

Effect of carboprost tromethamine in prevention of postpartum hemorrhage in cesarean section

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Abstract: Carboprost tromethamine is a synthetic prostaglandin derivative, which can effectively promote law contraction of the uterus and significantly reduce the amount of bleeding during and after delivery. In this study, we explored the effect of carboprost tromethamine on the prevention of postpartum hemorrhage after cesarean section and the effect on coagulation function and hemodynamics. At the same time, the effects of oxytocin and carboprost tromethamine were studied in different groups. The results showed that the amount of 2h bleeding (256.7±65.21) mL and the amount of 24h hemorrhage (308.3±78.3) after the operation were significantly decreased, and the difference was statistically significant (P<0.05). After the operation, the levels of APTT, TT and Fib in the two groups were significantly lower than those before the operation. The levels of SBP (119.4±8.24) mmHg and DBP (79.6±6.21) mmHg in the experimental group were significantly higher than those of the control group. In summary, carboprost tromethamine has a significant effect on the prevention of postpartum hemorrhage in cesarean section, and has a significant effect on improving the state of hypercoagulable blood and maintaining the stable hemodynamic state, which has clinical a value.

Keywords: Carboprost tromethamine, coagulation mechanism, oxytocin, incidence of hemorrhage.

INTRODUCTION

Postpartum hemorrhage is a serious complication of cesarean section. If it fails to stop bleeding in time, there may be a sharp decline in blood circulation, such as coagulation dysfunction, systemic ischemia, respiratory distress syndrome and so on (Kawamoto *et al.*, 2016). The disease continues to develop and even leads to death, which is one of the important causes of maternal death. After cesarean section, the postpartum hemorrhage is mainly caused by uterine contraction, and the previous clinical treatment is mainly treated with oxytocin, but the sensitivity of some parturients is poor, and it is easy to cause postpartum retention, which has a great influence on postpartum recovery (Khera *et al.*, 2015). The number of cesarean parturient has risen gradually and the excessive extension of the myometrium of the uterus and the injury of the uterine wall caused by the scar uterus caused by the pathological causes of the giant, multiple pregnancy and placenta previa, have a serious effect on the normal contraction of the uterus fiber and the contraction work of the postpartum womb, which causes the uterus to cause the uterus (Mavrides *et al.*, 2016). The contractile function is reduced, inducing uterine atony bleeding. Most of the clinical factors that the maternal postpartum hemorrhage is the main factor is uterine inertia, accounting for about 60% (Myslimi *et al.*, 2016). The key to the prevention and treatment of postpartum hemorrhage in clinic is the application of uterine contractions, especially in the 2h after puerperal postpartum. Therefore, for cesarean section, strengthening

uterine contractility has great significance for prevention of postpartum hemorrhage (Page *et al.*, 2017; Moncrieff, 2018).

The clinical medication for postpartum hemorrhage usually includes prostaglandins, oxytocin, and ERG. The pregnancy uterus has a larger individual difference in the uterine contractile hormone, and the drug only produces contractile stimulation on the upper uterine segment (Seto *et al.*, 2017). After the receptor site is full, the increase in the dose of the uterine contractile is not the effect of contractile is not very ideal if the puerperal woman has severe postpartum hemorrhage (Sanomura *et al.*, 2014).

The efficacy of prostaglandins in uterine contraction is obviously stronger than that of uterine contractile, but it can produce adverse reactions such as diarrhea, fever and shivering (Moncrieff, 2018; Perl *et al.*, 2015). It has adverse effects on the health of women, and there are also individual differences in prostaglandins. Carboprost tromethamine (Hemabate) is a synthetic prostaglandin derivative, which can effectively promote the law contraction of the uterus and significantly reduce the amount of bleeding during and after delivery (Pinas *et al.*, 2014). Carboprost tromethamine is a methyl derivative of PGF₂ alpha -15, which has a strong effect against the inactivation of 15- hydroxydehydrogenase, while the half-life is stronger than the traditional prostaglandin drugs, so the treatment and prevention of postpartum hemorrhage are more obvious (Page *et al.*, 2017). The effect of carboprost tromethamine on the contraction of the lower segment of the uterus is strong and lasting, and the application dose is small. The effect is very obvious for

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the prevention and treatment of postpartum hemorrhage of parturients and the reaction of carboprost tromethamine to the gastrointestinal tract is also small (Sanomura *et al.*, 2014). This study explored the effect of carboprost tromethamine on the prevention of postpartum hemorrhage after cesarean section, and the effect on coagulation function and hemodynamics. We studied the effect of oxytocin and carboprost tromethamine in groups.

