Rotation thromboelastometry (ROTEM) enables improved outcomes in the pediatric trauma population

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Abstract

Objective: We evaluated the role of rotation thromboelastometry (ROTEM) in managing acute traumatic coagulopathy in pediatric patients with trauma.

Methods: A retrospective cohort of pediatric patients with trauma from six institutes was studied during a 10-year period from 2007 to 2017. The associations between ROTEM-guided, goal-directed coagulation therapy and clinical outcomes were determined.

Results: Three hundred thirty-two pediatric patients (age $<$ 15 years) who were treated with ROTEM-guided, goal-directed coagulation therapy were matched to 332 control pediatric patients with conventional plasmatic coagulation tests. The ROTEM protocol was associated with a significant reduction in the interval for admission to acute traumatic coagulopathy treatment, less plasma transfusions in the first 24 hours of admission, and a favorable coagulopathy recovery. Furthermore, the median number of total hospital days was significantly shorter for patients who had the ROTEM protocol than for control patients.

Conclusions: There are significant favorable outcomes, including rapid acute traumatic coagulopathy treatment and a lower 24-hour blood product requirement, following ROTEM-guided, goal-directed coagulation therapy among pediatric patients with blunt trauma.

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Introduction

In patients with severe trauma, significant blood loss is frequently associated with coagulopathy, which causes approximately 40% of early mortality.[1,2] Therefore, this problem is a major challenge in trauma centers worldwide. Accurate and timely detection of the hemostatic potential to prevent and correct life-threatening bleeding is of clinical importance for optimizing prompt intervention of coagulopathy.[3,4]

Currently, management of coagulopathy for pediatric patients mainly relies on conventional laboratory coagulation tests,[5–7] including the prothrombin time (PT), activated partial thromboplastin time (APTT), and plasma fibrinogen levels. Pathological values in standard laboratory coagulation tests are rarely associated with acute, clinically relevant bleeding. Additionally, determining the PT and APTT is too time-consuming to provide prompt results, and might delay prompt hemostatic therapy. In contrast to plasmatic coagulation tests, viscoelastic assays, including thromboelastometry or thromboelastography, offer information not only for initiation of coagulation, but also for the clot formation process and clot stability. Therefore, these assays closely reflect the *in vivo* situation. Further, the first results for point-of-care methods (thromboelastography or thromboelastometry) are available within 10 minutes of initiating the test. Therefore, these results can provide a more rapid diagnosis than laboratory tests.[8,9] However, only a few studies that included a small number of patients have reported viscoelastic measurements in trauma patients. Studies focusing on the pediatric patient population, who might show specific pathology, are lacking.

In most trauma centers, a large amount of fresh frozen plasma (FFP) is part of the treatment protocol. FFP is associated with delayed correction of acute traumatic coagulopathy (ATC) and an increased incidence of infection, sepsis, acute lung injury, and multiorgan failure.[10,11] One advantage of coagulation factor concentrates is that they are immediately available, and thus eliminate time delays associated with preparation of allogeneic blood products for transfusion.[12,13] Another advantage is that coagulation factors contain high concentrations of the factor(s) of interest, thus enabling rapid restoration of hemostasis without volume expansion. This reduces adverse events of allogeneic transfusion.[14]

Since 2007, rotation thromboelastometry (ROTEM®, Pentapharm, Munich, Germany) has been performed in our institute as a point-of-care monitoring tool for monitoring and guiding goal-directed therapy of specific coagulation aberrations in pediatric patients. This study aimed to investigate and evaluate the potential usefulness of this technology for sufficiently restoring hemostasis and reducing blood product use in pediatric patients with major trauma.

Methods

Study population

This was a multicenter, retrospective cohort study for pediatric patients with a blunt

injury at six level 1 pediatric trauma centers, including Sanxian Hospital, Jinan Children's Hospital, Qingdao Municipal Hospital, Yongchuan Hospital, Linyi Municipal Hospital, and Children's Hospital of Chongqing Medical University. Patients who were admitted to one of these six institutions during the 10 years from 2007 to 2017 were included. Among the included trauma centers, comparable clinical routine guidelines were implemented to minimize variations in trauma care, including coagulation management, infection management, and restrictive transfusion. Eligible inclusion for this retrospective cohort study included age < 15 years; blunt injury to any region of the body excluding the brain; base deficit of ≥2 mmol/L of hemoglobin concentrations; and an Abbreviated Injury Scale (AIS) score of ≥2. Exclusion criteria were as follows: isolated traumatic brain injury; penetrating injuries; patients who were admitted to the study hospital later than 12 hours after trauma, patients who had pre-existing bleeding diathesis; and patients who received intravenous fluids before admission. To eliminate survivor bias, patients who died within 12 hours of admission and admission to the intensive care unit were excluded from analysis of transfusion outcomes. The study protocol was approved by the ethics committee of each institute that was involved. The need for written informed consent was waived because all of the patients were treated according to routine institutional treatment guidelines. Demographic data, laboratory data, trauma scores, and outcomes data were obtained from the electronic database.

