

## Markers of Fibrinolysis in Indian Patients with Isolated Head Trauma

### Abstract

**Context:** Head injury causes disseminated intravascular coagulation as the most severe complication which is associated with high mortality. Elevated levels of markers of fibrinolysis such as D-dimer and fibrinopeptide A (FPA) have been correlated with poor outcome in these patients. **Aim:** The study aimed to correlate the levels of plasma fibrinogen, D-dimer, and FPA with outcome in patients with isolated head trauma. **Settings and Design:** This cross-sectional descriptive study was conducted in the Departments of Pathology and Neurosurgery, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, on 100 patients admitted within 12 h of isolated head trauma. **Subjects and Methods:** Plasma fibrinogen, D-dimer, and FPA were measured in 100 patients admitted within 12 h of isolated head trauma. While plasma fibrinogen and D-dimer were estimated in all patients, FPA was measured in 45 patients. **Statistical Analysis:** SPSS (20.2) software was used for mean, standard deviation, and median values of the quantitative parameters, and for all qualitative parameters, their frequencies were obtained.  $P < 0.05$  was considered significant. **Results:** Elevated D-dimer ( $>250$  ng/ml) and FPA ( $>3$  ng/ml) were observed in 64% and 91.1% patients, respectively. Both D-dimer and FPA were elevated in 66.6% of patients. Disseminated intravascular coagulation (DIC) score, calculated using standard criteria, was  $\geq 5$  in 28% of patients indicating overt DIC. Hypofibrinogenemia was observed in 48% of patients. D-dimer, FPA, and DIC score was significantly ( $P < 0.001$ ) higher and plasma fibrinogen significantly ( $P < 0.001$ ) lower in nonsurvivors as compared to survivors. Elevated D-dimer and FPA and low fibrinogen levels were seen in patients irrespective of severity of injury. **Conclusions:** Elevated D-dimer and FPA were frequently observed in patients with isolated head trauma. As these markers rise soon after injury and indicate poor outcome, their measurement will help identify patients who will benefit with additional therapy, thus reducing morbidity and mortality.

**Keywords:** D-dimer, disseminated intravascular coagulation, fibrinopeptide A, Glasgow Coma Score, traumatic brain injury

### Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide which places a substantial economic burden on the health-care system.<sup>[1]</sup> These patients are prone to the early development of coagulopathy.<sup>[1,2]</sup> Disseminated intravascular coagulation (DIC) is the most severe complication characterized by formation of microthrombi in the cerebral vessels and eventual ischemia.<sup>[3]</sup>

Levels of D-dimer, a marker of fibrinolysis, are elevated in patients with DIC.<sup>[3]</sup> Fibrinopeptide A (FPA) levels provide a sensitive marker of *in vivo* hypercoagulability.<sup>[4]</sup> Hypofibrinogenemia has also been observed in these patients.<sup>[5]</sup> Changes in levels of plasma fibrinogen and D-dimer occur soon after head trauma. In a study of 20 patients evaluated

within 6 hours of isolated severe head injury and 4 controls, plasma fibrinogen was significantly ( $P < 0.005$ ) lower and D-dimer significantly ( $P < 0.005$ ) higher in patients as compared to controls.<sup>[4]</sup>

Elevated D-dimer levels and hypofibrinogenemia have both been associated with poor outcome.<sup>[3,5,6]</sup> However, only an occasional study has evaluated the role of FPA as a marker of fibrinolysis in patients with TBI.<sup>[4,7]</sup> Measurement of these markers will help in early identification of patients at risk which will aid in better management and improved prognosis. The present study aimed to measure the levels of fibrinogen, D-dimer, and FPA in patients admitted within 12 h of isolated head trauma and correlate them with outcome.

### Subjects and Methods

One hundred patients admitted within 12 h of isolated head trauma were included in

**How to cite this article:** Sikka M, Sodhi R, Kotru M, Singh G. Markers of fibrinolysis in Indian patients with isolated head trauma. *Asian J Neurosurg* 2019;14:118-21.

