Prospective Analysis of Coagulopathy Associated with Isolated Traumatic Brain Injury and Clinical Outcome

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Abstract

Introduction   Traumatic brain injury (TBI) affects the coagulation pathway in a distinct way than does extracranial trauma. The extent of coagulation abnormalities varies from bleeding diathesis to disseminated thrombosis.

Design   Prospective study.

Methods   The study included 50 patients of isolated TBI with cohorts of moderate (MHI) and severe head injury (SHI). Coagulopathy was graded according to the values of parameters in single laboratory. The incidence of coagulopathy according to the severity of TBI and correlation with disseminated intravascular coagulation (DIC) score, platelets, prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, and fibrinogen was observed. The comparison was also made between expired and discharged patients within each group. It also compared coagulation derailments with clinical presentation (Glasgow Coma Scale [GCS]) and outcome (Glasgow Outcome Scale [GOS]).

Results   Road traffic accident was the primary (72%) mode of injury. Fifty-two percent had MHI and rest had SHI. Eighty-four percent of cases were managed conservatively. The mean GCS was 12.23 and 5.75 in MHI and SHI, respectively. Sixty-two percent of MHI and 96% of the patients with SHI had coagulation abnormalities. On statistical analysis, DIC score ($p < 0.001$) strongly correlated with the severity of head injury and GOS. PT and APTT were also significantly associated with the severity of TBI. In patients with moderate TBI, D-dimer and platelet counts showed association with clinical outcome. Fibrinogen levels did not show any statistical significance. The mean platelet counts remained normal in both the groups of TBI. The mean GOS was 1.54 and 4.62 in SHI and MHI, respectively.

Keywords
► coagulopathy
► TBI
► DIC score
► head injury

Conclusion   Coagulopathy is common in isolated TBI. The basic laboratory parameters are reliable predictors of coagulation abnormalities in TBI. Coagulopathy is directly associated with the severity of TBI, GCS, and poor outcome.

Introduction

Traumatic brain injury (TBI) is a global health burden that affects people of all socioeconomic groups. It is a leading cause of mortality, morbidity, and disability in patients of trauma. Coagulopathy associated with TBI is well known for a long time; however, the exact pathophysiology is still poorly understood.[1,2]

However, several reports suggest coagulation derailments following TBI occur secondary to the release of tissue factor which is the physiological initiator of local and systemic coagulation and fibrinolytic pathways. Coagulopathy following TBI is a dynamic process of hypercoagulability followed by hemorrhagic diathesis.[1,3-5] The hypercoagulable state may be generalized in the form of disseminated intravascular coagulation (DIC) or localized with the development of microthrombi in the penumbra of contusion. The other mechanisms include platelet dysfunction, DIC, and activation of protein C pathways secondary to hypoperfusion.[3,4,6-8]

The state of DIC and consequent intravascular thrombosis in microvasculature can result in ischemic brain damage. This resultant secondary injury may lead to brain edema, progression of contusions, and hematoma. DIC can also be fulminant accompanied by uncontrolled hemorrhage, widespread necrosis, multiple organ failure, and death. The coagulation disorder in TBI is hence associated with poor outcome. Various authors in developed countries have reported the incidence of coagulation disorders in TBI.[8-21] However, data regarding the same is lacking for most low- and middle-income countries.

The extent of impact on TBI by the coagulation derailments is largely unknown. The present study was aimed to study the incidence of coagulopathy in TBI. The study also attempted to explore the extent of coagulation profile derangements, its correlation with the severity of TBI, and clinical outcome.

Materials and Methods

The study is of prospective design and compared incidence of coagulopathy in moderate and severe TBI. It also compared DIC score and other laboratory parameters among discharged and expired patients of both moderate head injury (MHI) and severe head injury (SHI).

The study was performed on patients with isolated head injury at a government referral center in North India. A total of 50 patients in the age group of 20 to 70 years were studied. Patients having other associated injuries (extracranial trauma) like long bone fractures, chest injuries, and abdominal injuries were not included in the study. Those with pre-existing coagulopathy or on anticoagulants, hypertension, diabetes, hepatic and renal dysfunction, or any other comorbidities were excluded.

All the selected patients were divided into subgroups of MHI and SHI based upon their Glasgow Coma Scale (GCS). Patients with GCS of 9 to 13 were classified as having MHI and < 8 as SHI.

Investigations including complete hemogram, prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimers, fibrinogen, computed tomography head, and ultrasonography of chest and abdomen were done. The blood was collected at the triage area itself upon arrival of the patient without any delay and processed immediately.

