Original Article

Diverse coagulopathies in a rabbit model with different abdominal injuries

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BACKGROUND: Although coagulopathy can be very common in severe traumatic shock patients, the exact incidence and mechanism remain unclear. In this study, a traumatic shock rabbit model with special abdomen injuries was developed and evaluated by examining indicators of clotting and fibrinolysis.

METHODS: Forty New Zealand white rabbits were randomly divided into four groups: group 1 (sham), group 2 (hemorrhage), group 3 (hemorrhage-liver injury), and group 4 (hemorrhage-liver injury/intestinal injury-peritonitis). Coagulation was detected by thromboelastography before trauma (T_0), at 1 hour (T_1) and 4 hours (T_2) after trauma.

RESULTS: Rabbits that suffered from hemorrhage alone did not differ in coagulation capacity compared with the sham group. The clot initiations (R times) of group 3 at T_1 and T_2 were both shorter than those of groups 1, 2, and 4 (P<0.05). In group 4, clot strength was decreased at T_1 and T_2 compared with those in groups 1, 2, and 3 (P<0.05), whereas the R time and clot polymerization were increased at T_2 (P<0.05). The clotting angle significantly decreased in group 4 compared with groups 2 and 3 at T_2 (P<0.05).

CONCLUSION: This study suggests that different abdominal traumatic shock show diverse coagulopathy in the early phase. Isolated hemorrhagic shock shows no obvious effect on coagulation. In contrast, blunt hepatic injury with hemorrhage shows hypercoagulability, whereas blunt hepatic injury with hemorrhage coupled with peritonitis caused by a ruptured intestine shows a tendency toward hypocoagulability.

KEY WORDS: Hemorrhagic shock; Multiple trauma model; Inflammation; Coagulopathy; Thromboelastography

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INTRODUCTION

Trauma is the leading cause of death worldwide; hemorrhage is a major contributor to this mortality and accounts for almost 50% of the deaths within the initial 24 hours.[1] Approximately 24% to 34% of trauma patients present with coagulopathy when they arrive in the emergency department.[2,3] Although traumatic coagulopathy may appear in an early or delayed form, the patients with traumatic shock have significantly different morbidity of coagulopathy.[4,5] Trauma-associated coagulopathy was originally thought to be primarily due to hypothermia, acidosis and consumption/dilution of clotting factors.[6] Current studies have revealed that neurohormonal activation, systemic inflammation and widespread endothelial damage may similarly have an important influential role, and the etiology of trauma-related coagulopathy is multifactorial.[7,8] Much mystery still surrounds changes in coagulation taking place in the period after injury. This study developed a rabbit model of traumatic shock with abdominal injuries to characterize

the changes in clotting and fibrinolysis function by whole blood thromboelastography. We hypothesize that changes in hemostatic function will be present shortly after trauma and will change as trauma severity increases.

METHODS

Animal care

This study was approved by the Institutional Ethics Committee of Guangxi Medical University. Forty New Zealand rabbits (male and female unlimited), aged 8–10 weeks, weighing between 2.30–2.65 kg, were provided by the Experimental Animal Center of Guangxi Medical University (registration number SCXK 2009–0002). The rabbits were equally randomized (simple randomization) into one of the following four groups: group 1 (sham), group 2 (hemorrhage), group 3 (hemorrhage-liver injury), or group 4 (hemorrhage-liver injury/intestinal injury-peritonitis). The blood samples were collected before trauma (T_0), at 1 hour (T_1) and 4 hours (T_2) after trauma. The rabbits had unlimited access to food and water before the experiment.

Animal preparation

Animals were intravenously anesthetized with 20% urethane (1 g/kg, Duly, Nanjing, China) via ear vein, and additional doses (0.2 g/kg) were administered as needed. The animals were maintained in a supine position. A temperature probe (MT-JC218, Shinland, Shenzhen, China) was placed rectally for continuous measurement of central body temperature. The left carotid artery was cannulated to allow for continuous recording of the mean arterial pressure (BL-420F, Bio-Medical Electronics Co., Chendu, China), blood laboratory sampling, and bleeding induction. The right internal jugular vein was cannulated for fluid resuscitation. Sham animals were only anesthetized and subjected to arterial, venous, and sham laparotomies.

