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Original Research Article

Effect of combined administration of carboprost tromethamine and ergometrine on uterine atony-induced postpartum hemorrhage

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Abstract

Purpose: *To determine the efficacy of the combined use of carboprost tromethamine and ergometrine in the prevention and treatment of postpartum hemorrhage induced by uterine atony.*
Methods: *A total of 66 pregnant women with postpartum hemorrhage due to uterine atony who were treated in Fuyang Women's and Children's Hospital from February 2019 to January 2022 were randomly and equally assigned to control and combination groups, respectively, based on the order of admission. The control group was treated with 0.2 mg of ergometrine maleate via intramuscular injection in the buttocks. In the combination group, the patients were also given 250 µg of carboprost tromethamine via cervical injection in addition to ergometrine. The two groups were compared in terms of volume of postpartum vaginal bleeding and hemoglobin levels, coagulation function index, clinical effectiveness and incidence of adverse reactions.*
Results: *There was a significant difference in total treatment effectiveness between the two groups (69.70 vs 90.91%; $\chi^2 = 4.694$, $p = 0.03$) with the combination group showing higher effectiveness. The volume of bleeding in the combination group at 2 h and 24 h after delivery were significantly lower than the corresponding values for the control group ($p < 0.05$). Comparison at 24 h postpartum showed significantly lower hemoglobin level in the combination group than in the control group ($p < 0.05$). Post-treatment levels of prothrombin time (PT) and thrombin time (TT) in the two groups were lower than the pre-treatment values, but the post-treatment levels in the combination group were lower than those in the control group ($p < 0.05$).*
Conclusion: *Combined administration of carboprost tromethamine and ergometrine may be a viable treatment strategy for uterine atony-induced postpartum hemorrhage. It has acceptable level of safety. However, further clinical trials are required prior to application in clinical practice.*

Keywords: *Carboprost tromethamine, Ergometrine, Postpartum hemorrhage, Uterine atony*

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INTRODUCTION

Postpartum hemorrhage is a serious obstetric disease which occurs 2 h after delivery. Approximately 70 – 90 % of postpartum hemorrhage is attributed to uterine atony, dysfunctional coagulation, and placental factors [1,2]. The clinical manifestations of postpartum hemorrhage are abnormal uterine contractions and vaginal bleeding, which may result in

respiratory distress syndrome or even shock, thereby constituting serious threat to the lives of the patients [3,4]. Therefore, it is important to develop effective prevention and treatment strategies for uterine atony so as to reduce or prevent postpartum hemorrhage.

At present, uterotonic drugs such as ergometrine and oxytocin are used clinically to treat postpartum hemorrhage caused by uterine atony. Although these drugs effectively induce uterine contraction, their duration of action is short, and complications result at high doses. In addition, the use of a single drug is not effective in some patients with uterine atjony [5,6]. Therefore, it is very necessary to use combination of ergometrine and other uterotonic agents to prevent and treat postpartum hemorrhage.

Studies have shown that carboprost, a derivative of natural prostaglandin F2α, exerts the pharmacological effect of continuously enhancing uterine contractions, and it also softens the cervix. Carboprost tromethamine has produced good therapeutic effect on postpartum hemorrhage caused by uterine atony [8,9]. This study investigated the efficacy of combination of carboprost tromethamine and ergometrine in the treatment of uterine atony-induced postpartum hemorrhage, in order to provide a reliable experimental basis for its subsequent use in clinical practice.

METHODS

Patients' baseline information

A total of 66 pregnant women with uterine atony-induced postpartum hemorrhage who were treated in Fuyang Women's and Children's Hospital from February 2019 to January 2022, were randomly and equally assigned to a control group and a combination group, based on order of admission. The control group had 1 to 2 gravidities (mean gravidity = 1.25 ± 0.24), and the mean age was 28.51 ± 4.20 years, while the gestational age ranged from 38 to 42 weeks (mean gestational age = 40.17 ± 1.23 weeks). The combined group had 1 to 2 gravidities (mean gravidity = 1.24 ± 0.19); their ages ranged from 21 to 41 years (mean age = 28.93 ± 4.46 years), and gestational age ranged from 37 to 41 weeks (mean gestational age = 40.13 ± 1.08 weeks). The baseline data of two groups were similar.