**Meera Sikka,  
Ruchika Sodhi,  
Mrinalini Kotru,  
Gurubachan Singh<sup>1</sup>**

Departments of Pathology  
and <sup>1</sup>Neurosurgery, University  
College of Medical Sciences  
and Guru Teg Bahadur Hospital  
Hospital, New Delhi, India

### Address for correspondence:

Dr. Meera Sikka,  
Department of Pathology,  
University College of Medical  
Sciences and Guru Teg Bahadur  
Hospital, New Delhi, India.  
E-mail: meerasikka55@gmail.  
com

### Access this article online

Website: [www.asianjns.org](http://www.asianjns.org)

DOI: 10.4103/ajns.AJNS\_278\_17

### Quick Response Code:



This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: [reprints@medknow.com](mailto:reprints@medknow.com)

the study. Patients with polytrauma/clinical evidence of infection/those on anticoagulants were excluded from the study. The severity of injury was assessed by Glasgow Coma Score (GCS).<sup>[8]</sup> A written informed consent was obtained from all patients. The study received clearance from the Institutional Ethics Committee for human research.

Complete blood counts with platelet count (automated hematology analyzer LH500) and tests of hemostasis including PT (Thromborel S, Siemens Healthcare Diagnostics Products), APTT (Siemens Healthcare Diagnostics Products), plasma fibrinogen (FIBROQUANT, Tulip Diagnostics), and markers of fibrinolysis: D-dimer (Biomedical Assay ELISA) and fibrinopeptide A (ZYMUTEST FPA, Hyphen BioMed ELISA) were measured. DIC score was calculated using standard criteria.<sup>[9]</sup> All patients were followed up till the time of discharge/death.

### Statistical analysis

SPSS (20.2) software was used for mean, standard deviation, and median values of the quantitative parameters, and for all qualitative parameters, their frequencies were obtained. For comparison between survivors and nonsurvivors, Chi-square test/Fisher's exact test was employed for the qualitative parameters and unpaired *t*-test for the quantitative parameters. The parameters not following the Gaussian distribution were normalized by log transformation, and then, the appropriate statistical test was used to compare. *P* < 0.05 was considered as significant.

### Results

The age of the patients ranged from 7 to 82 years with a mean  $\pm$  standard deviation of  $33.7 \pm 13.6$  years; majority (60%) of patients being in the age range of 21–40 years. The study included 78 (78%) males and 22 (22%) females. Road traffic accident was the most (74%) frequent cause of TBI, with fall from a height (13%) and physical assault (13%) contributing to the remaining cases. As assessed by GCS, mild, moderate, and severe injuries were seen in 45%, 28%, and 27% patients, respectively. The results of platelet count and screening tests of hemostasis and the abnormal result observed in each parameter are shown in Table 1.

Table 2 shows the levels of plasma fibrinogen, D-dimer, and FPA and the abnormality observed in each parameter. Hypofibrinogenemia (<150 mg/dl) was observed in 48% of patients. An elevated (>250 ng/ml) D-dimer was observed in 64% of patients. Of these patients, 36 (56.2%) showed moderate (251–500 ng/ml) and 28 (43.8%) showed marked (>500 ng/ml) elevation. Elevated (>3 ng/ml) FPA levels were observed in 41/45 (91.1%) patients. D-dimer and FPA were both elevated in 30/45 (66.6%) patients while only FPA was elevated in 11 (24.4%) patients.

DIC score calculated using standard criteria<sup>[9]</sup> was  $\geq 5$  in 28% patients indicating overt DIC. None of these patients had any clinical feature of DIC and scores were not repeated subsequently.

Hypofibrinogenemia and elevated D-dimer and FPA were seen in patients irrespective of the severity of injury and even in those with mild injury. The mortality in this study was 26%. Plasma fibrinogen was significantly (*P* < 0.001) lower and D-dimer and FPA significantly (*P* < 0.001) higher in nonsurvivors as compared to survivors [Table 3]. Mortality was significantly (*P* < 0.001) higher in patients with hypofibrinogenemia and elevated D-dimer and FPA as compared to patients in whom these parameters were normal [Table 4].