To aid the goal-directed treatment algorithms, viscoelastic assays was performed using ROTEM beginning from 8 February 2013 in our institution, from 9 January 2015 in Jinan Children's Hospital, and from 11 January 2013 in Qingdao Municipal Hospital. Samples were processed immediately following collecting blood at 37°C on a ROTEM delta instrument (Pentapharm GmbH, Munich, Germany). The ROTEM parameters of clotting time, alpha angle (α), clot formation time, clot amplitude at 5 minutes, and maximum clot firmness (MCF) were reported for each sample analyzed. Additional ROTEM tests were ordered on the basis of clinical assessment of bleeding to evaluate the response profile for coagulation parameters during treatment.

Transfusion of blood components and administration of coagulation factor concentrates

Among the included institutes, the general approach to coagulation management of trauma patients included FFP and cryoprecipitate administered as first-line hemostatic therapy in Chongqing, Qingdao and Linyi, whereas Yongchuan used fibrinogen concentrates. The trigger for fibrinogen administration differed between centers, with a fibrinogen level ≤150 to 200 mg/dL. Platelet concentrate and red blood cells (RBCs) were used as necessary.

For the protocol of ROTEM-guided, goal-directed coagulation management, prothrombin complex concentrate (PCC) or fibrinogen concentrate were used first for immediate treatment until FFP was available according to deficiency detected with viscoelastic testing. Usual thresholds for PCC were an extrinsically activated thromboelastometric test clotting time of > 90 s and/or an international normalized ratio (INR) > 1.5 as dosages of 25 units/kg, and PCC was repeated as necessary. Fibrinogen concentrate was used to correct low fibrinogen concentrations and/or poor fibrin polymerization (fibrinogen concentrations < 150–200 mg/dL = extrinsically activated thromboelastometric test with cytochalasin D [FIBTEM] MCF < 7 mm) at dosages of 25 to 50 mg/kg body weight.[1] The platelet concentrate was recommended to increase firmness of the

fibrin-based clot for platelet counts $< 50 \times 10^9$/L and/or poor clot firmness (FIBTEM MCF $\leq$10–12 mm) because fibrinogen could not fully compensate for decreased platelet levels. The target hemoglobin concentration levels should be > 8 to 9 g dL in actively bleeding trauma patients. Tranexamic acid was a principal component in the coagulation management protocols of all included institutes.

Data collection

Computerized medical records were collected and reviewed retrospectively. We collected information on the patients' demographics, type and injury severity scale (ISS), time elapsed between trauma and hospital admission, vital signs, standard plasmatic coagulation tests, blood cell count, lactate levels, and base excess at admission, as well as 24-hour transfused blood components, 24-hour dosage of coagulation factors, and 24-hour amount and type of intravenous fluids administered. We also evaluated the AIS, which quantifies injuries from a score of 1 (minor injury) to 6 (non-survivable) in various body regions. A patient's ISS score was calculated by summing the squares of the three highest AIS scores in three different body regions (values ranged from 1 to 75). The primary outcomes of interest were the time to coagulation management and amount of RBC transfusion. The time to coagulation management was defined as the time from arrival at trauma centers to the time of the first dosage of PCC, fibrinogen concentrate, or blood product use. The secondary outcomes were the proportion of patients with normalized coagulopathy within 24 hours and hemorrhage-related mortality within 24 hours. Other outcomes included 24-hour blood product use (RBCs, plasma, platelets, and cryoprecipitate) and hospital length of stay.

Propensity score matching

Propensity score analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) or R software 3.1.2 (www.r-project.org), and the MatchIt package (www.r-project.org). There was an imbalance in the number of subjects between groups and those receiving goal-directed coagulation therapy via ROTEM protocol were not randomly assigned. Therefore, propensity matching was performed using a 1:1 ratio nearest neighbor algorithm to minimize the effect of potential confounders on selection bias in baseline characteristics. The selected covariates entered into the propensity model included sex, admission INR, admission hemoglobin, initial base deficit, and ISS score. Propensity scores were estimated using a multivariable logistic regression model. A 0.2 caliper width was specified during the matching procedure and matching without replacement was performed on the basis of the estimated propensity score of each patient. Propensity model discrimination and goodness of fit were assessed for the balance of covariates used in propensity score estimation after matching using the C-statistic and the Hosmer–Lemeshow test, respectively.

