Effects of Blood Transfusion Amount on Coagulation Function and Safety in Patients with Severe Trauma
Running Tittle: Blood Transfusion Amount in Coagulation Function and Severe Trauma

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Objective:To investigate the effects of different blood transfusion volumes on coagulation function and safety in patients with severe trauma.

Patients and Methods:One hundred and ten cases with severe trauma were selected as the research subjects. They were admitted to our hospital from April 2016 to April 2018. Sixty patients who needed massive transfusion (1-1.5 times of their own blood volume level) were assigned to the study group, and another 50 patients who needed small amount of transfusion (less than their own blood volume level) were assigned to the control group. The blood coagulation function index, thrombelastogram index, blood gas analysis index and the influence of adverse reactions were compared between patients in the two groups before transfusion and 24h after transfusion. Results:Twenty fourhoursafter transfusion, prothrombin time (PT), activated partial thrombin time (APTT) and thrombin time (TT) were prolonged in both groups. Both platelet (PLT) and fibrinogen (FIB) decreased(p<0.05). Both response time of blood coagulation factor (R) and fibrin polymerization reaction time (K) decreased and were lowerin the study group than those in the control group, while fibrous protein aggregation function (Angle), platelet aggregation function (MA) elevated and were higherin the study group than those in the control group (p<0.05). pH in both groups decreased, oxygen partial pressure (PO2) and carbon dioxide partial pressure (PCO2) in both groups increased (p<0.05). PaCO2 and PaO2 in the study group were higher than those in the control group, and pH was lower than that in the control group (p<0.05). The incidence of total adverse reactions in the study group was higher than that in the control group (p<0.05).

Conclusion:In conclusion, massive transfusion for patients with severe trauma could reduce the patient's platelet and affect their coagulation function.

Key words: Severe trauma, massive transfusion, small amount of transfusion, coagulation function, blood gas analysis

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INTRODUCTION

Severe trauma is defined as trauma that threatens life or seriously affects the function of major organs of the body (1). Massive blood transfusion and small amount of transfusion can be definedby the amount of blood transfusion. When the amount of blood transfusion at one time exceeds 1-1.5 times of patient's own blood volume level, it is regarded as massive blood transfusion, and if the amount of blood transfusion at one time is less than patient's own blood volume level, it is regarded as small amount of transfusion (2). Clinical studies have found that (3, 4) most patients with severe trauma have extremely large blood loss and often require massive transfusion in a short time. Patients may go into shock or even life-threatening condition when transfusion is not given promptly enough. The immune system of patients with severe trauma may change at the same time of injury. (5). There is a certain relationship among massive transfusion, inflammatory response and immune system regulation (6).

In theory (7), patients with severe trauma need to be resuscitated by massive transfusion, which could improve the body's blood volume . Under the background of modern research, however, it has been found that (8) transfusing large amounts of blood to patients would affect the platelet coagulation function of patients with severe trauma, which is adverse to hemostasis. The amount of transfusion in patients with severe trauma will significantly affect the later treatment effect of patients (9). There are two sides of transfusion treatment. While solving the problem of blood loss, complications may also be induced (10), aggravating the patient's condition, which is not conducive to the later treatment and prognosis. It has been reported (11) that the risk of organ failure, sepsis and death in patients with severe trauma is bound up with increased transfusion. In order to control the adverse effects, it is necessary to take preventive measures to reduce the risk of complications in patients with severe trauma.

Although transfusion is the preferred first-aid treatment, there are few studies comparing the effects and safety of massive and small amounts of transfusion on patients with severe trauma. Therefore, this article aims to study the effect of massive and small amount of transfusion on the coagulation function and safety of patients with severe trauma, hoping to improve treatment efficiency.

