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Original Article

Trauma-Induced Coagulopathy: Incidence and Outcome in Patients with Isolated Traumatic Brain Injury in a Level I Trauma Care Center in India

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Abstract

Context: Trauma-induced coagulopathy (TIC) is life-threatening in head injury patients, and there is a lack of Indian data on its incidence and outcome. **Aims:** In this study, incidence and outcome related to coagulopathy were assessed in patients with moderate-to-severe isolated traumatic brain injury (iTBI). **Settings and Design:** A prospective observational study carried out in patients admitted within 24 h of injury. **Materials and Methods:** One hundred patients with moderate-to-severe iTBI were included. Samples for coagulation tests (prothrombin time [PT], PT index [PTI], international normalization ratio [INR], activated partial thromboplastin time, and platelet count) were collected at 5 points of time for 72 h. TIC was diagnosed if any three readings were abnormal during this period. Patients were also followed up posthospital discharge using the Glasgow Outcome Score (GOS) at 1 and 3 months. **Statistical Analysis:** Data were analyzed using SPSS ver. 21. Logistic regression analysis was employed to determine individual coagulation test as best predictors for mortality. $P < 0.05$ was considered statistically significant. **Results:** The incidence of TIC was found to be 62%; it was 63.75% in severe head injury and 55% in moderate head injury patients. Deranged INR at the time of hospital admission (odds ratio [OR] 4.38) and PTI at 24 h (OR 3.913) are highly predictive of mortality. There was no significant difference in GOS score at 1 and 3 months. **Conclusions:** The incidence of TIC in our study was 62% among iTBI patients. It contributes to increased mortality at 1 and 3 months. However, the neurological outcome was not different in between the groups.

Keywords: *Coagulopathy, GOS, isolated head injury*

Introduction

Traumatic brain injury (TBI) is the major cause of mortality and permanent disability in India and abroad. The primary and secondary injury affects its outcome. Primary insult of a brain cannot be altered, but secondary insults are preventable. Thus, the management of TBI should target measures that minimize the secondary injury.[1-4]

Coagulopathy is one of the causes of secondary insult.[5,6] Acute intrinsic coagulopathy arising in severely injured trauma patients is termed as trauma-induced coagulopathy (TIC).[7] TIC may result from dilution, dysfunction, or loss of the coagulation proteases. Its early identification through a set of coagulation tests along with its prompt intervention is the need of the hour.

There is a lack of Indian data on TIC in moderate-to-severe isolated TBI (iTBI) patients. Therefore, a study was planned to find out the incidence of TIC and its outcome in patients with moderate-to-severe iTBI.

Materials and Methods

After getting clearance from the Institutional Ethics Committee, the study was registered in Clinical Trial Registry-India (CTRI/2017/12/010836). A prospective observational study was carried out on patients admitted to intensive care units (ICUs) of a Level I Trauma Center in India. Patients of age group of 18–65 years with moderate-to-severe iTBI admitted to hospital within 24 h of injury were included in this study after taking informed consent from the nearest kin of the patient. Pregnant patients, pediatric patients, patients having the previous history of coagulation disorder, patients on anticoagulant therapy were excluded from the study. Patients with a history of liver or kidney disease or patients unwilling to participate in the study were not included in this study. Patients who were included

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in the study but have undergone an operation during the study were also excluded from the final analysis. All patients underwent detailed clinical evaluation followed by categorization into moderate and severe head injury group by GCS. Non-contrast CT scan of head (NCCT) head to diagnose the type of injury and Marshall scoring system to grade the severity of the injury were included in the assessment of the patients.

Samples for coagulation tests which included prothrombin time (PT), PT index (PTI), international normalization ratio (INR), activated partial thromboplastin time (aPTT), and platelet count were collected at 5 points of time namely at the time of admission and were repeated at the time of ICU/high dependency unit (HDU) admission, 24, 48, and 72 h of injury. If any patient had deranged coagulation in any 3 of the total readings during the 72 h period, was considered to have TIC. Our laboratory values which were considered normal for the above-mentioned test were as follows: PT – 12–14 s, PTI – 100%, INR <1.4, aPTT – 25–32 s, and platelet count – 1.5–4 lac/ml.

