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Early Use of Thrombelastometry is Associated with Improved Outcomes after Severe Traumatic Brain Injury

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Abstract

Introduction: Posttraumatic coagulopathy worsens outcomes of patients with severe traumatic brain injury (TBI). This study aimed to investigate whether the early use of thrombelastometry (TEM) was associated with better outcomes after TBI.

Methods: Between 3/2002 and 4/2012 17 Austrian centers enrolled TBI patients into 2 observational studies that focused on effects of guideline compliance (n=400) and on prehospital and early hospital management (n=777), respectively. Data on trauma severity, clinical status, prehospital and hospital treatment, and outcomes were collected prospectively. Information on use or non-use of TEM was missing in 278 cases. Data from patients with hopeless prognosis and patients with moderate TBI were excluded. Two groups of patients were created: the "TEM group" (TEM used within the first 2 h after admission, n=211) and the "no-TEM group" (211 matched patients selected from 610 possible cases). Demographic data and data on trauma severity, treatment and outcome were compared. Logistic regression models, corrected for the effects of age, Glasgow Coma Scale (GCS) scores, and Injury Severity Score (ISS) were constructed. A p-value of <0.05 was considered statistically significant.

Results: Age, sex, trauma mechanisms, and treatment were not significantly different. The "TEM group" had higher trauma severity. However, hospital mortality was significantly lower (20% vs. 31%, p=0.01) Logistic regression revealed that use of TEM, age, ISS and GCS score had significant influences upon hospital mortality and long-term outcome.

Conclusions: The early use of TEM is associated with significantly better outcomes after severe TBI.

Level of evidence: III, retrospective therapeutic study.

Keywords: Traumatic brain injury severe; Traumatic brain injury moderate; Traumatic brain injury outcome; Traumatic brain injury coagulopathy; Thrombelastometry

Introduction

Traumatic brain injury (TBI) is a major health and socioeconomic problem. The burden of TBI is highest in low-income and middle-income countries due to road traffic incidents and predominantly affects young individuals. In high-income countries TBI occurs mainly due to falls in the elderly [1,2]. The goals of the management of TBI patients are to prevent secondary insults to the injured brain and to transport the patients to a neurotrauma center for definitive treatment [3-5]. Assessment of clinical status, intubation, adequate ventilation, and fluid resuscitation are important treatment options to prevent and treat hypoxia, hypoventilation, and hypotension [5,6]. Coagulopathy is an important problem after TBI [7], and thrombelastometry (TEM) has been used to assess coagulation after trauma [8-10] as well as after TBI [11,12]. The goal of this retrospective analysis of prospectively collected data was to assess whether the early use of TEM would lead to improved outcomes as suggested in an earlier study on trauma patients [12].

Methods

Between 2001 and 2012 the International Neurotrauma Research Organization (INRO, a non-governmental research organization, founded 1999; based in Vienna, Austria) coordinated two observational projects that focused on Austrian patients with TBI. Projects enrolled TBI patients without age limit, with multiple trauma, and patients with low Glasgow Coma Scale (GCS) scores. Both projects collected data on epidemiology, prehospital care, and hospital treatment. First one focused on patients with severe TBI and analyzed the effects of guideline-based treatment [13] between 3/2002 and 6/2005 5 centers enrolled 400 patients. The second project included patients with moderate and severe TBI; between 3/2009 and 4/2012 16 centers enrolled 777 patients. Both projects were approved by the appropriate local Ethical Committees. All patients admitted to the participating hospitals were included if they fullfiled the following criteria for moderate/severe brain trauma

- GCS of 8 or less following resuscitation for severe TBI, GCS of 12 to 9 following resuscitation for moderate TBI.
- GCS score deteriorating to 8 or less within 48 h of injury for severe TBI, or to 12 to 9 for moderate TBI.

