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Head Trauma

Correlation between coagulopathy and outcome in severe head trauma in neurointensive care and trauma units☆

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Abstract

Background: Abnormal blood coagulation after traumatic brain injury is a common finding. Some studies have proposed these changes as useful predictors of outcome in patients with head trauma. This study aimed at evaluating the association of the routine tests of blood coagulation within the first hours after severe head trauma with prognosis of patients with severe head trauma.

Materials and Methods: A total of 52 patients with severe head trauma (Glasgow Coma Scale [GCS], ≤8) were admitted at Tabriz University Hospital for 1 year. Patients with major accompanying trauma were excluded. On admission, serum levels of hemoglobin and hematocrit as well as the platelet count, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) were documented. The relation between these parameters with final outcome and also with GCS at admission, 24 hours, 48 hours, and 1 week after admission and discharge time and Glasgow Outcome Scale (GOS) were studied.

Results: Thirty three patients were discharged, and 19 died. There were significant negative correlations between PT, PTT, and INR with all GCS and GOS scores. These correlations were significant and positive between the platelet count and all GCS and GOS scores. Median PT, PTT, and INR were significantly higher in nonsurvivors. Median serum platelets count was significantly lower in nonsurvivors.

Conclusion: On-admission PT, PTT, INR and platelet count may be used as predictors of outcome and prognosis of patients with severe head trauma.

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1. Introduction

Abnormal blood coagulation after brain injury was first reported by Penick and McLendon [1] in a newborn suffered during delivery. Soon, it was found that these abnormalities in

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coagulation system are very common in patients with head trauma because the routine coagulation tests were increasingly used [2-5]. The incidence of these abnormalities has been reported to vary between 15% and 100% depending on the severity of trauma [6-13]. Association between abnormalities in coagulation tests and poor outcome of patients with head injury was first reported by Pondaag [14] in 1979. Thereafter, a series of investigations confirmed the link between coagulopathy and adverse outcomes in head trauma in larger and more methodologically appropriate studies [15-20]. Although not fully recognized, it is proposed that the presence of abnormal coagulation tests in head trauma may be caused by cerebral vascular endothelial damage after direct damage, as well as indirect damage through inflammation, toxins, and ischemia. It seems that there is a disseminated intravascular coagulation condition in patients with head trauma [21]. It is assumed that the routine tests of blood coagulation are able to identify the earliest signs of coagulopathy, assess its severity, monitor its course, and predict the short-term and long-term outcome in patients with severe head trauma. However, supporting data are very scarce in the literature [22]. In this study, we aimed to assess the probable association of abnormalities in routine tests of blood coagulation within the first hours after severe head trauma with prognosis of patients.

2. Methods

In this cross-sectional study, 54 patients with severe head trauma (Glasgow Coma Scale [GCS], ≤8) were evaluated during a 1-year period from January 2009 to January 2010 at Tabriz University Hospital. Patients were enrolled in the study immediately after being examined by a neurosurgeon in the emergency ward. Patients included had a GCS of 8 or less and no severe chest and/or abdomen injury. Exclusion criteria were multisystem trauma, existing coagulation disorders, alcohol intoxication, drug overdose, liver disease, hypothermia, use of any medications affecting coagulation parameters, or presented to emergency ward with more than 3 hours after head injury. A critical care pharmacist screened patients on admission for any drug effects on coagulation. We were not able to follow up 2 patients; therefore, the study was performed on 52 patients. Demographic and clinical data collected included age; sex; mechanism of injury; admission to trauma step-down unit or intensive care unit; coexisting injuries; hospital length of stay; GCS score on admission and 24 hours, 48 hours, and 1 week after injury; Glasgow Outcome Score (GOS) score on discharge; GOS (discharged vs died); and final diagnosis. Routine serum laboratory tests on peripheral venous blood samples including the serum levels of hemoglobin and hematocrit as well as the coagulation panel including platelet count, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) were drawn at admission and every 6 hours until clinically stable. These markers were thereafter obtained on a daily basis. Initial admission readings were considered for predicting outcome. Computed tomography of the brain was performed on all patients, and its interpretation was performed by radiologists. Relation between the serum coagulation panel with the GCS and GOS scores, as well as the short-term outcome, was determined. Informed consents were signed by the first-degree relatives of the patients. This study was approved by the institutional review board committee at Tabriz University Hospital. Obtained data are presented as mean ± SD and frequency (percentage). The SPSS version 15 statistical software (SPSS, Inc, Chicago, Ill) was used for analysis. Quantitative variables were compared using Mann-Whitney U test. Qualitative variables were compared using contingency tables, χ^2 test, or Fisher exact test when appropriate. Correlation was evaluated by Spearman coefficient (ρ). Results with $P \leq .05$ were considered statistically meaningful in all studied items.

