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Evaluation for effects of severe acidosis on hemostasis in trauma patients using thrombelastography analyzer

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ABSTRACT

Objective: To investigate effects of metabolic acidosis on hemostasis function in trauma patients using thromboelastography analyzer.
Methods: 65 critically injured patients and 19 healthy volunteers were enrolled in the study. Three samples of whole blood were collected from each patient or healthy volunteer. These three samples were acidified with 50 mmol/l phosphate-buffered saline (PBS) (pH 5.8) or a neutral buffer (50 mmol/l phosphate, pH 7.4) and acidified blood sample with target pH of 6.95, 7.15 or 7.35 was obtained respectively. These three samples with target pH value were added into thrombelastography analyzer (TEG® 5000 Thrombelastograph Hemostasis Analyzers; Haemoscope Corporation, Niles, Illinois, USA) respectively and variables of Clot time (r), Rate of clot formation (α Angle), Clot formation time (K), Coagulation Index (CI) and Maximum strength (MA) were monitored at 37 °C. Besides, association between TEG® parameters and clinicopathological features was analyzed by the Pearson χ^2 test.
Results: In trauma patients, all 5 thrombelastographic variables, Clot time (r), Clot formation time (K), Maximum Amplitude (MA), Rate of clot formation (α Angle) and Coagulation Index (CI), were significantly affected by blood acidification, $F(1.321,83.213) = 88.960$, $P < 0.001$, $F(2,128) = 112.738$, $P < 0.001$, $F(1.199,76.748) = 37.964$, $P < 0.001$, $F(1.195,76.452) = 16.789$, $P < 0.001$ and $F(2,128) = 178.674$, $P < 0.001$. *Post hoc* tests showed that moderate acidosis (pH 7.15) significantly elongated K time (from 2.6 to 3.4 min, $P = 0.0013$) and increased α Angle (from 51.9°to 52.2°, $P = 0.0040$). r, MA and CI were not markedly influenced under moderate acidification. Comparing to mild acidosis (pH 7.15), severe acidosis (pH 6.95) induced more serious impairment to hemostasis and all 5 variables was substantially affected, r (from 5.9 to 6.8 min, $P < 0.001$), K (from 3.4 to 3.9 min, $P < 0.001$), α Angle (from 52.2°to 50.8°, $P = 0.002$), MA (from 52.9 to 51.6 mm, $P < 0.001$) and CI (from −2.3 to −4.2, $P < 0.001$). Additionally, higher r elongation under severe acidosis was significantly associated with an increased mortality rate and transfusion requirement ($P = 0.019$ and 0.031). In healthy volunteers, similar effects on hemostasis were detected. Inhibition ratios of thrombelastographic parameters were significantly higher in trauma patients than in healthy volunteers indicating severer impairment of metabolic acidosis to hemostasis in critically injured patients.
Conclusions: The degree of metabolic acidosis in trauma patients is positively correlated to the severity of hemostasis dysfunction. Additionally, acidosis induces more serious impairment to hemostasis in trauma patients than in healthy volunteers. Moreover, acidosis-induced r time elongation is positively related to a higher death rate and increased transfusion requirement and this indicates a predictive role of TEG® variables for prognosis of traumatized patients.

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1. Introduction

Trauma is the fourth leading cause of disability and death worldwide, and the top in youth [1]. Uncontrolled bleeding is a major cause for mortality in the early hours after trauma and thought to induce a "lethal triad of trauma" [2-6]. This triad including hypothermia, acidosis and coagulopathy is a detrimental prognostic factor and associated with a worse prognosis. The implementation of 'damage control' principles in surgery and resuscitation has alleviated these effects of trauma previously associated with high mortality [7,8]. However, the mortality rate of trauma patients remains high and a better understanding behind

Abbreviations: PBS, phosphate-buffered saline; r, Clot time; K, Clot formation time; α Angle, Rate of clot formation; CI, Coagulation Index; MA, Maximum strength; TEG, Thrombelastography; ATC, acute traumatic coagulopathy; TIC, trauma induced coagulopathy; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; VHA, viscoelastic hemostasis assays; ISS, injury severity score; t-PA, tissue plasminogen activator; ECA, endothelial cells activation; FDP, fibrin degradation products.

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the physiological mechanism of acidosis, hypothermia and coagulopathy is still necessary.

The coagulopathy associated with trauma was once thought primarily due to loss, dysfunction or hemodilution of hemostatic factors and platelets. Current studies have revealed that this acute trauma-related coagulopathy, now referred to as "acute traumatic coagulopathy (ATC)", is a distinct, endogenous coagulopathy within early post-trauma hours. ATC is the early phase of trauma induced coagulopathy (TIC) which is currently considered as a combination of primary (endogenous response) and secondary (effects of fluid resuscitation and consumption) events. ATC is associated with an increased mortality rate, transfusion requirement and a higher incidence of organ dysfunction [9]. Metabolic acidosis in trauma is believed to be secondary to tissue hypoxia in states of hypovolaemia and subsequent inadequate tissue perfusion. Acidosis decreases cardiac contractility, attenuates adrenergic receptor responsiveness to inotropic agents and impairs renal perfusion.