MATERIALS AND METHODS

General information

180 cases of puerperal women who underwent cesarean section in our hospital for 2016-2017 years were selected as the research subjects. According to random number table method, they were randomly divided into the experience group and the control group, 90 cases in each group. The experimental group comprised of 21-37 years old individuals, with an average age of (26.3±4.2), 37-42 weeks of pregnancy, mean gestational weeks as (37.14±0.81) weeks, 54 pregnant women and 36 parturients. The control group comprised of 20~36 years old individuals, with an average age of (27.1±3.9), 38-42 weeks of pregnancy, mean gestational weeks as (38.01±0.67) weeks, 56 primipara and 34 parturients. All patients were approved by ethics committee of our hospital, ethical approval number as 2015WYCHD2 and all patients signed on the informed consent.

Inclusion and exclusion criteria

Inclusion criteria: (1) conforming to the indications of cesarean section, all the subjects had uterine inertia. (2) inclusion of unwanted drugs, blood diseases, liver and kidney diseases, hypertension, uterine incision laceration and placental adhesion were included in the study. (3) the two groups were informed about the prevention of postpartum hemorrhage and were willing to participate in the study, and signed informed consent.

Exclusion criteria: (1) Combined with tumor, cardiovascular and cerebrovascular diseases, diabetes, coagulation dysfunction and other chronic diseases. (2) Congenital diseases or related family history. (3) Previous history of cesarean section or abnormal delivery history; (4) Allergic reactions to the drugs used in the study.

Therapeutic method

The two groups of parturients all underwent caesarean section, the control group was only treated with oxytocin, and the experimental group was treated with carboprost tromethamine on the basis of oxytocin treatment. After operation, the uterus was removed and the fetus was delivered after the amniotic fluid was cleared. The control group was given intravenous drip of Oxytocin Injection 20U, and oxytocin 20U was injected into the uterus (Singh *et al.*, 2016).

If contractions are not effective and postpartum hemorrhage (bleeding during cesarean section is above 1000mL) is present, then we needed to continue the injection of oxytocin 20U. The experimental group was given oxytocin injection 20U intravenous drip, and carboprost tromethamine 250 µg was injected into the uterus. If the effect of uterine contraction was not good, the symptoms of postpartum hemorrhage occurred, then the interval of 15min was continued to be injected with carboprost tromethamine 250 µg.

Detection index

After operation, a weighing method was used to measure the amount of water in the patient's body before operation, and a new absorbent cloth was replaced after the operation. The amount of 2h bleeding after the operation was counted, and the total amount of bleeding of 24h after the operation was accumulated. The formula was: [wet weight after delivery of the fetus (g) - dry weight (g) / 1.05 (blood ratio, g / mL)]. After the fetus was delivered, the amount of bleeding during cesarean section was above 1000mL, then the postpartum hemorrhage was determined, and the incidence of postpartum hemorrhage in the two groups was calculated.

Two groups of maternal venous blood were collected in EDTA tube before and after operation. The anticoagulant treatment was carried out with sodium citrate. After the plasma separation was completed in 2h, the indexes of coagulation function were detected by automatic coagulation analyzer: Activated partial thromboplastin time (APTT), plasma thrombin time (TT), fibrinogen (Fib). The hemodynamic indexes, such as systolic pressure (SBP), diastolic pressure (DBP), and heart rate (HR), were measured by heart rate blood pressure measuring instrument

STATISTICAL ANALYSIS

In this study, the amount of postoperative bleeding, various indexes of coagulation function and the level of hemodynamic indexes were measured, obeying the normal distribution and expressing ($x \pm s$). T test was used in group comparison and comparison between groups. The incidence of postpartum hemorrhage and other enumeration data was (n, %), using χ^2 test. Using statistical software SPSS 18.0 as data analysis tool, $P < 0.05$ shows significant difference, and has statistical significance.

