

Preventive effect and prognosis of carbetocin on postpartum hemorrhage

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Abstract: Objective: To investigate the clinical value of carbetocin in the treatment of postpartum hemorrhage (PPH) in the hospital. Methods: From 2018 to 2022, a total of 38948 high-risk parturients admitted to the hospital were enrolled in the study. All parturients were treated with carbetocin and the therapeutic results were compared and analyzed. Results: All the parturients suffered postpartum bleeding and their newborns were in good condition. Compared with the prenatal period, the postpartum hemoglobin (Hb), red blood cell volume (RCV) and red blood cell count (RBC) were both decreased after postpartum through vaginal delivery, regrettably there was no statistical difference ($P > 0.05$). In addition, the total incidence of adverse reactions was 0.1% (11/38948), which was low. Furthermore, we found that the annual dose of carbetocin were decreased year by year after 2019, which may be correlated with the decrease in the birth rate of newborns in China. Conclusion: The use of carbetocin alleviated the clinical indications of PPH in women undergoing vaginal delivery to a certain extent. However, there was no significant difference between prenatal and postnatal biomarkers.

Keywords: postpartum hemorrhage; Carbetocin; Preventive effect; prognosis

1. Introduction

Postpartum hemorrhage is a common and dangerous obstetrical complication, which may lead to maternal death. It is especially prevalent among women with complications, increasing the likelihood of caesarean section^{1, 2}. For the health and safety of women, prevention of postpartum bleeding is of critical significance³. The bleeding is associated with various factors, such as poor uterine contraction⁴, coagulation dysfunction⁵ and lacerations of the birth canal⁶. Current prevention and treatment methods include uterine artery embolization⁷, uterine massage⁸ and uterine cavity filling⁹. Adenosine and oxytocin are commonly used. Among these drugs, carbetocin, a new type of oxytocin receptor stimulant, demonstrates faster and more lasting efficacy compared with traditional oxytocin¹⁰⁻¹². However, there is limited research on the clinical effects of carbetocin in preventing and treating postpartum hemorrhage. Accordingly, this study aims to explore the values of carbetocin in the treatment of postpartum bleeding among women in the hospital.

2. Materials and Methods

2.1 General Information

We conducted a study involving 38948 high-risk pregnant women admitted to the hospital from 2018 to 2022. Their ages ranged from 18 to 51 years, with an average age of 31.9 ± 3.1 years old. In this study, we obtained approval from the hospital ethics committee (No.2023-40). The inclusion criteria consisted of: (1) having both a full-term and single pregnancy, (2) undergoing vaginal delivery, (3) obtaining informed consent from both the mother and her family members. On the other hand, the exclusion criteria included: (1) coagulation dysfunction, (2) impairment of important functional organs such as the liver and kidney, (3) drug allergy related to this study, (4) withdrawal from the study before completion. Further details about the specific information can be found in **Table 1**.

Table 1. General data analysis of all postpartum women (n=38948).

General information		Total proportion
Age (years)	Under 20 years old	43(0.09)
	20-30	16703(36.59)
	30-40	21342(61.24)
	Over 40 years old	860(2.08)
Pregnancy frequency (times)	≤ 3	33745(90.96)
	> 3	5203(9.04)
Production frequency	≤ 3	38853(99.74)
	> 3	95(0.26)
High risk factors	Prenatal high fever	1635(4.41)
	Giant	3395(9.14)
	With Gestational diabetes	990(2.67)
	Marginal Placenta praevia	7240(20.05)
	Long production process time	11148(26.51)
	Abnormal amniotic fluid volume	4705(13.63)
	History of Caesarean section	9835(23.60)
Route of administration	Intravenous infusion	220(0.59)
	intravenous injection	38553(98.94)
	other	175(0.47)
A single dose of carbetocin	1	37728(96.80%)
	2	917(2.30%)
	≥ 3	46(0.10%)

Values are number (proportion).