Due to the purely observational design of the projects informed consent of the patients was not mandatory; however, all patients that regained consciousness gave written permission to use their data for

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scientific purposes. The data were collected in 17 Austrian centers. All centers were able to provide state-of-the-art patient management. According to the prognostic IMPACT (International Mission for Prognosis and *Analysis* of Clinical Trials in *TBI*) core model [14] the centres achieved outcomes that were better than predicted [15]. Treatment in the field was provided by emergency physicians or paramedics, it included rapid examination with documentation of vital signs (GCS score, pupillary status, blood pressure, heart rate, oxygen saturation). Rapid sequence intubation facilitated by hypnotics, sedatives and relaxants, ventilation, treatment of hemorrhage, and fluid resuscitation were done as appropriate. After admission each patient was examined by a trauma team and a computed tomography (CT) scan was done. In centers where TEM was available the decision to use or not to use it was made by the attending physicians. The patients then underwent surgery as appropriate and/or were admitted to the intensive care unit (ICU). Neurosurgery was provided by neurosurgeons (6 centers) or by trauma surgeons (11 centers) who had the option of consulting neurosurgeons for more difficult cases. The specialty of the surgeon had no impact on outcomes of the patients [16]. Intensive care was provided by anesthesiologists in cooperation with neuro or trauma surgeons.

Basic demographic data of the patient, cause and location of trauma, prehospital status and treatment, mechanism and severity of trauma (Abbreviated Injury Score [AIS], Injury Severity Score [ISS]), results of CT scans, results of lab testing, use of TEM, and data on surgical procedures and outcomes were recorded in databases developed by INRO. Prehospital data were documented by emergency physicians/paramedics, and were then transferred into the databases. CT scans were interpreted by neurosurgeons, trauma surgeons and radiologists, and the following findings were entered into the CT sheet of the database: detailed data on basal cisterns, midline shift, main findings, and the Rotterdam CT score [17]. Data on duration of various treatments, on complications, and on outcomes were collected at discharge from the ICU and at hospital discharge. Information on status and location was recorded at 6 months after injury by phone calls to the patients and/or their relatives; in some cases the Glasgow Outcome Scale (GOS) score (18) was recorded at patients' follow-up visits to the centers. The full database had 1177 files. For this study, we used data of severe TBI patients only: 211 patients where TEM was used ("TEM group") were closely matched with 211 cases where TEM was not used. Ranked by importance, the criteria for selection were age, GCS score, pupillary reactivity, AIS of the region "head", ISS, and CT scan criteria (patency of basal cisterns, midline shift, predominant injury). The selected 211 cases formed the "no-TEM group". Data on trauma mechanism, trauma severity, CT findings, treatment, and outcomes were retrieved for each patient in both groups. "Unfavorable outcome" was defined as a GOS score of <4 at 6 months after trauma.

Statistical analysis

Data are given as means with standard deviations, medians with interquartile ranges (IQR), or as proportions. Two-tailed t-test, Fisher's exact test, Chi-square test, and analysis of variance were done as appropriate to identify differences between the groups. To check for associations with outcomes we constructed logistic regression models for ICU and hospital death and unfavorable long-term outcome where the effects of TEM use were corrected for age, GCS scores, and ISS. A p-value of < 0.05 was considered statistically significant.

Results

Demographic data and data on trauma severity are given in Table 1.

Variable	No-TEM group	TEM group	Total	P-value
Patients	211	211	422	
Age (mean, SD)	48.1 (22.4)	47.5 (22.7)	47.7 (22.5)	0.774
Sex (N, % male)	165 (78%)	148 (70%)	313 (74%)	0.076
Injury mechanism (N, %)				0.235
Traffic related	83 (41%)	79 (38%)	162 (40%)	
Fall<3 m	60 (30%)	59 (28%)	119 (29%)	
Fall>3 m	21 (10%)	28 (14%)	49 (12%)	
Sports	16 (8%)	20 (10%)	36 (9%)	
Violence	10 (5%)	3 (1%)	13 (3%)	
Other	12 (6%)	19 (9%)	31 (8%)	
Enrollment GCS (median, IQR)	4 (3-8)	3 (3-6)	3 (3-7)	<0.01
ISS (mean, SD)	26 (11.7)	28.6 (14.8)	27.3 (13.4)	0.048
AIS head and neck (mean, SD)	4.1 (0.7)	4 (0.8)	4.1 (0.8)	0.202
Pupils (N, %)				0.433
One reactive	28 (14%)	17 (9%)	45 (11%)	
Both reactive	155 (76%)	155 (80%)	310 (78%)	
None reactive	21 (10%)	20 (10%)	41 (10%)	
Not assessable	1 (1%)	2 (1%)	3 (1%)	
Prehospital hypoxia (N, % Yes)	5 (9%)	37 (22%)	42 (19%)	0.037
Prehospital hypotension (N, % Yes)	9 (5%)	18 (11%)	27 (7%)	0.044

SD: Standard Deviation; GCS: Glasgow Coma Scale; ISS: Injury Severity Score; AIS: Abbreviated Injury Score

Table 1: Demographics and trauma severity.