RESULTS

General situation comparison

There was no significant difference in mean age, mean gestational age and production status between the two groups ($P > 0.05$), as shown in table 1.

Table 1: General situation comparison

Group	Average age	Average week of pregnancy	Primiparas	Multiparas
Experience group	26.3±4.2	37.14±0.8	54	36
Control group	27.1±3.9	38.01±0.67	56	34

Table 2: Postoperative bleeding volume and incidence of postpartum hemorrhage

Group	Postoperative 2h bleeding	Postoperative 24h bleeding	Incidence of postpartum hemorrhage
Experience group	256.7±65.21	308.3 ±78.3	5(5.5%)
Control group	318.4±78.34	425.1±81.5	11(12.2%)

Table 3: Comparison of two groups of blood coagulation function levels

Group	Time	APTT(s)	TT(s)	Fib (g/mL)
Experience group	Preoperative	64.5 ±12.31	27.8 ±9.64	4.82 ±1.73
	Postoperatively	43.1 ±9.61	16.7 ±6.28	3.15 ±1.14
Control group	Preoperative	65.7 ±13.57	29.6 ±9.17	4.72 ±1.56
	Postoperatively	55.72 ±9.13	22.4 ±3.29	3.43 ±1.22

Table 4: Comparison of hemodynamic levels

Group	Time	SBP (mmHg)	DBP (mmHg)	HR (times/min)
Experience group	Preoperative	125.6 ±8.73	81.5 ±7.59	72.3 ±6.81
	Postoperatively	119.4 ±8.24	79.6 ±6.21	80.2 ±5.17
Control group	Preoperative	128.4 ±9.16	82.4 ±8.02	74.2 ±6.41
	Postoperatively	113.8 ±8.23	76.5 ±6.48	84.6 ±6.18

Table 5: Comparison of the occurrence of adverse reactions

Group	Diarrhea	Uterine contraction pain	Nausea and vomiting	Increased heart rate	Blood pressure rise	Total incidence
Experience group	0	2	2	2	1	7.7%
Control group	1	6	4	3	4	20.0%

Comparison of postoperative bleeding and postpartum hemorrhage

In the experimental group, the amount of 2H bleeding after operation was (256.7±65.21) mL, the amount of 24h bleeding after operation was (308.3 ±78.3) mL. Both were significantly decreased, and the difference was statistically significant (P<0.05). The incidence of postpartum hemorrhage in the experimental group was 6% significantly lower than that of the control group. The incidence of postpartum hemorrhage was 14%, and the difference was statistically significant (P<0.05), as shown in table 2.

Comparison of two groups of blood coagulation function levels

There was no significant difference in coagulation function indexes APTT, TT and Fib between the two groups before operation (P>0.05). After operation, the levels of APTT, TT and Fib in the two groups were significantly lower than those before operation, and the difference was statistically significant (P<0.05). After the operation, in experience group the level of APTT (43.1±

9.61)s, TT (16.7±6.28) s, Fib (3.15±1.14) g/mL were significantly lower than that of the control group (P<0.05), as shown in table 3.

Comparison of two groups of hemodynamic levels

There was no significant difference in SBP, DBP and HR between the two groups before operation (P>0.05). After operation, the SBP and DBP of the two groups were significantly lower than those before operation and the HR was significantly quicker, with a statistically significant difference (P<0.05). After the operation, the level of SBP (119.4±8.24) mmHg and the level of DBP (79.6±6.21) mmHg were significantly higher in the experience group than in the control group. The level of HR (80.2±5.17) times / min was significantly slower than that of the control group (P<0.05), as shown in table 4.