3. Results

The mean age of the patients was 32.3 ± 14.7 years (range, 22-43 years; median 28 years). Forty eight (92.3%) patients were male, and 4 (7.2%), female. Thirty three (63.5%) patients were hospitalized in step-down units, and 19 (36.5%), in the intensive care unit. Accompanied traumas existed in 8 (15.4%) patients, which were all bone fractures. Thirteen (46.2%) patients were traumatized in car accidents; 9 (17.3%), as pedestrians; 4 (7.7%), with fall accidents; and 2 (3.8%), in quarrel. The duration of hospital stay was 16.1 ± 10.8 days (range, 8-45 days). Regarding serum laboratory findings, the mean hemoglobin level was 12.7 ± 2.3 mg/dL (range, 8.4-19.2

Table 1 Final diagnoses in the studied population

Diagnosis	Percentage
Diffuse axonal injury	28.8
Brain contusion	17.3
Subdural hematoma	15.4
Subarachnoid hemorrhage	7.7
Subarachnoid hemorrhage and diffuse axonal injury	7.7
Diffuse axonal injury and brain edema	7.7
Subarachnoid hemorrhage and brain contusion	3.8
Epidural hemorrhage	1.9
Subarachnoid hemorrhage and brain edema	1.9
Diffuse axonal injury + brain contusion	1.9
Subarachnoid hemorrhage and intraventricular hemorrhage	1.9
Intraventricular hemorrhage and brain contusion	1.9
Subarachnoid hemorrhage and subdural hematoma	1.9

Table 2 Correlation between coagulation markers and GCS and GOS in the studied population

Variable		Base GCS	24 hours GCS	48 hours GCS	GCS After a week	GCS At discharge	GOS
Platelet count	ρ	0.335	0.102	0.108	0.100	0.142	0.188
	P	.015	.042	.048	.032	.038	.040
PT	ρ	−0.429	−0.369	−0.413	−0.432	−0.455	−0.456
	P	.002	.021	<.001	.002	.001	.001
PTT	ρ	−0.406	−0.428	−0.498	−0.419	−0.416	−0.450
	P	.003	.003	<.001	.002	.002	.001
INR	ρ	−0.411	−0.332	−0.481	−0.503	−0.324	−0.403
	P	.002	.032	.002	.001	.034	.032