DATA AND METHOD

General Data

A total of 110 cases with severe trauma were selected as the research subjects. They were admitted to our hospital from April 2016 to April 2018 and were grouped according to the volume of transfusion. Among them, 60 patients who needed a massive transfusion were set as the study group, and 50 patients who needed a small amount of transfusion were set as the control group. Thirty five males and 25 females in the study group were 20-50 years old, with an average age of (35.32±2.38) years old. There were 30 males and 20 females in the control group, with the mean age of 36.38±2.27 years old. There were no significant differences in age and gender between the two groups.

Inclusion criteria: Patients with severe trauma who needed transfusion were included. Exclusion criteria: patients with cardiopulmonary disease; patients with mental problems or communication problems; pregnant or lactating women; patients with coagulation dysfunction.

All patients and their families have agreed to participate in the experiment and signed informed consent. This study has been approved by the hospital ethics committee.

Methods

After admission, all patients in the two groups were given oxygen inhalation and wound cleaning adjuvant therapy. Blood oxygen saturation, central venous pressure, invasive arterial pressureand electrocardiogram were monitored. Multiple venous channels (>2) were opened. Sodium Lactate Ringer's (Siping jvneng pharmaceutical Co., Ltd., SFDA approval number: H20023075) was used to maintain blood volume. A rough assessment should be made according to the degree of injury, injury site, wound opening / closing, cause of injury, degree of shock if there is not enough time. Otherwise, an accurate assessment should be made through laboratory blood test if there is enough time. When blood loss of patients was more than 1L, concentrated red blood cells and fresh frozen plasma were injected to maintain the patient's hemoglobin at more than 80 $g{\cdot}L^{-1}$. For patients with blood loss over 80%, 2 $U{\cdot}10\ kg^{-1}$ platelets combined with 10 U cryoprecipitate were injected to maintain the central venous pressure at 12-15 cmH_2O. In the study group, the blood transfusion volume was 1-1.5 times of patient's own blood volume level. While in the control group, the amount of blood transfusion does not exceed the level of patient's own blood volume.

Experimental Materials

Thromboelastography (Haemoscope, USA) (37°C) was used to dynamically monitor the coagulation function. Among them, the R value refers to the time required for the blood sample to be placed in the TEG to the scan image width of

2 mm, K value refers to the time required from the end of the R time to the amplitude of the tracing chart of 20 mm, indicating the clot formation velocity. Angle refers to the rate of accumulation of blood clots, reflecting fibrinogen function, and MA value refers to the maximum amplitude on the TEG map, reflecting the maximum intensity of being formed blood clot and the stability of blood clot formation. The CA7000 automatic blood coagulation analyzer provided by Sysmex company was used to detect the activated partial thrombin time (APTT), fibrinogen (FIB), prothrombin time (PT), thrombin time (TT) and platelet (PLT), and all the detection were completed within 1 day. Blood gas analyzer Abbott i-STAT was used for the determination of pH, oxygen partial pressure (PO2), carbon dioxide partial pressure (PCO2). The levels of CD3+, CD4+ and CD8+ in patients' fasting venous peripheral blood were detected by BD-Facscalibur flow cytometry (USA).

Observational Indexes

[1] Comparison of general data of the two groups

[2] Indexes of coagulation function before transfusion and 24h after transfusion in the two groups

[3] Indexes of thrombelastogram before transfusion and 24h after transfusion in the two groups

[4] Indexes of blood gas analysis before transfusion and 24h after transfusion in the two groups

[5]T cell subset structure in peripheral blood in the two groups before transfusion and 24h after blood transfusion

[6] Number of adverse reactions 24h after transfusion in the two groups

Statistical Method

SPSS 20.0 software was used for statistical analysis. Enumeration data were expressed as n/%, comparison was qualified by x^2, and measurement data were represented by mean ± standard deviation ($\bar{x}\pm s$). Independent t test was used for comparison between the two groups, and paired t test was used for comparison before and after treatment. $p<0.05$ was considered statistically significant.

RESULTS

Comparison of general data of patients in the two groups

There were no significant differences in age and gender between the two groups ($p>0.05$). More details were shown in Table I.