Inclusion criteria

Patients in the following categories were included in the study: those who met the diagnostic criteria for postpartum hemorrhage as stipulated in *Guidelines for the Prevention and Management of Postpartum Hemorrhage* (2014), patients with bleeding volume ≥ 500 mL, those who experienced postpartum hemorrhage due to uterine atony, and those who were not allergic to the drugs used in the study.

Exclusion criteria

Patients who had dysfunctional coagulation, those with soft injury in the birth canal or diseases of the immune system, and patients who withdrew half-way during the study, were excluded from the study.

All patients in this study were informed about the purpose of the study and the procedures involved, and they signed informed consent letters. This study was carried out with the approval of the Ethics Committee of Fuyang Women's and Children's Hospital (approval no. 2016662). All the procedures were conducted in line with the principles in Declaration of Helsinki [10].

Treatments

Each of the patients in both groups was given massage on the uterus until the fetus was delivered, as well as intramuscular injection of 20 U oxytocin (Ningbo Renjian Pharmaceutical Group Co. Ltd, H33021019; specification: 10 U/mL). If bleeding still continued after placenta separation, 20 U oxytocin was intravenously infused. Patients in the control group were given 0.2 mg of ergometrine maleate (Sancai Shiqi Pharmaceutical Co. Ltd, H44023656; specification: 0.2 mg/mL) via intramuscular injection in the buttocks. In the combination group, the patients were given 250 μg of carboprost tromethamine (Zhejiang Xianju Pharmaceutical Co. Ltd, registration number = HJ20170146; specification: 250 μg/mL) via cervical injection. If the resultant hemostatic effect was not adequate, carboprost tromethamine was given every 15 min, with total amount not exceeding 2 mg.

Evaluations of parameters/indicators

Volume of postpartum vaginal bleeding and hemoglobin levels

Fasting venous blood (5 mL) was collected from each patient in both groups in the morning before and after treatment, and Hb level was determined using an automatic biochemical analyzer. Gravimetric method was used to calculate postpartum vaginal bleeding at 24 h.

Coagulation function index

Fasting venous blood (5 mL) taken from each patient in the morning was tested for coagulation function indexes. Following centrifugation at 3 000 rpm for 10 min, Japan Sysmex CA-1500 automatic coagulation analyzer was used to measure prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), and D-dimer (D-D) of prenatal and 2-h postpartum mothers. The reagents used were purchased from Dade Behring Company, and the operation was carried out in strict accordance with the instructions on the reagents. All samples were tested within 2 h.

Clinical effectiveness

After treatment, the clinical effects produced in the two groups of patients were evaluated according to the treatment standards for postpartum hemorrhage in *Routines of Diagnosis and Treatment of Obstetrics and Gynecology*. If the patient's uterus contracted significantly within 15-20 min of medication, and the amount of bleeding was significantly reduced, the treatment was *markedly effective*. If the uterus contracted significantly within 20-25 min of the medication, and the amount of bleeding was decreased, the treatment outcome was deemed *effective*. However, treatment outcome was regarded as *ineffective* if the uterus did not contract significantly after 30 min of medication, and the amount of bleeding did not decrease, or if the volume of bleeding was increased. Total treatment effectiveness (TE) was calculated as shown in Eq 1, where M represents markedly effective and E represents effective.

$$TE\ (\%) = \{(M + E)/\text{total number of patients}\}100 \quad \ldots\ldots\ldots (1)$$

Incidence of adverse reactions

The incidence of adverse reactions in the two groups was compared.

Statistical analysis

All data analyses were performed with SPSS version 22.0 software. Measurement data and count data were analyzed using *t*-test and chi-square test, respectively. Values of $p < 0.05$ indicated that the differences were statistically significant.

RESULTS

Clinical efficacy

There were 23 patients who showed treatment effectiveness in the control group, while the corresponding number in the study group (combination group) was 30. There was a significant difference in total treatment effectiveness between the two groups (69.70 vs 90.91 %; $\chi^2 = 4.694$, $p = 0.03$). These results are presented in Table 1.