All the blood investigations used to calculate DIC score (modified) were based on parameters as outlined by the International Society on Thrombosis and Haemostasis (ISTH) scoring system. APTT was also evaluated. The result of all the above blood investigations was graded on a score of 0 to 3 according to the range of normal values for a healthy population in the same laboratory (►Table 1). The sum of all the five blood investigations for a given patient was regarded as a DIC score. After calculation of the DIC score, the severity of DIC was graded as shown in ►Table 1.

Coagulopathy was defined as platelet counts less than 100,000 and PT > 15 seconds, APTT > 35 seconds, or a DIC score of more than 4. The outcome in each group was measured as per the Glasgow Outcome Scale (GOS).

Observations and Results

The study included 50 patients with isolated head injury. Age and sex distribution of patients is shown in ►Fig. 1.

Mechanism of Injury
The road traffic accident (RTA) was the most common mode of injury. Thirty-six patients (72%) sustained head injury by RTA. Six patients sustained the injury by assault (12%) and another six patients by fall. In 4% of cases mode of injury was unknown as these patients were found under unknown circumstances.

Table 1 Laboratory parameters with scoring system

Severity	Platelet count (in lacs)	PT (in seconds)	APTT (in seconds)	D-dimer (ng/mL)	Fibrinogen (g/L)	Score for laboratory parameter	DIC score
Normal	> 1.5	13.5	26–34	< 1,000	> 2	0	0–3
Mild derangement	1–1.5	13.5–15.0	> 34	1,000–2,000	< 2	1	3–6
Moderate derangement	0.6–1.0	15–18	> 39	2,000–4,000	< 1.5	2	7–10
Severe derangement	< 0.60	> 18	> 54	> 4,000	< 1	3	> 10

Abbreviations: APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; PT, prothrombin time.
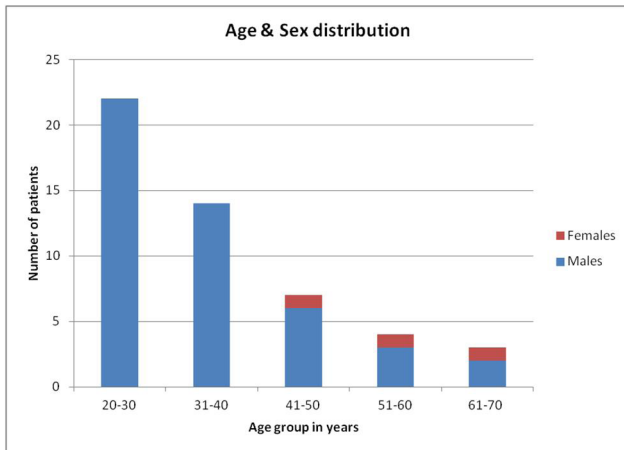
Fig. 1 Age and sex structure of study population.

Prehospital Time of Patients

Eighty percent of the patients were brought within 3 hours of trauma to the hospital. Another 12% were brought within 9 hours.

GCS at Presentation

Twenty-six (52%) patients had MHI with GCS 9 to 13 and 24 patients had SHI having GCS < 8 at presentation. The mean GCS was 12.23 and 5.75 in MHI and SHI patients, respectively. The overall mean GCS at presentation in the hospital was 9.12.

DIC Score of the Patients

Twelve patients (24%) had a DIC score of 0 to 3. Twenty-two (44%) patients had DIC score of 4 to 6 while 16 (32%) patients had DIC score of 7 to 10. In total, 76% of the patients had moderate to severe DIC scores.

Management

The various CT characteristics in population are depicted in pie-chart (►**Fig. 2**). Forty-two (84%) patients were conservatively treated while 8 (16%) patients underwent surgical intervention. Six patients of the SHI group and two of MHI were operated on.

Outcome of the Patients

Twenty-four patients with MHI were discharged with GOS 5 and two deaths were noted. On the other hand, 19 patients with SHI died, 4 were discharged with GOS 5 and one remained vegetative (GOS 2). Of the eight patients who underwent surgery four were discharged with GOS 5, one with GOS 3, and three patients expired after surgery.

The patients with SHI were divided into two groups. The first group included 20 patients and had GOS 1 or GOS 2. The second group included four patients and had GOS 5. p-Value for DIC score was < 0.001 and is statistically significant. p-Value in both PT and APTT was < 0.05 and was significant. However, it was not significant for D-dimer, fibrinogen, and platelet counts (►**Table 2**).

In patients with MHI, p-value in case of DIC score, platelet count, APTT, and D-dimer was < 0.001 and was highly significant. p-Value in PT was < 0.05 and found to be statistically

significant, however, it was not significant for fibrinogen (►**Table 3**).

