Research Paper

Comparison of Clinical Effects of Intravenous Tranexamic Acid and Carbetocin in the Treatment of Postpartum Hemorrhage

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Postpartum hemorrhage is one of the main causes of maternal death. This study compares clinical efficacy and adverse reactions rate between tranexamic acid injection and carbetocin in postpartum hemorrhage treatment. We selected 80 cases of postpartum hemorrhage after vaginal delivery who received therapy in the Affiliated Hospital of Guizhou Medical University from January 2019 to June 2020. And then randomly divided them into experiment group (40 cases receiving carbetocin treatment) and control group (40 cases receiving intravenous tranexamic acid treatment), compared the blood routine and coagulation function of both groups before and after treatment, and compared the postoperative clinical efficacy, blood pressure, heart rate and adverse reactions. The clinical efficiency of experimental group (95 %) was remarkably higher than control group (85 %) ($p<0.05$); experimental group had remarkably lower postpartum blood loss and hemoglobin reduction than control group ($p<0.05$); adverse reactions rate in experimental group (5 %) was remarkably lower than control group (17.5 %) ($p<0.05$). And after treatment heart rate of experimental group remarkably increased more than control group, so it possessed statistical significance ($p<0.05$). It had no obvious divergence in coagulation function (prothrombin time, activated partial prothrombin time, fibrinogen) and blood pressure between both groups before and after treatment, and it possessed no statistical significance ($p>0.05$). Carbetocin has a better clinical effect than tranexamic acid injection in postpartum hemorrhage treatment. It can effectively reduce postpartum blood loss. The clinical effect is greater and adverse reactions rate is less than that of tranexamic acid, which is worth popularizing in clinic.

Key words: Tranexamic acid, carbetocin, postpartum hemorrhage, clinical efficacy

Postpartum Hemorrhage (PPH) ranks third among most common cause of maternal death in USA and the leading cause of maternal death in developing countries. Approximately 530 000 women die from pregnancy or childbirth each year worldwide[1]. Approximately 14 million mothers experience PPH after childbirth each year. 2 % of them will die within 2-4 h after delivery of the fetus due to PPH. It is defined as vaginal bleeding ≥500 ml within 24 h after the baby is delivered, but for Severe Postpartum Hemorrhage (SPPH), the amount of vaginal bleeding exceeds 1000 ml[2,3]. The main cause of PPH is uterine weakness. Many studies have indicated that postpartum uterine weakness accounted for 90 %, reproductive tract injury accounted for about 7 %, placental residual hemorrhage and coagulation dysfunction accounted for 3 %, the above three aspects are the main reasons for PPH[3]. Although most deaths occur outside health care centers, a large proportion of maternal deaths still occur in hospitals and it is particularly important to need effective drugs to prevent PPH[4]. Usually, uterine contractile drugs or surgical ligation can reduce postpartum vaginal bleeding and effectively prevent PPH[5].

At present, there are various drugs to prevent PPH, but the drugs often have limited hemostatic effects, and we need combine some surgical methods to control PPH[6]. Tranexamic Acid (TXA) is a type of synthetic derivative of lysine amino acid, it inhibits fibrinolysis by reversibly blocking the lysine binding site on plasminogen[7]. It is reported that TXA has been used to treat menorrhagia, which will significantly reduce menstrual bleeding rate (45 %-54 %), but the effect on PPH is still unclear. However, the World Health

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Organization (WHO) also recommends us to use TXA for uncontrollable PPH[8]. Carbetocin is a long-acting synthetic oxytocin analog that also takes effect by stimulating uterus and generally causes drug side effects (for example, nausea or vomiting)[9]. Carbetocin has advantage of heat resistance and does not need to be refrigerated. Studies have indicated that compared with oxytocin, carbetocin has similar or better effects in preventing PPH[10]. This study attempts to discuss and compare the clinical efficacy of TXA and carbetocin in PPH treatment.