Age, sex, and injury mechanisms were not different. "TEM group" had higher rates of prehospital hypotension and hypoxia, higher ISS and lower GCS. No differences were observed regarding treatment (Table 2). Outcomes were better in the "TEM group": ICU mortality was lower (18 *vs.* 26%, not significant), hospital mortality was lower (20 *vs.* 31%, significant), and the rate of unfavorable outcome was lower (39 *vs.* 46%, not significant). The multivariate analysis revealed that use of TEM was significantly associated with improved ICU, hospital, and long-term outcomes. Older age, higher ISS and lower GCS score were associated with worse outcomes (Table 3).

Discussion

To the best of our knowledge this study is the largest study that investigated the association between use of TEM and outcomes after TBI. This study shows that the use of TEM during the first 2 h after hospital admission (i.e., during treatment in the trauma room and the operating theatre) was associated with better outcomes. This was most probably due to interventions based on TEM findings, e.g., use of fibrinogen, of platelets, of prothrombin complex concentrates, and/or of anti-fibrinolytic medication [18]. Unfortunately, we do not have any information which coagulation-related treatment the patients actually received because these data were not collected in the two observational studies from which we selected our cases. This is a major limitation of this study. The use of TEM together with the "platelet-mapping" technique has become a standard in large German as well as Austrian trauma centers, and management of coagulation has become a key element of the treatment of major trauma also elsewhere [19-21]. The use of TEM provides fast point-of-care information about significant post-traumatic coagulation problems. Using only 300 microliters of whole blood the technique measures the viscoelastic properties of a blood clot and provides the information on the speed of initiation of clotting, kinetics of the growth of the clot, strength of the clot and time to breakdown of the clot.

This information is provided numerically as well as graphically, and is therefore easy to read. The two most important tests are done using either activated thromboplastin ("extem") or cytochalasin D (to inhibit the action of platelets on the growing clot; "fibtem"). Initial test results are available 5 min after the start of the test, full test results are available after 20 min. If the initial test results show typical patterns (e.g., only small amplitude in "fibtem") treatment may be initiated within a few minutes after start of the test. A typical example is given in a case report by Schochl et al. [22]. To get continuous information a new test could be started every 5-10 min this means that two TEM devices are used in many centers. A third test ("aptem") uses aprotinin to inhibit fibrinolysis but is otherwise similar to "extem". Fibrinolysis is present if clot strength is normal on "aptem" and low on "extem". The most frequent finding after TBI is small amplitude on "fibtem" indicating decreased fibrinogen levels and/or impaired fibrin polymerization. Thus, administration of fibrinogen is usually the first-line treatment. If the maximum amplitude on "extem" does not increase after fibrinogen administration the use of platelet concentrates is indicated. Prolonged clotting time on "extem" warrants the use of prothrombin complex concentrates. In cases with increased fibrinolysis the use of tranexamic acid or other anti-fibrinolytic medications is necessary. This "goal-directed" treatment of coagulopathy after trauma avoids the need for large doses of fresh frozen plasma, and has been shown to improve outcomes after trauma [23]. TEM findings have also been used to identify patients with poor prognosis after TBI as well as after trauma. In both of these retrospective studies poor clot strength and hypocoagulability were associated with worse outcomes. In the TBI study [24] 8/78 patients (10%) were diagnosed by TEM to have hypocoagulability; this was confirmed by standard tests of coagulation in only 2/8 patients (25%). In the general trauma study [25] patients with poor clot strength had a significantly higher ISS than patients with normal clot strength (27 *vs.* 19; p=0.006).