Occurrence of adverse reactions

In the control group, 1 cases of diarrhea, 6 cases of uterine contraction pain, 4 cases of nausea and vomiting, 3 cases of heart rate quickening and 4 cases of blood pressure increased, the total incidence of adverse

reactions was 20%. In the experimental group, there were 2 cases of contractions pain, 2 cases of nausea and vomiting, 2 cases of heart rate acceleration, 1 case of elevated blood pressure and the total incidence of adverse reactions was 7.7%. The incidence of adverse reactions in the experimental group was slightly lower than that in the control group, but the difference was not statistically significant ($P>0.05$, table 5).

DISCUSSION

Postpartum hemorrhage is a common crisis in obstetrics, which means that the amount of bleeding in 24h or caesarean section is above 1000mL after birth of the fetus (Akhter *et al.*, 2009). The main cause of postpartum hemorrhage is the weakness of uterine contraction. The increase in the number of pregnant women's gestational weeks will be accompanied by the increase of intrauterine pressure, which leads to the changes in the muscle structure and the volume of the uterine cavity. For the parturient with abnormal birth canal and abnormal placental dissection, the uterine cavity is rapidly reduced after the birth of the fetus (Baldwin *et al.*, 2017). The normal muscle fiber and the compression of the muscle cannot reach the normal state of regulation, thus leading to postpartum (Balmadrid *et al.*, 2015). Cesarean section can cause the uterine contraction ability to weaken or disappear. The problem of postpartum hemorrhage is an important factor that threatens the safety of women, which seriously threatens the safety of mother and child. Therefore, strengthening the uterine contraction is the key method to reduce the amount of bleeding after cesarean section (Burguet *et al.*, 2017). The main measures for the treatment of postpartum hemorrhage are to promote rhythmic or tetanic contraction of the uterus, oppress the intrauterine blood vessels and reduce the amount of bleeding. Oxytocin is a contractile agent for the prevention of uterine atony postpartum hemorrhage. It can specifically excite the smooth muscle of the uterus, release calcium ions with the receptors on the uterine smooth muscle, make the uterus tetanic contraction, increase the contraction rapidly and reduce the symptoms of postoperative bleeding (Fischman *et al.*, 2015). A number of studies show that simple application Intravenous injection of oxytocin is not effective, and high dose may lead to abnormal blood pressure, pulse and so on, which is not conducive to maternal health.

Carboprost tromethamine is a derivative of prostaglandin F2 alpha, a kind of unsaturated fatty acid, which has many physiological functions, such as regulating blood vessels and relieving smooth muscle (Galasso *et al.*, 2015). It can affect the calcium ion in the uterine smooth muscle cells to improve the uterine pressure to improve the frequency and degree of uterine contraction, enhance the function of endothelial cells and platelets, and strengthen the mechanism of blood coagulation after the operation

(González *et al.*, 2015). Carboprost tromethamine can stimulate the tension of the uterine smooth muscle by inhibiting the activity of adenylate cyclase to enhance the tension of the smooth muscle of the uterus, thus promoting the rapid closure of the blood vessels and blood sinuses in the wound of the placenta, and exerting the hemostatic effect, and has the advantages of long half-life and strong biological activity. Intramuscular injection of carboprost tromethamine, after 7min can be effective, after 30min to achieve the highest efficacy peak and can maintain 2-3h and according to the situation of women's uterine contraction can be used many times. Studies have shown that carboprost tromethamine has better clinical effect, can induce and stimulate uterine myometrium contraction and prevent postpartum hemorrhage (Hurford *et al.*, 2015).

Carboprost tromethamine is a new type of uterine contractile drug, which can be injected directly into the uterine smooth muscle by intramuscular injection, effectively reducing peripheral interference (Espinel *et al.*, 2015). Compared with misoprostol, carboprost tromethamine has the following significant advantages in preventing postpartum hemorrhage: (1) The half-life is longer, reaching 2h, which can promote the contraction of uterine smooth muscle without repeated administration. (2) The body position is no longer confined to the upper part of the uterine body, and the uterine body and its lower segment are also receptor sites, which effectively reduces the dosage of drugs and improves the safety of medication. (3) The use of intramuscular injection is more effective, and the highest concentration of 15 min can be achieved. (4) Water solubility and absorbency are better than misoprostol, which can effectively reduce drug consumption and adverse reactions.

