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Original Article

Efficacy of misoprostol combined with mifepristone on postpartum hemorrhage and its effects on coagulation function

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Abstract: Objective: To explore the efficacy of misoprostol combined with mifepristone on postpartum hemorrhage and its effects on coagulation function. Methods: A total of 68 parturients with postpartum hemorrhage were enrolled and randomly assigned to a control group and an observation group (each n=34). The control group was treated with misoprostol, while the observation group was treated with mifepristone combined with misoprostol based on the treatment to the control group. The two groups were compared in heart rate and blood pressure before treatment, and blood loss and coagulation function after treatment. Results: Before treatment, there was no significant difference between the two groups in terms of systolic blood pressure, diastolic blood pressure, heart rate, plasma fibrinogen (FIB), D-dimer (D-D), prothrombin time (PT), and activated partial thromboplastin time (APTT) (all $P>0.05$), while after treatment, the observation group showed higher systolic blood pressure and diastolic blood pressure, lower heart rate, higher D-D level, and lower FIB, PT, and APTT levels than the control group (all $P<0.05$). In addition, the blood loss of the observation group during the third stage of labor, 2 hours after delivery, and 24 hours after delivery was lower than that of the control group during corresponding time period (all $P<0.05$). Conclusion: Misoprostol combined with mifepristone can effectively stabilize the heart rate and blood pressure of parturients with postpartum hemorrhage during treatment, and it can also reduce their blood loss and improve their coagulation function.

Keywords: Misoprostol, mifepristone, postpartum hemorrhage, coagulation function, blood pressure, heart rate

Introduction

Postpartum hemorrhage is the primary cause of death among pregnant women. There are many pathogenic factors for it, mainly including uterine inertia and placental factors. Massive hemorrhage will severely affect the physiological function, organs and tissues of parturients, and even threaten their life safety [1]. Misoprostol is a prostaglandin E1 derivative, with a strong inhibitory effect on gastric acid secretion, which can promote uterine contraction during pregnancy. It can not only be used to prevent early pregnancy and induce labor for intrauterine fetal death, but also be applied in gynecological operations such as the placement and removal of intrauterine device and endometrium sampling. Some studies revealed that misoprostol combined with mifepristone was commonly adopted in clinical treatment such as termination of early pregnancy, missed abortion and labor induction. The combination therapy has a good effect on promoting uterine contraction, and can effectively reduce uterine bleeding, but there are few studies on the combination therapy of them on coagulation function of patients [2]. This study has explored the effect of misoprostol combined with mifepristone on coagulation function in treatment of postpartum hemorrhage by taking parturients with postpartum hemorrhage as research objects, which is beneficial to the development of clinical research on the treatment of postpartum hemorrhage.

Materials and methods

Clinical data

A total of 68 parturients with postpartum hemorrhage from March 2018 to May 2019 were enrolled, and randomly assigned to a control

group and an observation group (each n=34). The control group consisted of 21 primiparas and 13 multiparas between 23 and 35 years old, with an average age of 28.8±1.7 years, gestational week of 36-42 weeks, and average gestational week of 39.2±1.8 weeks. The observation group consisted of 23 primiparas and 11 multiparas between 22 and 34 years old, with an average age of 27.3±1.9 years, gestational week of 36-42 weeks, and average gestational week of 38.8±2.0 weeks. This study has been approved by the Ethics Committee of Shandong Provincial Hospital.

Inclusion and exclusion criteria

The inclusion criteria were as follows: Parturients with blood loss of 300-800 mL during delivery; parturients having natural delivery; parturients with monocyesis, and parturients who understood the study and voluntarily participated in it (including their families).

The exclusion criteria were as follows: Parturients comorbid with pregnancy diseases such as pregnancy-induced hypertension, parturients with blood coagulation dysfunction or dysfunction of heart, liver, kidney or other organs; parturients allergic to drugs used in this study or with adverse reactions to the drugs.

Methods

The control group received treatment of misoprostol (Hubei Gedian Humanwell Pharmaceutical Co., Ltd., China) alone by sublingually taking 0.2 mg misoprostol after delivery, while the observation group received combined treatment of mifepristone (Shanghai New Hualian Pharmaceutical Co., Ltd., China) and misoprostol based on the treatment to the control group by additionally orally taking 25 mg mifepristone after delivery. If a parturient still suffered from massive bleeding after taking drugs, she would be surgically treated according to the actual situation.

