Tropical Journal of Pharmaceutical Research August 2023; 22(8): 1661-1666
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i8.17

Original Research Article

Effect of carboprost tromethamine and carbetocin on coagulation factors and prognosis in puerpera with postpartum hemorrhage due to uterine inertia

Hong Chen[1], Huifang Xiong[1]*, Chunmei Chen[2], Liping Fan[1]
[1]Department of Obstetrics, [2]Department of Pharmacy, Longyan First Hospital Affiliated of Fujian Medical University, Longyan, Fujian Province 364000, China

For correspondence:* ***Email:* *xhf_huifang99@163.com;* ***Tel:*** *+86-18396303603*

Sent for review: 10 March 2023 *Revised accepted: 23 July 2023*

Abstract

Purpose: *To determine the effect of carboprost tromethamine and carbetocin on coagulation factors and prognosis in puerpera with postpartum hemorrhage due to uterine inertia.*
Methods: *A total of 80 high-risk pregnant women with postpartum hemorrhage due to uterine inertia admitted to Longyan First Hospital Affiliated of Fujian Medical University, Longyan, China from June 2021 to June 2022 were randomly divided into control group (oxytocin + carboprost tromethamine, n = 40) and study group (oxytocin + carboprost tromethamine + carbetocin, n = 40). Vaginal bleeding volume was recorded for both groups at delivery, and 2 and 24 h after delivery. Decrease in hemoglobin level 24 h after delivery, as well as levels of coagulation factors, and adverse drug reactions before and after treatment were assessed.*
Results: *The third stage of labor, postpartum hemorrhage at 2 and 24 h, and decrease in hemoglobin 24 h after delivery in the study group were lower ($p < 0.05$). Compared with that before treatment, PLT and FIB levels also fell, while APTT and PT levels rose in both groups after treatment for 24 h ($p < 0.05$). Platelet count and fibrinogen levels in the study group were lower after treatment for 24 h, but APTT and PT levels were higher ($p < 0.05$). There was no statistically significant difference in the incidence of adverse drug reactions between both groups (15.00 vs 12.50 %; $p > 0.05$).*
Conclusion: *Co-administration of carboprost tromethamine with carbetocin prevents high-risk postpartum hemorrhage in pregnant women due to uterine inertia. It also reduces the level of bleeding, and promotes recovery of coagulation function. However, further clinical trials on a larger scale are recommended prior to the application of this treatment strategy in clinical practice.*

Keywords: *Uterine inertia, Postpartum hemorrhage. Carboprost tromethamine, Carbetocin, Coagulation factors*

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INTRODUCTION

Postpartum hemorrhage remains a common clinical delivery complication and a leading cause of maternal death [1,2], uterine inertia has emerged as the dominant causative factor of postpartum hemorrhage. Early judgment of risk in maternal postpartum hemorrhage, and preventive use of drugs are critical measures to improve its prognosis [3]. Factors affecting

postpartum hemorrhage due to uterine inertia entail systemic and local factors, and common triggers include: maternal physical weakness, mental stress, combined chronic diseases, as well as prolonged labor [4]. The treatment of postpartum hemorrhage due to uterine inertia is mainly comprised of general treatment, drug therapy, uterine tamponade and surgery. The use of drugs is the first choice treatment. Oxytocin is the drug of choice for postpartum hemorrhage due to uterine inertia, as it is cheap, with a rapid onset of action. However, its duration of action is short, with the key disadvantage being saturation of the receptors [5]. Carboprost tromethamine is a novel prostaglandin preparation that effectively improves uterine smooth muscle contraction [6]. Carbetocin is a synthetic long-acting oxytocin with agonistic properties, and potent uterotonic effects on pregnant or just delivered uteruses [7]. It has stronger biological activity and longer half-life. Besides, its efficacy is similar to that of natural oxytocin, and promotes rhythmic uterine contraction as well as a rapid onset of action. Moreover, carboprost tromethamine exerts a clear effect within 2 minutes of medication [8]. The aim of this study was to investigate the clinical effectiveness of the above drugs in the prevention of postpartum hemorrhage due to uterine inertia.

METHODS

Patients

A total of 80 pregnant women with postpartum hemorrhage due to uterine inertia were admitted to the hospital from June 2021 to June 2022, and were enrolled in the study.

Inclusion criteria

Patients were delivered vaginally, as well as risk factors of postpartum hemorrhage due to uterine inertia, including increased labor, intrauterine infection, polyhydramnios, placenta previa and so on.

Exclusion criteria

Patients with drug allergy; also, coagulation disorders, soft birth canal injury; as well as residual placenta.

