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Original Article

Effects of carbetocin combined with ergometrine maleate on blood loss and coagulation function of puerperae with postpartum haemorrhage

Hui Xue, Weijing Wang

The Fifth Department of Obstetrics, Harbin Red Cross Central Hospital, No. 415, Xinyang Road, Daoli District, Harbin 150076, Heilongjiang, China

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Abstract: Objective: To determine the effects of carbetocin combined with ergometrine maleate on blood loss and coagulation function of puerperae with postpartum haemorrhage (PH). Methods: In this retrospective study, the clinical data of 102 puerperae with PH treated in Harbin Red Cross Central Hospital from March 2019 to February 2022 were analyzed. Among them, 45 puerperae treated with carbetocin alone were assigned to the control group, and the other 57 treated with carbetocin combined ergometrine maleate were assigned to the observation group. After treatment, the blood loss, hemostasis time, changes of coagulation function and hemodynamic indexes, efficacy and incidence of adverse reactions were compared between the two groups. Results: The blood loss within 2 h and 24 h after treatment and hemostasis time of the observation group were greatly lower than those of the control group (P<0.05). After therapy, the coagulation function-associated indexes (fibrinogen (FIB), prothrombin time (PT), and activated partial thromboplastin time (APTT)) of the two groups were all improved, with greatly better coagulation function-associated indexes in the observation group than those in the control group (all P<0.05). After therapy, the observation group showed notably lower hemodynamic indexes (hear rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP)) than the control group (all P<0.05). Additionally, the observation group yielded a greatly higher effective treatment rate than the control group (P<0.05), and the incidence of adverse reactions in both groups was low, without significant difference (P>0.05). Conclusion: Ergometrine maleate combined with carbetocin can deliver favorable efficacy on PH, because it can effectively reduce the amount and duration of PH, improve the coagulation state of the body, and maintain the stability of hemodynamics, without increasing adverse reactions. Therefore, it is of high application value.

Keywords: Carbetocin, ergometrine maleate, postpartum hemorrhage, coagulation function

Introduction

Postpartum haemorrhage (PH) refers to the amount of bleeding ≥500 ml within 24 h after vaginal delivery or ≥1000 ml within 24 hours after caesarean section, which is the leading cause of maternal death worldwide, with an incidence of 2%-3% [1]. Because of the two-child policy and the postponement of childbearing age, the number of elderly puerperae in China is increasing. Age is one risk factor for PH, so the postponement of childbearing age further increases the incidence of PH. Clinical research has revealed that PH cases due to uterine weakness account for 70%-90% of all PH cases. Therefore, enhancing the postpartum uterine contraction ability of puerperae is the key to the prevention and treatment of PH [2, 3]. Currently, PH in vaginal delivery and caesarean section is usually prevented by gauze packing and oxytocin, etc. However, the incidence of PH is still high because of factors such as poor effectiveness of these methods and low dosage of the drugs. If the bleeding cannot be stopped in time, hysterectomy and uterine artery ligation will be adopted, which will seriously damage the physical and mental health of the puerpera [4, 5]. Carbetocin is a first-class drug for preventing and treating PH, which can effectively stimulate uterine smooth muscles and promote contractions [6]. Ergometrine maleate is a novel uterine contraction-promot-

Table 1. Comparison of general data

Items	Control group (n=45)	Observation group (n=57)	Statistical values	*P*
Age (years)	27.82±2.36	28.67±2.29	1.836	0.069
Gestational week (week)	38.33±0.67	38.24±0.62	0.703	0.484
Body mass index (kg/m^2)	23.25±2.71	23.41±2.58	0.304	0.762
Number of pregnancies (times)	2.36±0.51	2.47±0.63	0.951	0.344
History of abortion (cases)	7 (15.56)	9 (15.79)	0.001	0.974
Delivery mode				
Vaginal delivery	39 (86.67)	50 (87.72)	0.025	0.874
Cesarean section	6 (13.33)	7 (12.28)		
Newborn weight (g)	3365.82±433.63	3389.56±424.51	0.278	0.782
Blood loss before treatment (mL)	618.59±32.45	627.13±34.82	1.267	0.208

ing agent. With advantages of less adverse reactions and high stability, it has obvious effect in promoting uterine contraction in contrast to traditional ergodicine [7]. Because of different action parts and pharmacological properties of carbetocin and ergometrine maleate, they have their own advantages and disadvantages in the prevention and treatment of PH. Currently, the treatment of PH with ergometrine maleate combined with carbetocin is rarely reported at home and abroad. This study compared the effects of ergometrine maleate combined with carbetocin and carbetocin alone in the treatment of PH to provide the best treatment.