In patients with MHI, 62% of the study population had coagulopathy while 96% of the patients with SHI were found to have coagulation abnormalities (►**Fig. 3**).

Follow-Up

Two patients had facial nerve palsy at presentation which persisted at 1 month of follow-up. However, it recovered in one patient at 3 months' follow-up. No further mortality was noted.

Discussion

The incidence of head injury has exponentially increased in present times primarily due to an increase in the number of vehicles plying on the road.[22] Motor vehicle accidents, assault, and fall are three major modes of TBI. Most of the studies have shown accidents as the most common mode of injury.[13,23] The present study found RTA as the primary cause of TBI in 72% of the cases which may be ascribable to negligence in following the traffic norms. This is in contrast to western studies which have a relatively lower incidence of RTA due to better education, cognizance, and strict traffic regulations. In developing countries like India, safety and awareness regarding traffic regulations is still a matter of grave concern.

Most of the patients in the study were young between the ages of 20 to 40 years (72%) and predominantly males (94%) probably because this age group is more involved in outdoor activities, alcohol intoxication, driving, and other differential gender functions in India. In systemic review and meta-analysis of 82 studies, Nguyen et al[24] reported most TBIs among males and in the adult population. A similar data has been reported by Frost et al[25] in their meta-analysis and many other authors too.[26-29]

Coagulopathy in TBI

The factors responsible for coagulopathy in TBI patients are probably different from extracranial injury. Although isolated TBI does not have massive blood loss to induce coagulopathy, still it is commonly seen in clinical practice.[30] This suggests that TBI-induced coagulopathy follows a distinct pathogenic pathway that remains elusive. This also explains why the treatment and prevention of coagulopathy in TBI largely remains ineffective even today.[31]

The coagulation abnormalities in TBI have been studied earlier; however, the majority of them have included patients who sustained extracranial trauma too. The scoring system of ISTH was reviewed. Authors also added APTT in the study, the usefulness of which has been reported by multiple studies including Bakhtiari et al.[32] Yuan et al[33] also observed a significant correlation of APTT with poor outcome and mortality compared with other coagulation parameters.

We also noticed approximately 80% of the patients reported within 6 hours of trauma which is remarkable in this part of our developing country. Though the prehospital time is less in metro cities of the country.[34] Hulka et al[6] reported coagulopathy in TBI as early as first hour. Hence, the need

Table 2 Comparison of mean values and SD of DIC score as well as individual laboratory tests in expired and discharged patients of the SHI group

Parameter	Expired or vegetative (Group 1) (n = 20)	Discharged (Group 2) (n = 4)	p-Value	Mean value
DIC score	6.3 ± 1.97	4.0 ± 2.44	< 0.001	5.91 ± 2.18
Platelet	1.64 ± 0.58	1.55 ± 0.31	> 0.05	1.63 ± 0.54
PT	15.25 ± 2.98	12.92 ± 1.48	< 0.05	14.87 ± 2.90
APTT	35.84 ± 6.38	28.8 ± 3.85	< 0.05	34.67±6.53
Fibrinogen	0.71 ± 0.84	0.40 ± 0.284	> 0.05	0.66 ± 0.65
D-dimer	2812 ± 1351	2616 ± 1703.86	> 0.05	2779.73 ± 1375.57

Abbreviations: APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; PT, prothrombin time; SD, standard deviation; SHI, severe head injury.

Table 3 Comparison of DIC score as well as individual laboratory tests in expired and discharged (GOS 3–5) patients of the MHI group

Parameter	Expired (Group 1, n = 2)	Discharged (Group 2, n = 24)	p-Value	Mean value
DIC score	8.0 ± 1.4	3.92 ± 2.33	< 0.001	4.23 ± 2.51
Platelet	0.9 ± 0.42	1.75 ± 0.328	< 0.001	1.69 ± 0.40
PT	17.05 ± 1.76	13.75 ± 2.13	< 0.05	14.01 ± 2.26
APTT	24.05 ± 4.03	34.93 ± 10.71	< 0.001	34.1± 10.72
Fibrinogen	0.47 ± 0.60	0.68 ± 0.66	> 0.05	0.66 ± 0.78
D-dimer	4122 ± 883.17	1829.23 ± 1385.15	< 0.001	2005.63 ± 1478.05