Cutoff limits for the abnormal coagulation parameters were PT >16 s, PTI <80%, aPTT >32 s, INR >1.4, and platelets $<100 \times 10^3/mm^3$.

The patients who have deranged values at admission were assessed for D-dimer and fibrinogen levels with cutoff values for abnormal coagulation parameters being D dimer >260 ng/ml and fibrinogen level >4 g/L.

All patients recruited in the study were followed up till death in hospital or discharge from the hospital. During the hospital stay, they were assessed for the number of ventilator days, ICU days, and hospital days. All patients discharged from the hospital were followed up telephonically at 1 and 3 months interval to assess neurological outcome using the Glasgow Outcome Scale (GOS). GOS score ≤3 was taken as poor GOS and GOS ≥4 was taken as good GOS.

The data were analyzed using Statistical Package for the Social Sciences software version 21 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as the mean ± standard deviation or frequency (*n*) and percentage (%). Discrete variables were analyzed and presented as proportions. Categorical data were analyzed using the Chi-square test and Fisher's exact test. Parametric test such as *t*-test and Student's *t*-test was used to see the significance of different variables to the development of coagulopathy and to find their significance in the difference in the outcome. Logistic regression analysis was applied to determine the independent predictors of mortality among PT, PTI, INR, aPTT, and platelets count. The $P < 0.05$ was considered statistically significant.

Results

A total of 100 patients admitted to the hospital within 24 h of injury were included in the study. Road traffic accident (RTA) was the most common mode of trauma ($n = 90$), followed by fall from height ($n = 6$), and assault ($n = 4$). As per the definition of TIC, of 100, 62 patients were found to have deranged coagulation parameters in at least 3 readings in 72 h after admission while 38 patients did not have coagulopathy in the posttraumatic period. Patients were divided into two groups, those with coagulopathy and the others without coagulopathy. Demographic parameters of the two groups were comparable. Contusion was the most common computed tomography finding ($n = 63$), followed by Sub-dural haemorrhage; SDH ($n = 26$), Sub-arachnoid haemorrhage; SAH ($n = 10$), Diffuse axonal injury; DAI ($n = 18$). Based on the admission GCS score, patients were divided into moderate and severe head injury groups. The incidence of coagulopathy in severe head injury was more when compared to a moderate head injury (63.75% vs. 55%). Table 1 shows demographic parameters and the incidence of coagulopathy.

We found that deranged PT was present in 79% patients, PTI in 68%, INR in 33% of patients, aPTT in 41% of patients and deranged platelet count was found in 38% patients. Deranged coagulation parameters at five different points of time are mentioned in Table 2.

The pattern for the development of coagulopathy was also observed throughout 72 h. Figure 1 shows the time pattern for the development of deranged coagulation. The incidence of coagulopathy was maximum at 24 h while it gradually decreases at 72 h of injury.

The patients ($n = 35$) who had deranged coagulogram at admission, were assessed for D-dimer and fibrinogen levels, they were found to be abnormal in all these patients with the mean value of 2678.17 ± 1573.56 ng/ml and 5.613 ± 0.7374 g/L, respectively.

The incidence of in-hospital death in patients included in the study was 28% ($n = 28$), out of which 78.57% ($n = 22/28$) had coagulopathy. Out of all deaths in patients with coagulopathy, 90.9% ($n = 20/22$) of patients had severe iTBI. Figure 2 shows the flow chart of the incidence of coagulopathy, mortality, and outcome.

Increased Marshall score were also associated with increased mortality in patients having TIC (in Grade IV 50% and Grade V 100%).