Grouping of patients

Based on the medication regimen of parturients, the parturients were separated into control group (oxytocin + carboprost tromethamine) and study group (oxytocin + carboprost tromethamine + carbetocin). The parturients in the control group were 22 - 36 years old (mean, 27.86 ± 4.15 years). Gestational age was 38 - 42 weeks (mean, 40.11 ± 1.08 weeks); parturients in the control group were 21 - 35 years old (mean, 28.79 ± 5.04 years, while gestational age was 38 - 41 weeks (mean, 39.14 ± 1.09 weeks). There were no statistically significant difference in the general data between the two groups ($p > 0.05$).

Ethical approval

All procedures performed in the studies involving human participants were approved by the Ethics Committee of Longyan First Hospital Affiliated of Fujian Medical University (approval no. LYREC2023-k038-01), and followed the guidelines of the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [7]. Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Treatments

After delivery of the fetus, the parturients in both groups were given 10 U oxytocin (Anhui BBCA Pharmaceutical Co. Ltd, State Medical Permit no. H34020474) via intravenous drip. The parturients in the control group were given carboprost tromethamine (Changzhou Siyao Pharmaceuticals Co. Ltd, State Medical Permit no. H20094183) via cervical injection at a first dose of 250 μg. If the parturients showed further bleeding and failed to obtain the ideal hemostatic effect, carboprost tromethamine was applied again every 15 min. The total dose was controlled below 2 mg. The study group was treated with carbetocin based on the treatment of the control group, 100 μg carbetocin (Hybio Pharmaceutical Co. Ltd, State Medical Permit no. H20163023) was injected intravenously within 1 min.

Evaluation of parameters/indices

The vaginal bleeding volume during the third stage of labor and at 2 h and 24 h after delivery were compared between both groups. The amount of bleeding was calculated by weighing or volumetric methods to compare the level of hemoglobin decrease before delivery and 24 h after delivery between both groups. Cubital venous blood was collected before delivery and 24 h after delivery, and hemoglobin values were measured using colorimetry with an ABX Pentra-120 automatic hematology analyzer (HORIBA ABX, France).

Table 1: Comparison of bleeding volume at each time-point between the two groups (mean ± SD, mL)

Group	N	Third stage of labor	2h after delivery	24h after delivery
Study	40	91.58±16.87	50.69±10.57	189.57±20.33
Control	40	189.77±20.35	92.74±12.43	411.39±46.58
T		23.493	16.299	27.604
P-value		<0.001	<0.001	<0.001

Peripheral venous blood was collected before and 24 hours after delivery to compare coagulation factor levels between the two groups, which included platelet count (PLT), fibrinogen (FIB), activated partial thromboplastin time (APTT), and prothrombin time (PT). Adverse drug reactions were compared between both groups.

Statistical analysis

Data were processed using SPSS 19.0 statistical software. Measurement data are expressed as mean ± SD. Independent sample t-test was employed to compare mean values between the two groups while paired t-test was used to compare the mean before and after treatment. Enumeration data are presented as numbers and percentages. Chi squared test was used to compare the two groups, and $p < 0.05$ considered statistically significant.

RESULTS

Bleeding volume

Bleeding volume during the third stage of labor, and at 2 and 24 h after delivery in the study group were lower than in the control group ($p < 0.05$; Table 1).

Hemoglobin levels

The decrease in hemoglobin levels 24 h after delivery in the study group was lower than that in the control group ($p < 0.05$; Table 2).

Levels of coagulation factors

Compared with the values before treatment, PLT and FIB levels decreased, while APTT and PT levels increased in both groups after treatment for 24 h ($p < 0.05$). Platelet and FIB levels in the study group were lower than that in the control group after treatment for 24 h, while APTT and PT levels were higher than the control group ($p < 0.05$), as shown in Table 3.

Table 2: Comparison of hemoglobin levels between both groups (mean ± SD, g/L, n = 40)

Group	Decreased levels of hemoglobin 24h after delivery (g/L)
Study	10.36±1.65
Control	20.47±2.37
T	22.142
P-value	<0.001

Incidence of adverse drug reactions

There were no statistically significant differences in adverse drug reactions between the two groups ($p > 0.05$), as shown in Table 4.

DISCUSSION

The World Health Organization (WHO) statistics show that postpartum hemorrhage is a prominent factor in obstetric hemorrhage, and the prevention of postpartum hemorrhage is the key to solving obstetric hemorrhage [9]. As the leading cause of death due to obstetric hemorrhage, postpartum hemorrhage serves as the main reason for hysterectomy [10]. The etiology of postpartum hemorrhage is mainly linked uterine inertia, birth canal injury, coagulation dysfunction or placental abnormalities. Uterine inertia is the predominant factor in postpartum hemorrhage [11,12]. Factors affecting postpartum hemorrhage due to uterine inertia be divided into systemic factors and local factors.