mg/dL; median, 12.9 mg/dL); mean hematocrit level was 34.2 ± 6.6 (range, 22-43; median, 37); mean platelet count was 233.2 ± 70.0 $\times 10^3/\mu$L (range, 98-400 $\times 10^3/\mu$L; median, 220.5 $\times 10^3/\mu$L); mean PT was 14.2 ± 2.2 seconds (range, 10.4-20.0 seconds; median, 13.5 seconds); mean PTT was 36.9 ± 18.7 seconds (range, 23-120 seconds; median, 32 seconds); mean INR was 1.3 ± 0.5 (range, 1.0-3.4; median, 1.2); mean GCS at admission, 24 hours, 48 hours, 1 week, and at discharge time were 6.4 ± 1.5 (range, 3-8; median, 7), 6.8 ± 1.7 (range, 3-11; median, 7), 6.7 ± 2.5 (range, 0-14; median, 7), 6.4 ± 5.1 (range, 0-15; median, 7.1), 8.1 ± 6.1 (range, 0-15; median, 10.5), respectively; and the mean GOS was 2.6 ± 1.4 (range, 1-5; median, 3). Finally, 33 patients (63.5%) were discharged, and 19 (36.5%) died. The final diagnoses are summarized in Table 1. Accordingly, diffuse axonal injury, brain contusion, and subdural hematoma were the 3 leading underlying causes. The correlation between on-admission coagulation panel and GCS and GOS is summarized in Table 2. There were significant negative correlations between PT, PTT, and INR with all GCS and GOS scores. These correlations were significant and positive between the platelet count and all GCS and GOS scores. Different variables, as well as the coagulation markers, are compared between survivors and nonsurvivors in Table 3. There were no significant differences between the 2 groups regarding sex, hospitalization ward, and accompanying fractures in other parts of body. Median PT, PTT, and INR were significantly higher in nonsurvivors. Median serum platelet count was significantly lower in nonsurvivors. The receiver operating characteristic curve of the coagulation parameters in predicting mortality is shown in Fig. 1. Under-the-curve areas for all 4 markers were significant (0.648, P =.007 for PT; 0.722, P = .008 for PTT; 0.965, P = .020 for INR; and −0.810, P < .001 for platelet count). The optimal cutoff points were platelet count 229 $\times 10^3/\mu$L or less (sensitivity, 78.8%; specificity, 78.9%), PT 13.8 seconds or more (sensitivity, 57.9%; specificity, 63.3%), PTT 33.5 seconds or more (sensitivity, 63.2%; specificity, 81.8%), and INR 1 or greater (sensitivity, 73.7%; specificity, 72.7%) in this regard.

Table 3 Different variables and coagulation panel in survivors and nonsurvivors

Variable	Survivors (n = 33)	Nonsurvivors (n = 19)	P
Sex, male/female	30/3	18/1	.534
Age (y)	31.3 ± 12.2 (28)	33.3 ± 15.6 (29)	.302
Hospitalization word, ICU/trauma	13/20	6/13	.573
Accompanying fracture	7	1	.126
Platelet count ($\times 10^3/\mu$L)	247.1 ± 73.5 (237)	209.1 ± 57.4 (201)	.048
PT (s)	13.7 ± 1.7 (13.5)	15.2 ± 2.7 (14.5)	.044
PTT (s)	31.3 ± 4.6 (31)	46.8 ± 28.2 (36)	.008
INR	1.2 ± 0.3 (1.2)	1.5 ± 0.6 (1.3)	.042

Data are shown as mean ± SD (median) or frequency.
ICU indicates intensive care unit.

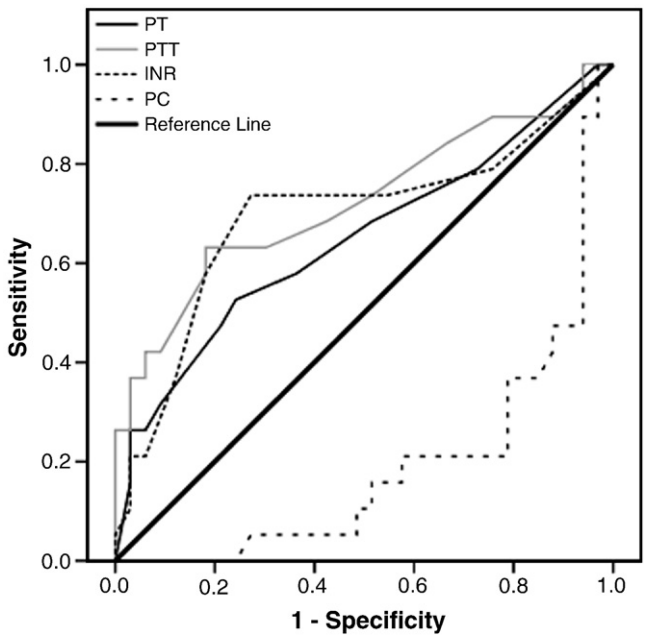

Fig. 1 Receiver operator characteristic curve of coagulation markers in predicting mortality in patients with severe head trauma.