Univariate analysis of the different coagulation parameters was done to assess the relation of coagulation tests to in-hospital mortality. Based on the analysis, abnormal values of PT at 24 h ($P = 0.002$), PTI at 24 h ($P = 0.001$), INR at admission ($P = 0.026$), INR at 24 h ($P = 0.048$), and INR at 48 h ($P = 0.046$) after injury were found to be significantly related to in-hospital mortality. On further multivariate analysis of these parameters, abnormal values of INR at admission (odds ratio [OR] 4.38) and PTI at 24 h (OR 3.913) are found to be strongly associated with in-hospital mortality [Table 3].

Table 1: Demographic parameters and incidence of coagulopathy

Characteristics	Total patients (*n*=100)	Patients with coagulopathy (*n*=62)	Patients without coagulopathy (*n*=38)	*P*
Age (years)	100	32.9±15.063	36.13±12.645	0.091
Gender (*n*)				
Male	100	47	34	-
Female		15	4	
GCS (at admission)	100	7.269±2.68	8.3080±2.67	0.169
The time interval between injury and admission (h)	100	7.179±5.08	7.797±6.8	0.606
Severity of HI				
Moderate	20	11	9	0.471
Severe	80	51	29	
CT scan				
Contusion	63	43	20	0.587
DAI	18	9	9	0.247
EDH	10	7	3	0.583
SDH	26	17	9	0.679
SAH	19	9	10	0.350
IVH	13	6	7	0.884

Continuous data are presented as mean±SD. Categorical data analyzed using Pearson Chi-square test. $P \leq 0.05$ was considered statistically significant. A single patient may have more than one CT findings. SD – Standard deviation; CT – Computed tomography; GCS – Glasgow Coma Scale; HI – Head injury; DAI – Diffuse axonal injury; SDH – Sub-dural haemorrhage; EDH – Epidural haemorrhage; SAH – Sub-arachnoid haemorrhage; IVH – Intraventricular haemorrhage

Table 2: Deranged coagulation parameters at different points of time

Parameter	Number of patients having deranged coagulation parameters				
	At hospital admission (*n*)	At ICU admission (*n*)	24 h after injury (*n*)	48 h after injury (*n*)	72 h after injury (*n*)
PT	49	50	47	42	34
PTI	38	47	44	27	24
INR	13	17	14	9	7
APTT	18	20	19	17	8
PLT	8	23	22	22	13

n – Number of patients. A single patient may have > one deranged parameter at one point of time. ICU – Intensive care unit; PT – Prothrombin time; PTI – PT index; INR – International normalization ratio; aPTT – Activated partial thromboplastin time; PLT – Platelet

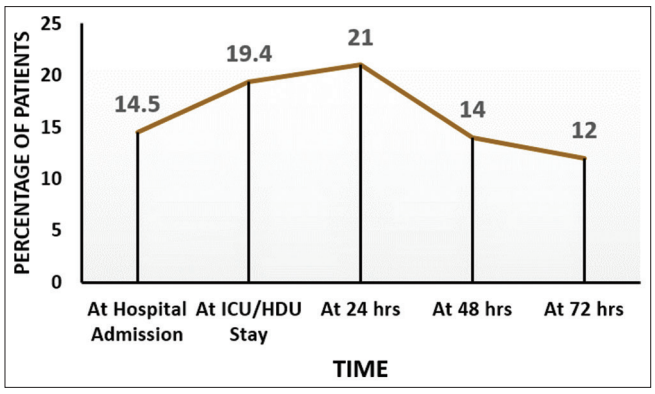

Figure 1: The time pattern for the development of deranged coagulation

The outcome of the patients having coagulopathy was also analyzed based on the number of ventilator days, ICU days, a total length of hospital stay. The parameters were comparable between the groups. GOS at 1 and 3 months after discharge were also noted. It was found to be comparable [Table 4].

Seventy-two out of 100 patients included in the study were discharged from the hospital, among which 40 patients had coagulopathy while 32 patients did not have a coagulopathy. Among patients with TIC, 64.51% of patients were discharged from the hospital. Sixty-seven patients discharged from the hospital were analyzed for the neurological outcome at 1 and 3 months using GOS. The incidence of poor GOS in patients with TIC at 1 month was observed in 32 (88.88%) patients. At 3 months' follow-up, the incidence of poor GOS among patients with TIC and the noncoagulopathy group was 43.75% and 40.74%, respectively. The incidence of total deaths during the study which includes 3 months after discharge was 43.54% in patients who had TIC while it was 26.31% in patients who did not have TIC with the risk ratio of 1.72 and 95% confidence interval of 0.94–3.12.