2.2 Methods

Immediately after the delivery of the fetus, pregnant women received 100ug of cabetocin (manufacturer: Huiling Pharmaceutical Co., Ltd., national drug approval number H20093500) via intravenous injection. Simultaneously, the midwife aids the mother with abdominal massage to facilitate the effective delivery of the placenta. The midwife should also be capable of promptly identifying and

addressing incomplete placental delivery. Once the placenta is fully delivered, uterine massage is conducted on the postpartum woman. This can be accompanied by the application of ice packs or other appropriate methods. Furthermore, close monitoring of postpartum vital signs should be prioritized.

2.3 Observation indicators

2.3.1 To evaluate postpartum bleeding and the condition of newborns, the following measures were undertaken. Firstly, the amount of bleeding was measured at three different time points, namely during labor, 2 hours after labor, and 24 hours after labor. This was done by collecting the concentrated bleeding using a graduated aspirator and then determining the amount of bleeding at each time point using the formula: amount of bleeding = (wet weight of postpartum dressing - wet weight of prenatal dressing)/1.05. To determine if postpartum bleeding had occurred, a threshold of 500mL was established based on the amount of bleeding 24 hours after delivery. Secondly, the weight of the newborn was recorded. Lastly, the newborn's muscle tone, stimulus response, pulse, and skin color were assessed using the Apgar score, which is a scale that assigns a total score of 10 points and relates the score to the newborn's overall condition.

2.3.2 Before delivery, the blood routine of all pregnant women should be tested and compared. To do this, 3mL of fasting venous blood should be extracted from each pregnant woman. The hemoglobin, hematocrit, and red blood cell (RBC) count of the pregnant women should then be detected and compared using a fully automated blood analyzer.

2.3.3 After medication, the adverse reactions of all pregnant women, such as arrhythmia and gastrointestinal reactions, should be recorded and compared.

2.3.4 We collected the data of annual dose of carbetocin in Obstetrics and Gynecology hospital of Fudan University from 2018 to 2022 shown in Figure 1.

2.4 Statistical methods

The analysis was performed using SPSS 19.0. The χ^2 (%) test was used for the count, and a t-test ($\bar{x} \pm s$) was used for the measurement. A p-value of less than 0.05 indicates a significant difference.

3 Results

3.1 Analysis of the amount of postpartum bleeding and newborn condition

Postpartum bleeding amount in all patients in different phases was minimal ($\leq 500\text{mL}$) and newborns were in good condition (**Table 2**).

Table 2. Analysis of the amount of postpartum bleeding and newborn condition (n=38948).

Index		Indicator value
Postpartum bleeding amount (mL)	During labor	233.5 ± 11.6
	2 hours postpartum	282.7 ± 12.1
	24 hours postpartum	338.4 ± 10.3
Newborn condition	Body mass (g)	3032.7 ± 23.6
	Apgar score 1 minute after delivery (points)	9.1 ± 0.4

Values are mean±SD.

3.2 Analysis of the blood routine indicators

We found that carbetocin alleviated the clinical indicators of PPH in women undergoing vaginal delivery to a certain extent, such as hemoglobin, red blood cell specific volume and red blood cell count. However, there were not statistic significance between the prenatal period and postpartum after 24h ($P>0.05$) (**Table 3**).

Table 3. Analysis of the blood routine indicators for all postpartum women (n=38948).

Blood routine		Indicator value	T	P
Hemoglobin (g/L)	Antenatal	137.7 ± 11.7	one point six three seven	$P > 0.05$
	24 hours postpartum	134.4 ± 12.0		
Red blood cell specific volume (%)	Antenatal	40.3 ± 3.0	two point zero zero one	$P > 0.05$
	24 hours postpartum	37.0 ± 2.9		
Red blood cell count (* 1012/L)	Antenatal	4.0 ± 0.3	one point nine six seven	$P > 0.05$
	24 hours postpartum	3.7 ± 0.2		

Values are mean±SD.

3.3 Analysis of adverse reactions

After treatment, a total of 11 cases of adverse reactions were observed in postpartum women, with 7 cases being arrhythmia and 4 cases being gastrointestinal reaction. The overall incidence rate of these reactions was 0.1% (11/38948), indicating a relatively low occurrence.