Multiple injuries and resuscitation

In group 3, a sterile laparotomy was performed via the right lower costal margin, and the liver was gently exposed. The right upper liver blunt-impact injury was established by hitting the exposed liver with a self-made iron bar (diameter=22 mm, length=39.5 mm, weight=100 g) from a height of 20 centimeters, according to AAST scale,[9] the liver injury grade was grade II. Group 4 also underwent blunt hepatic trauma, and the rabbits were subjected to five intestinal crushes and the injection of 5 mL of self-liquid feces into the peritoneal cavity to induce chemical peritonitis. The wound was temporarily closed with sutures. Finally, pressure-controlled hemorrhage was induced in groups 3 and 4 by bleeding approximately 33% of the total blood volume over a 15-minute period until a mean arterial blood pressure (ABP) of 40 mmHg was reached. ABP of 40 mmHg was maintained by controlling the carotid artery bloodletting. Blood pressure was allowed to fluctuate between 35 and 45 mmHg. Group 2 underwent only controlled hemorrhage and laparotomy. Hemorrhagic shock was maintained for 1 hour. The hemorrhage volume in trauma groups was 57.6±8.0 mL.

Fluid resuscitation was administered to the trauma groups (2, 3, and 4) at T_1, adjust speed with reference to ABP target 50–60 mmHg.[10] Fluid administration used hydroxyethyl starch 130/0.4 and a sodium chloride injection (6.9%, Kelun, Sichuan, China) at a volume equivalent to the blood loss volume. Fluid resuscitation was also administered to the sham group and was performed with the mean fluid volume of the trauma groups.

Blood samples

Blood samples were collected from the left carotid artery. Routine blood examination (e.g., platelets, hemoglobin, and NEUT%) was performed from 1 mL EDTA tubes (Jingzi, Jiangxi, China) with the URIT 3010 (Urit, Guilin, China). Samples for alanine aminotransferase (ALT) and lactate measurements were drawn into 4 mL vacuum tubes (Jingzi, Jiangxi, China) and 1 mL EDTA tubes respectively and were analyzed with the Hitachi automated biochemistry analyzer 7600 (Hitachi, Tokyo, Japan). Samples for thromboelastography (TEG 5000, Haemoscope, Niles, Illinois, America) were collected in 2 mL citrate tubes (Jingzi, Jiangxi, China).

Statistical analysis

Statistical analyses were performed using SPSS 16.0 software (SPSS, Inc., USA). The experimental data were expressed as mean±SD. One-way ANOVA was used to compare multiple groups and within a group between different time points. A difference with $P<0.05$ was considered significant.

RESULTS

Laboratory assessments

At the beginning of the experiment, physiologic variables were not different significantly among the groups (Table 1). At T_1, trauma resulted in comparable

impairment of physiologic variables in the three trauma groups (2, 3, and 4) compared with the sham group, with decreases in temperature, MAP and hemoglobin (P<0.05). Additionally, the hemoglobin levels in groups 3 and 4 were significantly decreased compared with group 2 (P<0.05), and the temperature of group 4 was significantly lower than that of group 2 (P<0.05). In all trauma groups (2, 3, and 4), the lactate levels increased from baseline and were significantly higher than those in group 1 (P<0.05).

At T_2, temperature, MAP and hemoglobin continuously decreased in the trauma groups (2, 3, and 4) until the end of the observation period, and the temperature of group 4 was significantly decreased compared with the other groups (P<0.05). The lactate values remained increased for the trauma groups (2, 3, and 4) compared with the sham group, and the ALT levels of groups 3 and 4 were significantly higher than those of groups 1 and 2 (P<0.05). The lactate and NEUT% values were increased significantly in group 4 and were significantly different from those of the other groups (P<0.05).

Two rabbits in group 4 died within 3.7 hours; blood samples were collected from the dying rabbits, and the values were incorporated into the T_2 results.