MATERIALS AND METHODS

Clinical data:

This study is a double-blind randomized clinical trial. We collected 80 PPH patients (500-1500 ml) diagnosed after caesarean section or normal delivery in the obstetrics department of the Affiliated Hospital of Guizhou Medical University and informed the patients that there would still be a small bleeding after drug treatment and they signed an informed consent form. Adopted sponge collection bag method to exam blood loss. And then randomly divided them into experiment group (40 cases receiving carbetocin treatment) and control group (40 cases receiving intravenous TXA treatment).

Selection criteria:

Inclusion criteria: The patients met the diagnosis of PPH in Obstetrics and Gynecology[11]; all patients were full-term singleton pregnancy; after childbirth, there were abnormalities such as unclear uterine contours, soft uterine texture and increased red bleeding.

Exclusion criteria: Patients with medical diseases (such as history of heart disease and hypertension) or major surgical history; allergy to TXA; thromboembolic diseases and high-risk pregnancy complications (severe preeclampsia). General data comparison is shown in Table 1. They are comparable.

Treatment methods:

After baby delivery, both groups received intravenous with oxytocin injection (Shanghai No.1 Biochemical Pharmaceutical Co., Ltd., GYZZ H31020861) 10 U+0.9 % sodium chloride injection 500 ml. Experiment group received intravenous with carbamic acid (Shanxi Pude Pharmaceutical Co., Ltd., GYZZ H14020886) 0.5 g+0.9 % sodium chloride injection 100 ml, 1 h later the same dose intravenously again. But applied control group with 100 mg (1 ml) of carbetocin intravenously after delivery. Then pressurize the lower abdomen of both groups with 1 kg self-made salt bag after delivery; according to the uterine contraction, if the uterine contractility was weak or there was no contraction, both groups would undergo one hand uterine compression and then both hands uterine compression. If the vagina did not continue to bleed through these methods, the patients would be included in the study. If there was still bleeding, the study would be excluded.

Observation index and curative effect evaluation standard:

AChecked PPH of both groups and then detected their routine blood test and coagulation function before and after surgery, including the concentration levels of Hemoglobin (HB), Activated Partial Prothrombin Time (APTT), plasma Fibrinogen (FIB) and plasma Prothrombin Time (PT). Recorded their postpartum blood pressure and Heart Rate (HR) changes, closely observed postpartum adverse reactions and the treatment effect. Clinical effective index evaluation, markedly effective was defined as vaginal bleeding less than 50 ml after 30 min of maternal medication; effective was defined as vaginal bleeding less than 100 ml after 60 min of maternal medication. Ineffectiveness was defined as the amount of vaginal bleeding less than 300 ml after 90 min of maternal medication[12]. Clinical effective rate=(markedly effective+effective)/total number of pregnant women in each group×100 %.

TABLE 1: COMPARISON OF GENERAL INFORMATION OF BOTH GROUPS ($\bar{x}$±s)

	Experimental group (n=40)	Control group (n=40)	t/χ^2	p
Age	25.18±5.04	24.22±6.12	0.27	0.76
Gestational age	39. 54±1. 23	39. 69±1. 21	0.25	0.66
Postpartum hemorrhage	798.72±25. 67	813.79±24.52	0.19	0.72

Statistical analysis:

Used Statistical Package for the Social Sciences (SPSS) 26.0 software to analyze all the data. Expressed the count data as n % and used Chi-square (χ^2) to test. Measurement data conformed to normal distribution and homogeneity of variance, used ($\bar{x}\pm s$) to indicate them and comparison between groups tested by independent sample t. Used paired t-test to compare the same group before and after treatment. Used the rank sum test for comparison between groups. $p<0.05$ was considered to possess statistical significance.

RESULTS AND DISCUSSION

It possessed no remarkable difference between both groups in terms of age, gestational age, PPH, etc., so it had no statistical significance ($p>0.05$). Both had comparability as shown in Table 1.

After carbetocin treatment, experiment group had remarkably less blood loss at 2 h and 24 h postpartum than control group, it had statistical significance ($p<0.05$) and also it had remarkably less HB decreased value than TXA group, so it possessed statistical significance ($p<0.05$), as shown in Table 2.