4. Discussion

In the present study, we evaluated early routine coagulation markers in patients with severe head trauma with regard to prognosis. Accordingly, PT, PTT, INR, and platelet count correlated significantly with GCS and GOS. Likewise, these parameters were significantly different between the survivors and nonsurvivors. There are many studies that have examined changes in the coagulation system, but only a limited number of researches have evaluated the predictive value of routine coagulation laboratory tests (INR, PT, PTT, and platelet count) in this regard [23-25]. In addition, these reports are heterogeneous maybe because of various limitations [26]. Engström et al [27] found that the significant fall in platelet counts after severe head trauma was related to prolonged mechanical ventilation [27]. Kaufman et al [28] reported dramatic changes in PTT and PT after head trauma and correlated them to multisystem damage, necrosis, and hemorrhage on head computed tomographic scan. Olson et al [29] evaluated the association between trauma outcome and hemostatic abnormalities by examining platelet count, PT, and PTT within 24 hours of head trauma. They reported that the prolonged PTT strongly correlated with poor outcome [29]. Bayir et al [30] evaluated coagulation markers in 62 patients with isolated head trauma. They found a negative relationship between GCS and PT and PTT ($P < .001$). Platelet levels did not correlate with GCS. Mortality was strongly related to PT. They found no relationship between mortality and platelet count or PTT. They concluded that only fibrinolytic markers measured within the first 3 hours are useful in determining the prognosis of patients with isolated head trauma [30]. It should be noted that they recruited patients with a wide range of age (2-76 years), which may have influenced the final conclusion. We only enrolled patients 22 to 43 years old. Auer and Ott [5] also found a significant relationship between PTT, PT, and platelet count and the severity of brain trauma in 30 patients 7 to 14 days after severe head trauma. Chiaretti et al [31] evaluated children with severe head injury and found a significant and independent association between delayed PTT and GOS. They concluded that a delayed PTT may predict worse outcome in children with severe head trauma [31]. The survivors and nonsurvivors were matched for age, sex, accompanying injuries, and ward of hospitalization. It may be concluded that the relation between coagulation markers and outcome is independent in our series, too. Harhangi et al [32] also concluded that coagulopathy after traumatic brain injury is an important independent risk factor related to prognosis. We conclude that the coagulation parameters within 3 hours after head injury are of value in determining the patient outcome. This is in line with previous reports [33-35]. Routine determination of the coagulation status, therefore, should be performed in all patients with traumatic brain injury [32]. The present study also determined the optimal cutoff point of coagulation markers in predicting mortality after severe head trauma. To the best of our knowledge, there is no similar data in the literature yet. The platelet count of 229 × $10^3/\mu$L or less (sensitivity, 78.8%; specificity, 78.9%), PT of 13.8 seconds or more (sensitivity, 57.9%; specificity, 63.3%), PTT of 33.5 seconds or more (sensitivity, 63.2%; specificity, 81.8%), and INR of 1 or greater (sensitivity, 73.7%; specificity, 72.7%) were the best cutoff points in prediction of mortality in our series. These values should be optimized in further studies with larger sample sizes. Although there is limited understanding of the mechanisms by which head trauma initiates coagulopathy, it should be born in mind that the acute coagulopathy of trauma should be considered distinct from disseminated intravascular coagulation as described in other conditions. Determining the exact underlying pathophysiology and rapid diagnosis are important areas for future research [36]. In addition, future studies focusing on early treatment of coagulation abnormalities should be performed to determine the effect on morbidity and mortality.

5. Conclusion

On-admission PT, PTT, INR, and platelet count may be used as predictors of outcome and prognosis of patients with severe head trauma.