Abbreviations: APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; GOS, Glasgow Outcome Scale; MHI, moderate head injury; PT, prothrombin time.
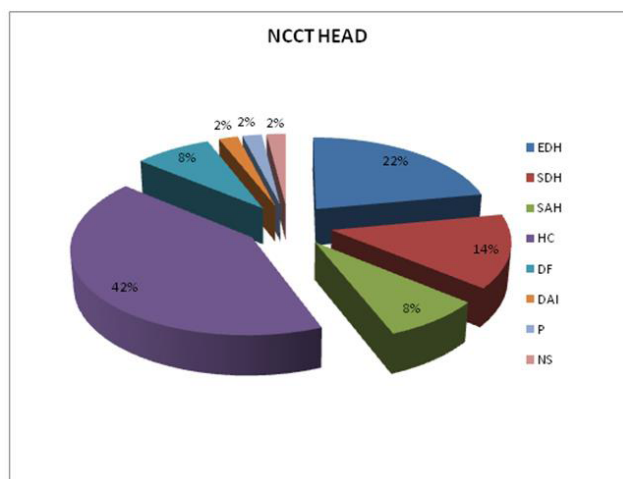
Fig. 2 Computed tomography findings along with their case distribution. DAI, diffuse axonal injury; DF, depressed fracture; EDH, extradural haematoma; HC, haemorrhagic contusion; NS, non specific (mixed haemorrhage); P, Pneumocephalus; SAH, subarachnoid haemorrhage; SDH, subdural haematoma.
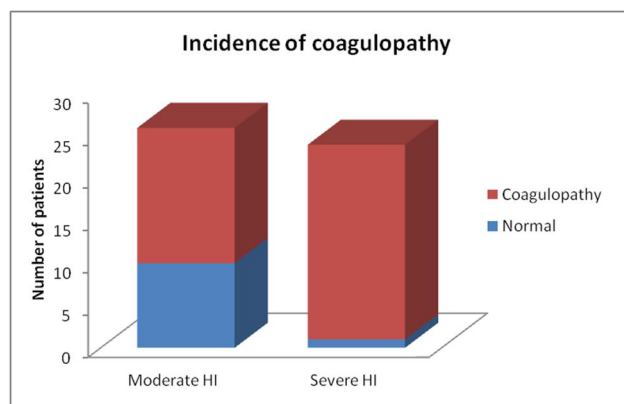
Fig. 3 Incidence of coagulopathy in moderate head injury (MHI) and severe head injury.

for urgent medical attention in TBI cannot be overemphasized. On the other hand, the onset of coagulation abnormalities can be delayed up to 72 hours of TBI[2] or up to 5 days.[35] Our study, however, did not find a significant association of prehospital time with the development of coagulopathy.

Platelet dysfunction in TBI is now being increasingly recognized. However, the mechanism related to their activation and dysfunction is poorly understood.[36] Several studies have found a significant prevalence of platelet dysfunction in severe TBI.[36,37] Wohlauer et al[38] reported early platelet dysfunction and significant differences in the platelet response between trauma patients and healthy volunteers. The response of the platelets in TBI is not related to platelet count.[37] Though many researchers have shown thrombocytopenia associated with TBI and poor outcomes.[39,40] In our study, we did not find significance of platelet count with the severity of TBI. Even in severe TBI, the platelet count remained > 100,000. We found high statistical significance of platelet count in MHI when outcomes were compared. We

Table 4 Statistical result of DIC score and GOS in MHI and SHI

	DIC score	GOS	*p*-Value
Severe head injury	5.91 ± 2.18	1.54 ± 1.98	< 0.001
Moderate head injury	4.23 ± 2.51	4.62 ± 1.09	> 0.05
All patients	5.04 ± 2.49	3.1 ± 1.9	< 0.001

Abbreviations: DIC, disseminated intravascular coagulation; GOS, Glasgow Outcome Scale; MHI, moderate head injury; SHI, severe head injury.

suggest that thrombocytopenia may not be associated with isolated head injury patients and platelet dysfunction may be the cause of coagulopathy. However, a large prospective/randomized trial is required for its validation.

PT is a measure of the function of the extrinsic and common coagulation pathways. The expired patients of both the moderate and severe TBI group had higher international normalized ratio (INR) values compared with discharged ones. The PT was found to be a statistically significant parameter in this study for both moderate and severe TBI. Saggar et al[41] also reported higher INR values in expired (2.28 ± 0.59) patients compared with the discharged group (1.33)± *0.47*. The IMPACT study (International Mission on Prognosis and Analysis of Clinical Trials) in TBI found that prolonged PT at admission was present in 26% of patients and was associated with a 64% increase in mortality risk.[12] Various other studies also found PT to be the most consistent coagulation abnormality in TBI.[35,42]

APTT was found to be a significant predictor of prognosis in this study and was found to be significant in both moderate and severe TBI among expired and discharged patients. This parameter has been reported as prolonged by various studies.[20,32,33,35,43] Multivariate logistic regression analysis by Yuan et al[33] found INR > 1.25, and APTT > 36 seconds were independently associated with in-hospital mortality. Macleod et al[42] too in his multiple regression model found PT and APTT as independent predictors of mortality.