Discussion

TBI is among the common causes of mortality and morbidity in the form of permanent disability among

trauma victims. Besides the primary insult, secondary insult which develops over time are also responsible for its eventual outcome. One of the causes of secondary complications is TIC.

In trauma, blood loss and tissue injury leads to tissue hypoperfusion and thus hypoxemia. During tissue hypoperfusion, endothelium releases thrombomodulin, which complex with thrombin and they, in turn, activates protein C, inhibiting factor V and VIII. These events inhibit the extrinsic pathway of coagulation. Tissue plasminogen activator is also released which activates fibrinolysis. The brain is rich in tissue factor "thromboplastin" and is released into circulation after the patient suffers from brain injury. It activates the extrinsic pathway of coagulation, causing a state of consumptive coagulopathy, which may cause multiple organ dysfunction and increase the risk of mortality. There is also a qualitative and quantitative compromise in platelet number and function, which increases patients' susceptibility for bleeding. Figure 3 shows the overall mechanism and series of events that leads to coagulopathy.

Table 3: Multivariate analysis for prediction of mortality by coagulation parameters

Variable	*P*	OR	95% CI
PTI, 24 h after injury	0.001	3.913	1.452-10.548
INR at the time of hospital admission	0.026	4.38	1.143-16.786

Data analyzed by multiple regression analysis. PT – Prothrombin time; PTI – PT index; INR – International normalization ratio; OR – Odds ratio; CI – Confidence interval

A prospective observational study was conducted in patients with iTBI admitted to a Level I Trauma center in India to find out the incidence of coagulopathy and its outcome.

RTAs are the most common mode of injury (90%), with the young population being affected the most. The incidence of TIC was found in 62% of patients. Of those with TIC, it was 63.75% in severe head injury and 55% in the moderate head injury. However, the incidence of TIC was almost 70.83% in patients who underwent a decompressive craniotomy. The incidence of TIC reported in various studies range between 10 and 97.3% depending on the limits and coagulation