Observation indexes

(1) Comparison of heart rate and blood pressure between the two groups before and after treatment. The heart rate, systolic blood pressure, and diastolic blood pressure of the two groups before treatment and after 24 hours of treatment were monitored using an electrocardiograph monitor (Jinan Biobase Medical Devices Co., Ltd., China, Comen STAR8000E). (2) Comparison of coagulation function between the two groups before and after treatment. Fasting venous blood (5 mL) was sampled from each parturient before treatment and after 24 hours of treatment, respectively, and the plasma fibrinogen (FIB), D-dimer (D-D), prothrombin time (PT), and activated partial thromboplastin time (APTT) of the sampled blood were determined using an automatic coagulation analyzer (Shenzhen Rayto Life and Analytical Sciences Co., Ltd., China, RAC-120). (3) Comparison of blood loss between the two groups. The amount of blood loss was calculated by the weighing method. The surgical dressings for cleanup of fetus and the parturient's vagina were weighted, and the amount of blood loss was calculated with each 1.05 g of dressings as 1 mL of blood. The blood loss of the two groups during the third stage of labor, 2 hours after delivery, and 24 hours after delivery was calculated and compared.

Statistical analysis

The detection data were statistically analyzed using SPSS18.0, and measurement data were expressed by $\bar{x} \pm sd$, and analyzed using the t test. $P<0.05$ indicates a statistic significant difference.

Results

Comparison of clinical data between the two groups

There was no significant difference between the two groups in age, gestational week, and delivery times (all $P>0.05$), so those parturients were suitable for treatment research. See **Table 1**.

Comparison of heart rate and blood pressure between the two groups before and after treatment

Before treatment, there was no significant difference between the two groups in terms of systolic blood pressure, diastolic blood pressure, and heart rate (all $P>0.05$), while after 24 hours of treatment, the observation group showed higher systolic blood pressure and diastolic blood pressure, and lower heart rate than the control group (all $P<0.05$). See **Table 2** and **Figures 1**, **2**.

Table 1. Comparison of clinical data between the two groups

Groups	Number of cases	Age (years)	Gestational week (weeks)	Unipara (n (%))	Multipara (n (%))
Observation group	34	27.3±1.9	38.8±2.0	23 (67.65)	11 (32.35)
Control group	34	28.8±1.7	39.2±1.8	21 (61.76)	13 (38.24)
t		0.083	0.079	0.126	0.147
P		0.467	0.469	0.451	0.443

Table 2. Comparison of heart rate and blood pressure between the two groups before and after treatment

Groups	Observation group	Control group	t	P
Number of cases	34	34		
Systolic blood pressure (mmHg)				
Before treatment	116.13±11.52	117.24±10.68	1.457	0.259
After 24 hours of treatment	118.27±10.67	115.92±10.48	8.125	0.003
Diastolic blood pressure (mmHg)				
Before treatment	78.26±8.33	77.93±8.75	1.562	0.148
After 24 hours of treatment	79.68±8.52	75.69±9.35	8.863	0.013
Heart rate (times/points)				
Before treatment	76.54±4.13	75.96±4.22	1.174	0.186
After 24 hours of treatment	74.76±3.59	76.24±5.02	7.693	0.025