D-dimer is a fragment of degradation products of cross-linked fibrin and is an indicator of ongoing fibrinolytic activity. This factor was found to be statistically significant in the MHI group; however, it was not significant in the case of SHI. The D-dimer concentration increases in head injury patients in comparison to other trauma patients.[5] Kuo et al[14] reported that D-dimer values > 1,496 mcg/dL were associated with poor prognosis in head injury patients.

In the meta-analysis by Epstein et al,[44] retrospective and prospective cohort studies were analyzed and an incidence of 35.2% of coagulopathy in TBI patients was found. A meta-analysis of 34 studies by Harhangi et al[10] reported an overall prevalence of coagulopathy in 32.7% after TBI. This incidence is very less compared with the present study which has observed 76% of coagulopathy in TBI cases which is similar to that reported by Affonseca et al.[13] Saggar et al[41] and Selladurai et al[45] reported 63 and 38% poor DIC score, respectively. The variation in the percentages of patients having such a wide range of DIC scores or coagulopathy can be explained based on differences in the severity of injuries of patients in the different studies, different criteria used for coagulopathy, and different combinations of laboratory parameters used. The incidence is

also dependent upon the cutoff laboratory value and the time lag between sample collection and trauma.

Outcome
In the MHI group the mortality was 8% while in the SHI group it was 79%. In those who developed coagulopathy, the mortality was 55%. The overall mortality was 42%. The prevalence of acute traumatic coagulopathy is directly associated with the severity of brain injury. van Gent et al[2] found coagulopathy in patients with TBI to be associated with the progression of hemorrhagic injury, surgical intervention, and increased in-hospital mortality.

Coagulopathy and GCS
The study observed severe coagulation abnormalities in patients with GCS < 8. This finding has implication in terms of predicting coagulopathy in TBI. May et al[46] reported coagulopathy in 81% of patients having GCS < 6 and 100% in those having GCS < 3. Pahatouridis et al[19] observed a correlation of severity of head injury with the severity of coagulation disorder and reported that patients with lower GCS were at higher risk of coagulation derailments. van Gent et al[2] found lower mean GCS (6.1) and worse prognosis in patients developing coagulopathy within 24 hours of trauma compared with patients without coagulopathy (10.1). Talving et al[47] reported that GCS score of < 8 is an independent risk factor for coagulopathy in isolated head injuries and TBI coagulopathy was associated with longer intensive care unit stay and 10 times increased mortality. These reports suggest that coagulopathy and GCS are interdependent.

Correlation of DIC Score to Outcome (GOS)
DIC score was found as an important predictor of the outcome of patients. On the statistical analysis of DIC score with GOS, the *p*-value was < 0.001 which is highly significant (►**Table 4**). We found that patients with poor DIC scores (> 4) within the first 24 hours had a worse prognosis (GOS 1). Affonseca et al[13] and Greuters et al[20] also observed that the presence of coagulopathy was related to a poor prognosis and on correlating the coagulopathy with the outcome the observed *p*-value was < 0.01 in the former and < 0.04 in the latter study. Macleod et al[42] also reported early coagulopathy as a predictor of mortality in trauma.

Merits of the Study
The study has included GCS and GOS both in the clinical assessment of the patients and excluded patients who had other associated injuries. The patients with comorbidities were also excluded. Follow-up clinical assessment was done.

The laboratory parameters used for the assessment of coagulopathy in the study are routinely available and can be used in institutions having basic laboratory facilities.

Limitations of the Study

Interval or sequential assessments of laboratory parameters were not done. As the time of sample collection affects the laboratory parameters, standardization of timing should be done to cut the observer bias. Thromboelastography parameters may have been included in this study.

Conclusion

The patients of isolated head injury are at high risk of developing coagulation abnormalities. Coagulopathy is directly associated with the severity of TBI, GCS, and is independently associated with poor outcome. DIC score is a useful parameter in the prediction of prognosis of head injury patients. The timely intervention in such patients can help improve prognosis. The analysis of coagulation parameters are useful predictors of outcome and can be used to explain the relatives about prognosis and course of the patient during the hospital stay.

Conflict of Interest

None declared.

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