Original Article

Fibrinolytic markers and neurologic outcome in traumatic brain injury

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Aims: To determine the usefulness of fibrinolytic markers as early prognostic indicators in patients with isolated head trauma. **Materials and Methods:** Sixty-two consecutive patients (26 women and 36 men; mean age 61 years, range 2-76 years) with isolated head trauma seen within the first three hours of the trauma were included in the study. The Glasgow Coma score (GCS), platelet counts (Plt), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, fibrin degradation products (FDP) and D-dimer levels were measured. Head computerized tomography (CT) findings were categorized as brain edema, linear fracture, depressed fracture, contusion and bleeding. Plt counts, PT, PTT, fibrinogen, FDP, D-dimer levels and CT findings were compared with both GCS and mortality in the first week. Statistical significance was accepted at $P \leq 0.05$. **Results:** A marked negative relationship was found between GCS and PT, PTT, FDP and D-dimer levels ($P<0.001$). Plt levels did not correlate with GCS. Mortality was most strongly related to GCS, PT, FDP and D-dimer levels ($P<0.001$, $P<0.001$, $P<0.001$ and $P<0.001$, respectively). We found no relationship between mortality and CT findings, nor was there any significant relationship between Plt, PTT and fibrinogen levels. **Conclusion:** GCS and fibrinolytic markers measured within the first three hours were useful in determining the prognosis of patients with isolated head trauma.

Key words: Disseminated intravascular coagulopathy, fibrinogen, Glasgow Coma score, prognosis, traumatic brain injury

Introduction

The head is the most frequently damaged part of the body in multiple trauma patients and the death rate in patients with head trauma is approximately 35%.[1] On postmortem examination, 75% of traffic accident victims had findings of brain damage.[2] The medical treatment and rehabilitation expenses of these patients together with the associated labor loss are enormous. In spite of their medical cure and rehabilitation, only 40-50% of these patients recover completely.[1,2] In addition to preventing head trauma, it is of vital importance to determine the factors that influence prognosis and mortality.

Miner *et al*. examined the relationships among clinical findings, head computerized tomography (CT) and systemic coagulation parameters within the first two hours of head trauma.[3] In their study, 71% of patients had abnormal coagulation parameters, with 32% meeting laboratory criteria for disseminated intravascular coagulopathy (DIC) or fibrinogen syndrome. The mortality rate of the patients with abnormal coagulation parameters was four times higher than that of patients with normal coagulation parameters and the prognosis of patients with severe brain damage, as determined by CT and abnormal neurological findings was worse. The authors concluded that mortality from head trauma might be reduced by treating DIC.[3]

Occurring as a complication in many disease states, DIC is a hemorrhagic disorder caused by the release of thromboplastin into the circulation with a resultant increase in platelet aggregation. Tissue factors are released in high concentrations after trauma, burns and surgery.[4]

The brain cortex contains large amounts of thromboplastin, which is released in high amounts after head trauma or in the presence of brain tumors.[5,6] Thromboplastin triggers coagulation, which leads to organ damage through disturbances of the microcirculation.[7,8] Widespread bleeding ensues from decreased platelet counts and insufficient coagulation factors.[4]

Multiple studies have found changes in coagulation parameters within 24 hours of severe head trauma to be reliable indicators of future hemorrhagic complications.[9,10] Engström *et al*. found the dramatic fall in platelet counts after severe head trauma to be related to longer periods of dependence on mechanical ventilation.[9] Stein *et al* found the changes in coagulation markers to correlate with the size of the damaged brain, as visualized on CT.[10]

This study was designed to investigate fibrinolytic changes within

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the first three hours of isolated head trauma and the prognosis of these patients.