Data and methods

Research subjects

This retrospective study was conducted to analyze the clinical data of 102 puerperae with PH treated in Harbin Red Cross Central Hospital from March 2019 to February 2022. The inclusion criteria: Puerperae who had a singleton pregnancy, full term, and gestational week ≥37 weeks; puerperae with blood loss ≥500 mL within 24 h after vaginal delivery, or puerperae with blood loss ≥1000 mL within 24 h after cesarean section; puerperae who were clinically diagnosed with PH because of uterine inertia; puerperae without PH history; and puerperae whose families signed an informed consent form. Exclusion criteria: Puerperae comorbid with complications of pregnancy including diabetes mellitus and hypertension; puerperae with coagulation dysfunction; puerperae comorbid with severe diseases of the heart, liver, kidney or other parts of the body; puerperae with placenta previa or placenta accreta; or puerperae with tear in the soft birth canal. This study was approved by the Medical Ethics Committee of Harbin Red Cross Central Hospital. The enrolled participants were assigned to the control group (n=45) or observation group (n=57) in the light of the medication methods. Their general data are summarized in **Table 1**.

Treatment means

After delivery, puerperae in the two groups were all injected intramuscularly with 10 u oxytocin (Shanghai Harvest Pharmaceutical Co., Ltd., State Food and Drug Administration (SFDA) approval no.: H31020850; specification: 1 mL:10 u), and their uterine contraction and PH were closely monitored. The puerpera in the control group were treated with 100 μg carbetocin alone (Ferring Pharmaceutical (China) Co., Ltd., SFDA approval no.: H2009-3500; specification: 1 ml:10 μg) immediately for more than 1 min. The puerpera in the observation group were treated with 0.2 mg additional ergometrine maleate (Tianjin Jinyao Pharmaceutical Co., Ltd.; SFDA approval no.: H12020612; specification: 1 mL:0.2 mg) via gluteal intramuscular injection for more than 1 min on the basis of control group. The administration was repeated once within 15-30 min based on patient's condition, and the maximum dose did not exceed 1 mg/d.

Close attention was paid to the physiological indicators of puerperae during medication, and targeted measures were taken to intervene immediately in case of an abnormal situation.

Outcome measures

The blood loss within 2 h and 24 h after treatment in the two groups was calculated using

Table 2. Comparison of blood loss and hemostasis time

Group	Number of cases	Blood loss (mL) within 2 h after treatment	Blood loss (mL) within 24 h after treatment	Hemostasis time (min)
Control group	45	153.76±14.52	281.95±27.35	23.64±4.38
Observation group	57	126.57±12.69	229.64±21.15	12.42±2.59
t		10.081	10.896	16.110
P		<0.001	<0.001	<0.001

the weighing method combined with volume method. The blood loss amount = (wet weight of blood dressing - dry weight of dressing before blood reception)/1.05. The hemostasis time was recorded. Venous blood (5 mL) was sampled from the upper limbs of every individual in the two groups before and 1 day after treatment, followed by centrifugation (3000 r/min) to take supernatant. Then an automatic biochemistry analyzer was adopted for determining the coagulation function-associated indexes including fibrinogen (FIB), prothrombin time (PT), and activated partial thromboplastin time (APTT). The changes of hemodynamic parameters, including heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), were monitored before and 2 hours after treatment.

Evaluation of efficacy

Markedly effective: obvious contractions occurred within 15 min after medication, and vaginal bleeding stopped or the blood loss decreased greatly, with stable vital signs; Effective: the contractions were strengthened within 30 min after medication, and vaginal bleeding decreased greatly, with stable vital signs; ineffective: within 30 min after medication, the contractions did not improve or the blood loss did not decrease, and the vital signs were unstable [8].

Adverse reactions

The incidence of blood pressure increase, heart rate increase, nausea and vomiting, and flushing in the two groups were evaluated.

Statistical analyses

SPSS19.0 software was used for statistical analyses. Counting data in terms of delivery mode and clinical efficacy, etc. were described by rate (%), and compared through the χ^2 test. Measurement data in terms of blood loss, coagulation function, etc. were described by ($\bar{x} \pm s$) and compared using the t test. $P<0.05$ suggested a significant difference.

Results

General data

No significant difference was found between the two groups in general data such as age, body mass index (BMI), delivery mode, newborn weight and blood loss before treatment ($P>0.05$, **Table 1**).

Blood loss and hemostasis time

The blood loss within 2 h and 24 h after treatment and hemostasis time of the observation group were significantly lower than those of the control group ($P<0.05$, **Table 2**).