Statistical analysis

After propensity score matching, the matched ROTEM protocol patients and controls (patients with plasmatic tests) were subjected to statistical comparisons using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp.). Continuous data are presented as mean $\pm$ standard deviation or median (minimum, maximum, or 25th and 75th interquartile range [IQR]) unless otherwise indicated. Categorical data are reported as percentages. For univariate comparisons, the Student's t-test, Shapiro–Wilk test, or Wilcoxon rank sum

(Mann–Whitney U test) was used to compare continuous variables. The χ^2 test or Fisher's exact test was used to compare categorical variables. A P value of ≤ 0.05 was considered significant with two-sided tests.

Results

At the time of the analysis, a total of 762 pediatric patients who were suffering from trauma injury were eligible for analysis. Among them, 366 patients received the ROTEM-guided, goal-directed coagulation therapy protocol (ROTEM group). The demographics, clinical characteristics, routine trauma panel values, and admission laboratory parameters are shown in Table 1.

Notably, there were no differences in sex, admission platelet levels, base deficit, lactate levels, PT, APTT, and INR at arrival between the ROTEM group and the plasmatic coagulation tests group. There were no significant differences in the ISS score and initial hemoglobin values between the two groups with unmatched patients (Table 1). With propensity score matching, 332 patients with ROTEM-guided, goal-directed coagulation therapy were well matched to 332 patients with plasmatic coagulation tests. After matching, several variables, including unstable hemodynamics, the ISS score, and initial hemoglobin levels, became more comparable after propensity score matching (Table 1).

After blood sampling, standard coagulation measurements were transmitted via

Table 1. Demographics, injury, and laboratory characteristics of patients before and after PS matching based on ROTEM compared with conventional plasmatic coagulation tests

	ROTEM before PS matching (n = 350)	Plasmatic tests before PS matching (n = 412)	p	ROTEM after PS atching (n = 332)	Plasmatic tests after PS matching (n = 332)	p
Male sex, n (%)	138 (39.43)	161 (39.08)	0.49	133 (40.06)	119 (35.84)	0.15
Weight, kg	21.89 ± 9.27	22.31 ± 9.29	0.53	22.28 ± 9.07	22.14 ± 9.39	0.85
Interval from injury (hours)	5.53 ± 4.68	5.79 ± 3.18	0.38	5.39 ± 3.04	5.74 ± 3.22	0.16
Fibrinogen (g/L)	1.57 ± 0.45	1.58 ± 0.46	0.71	1.57 ± 0.45	1.58 ± 0.46	0.74
Platelet count ($\times 10^9$/L)	251.70 ± 77.76	256.74 ± 78.79	0.38	255.91 ± 75.91	256.91 ± 79.60	0.87
Initial hemoglobin, g/dL	103.69 ± 16.30	106.52 ± 15.45	0.014	104.72 ± 14.96	106.24 ± 14.96	0.19
Lactate on admission, mmol/L	3.91 ± 1.04	3.82 ± 0.99	0.21	3.84 ± 0.97	3.85 ± 0.99	0.91
PT (seconds)	13.16 ± 2.02	13.04 ± 1.72	0.36	13.07 ± 1.78	13.08 ± 1.78	0.94
APTT (seconds)	27.81 ± 6.83	27.57 ± 5.33	0.60	27.63 ± 6.30	27.74 ± 5.50	0.81
INR, median (IQR)	1.09 (1.02, 1.16)	1.08 (1.02, 1.14)	0.75	1.09 (1.02, 1.15)	1.08 (1.02, 1.14)	0.96
Coagulopathy on admission, n (%)	74 (21.14)	82 (19.90)	0.43	65 (19.58)	65 (19.58)	0.50
ISS score, median (IQR)	11.75 ± 7.58	10.52 ± 6.38	0.015	11.06 ± 6.71	10.59 ± 6.58	0.36
Admission base deficit > 6 mmol/L, n (%)	73 (20.86)	74 (17.96)	0.18	61 (18.37)	60 (18.07)	0.50
Unstable hemodynamics, n (%)	56 (16.00)	49 (11.89)	0.063	43 (12.95)	42 (12.65)	0.50