Table 1. Mean (SD) for physiologic variables

Variables	T_0	T_1	T_2
Temperature (°C)			
Group 1	39.2 (0.6)	38.1 (0.6)	37.6 (0.7)
Group 2	39.0 (0.5)	37.3 (0.8)*	36.8 (0.8)*
Group 3	38.9 (0.3)	36.8 (0.5)*	36.1 (0.4)*#
Group 4	39.1 (0.5)	36.4 (0.6)*#	35.3 (0.6)*#Δ
Mean arterial pressure (mmHg)			
Group 1	97.4 (5.0)	97.8 (6.3)	91.1(4.1)
Group 2	97.0 (3.8)	55.2 (1.9)*	51.1 (3.2)*
Group 3	96.9 (3.9)	55.2 (2.7)*	51.0 (2.2)*
Group 4	96.8 (4.5)	55.7 (2.5)*	49.5 (1.7)*
Hemoglobin (g/L)			
Group 1	117.2 (5.9)	106.3(6.9)	110.7 (9.1)
Group 2	117.2 (9.1)	84.9 (7.0)*	78.5 (7.6)*
Group 3	114.8 (6.5)	76.6 (7.2)*#	72.7 (8.4)*
Group 4	110.0 (6.3)	78.5 (6.0)*#	69.7 (5.0)*#
Alanine aminotransferase (U/L)			
Group 1	34.8 (5.4)	33.1 (6.7)	34.5 (6.2)
Group 2	31.1 (8.5)	32.2 (6.8)	35.1 (5.4)
Group 3	37.6 (8.6)	37.2 (13.8)	65.7 (25.2)*#
Group 4	33.4 (10.1)	37.1 (15.9)	71.1 (12.0)*#
Lactate (mmol/L)			
Group 1	4.4 (0.8)	4.2 (0.5)	4.3 (0.7)
Group 2	4.5 (0.7)	7.4 (1.1)*	7.4 (0.8)*
Group 3	3.5 (1.1)	6.8 (1.3)*	8.8 (1.6)*
Group 4	4.4 (0.8)	10.9 (4.3)*	18.9 (8.2)*#Δ
Neutrophil (%)			
Group 1	17.1 (3.2)	15.4 (5.0)	16.9 (3.3)
Group 2	16.1 (4.6)	15.7 (5.0)	17.9 (4.6)
Group 3	16.0 (3.4)	17.9 (6.4)	18.2 (3.9)
Group 4	17.0 (4.3)	16.3 (5.3)	57.9 (11.3)*#Δ

When compared with group 1, *P<0.05; when compared with group 2, #P<0.05; when compared with group 3, ΔP<0.05; T_0: baseline; T_1: after trauma 1 hour; T_2: at the end of the experiment.

Thromboelastography

Before inducing the trauma, the thromboelastography values were not significantly different among the four groups.

Following trauma, clot initiation (R times) in group 3 was significantly shorter than that of the other groups (P<0.05) at T_1 and continuously shortened until the end of the observation period (P<0.05, T_2). The R time was significantly prolonged in group 4 compared with groups 1, 2, and 3 (P<0.05, T_2; Figure 1A).

Clot polymerization (K times) in group 4 was significantly longer than that of the other groups (P<0.05, T_2). No difference was observed among groups 1, 2, and 3 (Figure 1B).

Clotting angle (Ang) significantly decreased in group 4 compared with groups 2 and 3 (P<0.05, T_2; Figure 1C).

Clot strength (MA) significantly decreased in group 4 compared with that of the other groups (P<0.05) at T_1 and continuously decreased through T_2 (P<0.05; Figure 1D).

In groups 1 and 2, the thromboelastography values were not significantly different among the three time points. In group 3, the R and K times at T_1 and T_2 were significantly shorter than those at T_0, and Ang significantly increased at T_2 compared with T_0 (P<0.05). In group 4, the R and K times at T_2 significantly prolonged as compared with those at T_0, and MA significantly decreased at T_1 compared with T_0 and continuously decreased through T_2 (P<0.05, Table 2).