Changes of coagulation function-associated indexes

Before treatment, the two groups were similar in the levels of FIB, PT, and APTT (all $P>0.05$), while after treatment, the levels of FIB, PT, and APTT in both groups were greatly improved (all $P<0.05$), with significantly better levels in the observation group than those in the control group (all $P<0.05$, **Figure 1**).

Changes of hemodynamic indexes

Before treatment, the two groups were similar in the levels of HR, SBP, and DBP (all $P>0.05$), while after treatment, the levels of SBP and DBP in both groups declined greatly and HR in both groups increased greatly (all $P<0.05$), with significantly higher levels of SBP and DBP, and a significantly lower HR level in the observation group than those in the control group (all $P<0.05$, **Figure 2**).

Clinical efficacy

The effective treatment rate of the observation group (96.49%) was significantly higher than

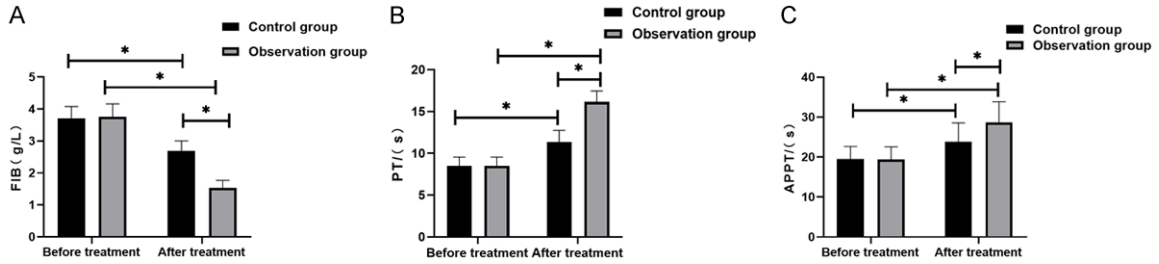

Figure 1. Changes of coagulation function-associated indexes in the two groups. A: Fibrinogen (FIB); B: Prothrombin Time (PT); C: Activated Partial Thromboplastin Time (APTT). **P<0.05.*

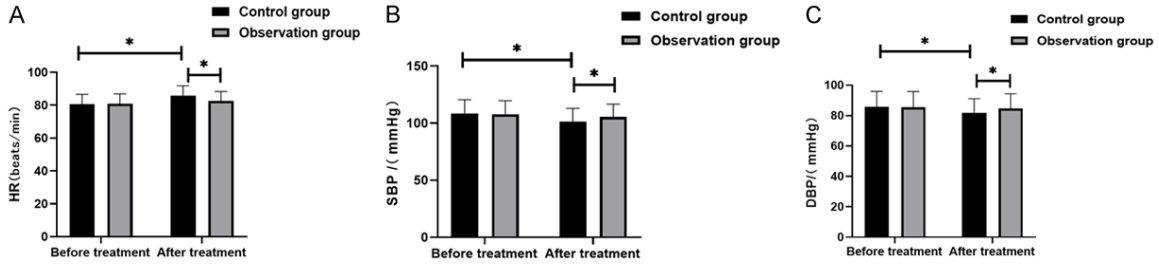

Figure 2. Changes of hemodynamic indexes before and after treatment in two groups. A: Hear Rate (HR); B: Systolic Blood Pressure (SBP); C: Diastolic Blood Pressure (DBP). **P<0.05.*

Table 3. Comparison of clinical efficacy

Group	Number of cases	Markedly effective (%)	Effective (%)	Ineffective (%)	Total effective (%)
Control group	45	20 (44.44)	18 (40.00)	7 (15.56)	38 (84.44)
Observation group	57	32 (56.14)	21 (36.84)	2 (3.51)	55 (96.49)
χ^2					4.536
P					0.033

Table 4. Comparison of adverse reactions

Group	Number of cases	Blood pressure increase (%)	Heart rate increase (%)	Nausea (%)	Flushing (%)	Incidence of adverse reactions (%)
Control group	45	0 (0.00)	1 (2.22)	1 (2.22)	1 (2.22)	3 (6.67)
Observation group	57	0 (0.00)	1 (1.75)	2 (3.51)	2 (3.51)	5 (8.77)
χ^2						0.154
P						0.695

that of the control group (84.44%) (*P*<0.05, **Table 3**).

Adverse reactions

The incidence of adverse reactions in the observation group (8.77%) was not greatly different from that in the control group (6.67%) (*P*>0.05, **Table 4**).