The systolic pressure and diastolic pressure of both groups did not change obviously before and after therapy, and compared with control group, there was no remarkable divergence, so it had no statistical significance ($p>0.05$). However, HR increasing in carbetocin group was remarkably higher than TXA group, it had significant difference ($p<0.05$), as shown in Table 3.

Adverse reactions (1 case of vomiting and 1 case of diarrhea) in experimental group was 5 %, which was remarkably lower than control group (1 case of hypertension, 3 cases of vomiting, 1 case of fever and 2 cases of diarrhea), which was 17.5 %. It possessed statistical significance ($p<0.05$), as shown in Table 4.

The coagulation function (PT, APTT, FIB) of both groups did not change remarkably before and after treatment, compared with control group, it had no remarkable divergence, so this had no statistical significance ($p<0.05$), as shown in Table 5.

After 24 h treatment for both groups, the total clinical effective rate (95 %) of experimental group was remarkably higher than control group (85 %). They

TABLE 2: COMPARISON OF BLOOD LOSS AND HB DROP VALUE BETWEEN BOTH GROUPS AFTER TREATMENT ($\bar{x}\pm s$)

Group	Cases	Bleeding volume at 2 h postpartum (ml)	Bleeding volume at 24 h postpartum (ml)	Hemoglobin decrease value (g/l)
Experimental group	40	214.45±20.25	285.37±12.55	14.75±3.54
Control group	40	305.07±23.01	401.11±21. 96	32.12±4.59
t		2.36	4.22	3.45
p		0.001	0	0

TABLE 3: COMPARISON OF SYSTOLIC PRESSURE, DIASTOLIC PRESSURE AND HR BETWEEN BOTH GROUPS BEFORE AND AFTER TREATMENT ($\bar{x}\pm s$)

Group	Cases	Systolic blood pressure			Diastolic blood pressure			Heart rate		
		Before treatment	2 h after treatment	24 h before treatment	Before treatment	2 h after treatment	24 h before treatment	Before treatment	2 h after treatment	24 h before treatment
Experimental group	40	115. 64±4.43	113.64 ±4.84	110.21 ±4.45	69.06 ±3.31	67.46 ±3.67	67.69 ±3.53	82.56 ±4.56	90.31 ±5.41	97.88 ±4.98
Control group	40	117. 54±4.16	112.64 ±4.03	109.54 ±4.31	69.97 ±3.39	68.12 ±3.324	68.19 ±3.28	80.54 ±3.67	78.27 ±4.02	79.02 ±4.12
t		0.38	112.64 ±4.04	0.62	0.19	0.95	0.29	0.76	2.53	4.09
p		0.7	112.64 ±4.05	0.42	0.91	0.68	0.87	0.94	0.02	0.005

TABLE 4: COMPARISON OF ADVERSE REACTIONS RATE IN BOTH GROUPS BEFORE AND AFTER TREATMENT (x̄±s)

Group	Cases	Hypertension	Vomiting	Fever	Diarrhea	Total incidence (%)
Experimental group	40	0	1	0	1	2 (5 %)
Control group	40	1	3	1	2	2 (17.5 %)
t				4.81		
p				0		

TABLE 5: COMPARISON OF COAGULATION FUNCTION (PT, APTT and FIB) BETWEEN BOTH GROUPS (x̄±s)

Group	Cases	PT (s)		APTT (s)		FIB (s)	
		Before treatment	24 h after treatment	Before treatment	24 h after treatment	Before treatment	24 h after treatment
Observation group	60	11.75±0.42	11.56±0.84	25.69±3.89	26.25±3.91	452.52±42.90	457.34±45.20
Control group	60	12.01±0.54	11.79±0.34	27.45±3.91	26.42±3.83	458.71±43.62	450.48±46.36
t		0.123	0.53	0.20	0.73	0.31	0.63
p		0.91	0.76	0.84	0.46	0.75	0.46

Note: PT: Prothrombin Time; APTT: Activated Partial Prothrombin Time and FIB: Fibrinogen