3.4 Analysis of annual dose of carbetocin

Our study suggested that the annual dose of carbetocin showed an upward trend between 2018 and 2019. However, the annual dose of carbetocin decreased year by year after 2019, which may be related to the decrease in the birth rate of newborns in China (**Figure 1**).

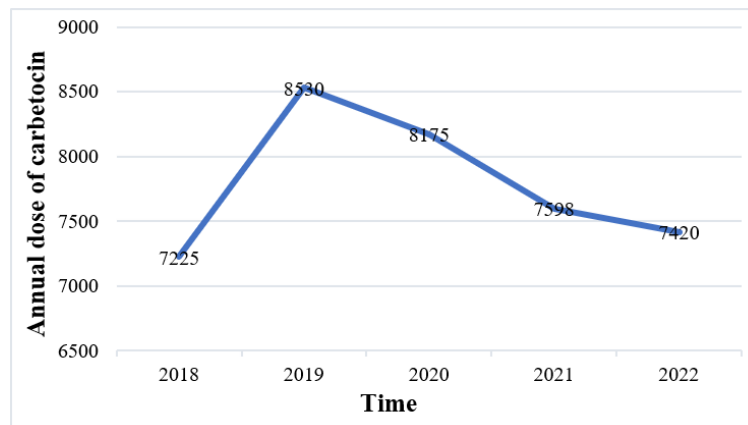


Figure 1. Annual dose of carbetocin in Obstetrics and Gynecology hospital of Fudan University from 2018 to 2022.

4. Discussion

Postpartum bleeding is one of the important factors leading to death among pregnant women. It can result from various factors such as uterine contraction, abnormal blood coagulation during pregnancy, lacerations of the birth canal and placenta issues¹³. Among these factors, uterine contraction fatigue is a common cause with an incidence rate of approximately 80%¹⁴⁻¹⁶. Therefore, effective prevention of uterine contraction fatigue is crucial for pregnant women to reduce the occurrence of postpartum bleeding and its associated mortality. Relevant studies have identified several important risk factors, including advanced maternal age¹⁷, macrosomia¹⁸, marginal placenta previa¹⁹, abnormal amniotic fluid²⁰, and prenatal high fever²¹. In light of this, it is imperative to address these high-risk factors in pregnant women to effectively prevent uterine contraction fatigue after delivery. This approach holds vital significance in reducing the incidence of postpartum bleeding and minimizing postpartum death.

Prostaglandin, oxytocin, and Ergometrine are currently the main drugs in the clinical treatment of postpartum bleeding²². Oxytocin, widely used and popularized for its short action time and fast onset, has a good promoting function for the contraction of the upper segment of the uterus^{23, 24}. However, its effectiveness is limited when the receptor site that binds to oxytocin is in a full state, regardless of increased dosage²⁵. Xinmupei, a kind of prostaglandin, can strengthen the tension of uterine smooth muscle and has a good hemostatic effect²⁶. However, its clinical promotion is constrained due to digestive tract side effects and high price²⁷. In recent years, carbetocin, a synthetic polypeptide hormone, has been gradually applied in clinical practice. By combining with the oxytocin receptor of uterine smooth muscle, carbetocin promotes myotonic contraction and effectively stops bleeding by compressing the blood vessels in the myometrium²⁸. Research has revealed that carbetocin injection can rapidly induce uterine contraction in pregnant women in a short period of time, with higher amplitude and frequency compared to conventional oxytocin²⁹. Moreo-

ver, carbetocin belongs to a long-acting oxytocin with a clearance half-life 4-10 times longer than conventional oxytocin³⁰. This study demonstrates reduced postpartum bleeding in all mothers and favorable conditions for newborns, thus indicating that carbetocin treatment effectively prevents postpartum bleeding among puerpera, contributing to newborn health.