Table 2. Mean (SD) for thromboelastgraphy values

Variables	T_0	T_1	T_2
R time (minutes)			
Group 1	3.0 (1.0)	3.9 (1.2)	2.8 (0.8)
Group 2	3.5 (1.7)	3.2 (1.3)	2.6 (0.6)
Group 3	3.3 (0.9)	1.9 (1.3)*	1.2 (0.8)*
Group 4	3.4 (1.1)	4.9 (3.4)	6.8 (3.2)*
K time (minutes)			
Group 1	1.2 (0.4)	1.2 (0.2)	1.3 (0.8)
Group 2	1.5 (1.1)	1.7 (0.7)	1.1 (0.3)
Group 3	2.1 (0.7)	1.1 (0.5)*	1.0 (0.5)*
Group 4	1.4 (0.7)	1.8 (1.1)	2.5 (0.8)*
Ang (°)			
Group 1	69.9 (9.2)	70.6 (6.2)	71.1 (9.2)
Group 2	70.7 (10.8)	70.6 (6.9)	75.9 (2.5)
Group 3	66.4 (6.9)	74.9 (4.0)	76.2 (2.3)*
Group 4	70.9 (7.7)	70.1 (10.9)	59.8 (16.1)
MA (mm)			
Group 1	70.4 (3.6)	71.1 (2.6)	71.2 (2.3)
Group 2	69.0 (2.8)	68.5 (4.8)	66.3 (7.0)
Group 3	69.8 (5.0)	69.7 (4.6)	68.5 (6.3)
Group 4	73.1 (4.3)	64.5 (3.5)*	48.7 (12.6)*#

When compared with T_0 in the same group, *P<0.05; when compared with T_1 in the same group, #P<0.05; T_0: baseline; T_1: after trauma 1 hour; T_2: at the end of the experiment.

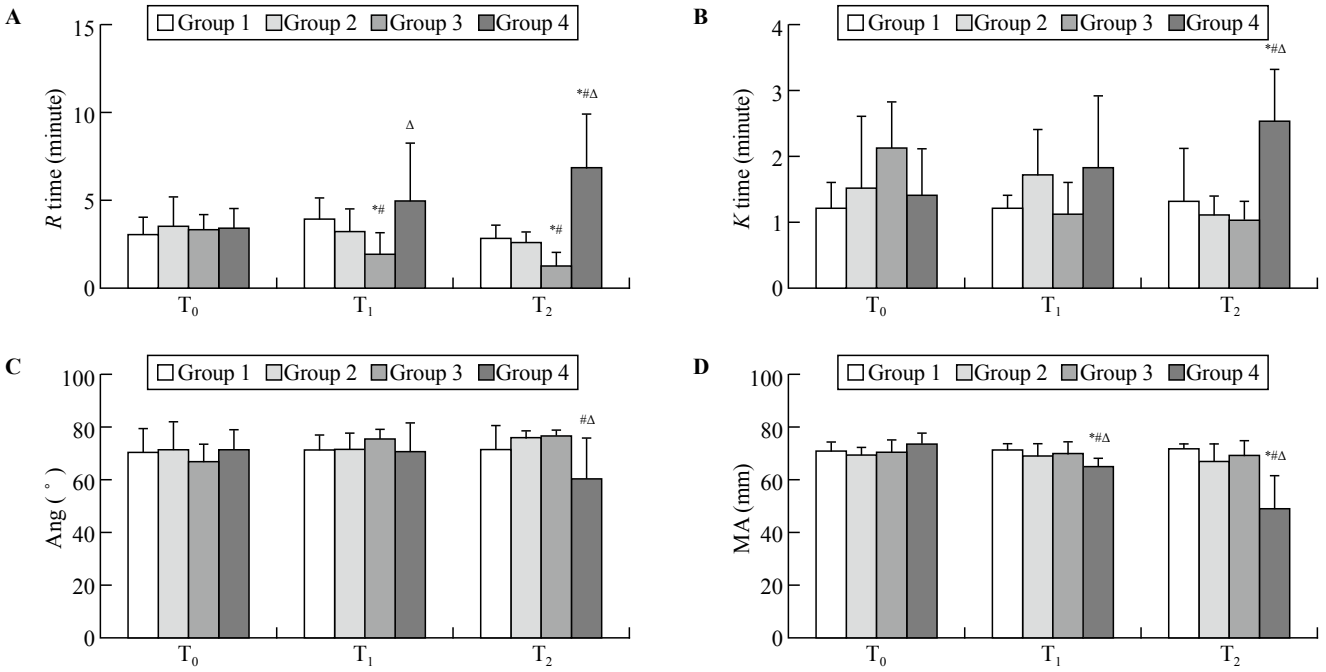

Figure 1. Mean (SD) for thromboelastography values. T_0: baseline; T_1: after trauma 1 hour; T_2: at the end of the experiment; *R* times: clot initiation; *K* times: clot polymerization; Ang: clotting angle; MA: clot strength; when compared with group 1, $^{*}P<0.05$; when compared with group 2, $^{\#}P<0.05$; when compared with group 3, $^{\Delta}P<0.05$.