Materials and Methods

The study protocol was approved by the ethics committee of the medical faculty. Prospectively, patients with isolated head trauma who presented to our hospital's emergency department over a six-month period (May 2004-October 2004) within three hours of the trauma were enrolled in the study. Exclusion criteria were multisystem trauma, existing coagulation disorders and presentation after the first three hours of the head trauma. Glasgow Coma score (GCS) was calculated upon initial examination and peripheral venous blood samples were taken from each patient to determine the platelet number (Plt), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, fibrin degradation products (FDP) and D-dimer levels. Head CT was performed on each patient and its reading performed by emergency physicians. CT findings were classified as brain edema, linear fracture, depressed fracture, contusion and bleeding (epidural, subdural, subarachnoid or intracerebral bleeding). Patients were then transferred to the intensive care unit and from there to the neurosurgery ward.

Statistical analysis

GCS, age, Plt, PT, PTT, fibrinogen, D-dimer values and CT findings were compiled using SPSS for Windows® v.13 (SPSS Inc, Chicago, USA) software at admission and discharge. Spearman's rho (r_s) correlation coefficients were calculated. In addition, GCS, Plt, PT, PTT, fibrinogen and D-dimer values were correlated with gender and mortality using the Mann-Whitney U test. Findings were considered statistically significant at $P \leq 0.05$.

Results

During the study period, 62 patients (41% female, mean age 61 ± 8 years, range 2-73 years) with isolated head trauma were enrolled in the study, with a mean time lapse from trauma to presentation at the emergency department of 113 ± 28 min. Fifteen patients (24%) were younger than 18 years (pediatric age group), with a mean age of 7 ± 2 years (range 2-18 years). On admission, the GCS was over 8 in 40% of patients (mean 8 ± 3, range 3-13).The mean Plt count, PT, PTT, fibrinogen and FDP were 153,000 ± 37 000 $10^3/\mu L$, 2.14 ± 0.6 sec, 73 ± 27 sec, 178 ± 43 mg/dl and 20 μg/ml respectively. The mean D-dimer level was greater than 1 μg/ml.

Patients were divided into five groups according to CT findings (brain edema, linear fracture, depressed fracture, contusion, hemorrhage).

Patients with GCS of 8 or below had a mean Plt count, PT, PTT, fibrinogen, FDP and D-dimer level of 98,000 ± 24,000 $10^3/\mu L$, 2.7 ± 0.5 sec, 89 ± 12 sec, 128 ± 33 mg/dl, >20 μg/ml and >1 μg/ml, respectively. Half of the patients in this group (n=19) were lost during follow-up.

A positive relationship (r_s=0.688) was found between GCS and fibrinogen levels ($P<0.001$), but a markedly negative relationship between GCS and PT, PTT, FDP and D-dimer levels [Table 1]. Mortality strongly correlated with GCS, PT, FDP and D-dimer ($P<0.001$, $P<0.001$, $P<0.001$ and $P<0.001$, respectively). The relationship between GCS and Plt levels was not statistically significant ($P=0.051$). The relationship between GCS and CT findings was also not statistically significant ($P=0.055$). We found no relationship between mortality and CT findings, nor was there any significant relationship between Plt, PTT and fibrinogen levels.

A significant decrease in Plt and fibrinogen values and a significant elevation in PTT, FDP and D-dimer values were determined. Parameters of survivors and non-survivors are compared in Table 2.

Discussion

Many researchers have examined changes in the fibrinolysis system that occur in some patients with isolated head trauma.[11-22] Decreased levels of antithrombin (AT), fibrinogen and protein C were common, but levels of tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor did not appear to change. D-dimer levels were also altered in these patients. Elevated FDP was an indicator of poor prognosis in children with isolated head injury.[12] A significant association between GCS and clinical outcome in patients developing DIC has also been reported.[11]

Olson *et al* evaluated the association between trauma outcome and hemostatic abnormalities by examining Plt, PT, PTT, thrombin coagulation time (TCT), fibrinogen, FDP and DIC within 24 hours of head trauma. A comparison between

Table 1: Correlation (Spearman's rho coefficient, r_s) between GCS and fibrinolytic markers in patients with traumatic brain injury (n=62).