References

[1] Penick GD, McLendon WW. Disorders of the hemostatic mechanism. Int Rec Med 1960;173:491-6 PMID: 14431589.
[2] Goodnight Jr SH. Defibrination following head injury. Compr Ther 1977;3(3):25-8 PMID: 844269.
[3] van der Sande JJ, Veltkamp JJ, Boekhout-Mussert RJ, Bouwhuis-Hoogerwerf ML. Head injury and coagulation disorders. J Neurosurg 1978;49(3):357-65 PMID: 681997.
[4] Auer L. Disturbances of the coagulatory system in patients with severe cerebral trauma. Acta Neurochir (Wien) 1978;43(1-2):51-9 PMID: 707171.
[5] Auer LM, Ott E. Disturbances of the coagulatory system in patients with severe cerebral trauma II. Platelet function. Acta Neurochir (Wien) 1979;49(3-4):219-26 PMID: 517179.
[6] Sawada Y, Sadamitsu D, Sakamoto T, Ikemura K, Yoshioka T, Sugimoto T. Lack of correlation between delayed traumatic intracerebral haematoma and disseminated intravascular coagulation. J Neurol Neurosurg Psychiatry 1984;47(10):1125-7 PMID: 6502169.
[7] Piek J, Chesnut RM, Marshall LF, van Berkum-Clark M, Klauber MR, Blunt BA, et al. Extracranial complications of severe head injury. J Neurosurg 1992;77(6):901-7 PMID: 1432133.
[8] Stein SC, Young GS, Talucci RC, Greenbaum BH, Ross SE. Delayed brain injury after head trauma: significance of coagulopathy. Neurosurgery 1992;30(2):160-5 PMID: 1545882.
[9] Sørensen JV, Jensen HP, Rahr HB, Borris LC, Lassen MR, Fedders O, et al. Haemostatic activation in patients with head injury with and without simultaneous multiple trauma. Scand J Clin Lab Invest 1993;53(7):659-65 PMID: 8272754.
[10] May AK, Young JS, Butler K, Bassam D, Brady W. Coagulopathy in severe closed head injury: is empiric therapy warranted? Am Surg 1997;63(3):233-6 [discussion 236-7], PMID: 9036890.