Postpartum hemorrhage, vaginal bleeding and Hb levels

The amount of vaginal bleeding and the level of hemoglobin in the two groups were decreased significantly over time. The amounts of bleeding in the combined group at 2 h and 24 h after delivery were significantly lower than those in the control group ($p < 0.05$). There was no significant difference in the hemoglobin level between the control group and the combination group at 2 h postpartum. However, comparison at 24 h postpartum showed that the hemoglobin level in the combination group was significantly lower than that in the control group ($p < 0.05$). These results are shown in Table 2.

Coagulation function indices

The levels of PT and TT in the two groups after treatment were lower than the corresponding pre-treatment values ($p < 0.05$), while PT and TT levels in the combination group were lower than those in the control group post-treatment ($p < 0.05$). The levels of FIB and D-D in the two groups were significantly increased after treatment, but the degrees of increase in the combination group were significantly greater than those in the control group ($p < 0.05$; Table 3 and Table 4).

Table 1: Comparison of clinical treatment effects between the 2 groups of patients {n (%), N = 66)}

Group	Markedly effective	Effective	Ineffective	Total effectiveness (%)
Control	16	7	10	23 (69.70%)
Combined	24	6	3	30 (90.91%)
χ^2				4.694
P-value				0.03

Table 2: Comparison of volume of postpartum hemorrhage and Hg levels between the 2 groups of patients (mean ± SD, N = 33)

Group	Vaginal bleeding		Hb level	
	2 h postpartum	***24 h postpartum***	***2 h postpartum***	***24 h postpartum***
Control	314.22±58.73	193.21±51.38	126.82±9.11	22.34±4.85
Combined	261.39±50.18	133.62±45.85	126.79±9.71	12.18±3.70
t	3.836	4.971	0.852	9.671
P-value	<0.001	<0.001	1.303	<0.001

Table 3: Comparison of coagulation function indexes (PT and TT) between the 2 groups of patients (mean ± SD, N = 33)

Group	PT (s)		TT (s)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
Control	12.54±1.21	11.24±0.76*	16.42±1.06	14.27±1.93*
Combined	12.52±1.17	10.14±1,35*	16.82±1.29	12.14±1.72*
t	0.068	4.079	1.376	4.733
P-value	0.946	<0.001	0.174	<0.001

Table 4: Comparison of coagulation function indices (FIB and D-D) between the 2 groups of patients (mean ± SD, N = 33)

Group	FIB（g/L）		D-D（mg/L）	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
Control	2.26±0.97	3.01±0.65*	0.22±0.03	0.31±0.06*
Combined	2.23±0.81	4.03±0.61*	0.22±0.05	0.51±0.08*
t	0.136	6.573	0.0	11.489
P-value	0.892	<0.001	1.0	<0.001

**P* < 0.05, compared with the same group before treatment; FIB, fibrinogen; D-D, D-dimer

Table 5: Comparison of the incidence of adverse reactions between the two groups {n (%), N = 33}

Group	Nausea and vomiting	Chest tightness	Dizziness and headache	High blood pressure	Rapid heartbeat	Total incidence (%)
Control	2	2	3	1	2	10 (30.30%)
Combined	2	2	1	1	1	7 (21.21%)
χ^2						0.713
P-value						0.398

Incidence of adverse reactions

In the control group, there were 2 cases of nausea and vomiting, 2 cases of chest tightness, 3 cases of dizziness and headache, 1 case of elevated blood pressure, and 2 cases of rapid heartbeat. In the combination group, there were 2 cases of nausea and vomiting, 2 cases of chest tightness, 1 case of dizziness and headache, 1 case of elevated blood pressure, and 1 case of rapid heartbeat. There was no significant difference in the incidence of adverse reactions between the control group and the combined group (30.30 % vs 21.21%; $p > 0.05$). These results are shown in Table 5.

DISCUSSION

During pregnancy, expectant mothers are easily affected by factors (such as fetus and placenta) which leads to changes in the uterus, resulting in atony and postpartum hemorrhage [10]. Atony-induced postpartum hemorrhage is common in clinical practice. At present, the main treatment strategies for the disease comprise drug therapy, uterine packing, surgery and interventional therapy, among which drug therapy is frequently used [11]. At present, oxytocin and ergometrine are the first-line drugs for the prevention and treatment of postpartum hemorrhage worldwide. When administered, the drugs diffuse rapidly through the uterine muscle tissue, and they have rapid-action profiles. However, the efficacy of these drugs is receptor-dependent and of short duration [11].