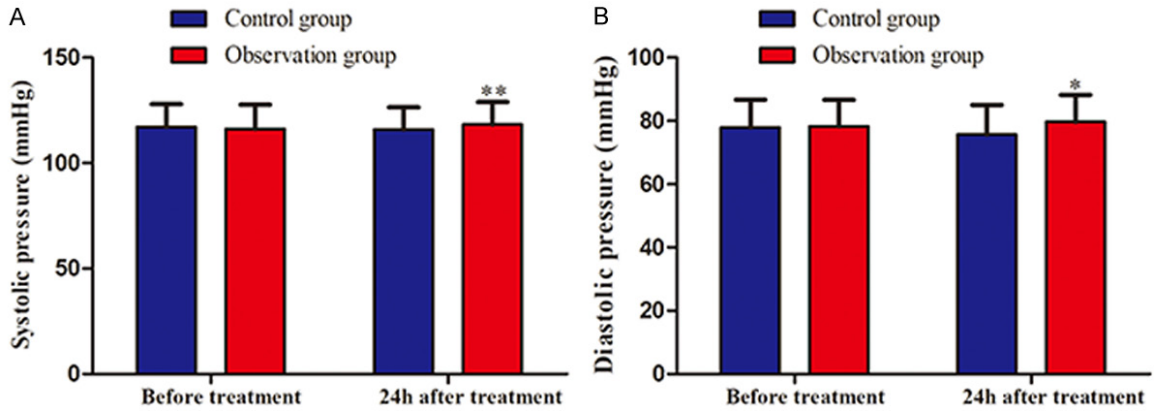

Figure 1. Comparison of blood pressure between the two groups before and after treatment. A. Comparison of systolic blood pressure between the two groups before and after treatment. B. Comparison of diastolic blood pressure between the two groups before and after treatment. *P<0.05, **P<0.01, compared with the control group.

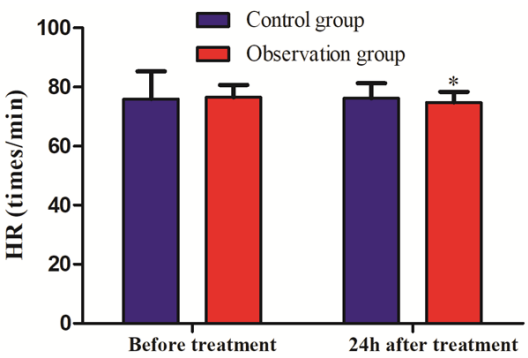

Figure 2. Comparison of heart rate between the two groups before and after treatment. *P<0.05, compared with the control group. HR: heart rate.

Comparison of coagulation function between the two groups before and after treatment

Before treatment, there was no significant difference between the two groups in terms of FIB, D-D, PT, and APTT levels (all P>0.05), while after 24 hours of treatment, the observation

Table 3. Comparison of coagulation function between the two groups before and after treatment ($\bar{x}$ ± sd)

Groups	Observation group	Control group	t	P
FIB (g/L)				
Before treatment	4.84±1.21	4.79±1.24	0.527	0.382
After 24 hours of treatment	3.37±1.10	4.26±1.08	7.605	0.021
D-D (mg/L)				
Before treatment	2.89±0.21	2.78±0.27	1.342	0.643
After 24 hours of treatment	3.78±0.45	3.15±0.29	6.249	0.030
PT (s)				
Before treatment	14.08±1.53	13.82±1.24	1.013	0.297
After 24 hours of treatment	10.54±1.26	13.24±1.08	8.921	0.025
APTT (s)				
Before treatment	27.93±8.72	28.43±8.57	1.428	0.346
After 24 hours of treatment	24.16±3.76	26.36±3.49	9.837	0.024

Note: FIB: fibrinogen; D-D: D-dimer; PT: prothrombin time; APTT: activated partial thromboplastin time.

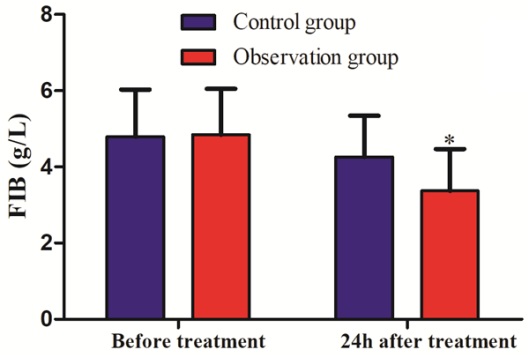

Figure 3. Comparison of FIB level between the two groups before and after treatment. *P<0.05, compared with the control group. FIB: fibrinogen.

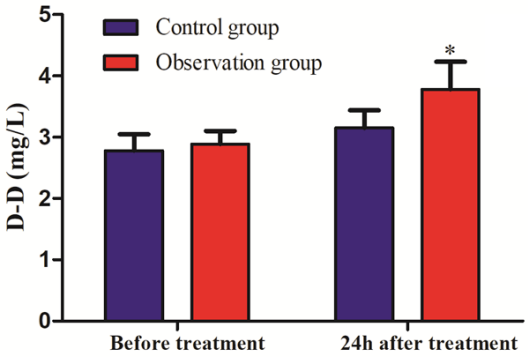

Figure 4. Comparison of D-D level between the two groups before and after treatment. *P<0.05, compared with the control group. D-D: D-dimer.

group showed higher D-D level and lower FIB, PT and APTT levels than the control group (all P<0.05). See **Table 3** and **Figures 3**-**5**.