Data are mean ± standard deviation, median (IQR), or n (%) as indicated.
ROTEM: rotational thromboelastometry; PS: propensity score; INR: international normalized ratio; IQR: 25th to 75th interquartile range; ISS: injury severity scale; PT: prothrombin time; APTT: activated partial thromboplastin time.

the hospital electronic record system with a median time of 47.5 minutes (IQR: 38.0–63.0), whereas ROTEM results were available online after 21.5 minutes (IQR: 15.0–28.0) (p < 0.001). Outcomes of the matched trauma population are shown in Table 2. Patients in the ROTEM group were associated with a significant reduction in interval from admission to RBC use (p = 0.015), while the time to the first plasma use was similar between the two groups. Significantly less plasma transfusion overall and in the first 24 hours of admission

was observed in patients in the ROTEM group than in patients in the plasmatic coagulation tests group (p = 0.005 and p = 0.021, respectively). RBC transfusion was similar in the two groups. In patients in the ROTEM group, 60 of 332 (18.01%) patients received RBC transfusion (median, 150 mL) compared with 75 of 332 (22.6%) patients in the plasmatic coagulation tests group (median, 200 mL). Plasma was administered to 40 (12.04%) patients in the ROTEM group compared with 65 (19.58%) patients in the plasmatic coagulation tests group (p = 0.005).

Table 2. Outcomes of the matched trauma population who were treated on the basis of ROTEM compared with conventional plasmatic tests

Characteristic	ROTEM (n = 332)	Plasmatic tests (n = 332)	p value
Interval from sampling to results, minutes (IQR)	21.50 (15.00–28.00)	47.50 (38.00–63.00)	<0.001
24-hour crystalloid, mL/kg	77.84 ± 26.99	81.14 ± 27.79	0.12
RBC transfusions, n (%)	60 (18.01)	75 (22.6)	0.088
Interval from admission to RBC use, minutes	88.20 ± 17.23	96.00 ± 19.60	0.015
24-hour RBC, mL, median (IQR)	150 (50–500)	200 (100–400)	0.075
Plasma transfusions, n (%)	40 (12.04)	65 (19.58)	0.005
Interval from admission to plasma use, minutes	134.92 ± 65.36	141.09 ± 75.44	0.66
24-hour plasma, mL	147.50 ± 50.57	175.38 ± 96.87	0.021
Interval from admission to determining fibrinogen levels or PCC, minutes	57.50 ± 21.32	–	
Determination of fibrinogen levels or PCC, n (%)	65 (19.58)	23 (6.93)	<0.001
Coagulopathy after 24 hours, n (%)	21 (6.33)	35 (10.54)	0.034
ARDS, n (%)	3 (0.90)	2 (0.60)	0.50
Total number of hospital days	11.22 ± 4.39	12.09 ± 5.38	0.021
Emergent operation after 12 hours, n (%)	10 (3.01)	12 (3.61)	0.41
Platelet nadir <100 ($\times 10^9$/L), n (%)	13 (3.91)	9 (2.71)	0.26
Hemoglobin nadir < 8 g/dL, n (%)	9 (2.71)	11 (3.31)	0.41
Mortality (%)	1 (0.30)	0 (0)	0.50

Data are mean ± standard, median (IQR), or n (%) as indicated. ROTEM: rotational thromboelastometry; IQR: interquartile range; RBC: red blood cell; ARDS: acute respiratory distress syndrome; PCC: prothrombin complex concentrate.

After the final therapy step, more favorable recovery of coagulopathy was observed in patients in the ROTEM group than in those in the plasmatic coagulation tests group (p = 0.034). Furthermore, both groups had comparable emergent operations performed. The ROTEM group appeared to receive lower 24-hour crystalloid volume than did the plasmatic coagulation tests group (p = 0.12), although this did not reach statistical significance. The median number of total hospital days was significantly shorter for patients in the ROTEM group compared with patients in the plasmatic coagulation tests group (p = 0.021). The effect of the resuscitative strategy on mortality could not be determined because of its rare occurrence.

Discussion

This retrospective cohort study showed a reduction in the time to the first transfusion of blood products after implementation of an ROTEM-guided hemostatic therapy. Furthermore, ROTEM-guided hemostatic therapy of patients with bleeding trauma who used PCC, fibrinogen, or a combination with FFP was associated with a reduced total number of hospital days.