Recently, there are reports revealing that acidosis causes a significant impairment to hemostasis [10]. However, effects of metabolic acidosis on hemostasis system in trauma patients have not been fully elucidated. Additionally, for many studies, traditional assays were chosen for hemostasis status evaluation, including prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, international normalized ratio (INR), D-dimer and fibrinogen. Most of these assays were developed for assessment of hemophilia and anticoagulation therapy. None is satisfactory in a trauma setting, as each represents a single point in a potentially ongoing progress of bleeding. Thrombelastography is one of viscoelastic hemostasis assays (VHA) and has been widely applied in hemostasis evaluation in trauma. TEG® can reproduce the progress of clotting in graphical and numerical format and has many advantages. In current study, hemostasis function was evaluated in 65 severe trauma patients and 19 healthy volunteers using thrombelastography analyzer and effects of acidosis on coagulation system were fully investigated. Moreover, clinicopathological features have been shown to be significantly correlated to acidosis-induced r time elongation indicating that thrombelastographic variables may be served as a predictor for clinical outcomes of traumatic patients.

2. Patients and methods

2.1. Ethics statement

Written informed consent in the study was obtained from all participants. This study was approved by the ethics committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine.

2.2. Patients

A priori was performed and the required sample size was computed by G*Power software. After calculation, a sample size of at least 26 was required for repeated-measures design. Therefore, 65 cases of critical injuries (10 women, 55 men, average age of 37.2 years) transferred to Intensive Care Unit were included in our study between June 2013 to June 2014. These patients were aged between 17 years to 52 years and injury severity score (ISS) was assessed on arrival day. All ISSs were above 18 and the average score was 25.4. 20 were cases of high falling injuries, 45 cases of traffic accident injuries. All patients had a wound number of 2–5 and the average number was 3.1. Exclusion criteria included a known history of severe liver dysfunction, congenital hemostatic disorders, or pre-existing anticoagulants usage (such as clopidogrel, non-steroidal anti-inflammatory drugs and heparin). On the basis of these criteria, 9 patients were excluded and 65 were included in our study. All included patients received therapies including damage control surgery, antibiotics usage, blood products transfusion (red cell concentrates, platelets and plasma) and coagulation factor concentrates (fibrinogen concentrates and other factor products), fluid resuscitation, acidosis correction by dicarbonate, body brake and so on. 56 patients (8 women, 48 men) survived and 9 patients (women 2, men 7) died eventually. In addition, 19 healthy volunteers (10 men, 9 women, age range 19–35 years) were also included into study aiming to investigate effects of metabolic acidosis on hemostasis in healthy people.

2.3. Methods

To obtain the desired pH value, 50 mmol/l PBS (pH 5.8) was used for blood acidification and preliminary experiment was carried out with 6 whole blood samples from healthy volunteers. pH value under gradient volumes of acidifier was detected by blood gas analyzer (ABL 80 FLEX blood gas analyzer, Radiometer, Copenhagen, Denmark) and titration curves were drew (Appendix).

For each patient, three samples of 9 ml whole blood were drawn from femoral veins on arrival day. To avoid the dilutional effects of fluid resuscitation, blood samples were collected before aggressive transfusion. The first 5 ml blood was discarded to avoid sample contamination. 50 mmol/l PBS (pH 5.8) was pumping into 4 ml blood sample at the rate of 0.2 ml/h after a conservative volume of bolus injection and pH value was monitored constantly as acidification proceeded. Pumping suspended as target pH was achieved and the volumes added into blood sample were recorded. Collectively, a volume of 1.14–1.77 ml of PBS (pH 5.8) was required for target pH 6.95 and 0.65–1.11 ml was needed as pH 7.15 was achieved. Moreover, 1 ml of a neutral buffer (50 mmol/l phosphate, pH 7.4) was added into the third sample as the control whose average pH value was 7.35 ± 0.4. Additionally, blood samples were collected from 19 healthy volunteers and target pH of 6.95, 7.15 and 7.35 was achieved in the same manner.

4.5 ml of each blood sample with target pH was transferred into a non-wettable surface tube containing 0.5 ml of 3.2% (0.105 M) sodium citrate, mixed with the citrate by gentle inversion for three times and then citrated blood sample was obtained. After a fixed time of 15 min, each citrated sample of 340 μl was transferred into a cup into which 20 μl of 0.2 M calcium chloride was added. Afterwards, thrombelastography analyzer were running the samples at 37 °C and thrombelastographic variables were measured (Table 1).

2.4. Measured thrombelastographic variables

The measured thrombelastographic variables include Clot time (r), Clot formation time (K), Rate of clot formation (α Angle), Maximum Amplitude (MA)and Coagulation Index (CI) (Table 1). r is the time from the beginning of a sample run to the point at which the first significant clot formation is detected. Thus, r time represents the enzymatic portion of coagulation (normal range 5–10 min). The time from the closure of r to the point when certain clot firmness is reached is K time which represents clot kinetics (normal range 1–3 min). α Angle measures the speed of fibrin build-up and cross-linking and represents fibrinogen level (normal range 53°–72°) . MA is the measurement of maximum strength of the developed clot and reflects fibrin and platelet function (normal average 50–70 mm). Coagulation Index that derived from r, K, MA and α Angle describes a patient's overall coagulation and its normal value lies between -3 and $+3$.

2.5. Statistics analysis

All statistical analyses were performed using the SPSS 16.0 software package. All data was checked for normal distribution. Repeated-measures ANOVA was chosen to analyze whether thrombelastographic variables were statistically affected by metabolic acidosis. Greenhouse-Geisser correction was performed when sphericity assumption was violated. As to *post hoc* tests, when sphericity assumption met, Turkey's test was used, and when sphericity violated, Bonferroni method was performed. The relationship between thrombelastographic variables and

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