Comparison of blood loss between the two groups after treatment

After treatment, the blood loss of the observation group during the third stage of labor, 2 hours after delivery, and 24 hours after delivery was lower than that of the control group during corresponding time period (all P<0.05). See **Table 4** and **Figure 6**.

Discussion

Characterized by massive hemorrhage, postpartum hemorrhage is a labor complication with high incidence and mortality. Massive hemorrhage during a short period of time poses a great threat to the life safety and body function of parturients, which calls for good judgment ability of medical staff. Clinical postpartum hemorrhage is usually driven by uterine inertia, placental factors, soft birth canal laceration, and blood coagulation dysfunction [3, 4], and it is affected by many factors including spirit, emotion, constitution, heredity, uterine development, fetal development, and drug administration. Postpartum hemorrhage is conventionally treated with oxygen inhalation, transfusion, fluid infusion, and massage, which can stabilize the vital signs and bleeding of parturients. However, appropriate medicines could more effectively stop bleeding through drug effect [5, 6].

Massive hemorrhage of parturients will reduce the effective circulatory blood volume in their body and deprive their multiple organs and tissues of enough running blood support, causing

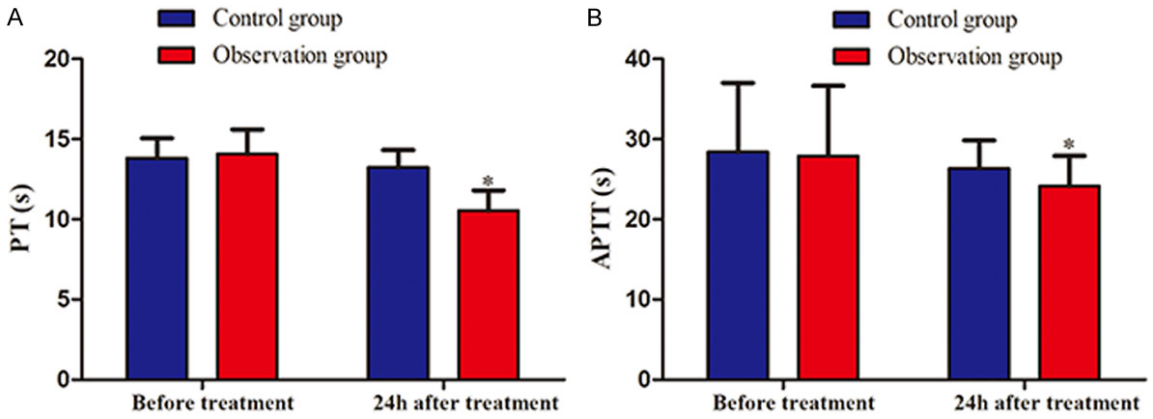

Figure 5. The levels of PT and APTT before and after treatment were compared between the two groups. A. Comparison of PT level between the two groups before and after treatment. B. Comparison of APTT level between the two groups before and after treatment. *P<0.05, compared with the control group. PT: prothrombin time; APTT: activated partial thromboplastin time.

Table 4. Comparison of bleeding volume between the two groups after treatment (mL, $\bar{x} \pm sd$)

Groups	Observation group	Control group	t	P
Numbers of cases	34	34		
Amount of bleeding during the third stage of labor	313.56±74.61	514.37±117.62	4.613	0.020
Postpartum 2 h bleeding volume	97.36±24.51	124.78±63.29	4.580	0.021
Postpartum 24 h bleeding volume	451.36±125.57	786.64±158.39	5.734	0.000

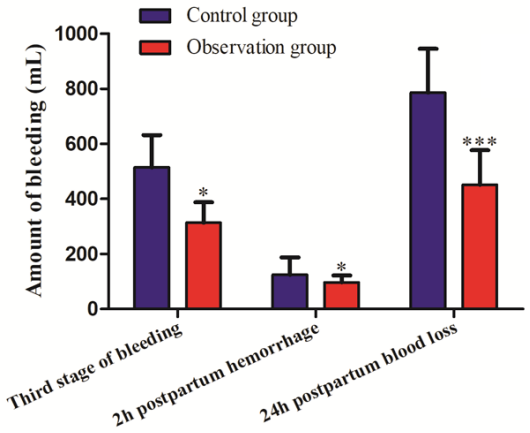

Figure 6. Comparison of amount of bleeding between the two groups. *P<0.05, ***P<0.001, compared with the control group.