Evidence suggests that carboprost tromethamine is effective in promoting uterine contraction. Its bioactive derivative is 15-methyl prostaglandin F2α which has higher biological activity and a longer drug half-life than the parent drug. The

plasma concentration of the drug peaked 20 min after it was administered; it effectively increased the frequency of uterine contractions, and rapidly produced hemostasis by closing open blood sinuses [12,13].

The results of this study showed that 23 patients showed treatment effectiveness in the control group, while the corresponding number of patients in the study group was 30. Vaginal bleeding volume and hemoglobin level in the two groups were decreased significantly with time, and the volumes of postpartum bleeding at 2 h and 24 h in the combination group were significantly lower than those in the control group. There was no significant difference in the level of hemoglobin between the control group and the combination group at 2 h postpartum. However, at 24 h postpartum, the level of hemoglobin in the combination group was significantly lower than that in the control group. This finding suggests that the combined use of ergometrine and carboprost tromethamine produces a significant and beneficial effect in the treatment of postpartum hemorrhage caused by uterine atony by significantly reducing the amount of postpartum vaginal bleeding. The possible explanation for this finding is that ergometrine is a uterine contraction drug with relatively powerful and selective pharmacological effect on uterine smooth muscle. Ergometrine acts directly on uterine smooth muscle and significantly enhances the tonic contraction of uterine fibers and vascular tissue, thereby producing the therapeutic effect of hemostasis [14].

Carboprost tromethamine is an oxytocin receptor agonist with a longer half-life and more powerful biological activity than ergometrine. It effectively blocks the physiological pathway of cyclic adenosine monophosphate synthesis, significantly reduces the degree of phosphorylation of sarcoplasmic reticulum proteins, and reduces binding of calcium ions. As a result, there is marked increase in the level of calcium ions in the cytoplasm, which in turn promotes the contraction of uterine myofibrillar tissue, significantly increases the level of intrauterine pressure, and closes open blood vessels and sinusoids [15].

Carboprost tromethamine produces hemostasis by enhancing platelet aggregation under endothelial collagen fibers, promoting the synthesis and release of bioactive vasoconstrictor substances, promoting the contraction and movement of vascular tissue, and causing thrombosis [16]. The present study also found no significant difference in the incidence of adverse reactions between the control group and the combination group, indicating that the combined use of the two drugs was of acceptable safety. Complications such as obstetric hemorrhage can be effectively prevented and treated through coagulation function test. The shortening of PT and TT is related to increased concentrations of coagulation factors during pregnancy. An increase in FIB enhances the aggregation of cells and platelets and promotes hemostasis. However, high FIB easily results in thrombosis. It is known that D-D, a molecular marker of secondary hyperfibrinolysis, increases with increase in FIB. In pregnant women, increased D-D content may activate thrombin [17].

In the present study, the levels of PT and TT in two groups of patients after treatment were lower than the corresponding pre-treatment values, and the levels in the combination group were lower than those in the control group post-treatment. The levels of FIB and D-D in the two groups were significantly increased after treatment, but the degree of increase in the combination group was significantly greater than that in the control group. This suggests that the combined use of the two drugs effectively improved coagulation function in puerperae, thereby reducing the amount of postpartum hemorrhage [18,19].

Limitations of the study

However, there are some limitations in this study. The sample size used was small. The small sample size will affect the robustness and generalizability of the findings. Therefore, there is need for further studies with a larger sample size to validate the current findings.

CONCLUSION

The combined administration of carboprost tromethamine and ergometrine may be a viable strategy in the treatment of postpartum hemorrhage caused by uterine atony. It is of acceptable safety, however, further clinical trials are required prior to its introduction into clinical practice.

DECLARATIONS

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Ethical approval

This study was carried out with the approval of the Ethics Committee of Fuyang Women's and Children's Hospital (approval no. 2016662).

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.

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