TABLE 6: COMPARISON OF CLINICAL EFFICACY BETWEEN BOTH GROUPS AFTER TREATMENT

	Markedly effective	Effective	Ineffective	Total effective rate
Experimental group	22 (55 %)	16 (40 %)	2 (5 %)	38 (95 %)
Control group	20 (50 %)	14 (20 %)	6 (15 %)	34 (85 %)
x^2	4.63	0.123	0.123	0.123
p	0.03	0.123	0.123	0.123

were obviously different so it possessed statistical significance ($p<0.05$), as shown in Table 6.

Severe PPH is the main reason for the emergence of critical illness in pregnant women and reducing its incidence is the main challenge facing obstetrics today[13]. At present, it is often necessary to combine drugs and surgical treatment to achieve a good prevention of PPH that threatens the life of the lying-in woman. A clinical study reported that sublingual misoprostol and intravenous oxytocin had a good clinical effectiveness in controlling PPH[14]. The study results showed that PPH patients treated with misoprostol had remarkably lower incidence than those treated with oxytocin. Although our study compares the effects of TXA and carbetocin in controlling PPH, carbetocin has better effect than TXA on PPH treatment. In another study, it showed that TXA could reduce PPH after laparotomy and any side effects or complications were not related to TXA.

Carbetocin is a drug introduced in 1987. It is a long-acting synthetic oxytocin analog and its half-life period is about 40 min. The bioavailability of intramuscular injection is 80 %. After intramuscular or intravenous injection of the drug, significant uterine contractions will occur within 2 min[15]. Common side effects of carbetocin are nausea, vomiting, abdominal pain, hypotension, headache, chills and fever. Its contraindications are bleeding caused by rupture of the uterus, vagina or cervix. Carbetocin produces a stronger frequency and amplitude of uterine contractions than oxytocin[16]. Our study shows that after delivery HB decrease remarkably lower in carbetocin group than TXA group. They were obviously different, indicating that intravenous injection of carbetocin has better effect than TXA on preventing PPH. Some studies have indicated that TXA group has higher HB levels than carbetocin group[17,18]. The findings are almost the same as our results and show that carbetocin has better effect than TXA.

According to the results of this study, both groups had no difference in the effects on systolic and diastolic pressure after administration. At the same time, our results showed that the average HR value between both groups was not statistically significant after administration. Previous studies have reported that carbetocin could cause maternal tachycardia[19]. Another study showed that tachycardia occurred in 21 % of

mothers receiving carbetocin, which was significantly higher than that in other groups[20]. Our study also found that carbetocin group had remarkably higher tachycardia incidence than TXA group, which was almost the same as the results of previous studies. In this study, adverse reactions rate such as hypertension, vomiting, diarrhea and fever in carbetocin group was lower than that in TXA group. Some studies have also shown that vomiting condition in women in carbetocin group is low. Our study found that 1 case of vomiting in the carbetocin group and 3 cases of vomiting in TXA group, the difference is statistically significant.

Our study also has some design deficiencies. It is possible that the effect of carbetocin combined with oxytocin treatment is better than that of carbetocin alone and more case designs are needed in the later stage to compare the clinical efficacy of oxytocin alone and combined oxytocin in the treatment of PPH. At the same time, some predecessors have studied the difference between the different administration methods of rectal misoprostol for the treatment of PPH and we obtained a conclusion that the rectal suppository misoprostol was more effective and less harmful than injection misoprostol in reducing PPH[21]. Therefore, we can select misoprostol to become a drug to prevent PPH. Our later study needs to prove the comparison of clinical efficacy of misoprostol or carbetocin in treating PPH.

In conclusion, our research shows that carbetocin has a better clinical effect than injection of TXA in PPH treatment. It can effectively reduce postpartum blood loss, the clinical effect is greater and adverse reactions rate is less than that of TXA, but carbetocin can increase patients' HR, so it is still worth popularizing of in clinic.

Conflict of interests:

The authors declared no conflicts of interest.

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