Timely administration of hemostatic therapy is critical for survival.[15–17] In our study, viscoelastic assays could be obtained within a few minutes, and closely reflected the *in vivo* situation and enabled differentiated diagnosis of primary underlying pathologies, including hyperfibrinolysis. However, the first dose of fibrinogen concentrate is administered at a median time of 57 minutes, and over half of patients receive the first dose of FFP over 2 hours after availability of plasmatic coagulation tests.[8] Furthermore, typical doses of fibrinogen concentrate and PCC only require less than 10 minutes[18,19] for intravenous infusion. However, extra time is required for blood group matching, thawing, and warming of FFP before administration (thawing and warming usually take approximately 30 minutes), and one unit of FFP is recommended over a period of 30 minutes for administration.

Acquired coagulopathy for patients with trauma is predominantly characterized by poor fibrinogen polymerization, and consequently poor clot firmness, followed by hyperfibrinolysis and prolonged initiation of coagulation. From a pathophysiological point of view, because of low fibrinogen levels (main protein of interest), transfusing FFP as the first-line treatment is questionable because small quantities of FFP are not effective in correcting coagulopathy.[20,21] Furthermore, administration of FFP may have a dilutional effect on hematocrit, and unavoidably leads to thrombocytopenia. Thrombocytopenia weakens clot strength and aggravates anemia, thereby leading to an increase in RBC transfusion. Successful use of PCC or fibrinogen concentrate to treat acquired coagulopathy has previously been reported in other settings involving extensive surgery and blood loss (e.g., cardiovascular surgery), albeit in limited numbers of patients.[22–24] The present study showed that coagulation factor treatment effectively corrected coagulopathy and maintained clot firmness, confirming this notion. Transfusion of FFP, carries the risk of noninfectious side effects, such as immunomodulation and pathogen transmission, transfusion-related lung injury, circulatory overload, and development of blood stream infection or multiple organ failure.[25] However, these findings were not observed in our study. Our study showed a reduction in RBC transfusion among patients who were treated with fibrinogen concentrate and PCCs (ROTEM group) compared with patients who had plasmatic coagulation tests. The faster cessation of bleeding by fibrinogen concentrate and PCCs and relatively low volume of administration for

hemodilution might provide an explanation for reduced RBC transfusion.

There is increasing evidence that thromboelastometry might provide a more clinically relevant definition of ATC with a characteristic clot strength parameter to accurately predict the need for blood product transfusion.[26,27] Several reports have described a reduction in the amount of allogeneic blood product transfusion in patients with trauma or liver transplantation following ROTEM-guided coagulation management algorithms[28,29] compared with standard laboratory tests. A previous study also suggested that the maximum amplitude of thromboelastography within the first 24 hours was a predictor of transfusion.[30] Austrian guidelines recommend PCC administration in bleeding patients if clotting time as measured by thromboelastography/thromboelastometry is prolonged.[31] In the present study, PCC was administered to treat bleeding when the clotting time in the ROTEM assay was prolonged and these patients predominantly showed low fibrinogen concentrations and impaired polymerization.

Fibrinogen/fibrin is critically consumed by the clotting process and is consequently required more than other coagulation factors during perioperative hemorrhage and dilutional coagulopathy.[32] There is growing evidence that considerably higher fibrinogen levels are necessary to control bleeding. Although a minimum plasma fibrinogen level of 1 g/L was recommended by older guidelines,[33] our clinical experience with ROTEM assays suggests that profuse bleeding commonly occurs at an FIBTEM MCF of 7 mm. This value corresponds to a fibrinogen concentration of 150 mg/dL. Based on the evidence from this study and other studies, viscoelastic assays appear to be more appropriate than standard coagulation assays for diagnosing and treating ATC in patients with blunt trauma.[34,35]

The present study has certain limitations that need to be taken into account. Primarily, data were retrospectively collected over a long study interval. In practice, there is no executable guideline, and transfusion therapy was not solely based on laboratory findings, but additionally related to clinical observations. We are inclined to perform ROTEM-guided coagulation management in some patients who are prone to more blood loss, which might be associated with severe coagulopathy, and the patients tend to be transferred into the intensive care unit. Therefore, detecting a significant difference in so many heterogeneous variables in our study might have been difficult.

In conclusion, ROTEM assays reliably detect deficiencies, which can affect timely monitoring and guiding coagulation therapy in patients with severe blunt trauma. Early administration of fibrinogen concentrate and FCC should be predominately used to reduce blood loss in pediatric patients with blunt trauma.

Author contributions

Qin Deng designed the study, analyzed the data, and evaluated the manuscript. Fabao Hao performed statistical measurements and analyzed the data. Chunbao Guo analyzed the data and wrote the paper.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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