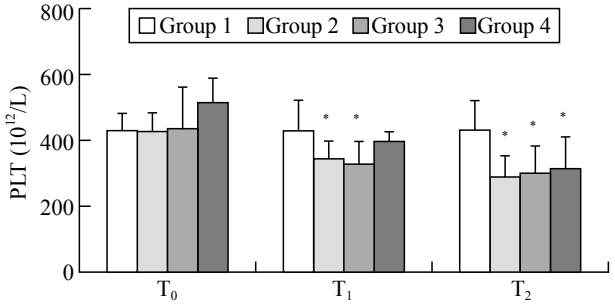

Figure 2. Mean (SD) for platelets. T_0: baseline; T_1: after trauma 1 hour; T_2: at the end of the experiment; when compared with group 1, $^{*}P<0.05$.

Platelet count

The baseline platelet counts were not different among the groups. Following trauma induction, the platelet counts in trauma groups 2 and 3 were significantly decreased compared with that in the sham group ($P<0.05$, T_1). At the end of the observation period, the platelet counts in all trauma groups (2, 3, and 4) were significantly decreased compared with the sham group ($P<0.05$, T_2; Figure 2).

Macroscopic results

After experiment, careful exploration of the injured liver and intestines were performed. In groups 3 and 4, we were not able to detect macroscopic or petechial bleeding in the peritoneal cavity.

DISCUSSION

Injured patients who develop coagulopathy have an increased mortality risk, but the pathogenesis of traumatic coagulopathy is still not fully elucidated. The primary reasons were originally thought to be the loss of hemostatic factors resulting from severe hemorrhage and consumption, dilution by fluid resuscitation, hypoperfusion and acidosis attributed to shock.[11] The current explanation of traumatic coagulopathy is based on the concept of homeostasis; when hemostatic balances were breakdown, the phenotype of coagulation is depending on the injury, shock, or infection.[12] Our study shows that nontraumatic hemorrhagic shock has no obvious effect on blood coagulation, blunt hepatic injury with hemorrhage induces hypercoagulability, and blunt hepatic injury with hemorrhage coupled with peritonitis caused by a ruptured intestine shows a tendency toward hypocoagulability. Thus, it remains unclear whether traumatic coagulopathy is correlated with injury, infection and inflammation.

In this study, the hemorrhage volume in trauma groups was approximately 30% to 35% of the rabbit blood volume[13] and is equivalent to adult severe shock.[14] Hemorrhagic shock was the only trauma factor in group 2; therefore, we could observe the change of coagulation in the pathological state of shock. In our study, group 2 had a remarkably decreased platelet count, lower

temperature and acidosis. However, coagulation was not significantly changed until the end of T_2. To date, only a few studies have examined coagulation in isolated experimental hemorrhagic shock models. Fung et al[15] also evaluated nontraumatic hemorrhage without impairing coagulation in an ovine model. Some reports have shown that hemorrhagic shock may play an integral role in the progression of early coagulopathy,[16,17] but our results revealed that hypoperfusion, lower temperature and acidosis may exacerbate the development of coagulopathy. Coagulation dysfunction was not initiated by the isolated hemorrhagic shock.