dysfunction of microcirculation and metabolism and seriously damaging cells, tissues, and organs [7, 8]. The blood loss and body function of parturients can be roughly evaluated by paying close attention to their blood pressure and heart rate, because when the amount of blood loss is large and the blood volume is insufficient, the blood pressure will significantly decrease, and the heart rate will accelerate in the early stage and then decline in the later stage. Therefore, the monitored blood pressure and heart rate of parturients treated with drugs can reflect the efficacy of the drugs on postpartum hemorrhage [9, 10]. In this study, after treatment, the diastolic blood pressure of the observation group was higher than that of the control group, and both diastolic blood pressure and heart rate of the observation group were improved. In addition, the blood loss of the observation group during the third stage of labor, 2 hours after delivery, and 24 hours after delivery was lower than that of the control group during corresponding time period. It implied that misoprostol combined with mifepristone could effectively stabilize the vital signs of parturients with postpartum hemorrhage and reduce their blood loss.

Misoprostol is an artificially synthesized prostaglandin E1 derivative with efficacy of inhibiting collagen synthesis, loosening collagen fiber arrangement, and stimulating cervical fibrocytes. It can promote uterine contraction through selective action on uterine prostaglandin receptor, and effectively shorten the third delivery

process, which is not only conducive to shortening the third stage of labor and the uterine vessel opening time after placenta expulsion by facilitating placenta expulsion, but also beneficial to improving the parturients' coagulation function, promoting blood coagulation, and reducing blood loss [11, 12], thus treating postpartum hemorrhage. Sublingual administration contributes to high drug absorptivity and fast onset, and is convenient, so it is suitable for emergency treatment. Mifepristone is a common drug for termination of early pregnancy in clinical practice. Its competitive effect on progesterone is also applicable to the treatment of postpartum hemorrhage due to placental factors. It can shorten the third stage of labor and reduce postpartum hemorrhage of parturients by contributing to the complete and smooth delivery of placenta [13, 14]. Therefore, misoprostol combined with mifepristone therapy can take advantages of pharmacodynamic effects of the two drugs to shorten the third stage of labor by promoting the smooth placental expulsion and reduce uterine bleeding by promoting uterine contraction meantime. Such an interaction can stabilize the blood pressure and heart rate of parturients, significantly reduce parturients' postpartum hemorrhage, and lessen their body function damage [15, 16].

Coagulation function is the mechanism by which blood changes from a flowing state to a gel state. After smooth placental expulsion, the uterus closes off open vessels by contraction and compression, and the blood coagulates at the open blood vessels through the coagulation function, thus stopping bleeding. Coagulation dysfunction is one of the four major causes of postpartum hemorrhage. Hormone changes during pregnancy will give rise to corresponding changes of the concentration and activity of coagulation factors, resulting in coagulation abnormalities of pregnant women, so the pregnant women will lose the ability of coagulating blood and suffer from postpartum hemorrhage [17]. FIB is a protein synthesized by the liver, with a significant effect on coagulation, and D-D is a specific degradation product of fibrin, with ability of reflecting the dissolution function and degree of fibrin. PT refers the time consumed by prothrombin for blood coagulation in converting to thrombin in blood with a large number of tissue thromboplastins and calcium ions, but lacking platelet, which is an important indicator for blood coagulation function detection [18, 19]. APTT is an indicator for comprehensive activity detection of coagulation factors, and too high or too low APTT level will result in abnormal body function [20, 21]. In this study, the coagulation function of the observation group treated with misoprostol combined with mifepristone was significantly better than that of the control group, which implied that the combination therapy could more strongly improve the coagulation function of parturients, and could promote their blood coagulation and reduce their blood loss. The parturients whose blood loss cannot be effectively reduced after treatment should be surgically treated according to their actual situation.

The study only covers a small number of research objects, and those research objects are all selected from those admitted to our hospital, bringing about a regional limitation. However, under this limitation, the therapeutic effect of misoprostol combined with mifepristone is of representative significance, and is worthy of further study in other regions. The further study can provide a more comprehensive analysis on the efficacy of the combination therapy for postpartum hemorrhage.

To sum up, misoprostol combined with mifepristone can effectively stabilize the heart rate and blood pressure of parturients with postpartum hemorrhage during treatment, and it can also reduce their blood loss and improve their coagulation function.

Disclosure of conflict of interest

None.

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