### Discussion

TBI is an acute brain injury arising from an external physical force to the head. The final injury to the brain results from a combination of primary and secondary insults. Coagulopathy which is frequently observed in these patients contributes to secondary brain injury and is associated with an adverse

**Table 1: Platelet count, prothrombin time, international normalized ratio, and activated partial thromboplastin time and abnormal results in each parameter**

Parameter	Range	Mean $\pm$ SD	Abnormal result (%)
Platelet count ( $\times 10^9/L$ )	46-274	152.8 $\pm$ 58.4	<150 (48)
PT (s)	10.9-52.6	14.4 $\pm$ 5.5	>14 (31)
APTT (s)	28.0-61.0	32.5 $\pm$ 5.0	>34 (26)
INR	1.0-4.8	1.3 $\pm$ 0.5	>1.3 (27)

PT - Prothrombin time; INR - International normalized ratio; APTT - Activated partial thromboplastin time; SD - Standard deviation

**Table 2: Levels of plasma fibrinogen, D-dimer, and fibrinopeptide A and abnormal results in each**

Parameter (n)	Range	Mean $\pm$ SD	Abnormal test result (%)
Fibrinogen (mg/dl) (100)	50.0-264.0	150.8 $\pm$ 37.6	<150 (48)
D-dimer (ng/ml) (100)	77.9-950.0	382.0 $\pm$ 243.4	>250 (64)
FPA (ng/ml) (45)	1.0-110.0	41.6 $\pm$ 37.4	>3 (91.1)

Figures in parentheses indicate the number of patients in whom the parameter was measured. FPA - Fibrinopeptide A; SD - Standard deviation

**Table 3: Plasma fibrinogen, D-dimer, and fibrinopeptide A levels in survivors and nonsurvivors**

Parameter	Mean $\pm$ SD	
	Survivors	Nonsurvivors
Fibrinogen (mg/dl)	161.6 $\pm$ 33.8	120.3 $\pm$ 31.1*
D-dimer (ng/ml)	277.0 $\pm$ 165.5	681.1 $\pm$ 169.6*
FPA (ng/ml)	20.71 $\pm$ 22.4	83.4 $\pm$ 23.4*

\**P*<0.001 for all parameters. SD - Standard deviation; FPA - Fibrinopeptide A

**Table 4: Mortality in patients with and without changes in plasma fibrinogen, D-dimer, and fibrinopeptide A**

Parameter (n)	Mortality (%)
Plasma fibrinogen	
Reduced (48)	43.7
Normal (52)	9.6
D-dimer	
Elevated (64)	39.1
Normal (36)	2.8
FPA	
Elevated (41)	36.6
Normal (4)	0

$P < 0.001$  for all parameters. FPA - Fibrinopeptide A

outcome.<sup>[10]</sup> DIC remains the most severe complication of TBI<sup>[3]</sup> in which there is depletion of coagulation factors and activation of coagulation. This study aimed to correlate the levels of plasma fibrinogen, D-dimer, and FPA with outcome in patients with isolated head trauma.

Hypofibrinogenemia was observed in 48% of patients in this study. In a previous study on 100 patients with isolated TBI, hypofibrinogenemia was reported in 7% of patients. The authors attributed the low incidence to genetic variation of the Indian population.<sup>[5]</sup> Kuo *et al.* observed hypofibrinogenemia in 23% of patients.<sup>[11]</sup>

The present study observed elevated levels of D-dimer and FPA in 64% and 91.1% of patients, respectively. Elevated levels denote increased thrombotic activity with consequent secondary fibrinolysis and have been commonly observed after TBI.<sup>[4,6,10,11]</sup> In a study on 42 patients with head injury, elevated D-dimer was the most frequent coagulation abnormality seen in 48.5% of patients with severe injury. Even in patients with normal coagulation profile at admission, levels of D-dimer were elevated. The authors concluded that these levels must be measured at admission as early transfusion of Fresh Frozen Plasma (FFP) and platelets to these patients improved the prognosis.<sup>[12]</sup>

Levels of D-dimer rise soon after head trauma.<sup>[4,11]</sup> Gando *et al.* studied 40 patients with trauma; 15 with and 25 without DIC. FPA and D-dimer were measured at days 0, 3, and 6. Both markers were elevated immediately after trauma, and though the levels decreased after the initial phase, the activity was higher than normal.<sup>[13]</sup>

Although not many studies have measured FPA in patients with head injury, increased levels have been observed following isolated head injury.<sup>[4,13]</sup> In this study, FPA was elevated in a greater number (91.1%) of patients than D-dimer (64%), and 24.4% of patients had only elevation of FPA. The high levels are in agreement with those reported by Risberg *et al.*<sup>[7]</sup> The increased levels result from thrombin production which occurs after trauma.