In groups 3 and 4, the injuries of trauma and shock were combined, but the clotting function changed significantly. During the experiment, the R time was shorter in group 3 than in other groups, whereas temperature, lactate and platelet count were comparable. Mulier et al[18] also found an increased rate of clot formation in a swine multitrauma and hemorrhage study. With minor trauma, tissue-type plasminogen activator (tPA) and activation of the protein C (PC) pathway could counterbalance the hemostatic activation, and the coagulation display a normal phenotype.[19] However, with increasing tissue trauma, the progressively increasing catecholamine level further enhances thrombin generation, which exceeds the released level of tPA and PC; the net hemostatic effect is hypercoagulability.[19,20] This pathway may underlie the changes in coagulation function in group 3. In group 4, both R time and K time were significantly prolonged compared with those of the other groups, and MA significantly decreased. In addition, experimental results similar to ours were found in the study reportedn by Martini et al.[21,22] Regarding trauma duration, in group 4, the R and K times at T_2 significantly prolonged as compared with those at T_0, and MA continuously decreased through T_2. It suggests the impact of intestinal injury and peritonitis in a traumatic rabbit model was increasingly severe in group 4. At T_2, the temperature was significantly decreased, and the lactate was significantly increased in group 4; these results were significantly different from those in the other groups. Hypothermia and acidosis are important factors that affect clotting factor and platelet activity; as temperature decreases and acidosis is aggravated, the incidence of coagulopathy will increase. Clotting factor activity and platelet aggregation may be reduced by hypothermia (<33–34 °C).[11,23] White et al[24] found that acidosis may reduce the activity of the factor Xa/Va complex, and the activity will be persistently reduced by the increasing acidosis severity. NEUT% values were significantly increased in group 4, implying that group 4 had inflammation. Although not fully elucidated, there is evidence that these values indicate cross-talk between inflammation and coagulation. Tissue factor, the thrombin-thrombomodulin protein C pathway, endothelium, complement proteins, proinflammatory cytokines, and platelets play important roles in this interaction between inflammation and coagulation.[23,25–27] The inflammation cytokines enhance endothelial expression/release of thrombomodulin resulting in enhanced activation of PC.[28] With increasingly severe trauma, the excessive increases in plasma catecholamine increase the release of tPA and PC, and the excessive consumption of coagulation factors and platelets, resulting in predominant hypocoagulability.[29] With increasing trauma severity (as measured by ISS), the coagulation monitored by TEG changes from normal (minor tissue injuries) to hypercoagulable (ISS 10–25), to hypocoagulable (ISS 20–35) and hyperfibrinolytic (ISS > 35).[1]

We observed that at T_2, coagulation differed prominently among the three trauma groups (2, 3, 4), even though the platelets count in the trauma groups (2, 3, and 4) were significantly decreased compared with that in the sham group and were not different among the groups. The results suggest that platelet count was not the key factor in coagulopathy, although one of the current debates on traumatic coagulopathy is the decrease or consumption of platelets. Early platelet dysfunction might be positively correlated with the severity of coagulopathy. In a clinical study, Ostrowski et al[30] found that trauma-induced platelet excessive activation may lower platelet responsiveness or hemostatic potential, so the remaining platelets cannot adequately support clot formation. In addition, adenosine diphosphate (ADP) is one of the main activators of platelet aggregation, but traumatic shock-induced acidosis causes excess ADP generation, which also lowers platelet responsiveness.[31]

There are several limitations in this study. First, rabbits have a different coagulation system from humans, which may have impacted our results. Second, we induced a multiple injuries model focused on abdominal trauma, and the observation period ended 4 hours post-trauma (T_2) or rabbits death; the impact of injury to different regions of the body and the later effect of trauma on coagulopathy was not considered in the present study. Third, with the limitation of experimental conditions, many impact factors regarding traumatic coagulopathy were not assayed such as pH, base excess and PaO_2. Lactate is the earliest marker seen in blood during hypoxia and oxidative stress, so we used lactate to reflect the severity of hypoxia. Fourth, traditional

coagulation tests [prothrombin time (PT), activated partial thromboplatin time (APTT), international normalized ratio (INR)] end once fibrin formation starts; thus, these assays are only sensitive to identify hypocoagulation. Therefore, we only used TEG to evaluate coagulation.

CONCLUSION

The present study suggests that shock combined with different abdominal traumas causes diverse coagulopathies in the early phase. Nontraumatic hemorrhagic shock shows no obvious effect on blood coagulation, hemorrhagic shock combined with blunt hepatic injury shows hypercoagulability, and hemorrhagic shock with hepatic blunt-impact injury coupled with peritonitis caused by intestinal rupture demonstrates a tendency toward hypocoagulability.

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Contributors: Wu R proposed the study and wrote the first draft. All authors read and approved the final version of the paper.

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