Table I
Comparison of general data of patients in the two groups (n%)

Factors	Study group (n=60)	Control group n=50	t/X^2	*p*
Age (years old)	36.32±2.38	36.38±2.27	0.134	0.893
BMI(kg/m^2)	21.4±2.56	21.5±2.73	0.197	0.843
Gender				
Male	35(58.33)	30(60.00)		
Female	25(41.67)	20(40.00)	0.031	0.859
Cause of injury				
Traffic injury	32(53.33)	25(50.00)	0.728	0.121
High fall injury	18(30.00)	17(34.00)	0.654	0.201
Blunt force injury	8(13.33)	6(12.00)	0.044	0.835
Explosion injury	2(3.33)	2(4.00)	0.035	0.852
Emergency operation	42(70.00)	38 (76.00)	0.495	0.482
ICU length of stay	8.3±2.5	9.2±3.2	1.656	0.101
Length of stay	11.5±3.5	12.2±3.9	0.991	0.323
Hypertension				

with	32	28		
without	28	22	0.078	0.779
Smoking history				
with	41	37		
without	19	13	0.425	0.515

Indexes of Coagulation Function before Transfusion and 24h after Transfusion in the Two Groups

There were no significant differences in coagulation function between the two groups before transfusion (p>0.05). Twenty four hoursafter transfusion, PT, APTT and TT were prolonged in both groups, and patients in the study group were higher than those in the control group. Both PLT and FIB decreased, and the study group was lower than the control group, with statistically significant differences (p<0.05). More details were shown in Figure 1.

Figure 1
indexes of coagulation function before and after transfusion of patients in the two groups