DIC score was  $\geq 5$  in 28% of patients indicating overt DIC. None of these patients had any clinical feature of DIC

and scores were not repeated subsequently. Similar results have been reported by other authors.<sup>[3,14]</sup> Even though manifestations of DIC are not present initially, studies have shown that if fibrinolytic markers are elevated, early administration of heparin provides additional protection against cerebral ischemia as fibrinolytic turnover may spark DIC.<sup>[14]</sup>

The present study observed that hypofibrinogenemia and elevated D-dimer and FPA were associated with a worse outcome. Similar results have been reported by other authors.<sup>[5,11,12,15]</sup>

Hypofibrinogenemia and elevated D-dimer and FPA were seen in patients irrespective of the severity of injury and even in those with mild injury. Measurement of these parameters in all patients with TBI irrespective of severity of injury at admission will help identify patients in need of additional therapy. Gando *et al.* treated patients of head trauma with DIC and elevated FPA levels with gabexate mesilate. There was no difference in the level from the non-DIC group.<sup>[13]</sup> This will help reduce morbidity and mortality.

#### Acknowledgment

We would like to thank hematology staff members of our department for their help in the laboratory procedures of our project.

#### Financial support and sponsorship

Nil.

#### Conflicts of interest

There are no conflicts of interest.

#### References

- Levine JM, Kumar MA. Traumatic brain injury. Neurocritical Care Society Practise Update; 2013.
- Carrick MM, Tyroch AH, Youens CA, Handley T. Subsequent development of thrombocytopenia and coagulopathy in moderate and severe head injury: Support for serial laboratory examination. *J Trauma* 2005;58:725-9.
- Vecht CJ, Sibinga CT, Minderhoud JM. Disseminated intravascular coagulation and head injury. *J Neurol Neurosurg Psychiatry* 1975;38:567-71.
- Scherer RU, Spangenberg P. Procoagulant activity in patients with isolated severe head trauma. *Crit Care Med* 1998;26:149-56.
- Chhabra G, Rangarajan K, Subramanian A, Agrawal D, Sharma S, Mukhopadhyay AK, *et al.* Hypofibrinogenemia in isolated traumatic brain injury in Indian patients. *Neurol India* 2010;58:756-7.
- Antovic J, Bakic M, Ignjatovic G, Milenkovic Z, Djuric S, Tasic J, *et al.* Blood coagulation and fibrinolysis parameter changes after various types of brain damage. *J Facta Univ* 1998;5:44-9.
- Risberg B, Medegård A, Heideman M, Gyzander E, Bundsen P, Odén M, *et al.* Early activation of humoral proteolytic systems in patients with multiple trauma. *Crit Care Med* 1986;14:917-25.
- Jennett B, Teasdale G, Galbraith S, Pickard J, Grant H,

- Braakman R, *et al.* Severe head injuries in three countries. *J Neurol Neurosurg Psychiatry* 1977;40:291-8.
9. Taylor FB Jr., Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH), *et al.* Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001;86:1327-30.
  10. Saggar V, Mittal RS, Vyas MC. Hemostatic abnormalities in patients with closed head injuries and their role in predicting early mortality. *J Neurotrauma* 2009;26:1665-8.
  11. 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; 11:710-4.
  12. Subramaniam PC, Bogra J, Chandra G, Kumar A, Kohli M, Dasmana S, *et al.* Coagulation profile as predictor of recovery status in patients of head injury. *Int J Sci Innov Res* 2013;1:39-50.
  13. Gando S, Tedo I, Kubota M. Posttrauma coagulation and fibrinolysis. *Crit Care Med* 1992;20:594-600.
  14. Pahatouridis D, Alexiou GA, Zigouris A, Mihos E, Drosos D, Voulgaris S, *et al.* Coagulopathy in moderate head injury. The role of early administration of low molecular weight heparin. *Brain Inj* 2010;24:1189-92.
  15. Inaba K, Karamanos E, Lustenberger T, Schöchl H, Shulman I, Nelson J, *et al.* Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. *J Am Coll Surg* 2013;216:290-7.