In the results of this study, compared with the control group, the amount of 2h bleeding (256.7 ± 65.21) mL and the amount of 24h hemorrhage (308.3 ± 78.3) mL after the operation were significantly decreased, and the difference was statistically significant ($P<0.05$). The incidence of postpartum hemorrhage in the experimental group was 5.5% significantly lower than that of the control group. The results showed that carboprost tromethamine was better than the oxytocin in reducing the total amount of bleeding and avoiding postpartum hemorrhage after cesarean section, which was in agreement with the previous study. The reason is that the injection of carboprost tromethamine after delivery of the placenta can regulate the intracellular calcium concentration, enhance the efficacy of oxytocin, promote the formation of intercellular space connection, direct the contraction of the uterine contraction and stimulate the aggregation of the blood platelets at the injury, thus promoting the effect of vasoconstriction (Hofmeyr *et al.*, 2016). Oxytocin only promotes contraction of the uterine smooth muscle. Carboprost tromethamine can stimulate uterine

contraction and stimulate the smooth muscle of the uterus, bladder and gastrointestinal tract. Therefore, the latter is more effective and effective and has longer time.

Studies have shown that coagulation dysfunction is an important inducement of postpartum hemorrhage (Heer *et al.*, 2015). APTT is an indicator of whether the endogenous coagulation function is normal. The decrease of the level indicates that the patient is in a hypercoagulable state and even forms a thrombus, which is not conducive to postpartum hemostasis if it exceeds the normal level (Isorni *et al.*, 2015). TT is an index reflecting the anticoagulant substances in the body, and its level increases indicate abnormal coagulation function. Fib is one of the effective indexes to reflect the hypercoagulable state of the body. It is easy to form a thrombus at the level of high level, suggesting that the body's plasma viscosity is not normal, indicating that the body may be in hyperfibrinolysis and hypercoagulability.

In this study, the levels of APTT, TT and Fib in the two groups were significantly lower than those before the operation, and the difference was statistically significant ($P < 0.05$). It indicates that carboprost tromethamine can effectively improve coagulation function and promote uterine contraction and hemostasis. The reason is that it can accelerate the aggregation of platelets, improve the blood microcirculation, enhance the contraction of the uterus quickly, help to peel off the placenta, reduce the bleeding, and then improve the state of the blood coagulation function of the parturient (Vagnarelli *et al.*, 2015).

In this study, the two groups of SBP and DBP were significantly lower than those before the operation, and the HR was significantly accelerated. The difference was statistically significant ($P < 0.05$). The results showed that all two groups of drugs had a significant influence on the hemodynamics of parturients, but the postoperative recovery of the experience group was significantly better than that of the control group. It indicated that the carboprost tromethamine was superior to the oxytocin in maintaining the hemodynamic stability of the patients, which may be due to the longer half-life and long duration of the drug effect. Rapid and efficient, compared with oxytocin alone, has little effect on the systemic circulatory system, so the hemodynamic state is recovered faster.

CONCLUSION

Carboprost tromethamine can produce greater irritation to the contraction of the uterine smooth muscle, and the hemostatic effect is obvious, but the gastrointestinal smooth muscle of the patient will be stimulated obviously during the period of drug use, causing discomfort of the digestive tract. At the same time, this product has a definite promoting effect on the contraction of vascular smooth muscle, which can easily cause blood pressure to

rise. However, these adverse reactions are not serious, and can be restored to normal after symptomatic treatment. It is safe and reliable, and its prevention and treatment of postpartum hemorrhage is better than oxytocin. In summary, carboprost tromethamine has a significant effect on the prevention of postpartum hemorrhage in cesarean section, and it has a significant effect on improving the state of hypercoagulable blood and maintaining the stable hemodynamic state. Therefore, it has clinical application value.

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