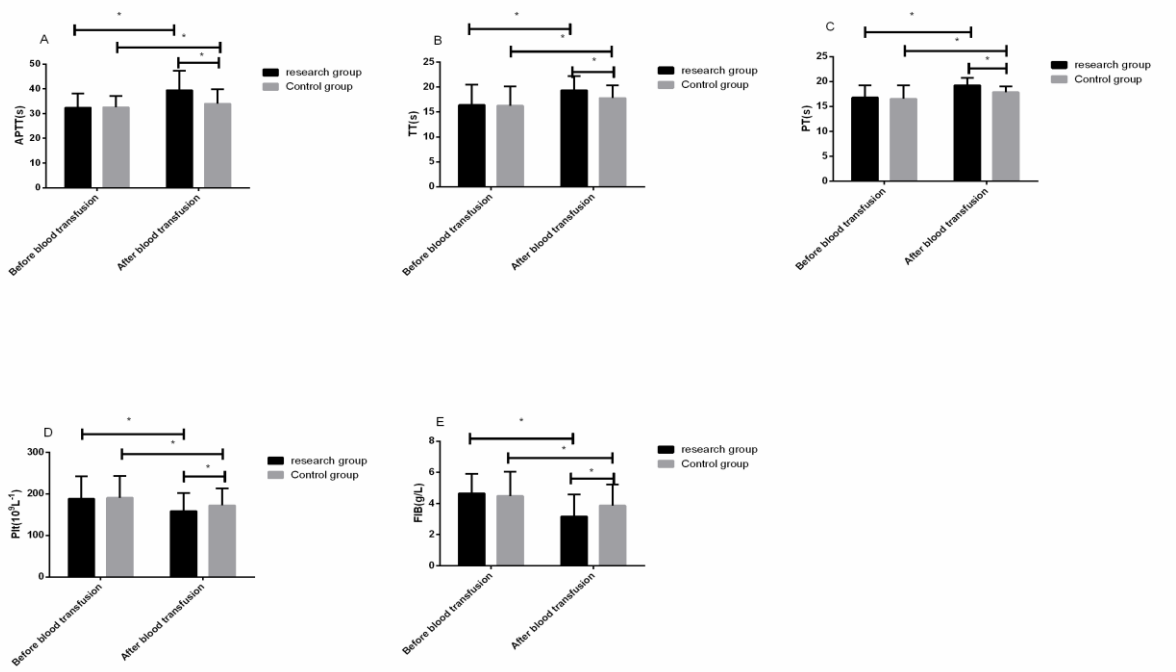

Figure 1-a: After operation, APTT was increased in both the study group and the control group, but the index in the study group was higher than that in the control group. Figure 1-b: After operation, TT was increased in both the study group and the control group, but the index in the study group was higher than that in the control group. Figure 1-c: After operation, PT was increased in both the study group and the control group, but the index of the study group was higher than that of the control group. Figure 1-d: After operation, PLT was decreased in both the study group and the control group, but the index of the study group was lower than that of the control group. Figure 1-e: After operation, FIB was decreased in both the study group and the control group, but the index of the study group was lower than that of the control group.

Note: * means p<0.05.

Indexes of Thrombelastogram before Transfusion and 24h after Transfusion in the Two Groups

Before transfusion, there were no significant differences between the two groups (p>0.05). Twenty four hoursafter transfusion, both R and K decreased, while Angle and MA increased in both groups, with statistically significant differences (p<0.05). However, R and K in the study group were lower than those in the control group, while Angle and MA were higher than those in the control group. The differences were statistically significant (p<0.05). More details were shown in Table II.

Table II
Thrombelastogram indexes before and after transfusion in the two groups

Indexes	R value	K value	Angel value	MA value
Study group (n=60)				
Before transfusion	8.52±1.21	3.85±0.48	44.39±5.32	45.66±4.21
24h after transfusion	7.37±1.24	3.08±0.65	49.74±4.32	52.32±4.32
t	5.142	7.381	6.047	8.552
p	<0.001	<0.001	<0.001	<0.001
Control group n=50				
Before transfusion	8.48±1.32*	3.75±0.52*	44.24±4.38*	45.23±4.23*
24h after transfusion	7.86±1.12#	3.53±0.42#	46.32±3.78#	48.42±4.12#
t	2.532	2.327	2.542	3.820
p	<0.001	<0.001	<0.001	<0.001

Note: * means compared with that before transfusion in the study group, $p>0.05$; # means compared with that after 24h of transfusion in the study group, $p<0.05$.

Blood Gas Index before Transfusion and 24h after Transfusion in the Two Groups

Before transfusion, there were no significant differences in p H, PaO2 and PaCO2 between the two groups ($p>0.05$). Twenty four hoursafter transfusion, p H decreased and PaO2 and PaCO2 increased in both groups, with statistically significant differences ($p<0.05$). Moreover, after 24h of transfusion, PaCO2 and PaO2 in the study group were higher than that in the control group, and pH was lower than that in the control group, the differences were statistically significant ($p<0.05$). More details were shown in Table III.

Table III
Blood gas index between patients in the two groups

Groups	PH	Pa O2(KPa)	Pa CO2(KPa)
Study group (n=60)			

Before transfusion	7.45±0.05	5.96±1.24	7.55±1.25
	7.24±0.04	9.54±2.13	10.38±1.35
t	25.40	11.25	11.58
p	<0.001	<0.001	<0.001
Control group n=50			
Before transfusion	7.46±0.04*	5.92±1.21*	7.51±1.32*
24h before transfusion	7.38±0.16#	8.23±2.21#	9.50±1.21#
t	5.145	6.483	9.438
p	<0.001	<0.001	<0.001

Note: * means compared with that before transfusion in the study group, $p>0.05$; # means compared with that after 24h of transfusion in the study group, $p<0.05$.

T Cell Subset Structure in Peripheral Blood in the Two Groups before Transfusion and 24h after Blood Transfusion

Before transfusion, there were no significant differences in indexes of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ between the two groups ($p>0.05$). Indexes of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ increased in both groups 24 hafter transfusion, but these indexes in the study group was higher than those in the control group ($p<0.05$). More details were shown in Table IV.