Carbetocin is an effective preventive measure for postpartum bleeding in high-risk pregnant women, as it reduces the amount of bleeding and avoids its occurrence³¹. Conventional oxytocin is commonly used in most hospitals for uterine contraction enhancement due to its efficacy and low cost²⁹. However, when patients have high-risk factors for postpartum uterine inertia, the use of conventional oxytocin may not effectively control postpartum vaginal bleeding³⁰. In such cases, intervention measures such as ice pack application, uterine massage, and drug combinations are required. In severe cases, blood transfusion or surgical hemostasis may be necessary, increasing the burden on patient postpartum recovery, life safety, medical costs, and nursing resources¹. Research shows that the intravenous drip of oxytocin and the assistance of carbetocin injection effectively prevent postpartum bleeding, especially in parturients who have undergone Caesarean section³². The use of carbetocin further strengthens uterine contraction, reducing postoperative bleeding significantly compared to conventional treatment³¹. Carbetocin is also effective in preventing postpartum bleeding in parturients with high-risk factors such as placenta previa and scar uterus³³. Some scholars argue that carbetocin is more effective than conventional oxytocin in preventing or treating postpartum bleeding, especially when uterine atony or oxytocin's hemostatic effect is not ideal³⁴. However, repeated use of oxytocin may lead to depleted oxytocin receptor positions, reducing the effectiveness of carbetocin for stopping bleeding³⁵. These factors require further investigation. This study found that postpartum women had lower hemoglobin, hematocrit, and red blood cell count compared to prenatal women, but the difference was not statistically significant ($P>0.05$). This indicates that carbetocin has a positive effect on preventing and treating postpartum bleeding without significantly impacting blood routine indicators. However, the occurrence of this situation may depend on the level of medical and nursing technology at the hospital. Active intervention and treatment of patients with increased postpartum bleeding effectively suppress bleeding and maintain stable maternal vital signs.

This study further confirmed the safety and relatively good implementation effect of carbetocin during its treatment. The total incidence of adverse reactions is 0.1% (11/38948), with a lower overall incidence. Although some patients may experience arrhythmias, gastrointestinal reactions, etc., their symptoms are relatively mild and last for a short period of time, and they can improve without special treatment, which fully explains the safety of the use of carbetocin. In addition, it is not only simple and convenient but also relatively safe to treat vaginal delivery mothers with carbetocin³⁶. For some high-risk patients with postpartum bleeding, after completing the intravenous injection of carbetocin,

relevant venous pathways can be directly established to facilitate timely administration when necessary, thus ensuring the feasibility of the follow-up treatment scheme³⁷. This study shows that the safety of carbetocin in the prevention and treatment of postpartum bleeding is relatively high, as the incidence of adverse reactions is low. However, more clinical research is needed for the application of carbetocin in vaginal delivery, as the current research is limited and the dosage is not uniform. Nonetheless, recent studies have shown that carbetocin has been effectively used in vaginal delivery, providing promising results for its future widespread use in clinical practice³¹. Furthermore, the use of carbetocin in vaginal delivery reduces the pain caused by repeated intramuscular injection of oxytocin, leading to improved treatment compliance among patients³⁷. Therefore, the application of carbetocin in the prevention and treatment of postpartum bleeding in vaginal delivery emerges as a relatively safe and convenient treatment option, with high clinical application and promotion value.

When it comes to high-risk pregnant women with postpartum uterine contractions and fatigue, carbetocin can be used as a routine drug to reduce the ineffective and repeated use of oxytocin and prevent the consumption of oxytocin receptor sites². Additionally, immediate administration of carbetocin after delivery in high-risk mothers can promote continuous intensification of uterine contractions, thereby minimizing postpartum bleeding, reducing medical costs, and avoiding the waste of nursing resources³³. This approach can also play a positive role in promoting postpartum recovery and is safer and more acceptable for mothers³⁸. However, further optimization of the specific dosage of carbetocin will need to be confirmed through large-scale, multicenter experiments in the future, which is one of the important goals of our research.

In summary, carbetocin can effectively prevent postpartum bleeding in hospitalized puerpera. It significantly reduces bleeding, ensuring the safety of the puerpera and improving their prognosis.

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