Variable	No-TEM group	TEM group	Total	P-value
Patients	211	211	422	
Prehospital intubation (N, % Yes)	191 (91%)	186 (88%)	377 (89%)	0.528
Secondary transport (N, % Yes)	31 (15%)	26 (13%)	57 (14%)	0.68
Prehospital pulse oximetry (N, % Yes)	193 (97%)	171 (97%)	364 (97%)	0.945
Neurosurgical procedure (N, % Yes)	140 (66%)	137 (65%)	277 (66%)	0.89
EDH evacuation (N, % Yes)	23 (11%)	18 (9%)	41 (10%)	0.553
SDH evacuation (N, % Yes)	44 (22%)	41 (20%)	85 (20%)	0.846
Parenchymal hemorrhage evacuation (N, % Yes)	4 (2%)	2 (1%)	6 (1%)	0.698
Days of ICP monitoring (median, IQR)				
All patients	1 (0-8)	3 (0-8.75)	2 (0-8)	0.173
Survivors	1 (0-8)	3.5 (0-10)	3 (0-9)	0.199
Dead	1 (0-5.5)	1 (0-5.3)	1 (0-5.5)	0.867
Days of ventilation (median, IQR)				
All patients	5 (2-14)	5 (1-15)	5 (1-14)	0.282
Survivors	7 (1-14)	7 (0-16)	7 (1-16)	0.412
Dead	4.5 (2-10.5)	3 (2-7)	4 (2-9)	0.388
Days at ICU (median, IQR)				
All patients	10 (4-20.5)	10 (2.5-21.3)	10 (3-21.2)	0.686
Survivors	13 (5.5-24)	13.5 (4-22.9)	13 (5-23)	0.43
Dead	4.5 (2-10.4)	2.4 (0.9-8.9)	4 (2-10)	0.118
Days at hospital (median, IQR)				
All patients	18 (6-33.6)	18.5 (7-33.4)	18.4 (6.6-34)	0.412
Survivors	23 (13.8-41.5)	21.2 (14-39.4)	22.2 (14-42)	0.577
Dead	5 (2-12)	3.2 (1.3-8.9)	4 (2-12)	0.32
ICU mortality (N, %)	54 (26%)	38 (18%)	92 (22%)	0.068
Hospital mortality (N, %)	66 (31%)	42 (20%)	108 (26%)	0.01
Six months unfavorable outcome (N, %)	96 (46%)	82 (39%)	178 (42%)	0.2

EDH: Epidural Hematoma; SDH: Subdural Hematoma; ICP: Intracranial Pressure; ICU: Intensive Care Unit; IQR: Interquartile Range; ICU: Intensive Care Unit

Table 2: Treatment factors and outcomes.

Conclusions

In conclusion, our study showed that the early use of TEM was associated with improved outcomes after TBI. Unfortunately, due to the retrospective nature of our study we were unable to provide information on the coagulation-related treatment. A large prospective study should be done to investigate and define the possible benefits of "goal-directed" management of coagulation after severe TBI.

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Author Contribution Statement

Alexandra Brazinova: project manager for the second project, entered the data

	ICU outcome (Alive=1)		Hospital outcome (Alive=1)		Long Term outcome (Favorable=1)	
	OR (CI95%)	P-value	OR (CI95%)	P-value	OR (CI95%)	P-value
Rotem (Used *vs.* No)	2.1 (1.2-3.5)	<0.01	2.5 (1.5-4.1)	<0.001	1.6 (1.02-2.4)	0.039
ISS	0.95 (0.94-0.96)	<0.001	0.97 (0.95-0.98)	<0.001	0.97 (0.95-0.99)	<0.001
GCS	1.2 (1.07-1.32)	<0.01	1.2 (1.1-1.3)	<0.001	1.1 (1.03-1.19)	<0.001
Age	0.97 (0.96-0.98)	<0.001	0.97 (0.96-0.98)	<0.001	0.97 (0.96-0.98)	<0.001

GCS: Glasgow Coma Scale; ISS: Injury Severity Score; OR: Odds Ratio; CI: Confidence Interval

Table 3: Multivariate analysis.

collected by the local investigators, analyzed data quality, and wrote part of the paper

Walter Mauritz: developed both observational projects, analyzed data, and wrote part of the paper

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Conflicts of interest

The authors do not have any conflicts of interest.

Previous presentations

This study has not been presented anywhere.

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