[11] Scherer RU, Spangenberg P. Procoagulant activity in patients with isolated severe head trauma. Crit Care Med 1998;26(1):149-56 PMID: 9428558.
[12] Jacoby RC, Owings JT, Holmes J, Battistella FD, Gosselin RC, Paglieroni TG. Platelet activation and function after trauma. J Trauma 2001;51(4):639-47 PMID: 11586152.
[13] Murshid WR, Gader AG. The coagulopathy in acute head injury: comparison of cerebral versus peripheral measurements of haemostatic activation markers. Br J Neurosurg 2002;16(4):362-9 PMID: 12389889.
[14] Pondaag W. Disseminated intravascular coagulation related to outcome in head injury. Acta Neurochir Suppl (Wien) 1979;28(1): 98-102 PMID: 39428.
[15] Stein SC, Spettell C, Young G, Ross SE. Delayed and progressive brain injury in closed-head trauma: radiological demonstration. Neurosurgery 1993;32(1):25-30 PMID: 8421553.
[16] Stein SC, Spettell CM. Delayed and progressive brain injury in children and adolescents with head trauma. Pediatr Neurosurg 1995;23 (6):299-304 PMID: 8743998.
[17] Kearney TJ, Bentt L, Grode M, Lee S, Hiatt JR, Shabot MM. Coagulopathy and catecholamines in severe head injury. J Trauma 1992;32(5):608-11 PMID: 1588649.
[18] Gando S, Nakanishi Y, Tedo I. Cytokines and plasminogen activator inhibitor-1 in posttrauma disseminated intravascular coagulation: relationship to multiple organ dysfunction syndrome. Crit Care Med 1995;23(11):1835-42 PMID: 7587259.
[19] Becker S, Schneider W, Kreuz W, Jacobi G, Scharrer I, Nowak-Göttl U. Post-trauma coagulation and fibrinolysis in children suffering from severe cerebro-cranial trauma. Eur J Pediatr 1999;158(Suppl 3):S197-202 PMID: 10650869.
[20] Vavilala MS, Dunbar PJ, Rivara FP, Lam AM. Coagulopathy predicts poor outcome following head injury in children less than 16 years of age. J Neurosurg Anesthesiol 2001;13(1):13-8 PMID: 11145472.
[21] Yokota H, Naoe Y, Nakabayashi M, Unemoto K, Kushimoto S, Kurokawa A, et al. Cerebral endothelial injury in severe head injury: the significance of measurements of serum thrombomodulin and the von Willebrand factor. J Neurotrauma 2002;19(9):1007-15 PMID: 12482114.
[22] Lustenberger T, Talving P, Kobayashi L, Inaba K, Lam L, Plurad D, et al. Time course of coagulopathy in isolated severe traumatic brain injury. Injury 2010 [Epub ahead of print], PMID: 20471013.
[23] Copes WS, Sacco WJ, Champion HR, Bain LW, "Progress in Characterising Anatomic Injury", In Proceedings of the 33rd Annual Meeting of the Association for the Advancement of Automotive Medicine, Baltimore, MD, USA, 1993;205-18
[24] Gando S, Tedo I, Kubota M. Posttrauma coagulation and fibrinolysis. Crit Care Med 1992;20(5):594-600 PMID: 1533358.
[25] Bredbacka S, Edner G. Soluble fibrin and D-dimer as detectors of hypercoagulability in patients with isolated brain trauma. J Neurosurg Anesthesiol 1994;6(2):75-82 PMID: 8012177.
[26] Stein SC, Smith DH. Coagulopathy in traumatic brain injury. Neurocrit Care 2004;1(4):479-88 PMID: 16174954.
[27] Engström M, Romner B, Schalén W, Reinstrup P. Thrombocytopenia predicts progressive hemorrhage after head trauma. J Neurotrauma 2005;22(2):291-6 PMID: 15716634.
[28] Kaufman HH, Hui KS, Mattson JC, Borit A, Childs TL, Hoots WK, Bernstein DP, Makela ME, Wagner KA, Kahan BD, et al. Clinico-pathological correlations of disseminated intravascular coagulation in patients with head injury. Neurosurgery 1984;15(1):34-42 PMID: 6472592.
[29] Olson JD, Kaufman HH, Moake J, O'Gorman TW, Hoots K, Wagner K, et al. The incidence and significance of hemostatic abnormalities in patients with head injuries. Neurosurgery 1989;24(6):825-32 PMID: 2747858.
[30] Bayir A, Kalkan E, Koçak S, Ak A, Cander B, Bodur S. Fibrinolytic markers and neurologic outcome in traumatic brain injury. Neurol India 2006;54(4):363-5 PMID: 17114843.
[31] Chiaretti A, Pezzotti P, Mestrovic J, Piastra M, Polidori G, Storti S, et al. The influence of hemocoagulative disorders on the outcome of children with head injury. Pediatr Neurosurg 2001;34(3):131-7 PMID: 11359101.
[32] Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. Acta Neurochir (Wien) 2008;150 (2):165-75 PMID: 18166989.
[33] Kuo JR, Chou TJ, Chio CC. Coagulopathy as a parameter to predict the outcome in head injury patients—analysis of 61 cases. J Clin Neurosci 2004;11(7):710-4 PMID: 15337130.
[34] Zehtabchi S, Soghoian S, Liu Y, Carmody K, Shah L, Whittaker B, et al. The association of coagulopathy and traumatic brain injury in patients with isolated head injury. Resuscitation 2008;76(1):52-6 PMID: 17706857.
[35] Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D. Coagulopathy in severe traumatic brain injury: a prospective study. J Trauma 2009;66(1):55-61 PMID: 19131806.
[36] Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma 2008;65(4):748-54 PMID: 18849786.