Table IV
T cell subset structure in peripheral blood in the two groups before transfusion and 24h after blood transfusion

Groups	$CD3^+$	$CD4^+$	$CD4^+/CD8^+$
Study group (n=60)			
Before transfusion	53.4±3.42	25.2±2.21	0.78±0.17
24h before transfusion	64.5±2.56	43.4±2.56	1.57±0.12

t	20.13	41.68	29.41
p	<0.001	<0.001	<0.001
Control group n=50			
Before transfusion	52.4±3.35*	25.4±2.43*	0.82±0.14*
24h after transfusion	60.6±2.45#	36.8±2.12#	1.23±0.13#
t	13.97	24.54	15.17
p	<0.001	<0.001	<0.001

Note: * means compared with that before transfusion in the study group, $p>0.05$; # means compared with that after 24h of transfusion in the study group, $p<0.05$.

Number of Adverse Reactions in Two Groups

There were no significant differences in the number of patients with hypothermia, sodium citrate poisoning and bleeding tendency after transfusion between the two groups, but the incidence of total adverse reactions in the study group was higher than that in the control group, with statistically significant differences ($p<0.05$). Adverse reactions were welltreated. More details were shown in Table V.

Table V
Number of adverse reactions of patients in two groups

Factors	Study group (n=60)	Control group n=50	t	*p*
Hypothermia	15(25.00)	7(14.00)	2.063	0.151
Sodium citrate poisoning	9(15.00)	4(8.00)	1.282	0.258
Bleeding tendency	5(8.33)	1(2.00)	2.121	0.145
Total number of adverse reactions	29(48.33)	12(24.00)	6.907	0.009

DISCUSSION

Severe trauma is characterized by severe stress response, rapid disease change and high mortality (12). Resuscitation in patients with trauma and hemorrhagic shock has improved in recent years, but bleeding, especially coagulopathy bleeding, cannot be surgically corrected. It has to be controlled to reduce morbidity and mortality

associated with severe trauma (13).

A large number of studies have found that (14) massive transfusion for patients with severe trauma may damage the patients' coagulation system. Hence, more attention should be paid to the changes in various indexes of coagulation function in the treatment process, and blood transfusion strategies should be reasonably adjusted. After massive transfusion, patients may not only have coagulation disorder affecting coagulation function, but also have platelet dysfunction (15). Therefore, we compared the indexes of coagulation function before transfusion and 24h after transfusion of patients in the two groups. The results showed that PT, APTT and TT were prolonged and PLT and FIB were decreased in the two groups after transfusion, while PT, APTT and TT were higher in the study group than those in the control group, and PLT and FIB were lower in the study group than those in the control group. It indicated that massive transfusion to patients would cause damage to coagulation factors and platelets. Davidson et al (16) also reached the same conclusion, and pointed out that the patient's activity factor was also significantly reduced. And there are also studies pointing out that due to the combination of coagulation factors and procoagulant activated platelets, a membrane-dependent enzyme complex is then produced, which plays an important part in the process of blood clotting (17). Therefore, patients' coagulation function would be affected. There were also changes in the control group, but the fluctuation intervals were small, suggesting that a small amount of transfusion had little effect on coagulation. In the study of Son et al (18), it was pointed out that salvage transfusion exceeding 18.5% of the total blood volume for patients undergoing cardiac surgery may have a negative impact on coagulation function, which inspired us that the optimal cut-off point for blood transfusion under different treatment backgrounds will be different. Therefore, timely detection of patients with abnormal coagulation function and corresponding intervention measures are important for prognosis.