Table 3: Comparison of coagulation factor levels between both groups (mean ± SD)

Group	Time	PLT (×10^9/L)	FIB (g/L)	APTT (s)	PT (s)
Study (n=40)	Pre-medication	340.57±46.58	3.37±0.37	23.47±4.17	9.68±1.85
	24 h after medication	167.58±25.17[a]	2.11±0.45[a]	29.66±5.02[a]	11.43±2.09
Control (n=40)	Pre-medication	341.15±50.34	3.28±0.56	24.02±4.22	9.48±1.93
	24 h after medication	263.47±33.76	2.57±0.28	26.41±5.11	10.21±2.21
Comparison between both groups after 24h of medication	*t*	14.402	5.489	2.869	2.537
	P-value	<0.001	<0.001	0.005	0.013

[a]$P < 0.05$, compared with the same group before treatment

Table 4: Incidence of adverse drug reactions in the two groups {n (%)}

Group	n	Diarrhoea	Hypertension	Hot flashes	Chest tightness and headache	Nausea and vomiting	Metallic taste in mouth	Total
Study	40	1 (2.50)	1 (2.50)	2 (5.00)	0 (0.00)	1 (2.50)	1 (2.50)	6 (15.00)
Control	40	0 (0.00)	0 (0.00)	3 (7.50)	1 (2.50)	0 (0.00)	1 (2.50)	5 (12.50)
χ^2		--	--	--	--	--	--	0.105
P-value		--	--	--	--	--	--	0.745

The common triggers are maternal physical weakness, chronic diseases, mental stress, use of excessive anesthetics/sedatives/tocolytics, prolonged labor, preeclampsia, polyhydramnios, and infection of the amniotic cavity.

At present, the treatment of postpartum hemorrhage resulting from uterine inertia is divided into general treatment, drug treatment, uterine tamponade and surgery with the use of drugs being the optimal treatment [13-15]. Oxytocin is the most widely used drug in clinical practice, as it has a rapid onset of action and is safe, but its duration of action is short. The half-life of the drug is 1 - 6 min, and the effect of oxytocin depends on the number of oxytocin receptors in the body. When the receptor is saturated, increasing the dose does not enhance uterine contraction, but gives rise to various adverse reactions which limit the clinical application of oxytocin [16].

It is essential to identify more effective uterotonic drugs for use in the prevention and treatment of postpartum hemorrhage due to uterine inertia. Carboprost tromethamine, a natural prost methyl salt solution, is a Ca^{2+} carrier that increases intracellular Ca^{2+} concentration, inhibits adenylyl cyclase activity, activates myosin light-chain kinase, and persistently stimulates uterine smooth muscle contraction [17]. Compared with traditional prostaglandin drugs, carboprost tromethamine uses methyl to replace 15-hydroxy and it has stronger biological activity and a longer half-life. In addition, it is widely used in the prevention and treatment of postpartum hemorrhage [18]. Numerous studies have indicated that carboprost tromethamine is more effective than oxytocin in the prevention and treatment of postpartum hemorrhage due to uterine inertia [19-21].

However, the present work did not include a group using oxytocin alone. Nonetheless, the level of bleeding during the third stage of labor, and 2 and 24 h postpartum in the control group which used oxytocin combined with carboprost tromethamine was lower than the level of bleeding in previous studies where oxytocin alone was used.

Carbetocin is a synthetic long-acting oxytocin with agonist properties that has similar efficacy to natural oxytocin; it also promotes rhythmic uterine contraction, and increases contraction frequency and uterine tone [22]. Carbetocin has a rapid onset of action and exerts a rapid effect within 2 min of medication, with a drug half-life of 40 min. Its duration of action on uterine activity is significantly longer than that of oxytocin [23]. As discovered in the current study, the use of carbetocin based on the application of oxytocin combined with carboprost tromethamine further reduced vaginal bleeding during and after delivery, and decreased the level of hemoglobin 24 h after delivery.

Cases of postpartum hemorrhage due to uterine inertia are often accompanied by coagulation dysfunction. The present work found that the levels of coagulation factors (PLT, FIB, APTT and PT) in the study group significantly improved after 24 h of treatment, compared with that before the treatment. The improvement was higher than in the control group. This suggests that the combination of carboprost tromethamine and carbetocin has a synergistic effect, facilitates regular uterine contraction, and prevents postpartum hemorrhage. Furthermore, it reduced bleeding volume and improved medication safety.

CONCLUSION

The combined use of carboprost tromethamine and carbetocin prevents postpartum hemorrhage due to uterine inertia in high-risk pregnant women, reduces the level of bleeding, and facilitates the recovery of coagulation function. However, further clinical trials are required prior to the use of combination therapy in clinical practice.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

This study was approved by the Ethics Committee of Longyan First Hospital Affiliated of Fujian Medical University, China (approval no. LYREC2023-k038-01).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Hong Chen and Huifang Xiong designed the study and carried them out; Hong Chen, Huifang Xiong, Chunmei Chen and Liping Fan supervised the data collection, analyzed and interpreted the data, prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript.

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