uterotonics than oxytocin for prevention of PPH after elective cesarean section in Chinese high risk women.

A study concluded by Maged *et al.* [21] among pregnant women who had at least two PPH risk factors showed that carbetocin was superior to oxytocin regarding postpartum blood loss, the change in hemoglobin level, and the need for uterine massage after vaginal delivery. In addition, several previous studies had showed that carbetocin reduced the blood loss and the risk of PPH in caesarean section compared to oxytocin [9,10,22]. However, similar results were not found in our research. The present study showed that no significant differences in the postpartum blood loss, postpartum hemoglobin, hemostatics, blood transfusion, additional surgical interventions or uterine massage was found between the two groups. The discrepancy between previous reports and our findings may be result from the method of calculation of blood loss during caesarean section and the population involved in this study. In present study, blood loss was calculated by measuring the volume in the suction bottle and the absorption in the surgical drapes, gauzes, and pads. The measurement inevitably included a certain amount of amniotic fluid, making the assessment less accurate. In addition, when a pregnant woman had a tendency to develop PPH, in order to deal with it in time, the cut-off value of 800 mL was used in our

study to avoid the occurrence of PPH. Besides, pregnant women with one or more PPH risk factors (scarred uterus, uterine fibroid, breech position, age $\geq$35 years) were eligible to enter this study. Cesarean section, scarred uterus and hysteromyomectomy may cause uterine damage, which increased the incidence of placental diseases and uterine atony, and thus increased the risk of PPH [23]. Previous study showed that breech position was more likely to cause difficulty of fetal delivery during cesarean section than head position and affect uterine contractions, which may be the main reason for increasing the risk of PPH [24]. Maternal age $\geq$35 was also identified as a risk factor of PPH [25]. Compared with younger pregnant women, elderly pregnant women (maternal age $\geq$35 years) had higher risk of spontaneous abortion, preterm birth, placenta previa, stillbirth, congenital disorders, and cesarean section [26]. Lastly, this study excluded women with multiple gestations and placenta previa which were associated with high risk of severe hemorrhage [27–29]. For these women, we generally use many methods to avoid PPH during cesarean section, including arterial ligation and B-Lynch suture, which could not be achieved with 30 IU oxytocin. The risk of these women was too high to be used as a randomized controlled study, especially the women in the oxytocin group. All the aforementioned factors might result in the discrepancy findings.

Several notable limitations exist in our study. First of all, our study was conducted at a single institute, which had certain limitations in clinical application. Secondly, the safety was evaluated only by the maternal and neonatal outcomes, and the drugs side effects in this study were ignored. Thirdly, the blood loss could not be measured precisely. This study needs to be repeated in a multicenter setting to further identify the impact of carbetocin on the aforementioned factors and verify our findings and hypothesis.

5. Conclusions

Carbetocin required lower rate of additional uterotonics than oxytocin for prevention of PPH after elective cesarean section in Chinese high risk women. Carbetocin was comparable to oxytocin in postpartum blood loss, postpartum hemoglobin, hemostatics, blood transfusion, additional surgical interventions or uterine massage.

Author contributions

LPZhu and YW—designed the research study. SYK, LPZhou, YFY and LY—collected data. SYK, LPZhou, YFY and LY—analyzed the data. LPZhu and YW—provided administrative support. SYK, LPZhou, LPZhu and YW—drafted the article. All authors contributed to editorial changes in the manuscript. All—final approval of the manuscript submitted.

Ethics approval and consent to participate

The protocol had been approved by ethics committee institutional review board of participating center (K2016062), and written informed consent was obtained from each participant.

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Conflict of interest

The authors declare no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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