Discussion

PH is one of the complications that occur after vaginal delivery and cesarean section. The prevention guidelines of PH worldwide all suggest that uterine contraction agents should be adopted to prevent PH [9]. In China, oxytocin is the first choice for the prevention of PH. Many studies have confirmed that oxytocin can promote effective postpartum contractions, accelerate the recovery of uterine function damage and maintain the normal circulation of intrauterine blood flow [10, 11]. However, clinical practice shows that excessive use of oxytocin can easily cause excessive uterine contraction and further damage the uterus. Therefore, the dosage of oxytocin in clinical prevention of PH

is relatively low [12]. Limited by the influence of single medication and low dose, the effect of oxytocin in the prevention of PH after vaginal delivery or cesarean section is not ideal, and the incidence of PH is high. Reportedly, uterine inertia is the leading cause of PH, and the key to treat PH is to enhance the ability of postpartum contraction [13].

Carbetocin is a new type of long-acting manufactured hormone like oxytocin, which can act on the smooth muscle of uterus. In combination with oxytocin receptors of the smooth muscle, it can promote the rhythmic contraction of uterus, thus enhancing the contractility and tension of uterus and accelerating the contraction frequency. It is clinically adopted for preventing PH and treating PH caused by insufficient tension after cesarean section [14, 15]. However, oxytocin drugs mainly act on the outer myometrium of the uterus, and carbetocin has a poor effect on enhancing the contractility of the lower uterine segment. Ergometrine maleate is a semi-synthetic ergot alkaloid. With main action sites including uterine body and uterus cervix, it can simultaneously stimulate uterine smooth muscle and internal myometrium of the uterus, promote the overall continuous contraction of uterus, and enhance contractility. Many studies have confirmed the crucial role of ergometrine maleate in preventing PH in women with uterine inertia [16]. However, ergonovine maleate has poor thermal stability. Compared with ergometrine maleate, Li Xiaofen and other researchers have confirmed that carbetocin can significantly reduce postpartum hemorrhage and improve blood coagulation function, and it is relatively cheap, so it can be used as a priority choice for medication of postpartum haemorrhage [17]. In this study, after treatment, the observation group experienced significantly less blood loss and shorter hemostasis time than the control group and showed a significantly higher total effective treatment rate than the control group. The results suggest that ergonovine maleate combined with carbetocin can give full play to their respective advantages in the treatment of PH to effectively reduce the amount and duration of PH, and deliver a high efficacy on PH. This is consistent with the conclusion of Zhao Jie et al. [18]. The reason is that the advantages of different action sites of cabesin and ergometrine maleate can play a synergistic role to improve the therapeutic effect.

Coagulation dysfunction is also one crucial cause of PH. Improving postpartum coagulation function and shortening coagulation time can both prevent and reduce the occurrence of PH. Reportedly, enhancing postpartum uterine contractility can improve maternal coagulation function [19]. Coagulation function-associated indexes such as FIB, PT, as well as APPT are frequently adopted for diagnosing coagulation dysfunction and assessing the risk of PH. In this study, after treatment, FIB, PT, and APTT of the two groups were all improved, with significantly better levels in the observation group than those in the control group, suggesting that ergonovine maleate combined with carbetocin can substantially improve the coagulation state of the body and reduce the occurrence of PH due to enhanced postpartum uterine contractility.

As a powerful vasoconstrictor, ergonovine maleate has been reported to increase the occurrence of cardiovascular events [20]. In this study, after treatment, hemodynamic indexes like SBP, DBP, and HR of the two groups all changed, but the changes in the observation group were milder than those in the control group, indicating that ergonovine maleate combined with carbetocin can effectively maintain stable hemodynamics in the treatment of PH. The reason might be that the two drugs are highly selective in promoting uterine contraction, and the combined application of them can speed up the recovery of uterine contraction function, with little impact on its own circulatory system, thus ensuring a stable hemodynamics. In addition, the incidence of adverse reactions in the two groups was low, without significant difference, verifying that ergonovine maleate combined with carbetocin is safe in the treatment of PH.

Still, this study has some limitations. The sample size of the study is small, so it is necessary to further expand the sample size to verify the conclusion. In addition, all the puerperae with postpartum hemorrhage selected in this study had no history of postpartum hemorrhage, and the application effect and medication standard of carbetocin combined with ergonovine maleate in puerperae with a history of postpartum

hemorrhage are also one of the future research directions.

To sum up, ergometrine maleate combined with carbetocin can deliver favorable efficacy for treatment of PH, because it can effectively reduce the amount and duration of PH, improve the coagulation function of the body, and maintain the stability of hemodynamics, without increasing adverse reactions. Therefore, it has high application value.

Disclosure of conflict of interest

None.

Address correspondence to: Hui Xue, The Fifth Department of Obstetrics, Harbin Red Cross Central Hospital, No. 415, Xinyang Road, Daoli District, Harbin 150076, Heilongjiang, China. Tel: +86-13804600759; E-mail: xh19930710@163.com

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