	r_s	*P*
Plt ($10^3/\mu L$)	0.248	0.051
PT (sec)	-0.472	<0.001
PTT (sec)	-0.595	<0.001
Fibrinogen (μg/dl)	0.688	<0.001
FDP (μg /ml)	-0.573	<0.001
D-dimer (μg /ml)	-0.573	<0.001

Plt: Platelets, PT: Prothrombin time, PTT: Partial thromboplastin time. FDP: Fibrin degradation products, GCS: Glasgow coma score

Table 2: GCS, Plt, PT, PTT, fibrinogen and D-dimer levels (mean ± SD) in survivors and non-survivors in the first week of follow-up

	Survivors	Non-survivors	*P*
GCS	10.1 ± 3.1	5.1 ± 1.4	0.160
Plt ($10^3/\mu L$)	272249 ± 137651	211961 ± 63993	0.007
PT (sec)	1.7 ± 0.4	2.2 ± 1.2	0.155
PTT (sec)	32.4 ± 5.4	35.7 ± 8.0	<0.001
Fibrinogen (μg/dl)	272.1 ± 93.1	151.2 ± 31.3	<0.001
FDP (μg/ml)	12.3 ± 7.6	20.0 ± 0.0	<0.001
D-dimer (μg/ml)	0.7 ± 0.3	1.0 ± 0.0	<0.001

Plt: Platelets, PT: Prothrombin time, PTT: Partial thromboplastin time, FDP: Fibrin degradation products, GCS: Glasgow coma score

coagulation parameters and clinical outcome (discharge or death) was also made and the authors found a strong association between increased FDP and TCT levels and poor clinical outcome. Long PTT times also strongly correlated with poor outcome.[14] We verified these findings and also found especially long PT and PTT times, low fibrinogen levels and increased FDP and D-dimer in non-survivors.

Bredbacka *et al* measured soluble fibrin, D-dimer and AT and stated that high levels of soluble fibrin and D-dimer, as well as a secondary decrease in AT at admission in patients with isolated skull trauma were associated with a poor prognosis.[15]

Trauma to the brain may cause coagulation disorders at various levels.[16] After head trauma, prothrombin fractions 1 + 2 (F1+2) and thrombin-antithrombin complex taken from the internal jugular vein were higher than those in samples taken from peripheral veins and arteries. Plasma fibrinogen levels were significantly decreased, resulting in a generalized lack of hemostasis after a localized injury to the head.

Scherer *et al*. also examined blood samples from the vena cava, jugular vein and a peripheral artery.[17] They found that within six hours of severe isolated skull trauma, the release of procoagulation factors from the cerebral microvascular system increased the level of thrombin and inhibition of AT III. The increased systemic and local procoagulation speeds fibrinogen turnover and causes DIC.

Studies that have examined the relationship between fibrinogen and CT findings in patients with head trauma have demonstrated good correlation.[18,19] In the study by Ueda *et al*, 26 patients with head trauma were evaluated to determine the relationships among fibrin, FDP and CT findings.[18] Patients with brain contusion on CT had higher FDP levels than patients with epidural hematoma. In addition, FDP levels in the patients with severe contusion were higher than in those with mild contusion and these high FDP levels persisted for an extended period.[18]

In the study by Kaufmann *et al*. on patients with head trauma, changes in fibrinogen, FDP, PTT, PT and thromboplastin time (TT) were found and some patients who developed DIC had multisystem damage and necrosis and hemorrhage on head CT scan.[19] Future studies focusing on early treatment of coagulation abnormalities should be performed to determine the effect on morbidity and mortality.

Auer found a significant relationship between TT, PTT, PT, fibrinogen and Plt count and the severity of brain trauma in 30 patients 7-14 days after severe head trauma.[20]

Conclusion

Decreased Plt count, prolonged PT and PTT, decreased fibrinogen and increased D-dimer levels were observed in patients within the first three hours of acute isolated head trauma. PT, PTT, FDP and D-dimer levels in particular may be useful prognostic indicators in these patients.

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