At the same time, due to excessive blood loss, the blood would take away a large number of coagulation factors, waking up the coagulation system and consuming a large number of platelets and coagulation factors, which is the main cause of vascular microthrombus. Diffuse intravascular coagulation may occur in case of severe organism secondary hyperfibrinolysis (19,20). In the report of Lawson et al (21), the dynamic monitoring of thrombus elasticity index using TEG helps to provide surgical guidance and improve the efficiency of blood transfusion. The study also pointed out that higher MA is of great value for assisting the prediction of massive blood transfusion during liver transplantation. We compared thrombelastogram index of patients in the two groups before transfusion and 24h after transfusion. The results showed that there were no significant differences before transfusion. After 24h of transfusion, both R and K decreased and Angle and MA increased in the two groups, while patients in the study group had lower R and K than those in the control group, and Angle and MA were higher than those in the control group. It suggests that massive transfusion has a great influence on the coagulation state of the body. Hence, the application of thrombelastogram index in the monitoring of dynamic coagulation function in patients requiring massive transfusion with severe trauma has positive significance for the treatment and prognosis of patients.

The substantial lose of blood due to severe trauma may lead to abnormal blood gas index and affect the coagulation function (22). According to the blood gas analysis, pH value decreased and PaO2 and PaCO2 increased 24h after transfusion, while the content of PaCO2 and PaO2 in the study group was higher than that in the control group, and the pH value was lower than that in the control group. The mechanism might be that there was a large amount of lactic acid in the stored blood, and massive transfusion can reduce the pH value of the blood. After the infusion of stored blood, lactic acid further neutralizes HCO3 in the blood, resulting in metabolic acidosis in patients after transfusion (23,24). The mechanism of increased PaO2 and PaCO2 after transfusion was speculated to be that transfusion increased blood volume, improving hypoxia to a certain extent (25). Hence, it was of great significance to monitor the blood gas index during transfusion.

There are a large amount of inflammation reactions in patients with trauma, and severe inflammation reaction can affect the immune system. T cell subset structure is an important index of cellular immune function (26). Studies have shown that (27) there are more types of immune-related substances in the transfused blood. According to the results of the study, $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ were increased in both groups 24h after blood transfusion, and these factors in the study group were higher than those in the control group. It was speculated that massive transfusion had changed the internal environment of the body and played a positive role in the recovery of the patient's immune system. Meanwhile, the blood also contained substances that enhanced the body's immunity. However, some studies have also shown that excessive transfusion would lead to the suppression of the immune system of the body, making blood transfusion ineffective (28), which needs to be further studied and discussed in follow-up studies.

Massive transfusions can replenish patient's blood volume. However, due to the differences between massive transfusion and conventional blood transfusion, the composition of blood cells in the stored blood may have changed, so patients underwent massive transfusion could easily have a variety of complications or adverse reactions (29). Comparing the adverse reactions caused by transfusion in each group, there were no significant differences in the number of patients in the two groups suffering from hypothermia, sodium citrate poisoning and bleeding tendency after blood transfusion. However, the incidence of total adverse reactions was higher in the study group than that in the control group, suggesting that the likelihood of complications due to transfusion was significantly higher than that of a small amount transfusion. In addition, low body temperature could worsen the degree of acidosis and affect the normal operation of the coagulation system, resulting in coagulation system diseases, and these three factors could reinforce each other (30). Therefore, it is also important to reduce the incidence of adverse reactions and improve the outcome of transfusion.

CONCLUSION

In conclusion, massive transfusion for patients with severe trauma has a greater impact on the changes of coagulation and blood gas analysis than a small amount of transfusion, which may cause coagulation dysfunction in patients. In the process of transfusion, patients' coagulation status should be timely monitored to effectively maintain blood coagulation function, avoid related complications and improve the success rate of massive transfusion, in order to reduce mortality.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

KY, LR, FZ, HL and XY led the conception and design of this study. KY, FZ, HL, JZ and XY were responsible for the data collection and analysis. LR, FZ and XY were in charge of interpreting the data and drafting the manuscript. KY and LR made revision from critical perspective for important intellectual content. The final version was read and adopted by all the authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Huangshi Central Hospital. Signed written informed consents were obtained from the patients and/or guardians.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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