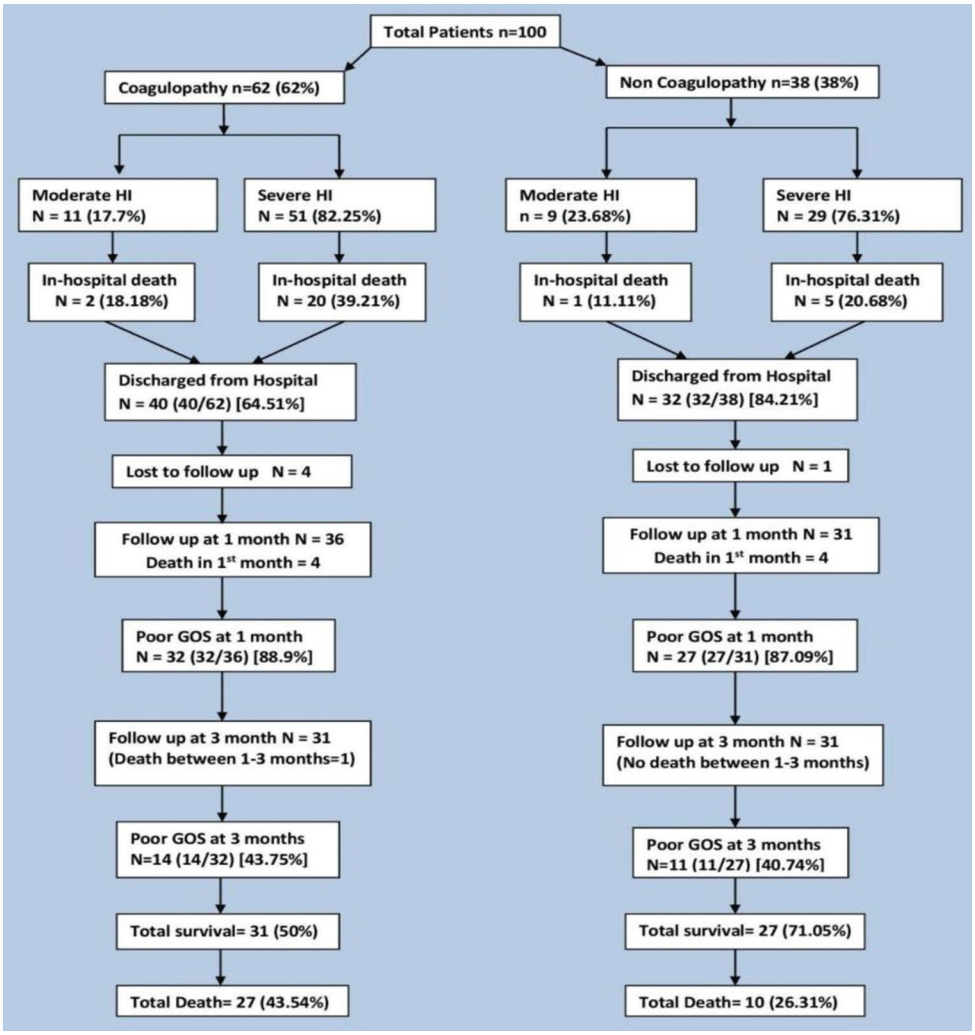

Figure 2: The flow chart of incidence of coagulopathy, mortality, and outcome

Table 4: Outcome in patients with or without coagulopathy

Parameter	Mean±SD		*P*
	Patients with coagulopathy	Patients without coagulopathy	
Ventilator days	7.51±6.07	6.37±4.69	0.328[a]
ICU days	8.87±6.82	7.87±5.04	0.439[a]
Hospital days	13.2±8.8	10.79±6.86	0.153[a]
In Hospital mortality (*n*)	22	6	0.041[b]
Poor glasgow outcome score (GOS) at 1 month, *n* (*n*/*n*1), %	32 (32/36), 88.9	27 (27/31), 87.09	1.00[b]
Poor GOS (at 3 months, *n* (*n*/*n*1), %	14 (14/32), 43.75	11 (11/27), 40.74	0.726[b]

[a]Data analyzed by unpaired *t*-test; [b]Data analyzed by Fischer's test; *n* – Number; *n*1 – Total number in that group. ICU – Intensive care unit; SD – Standard deviation

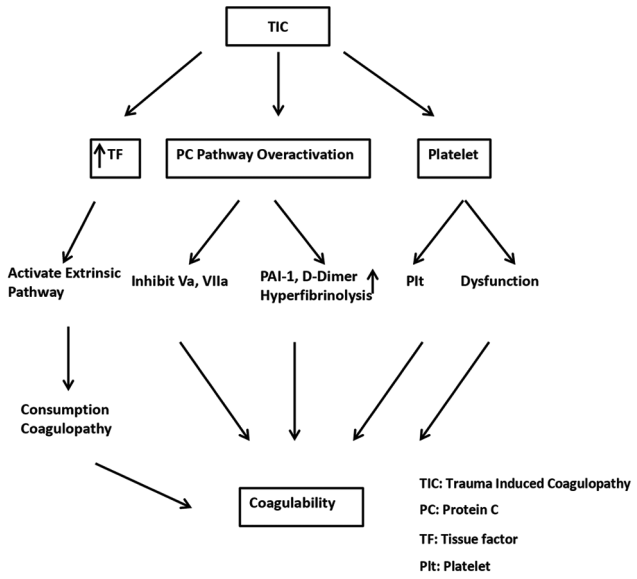

Figure 3: Overall mechanism and series of events that leads to coagulopathy

parameter chosen and also according to the variations in the definition of coagulopathy.[8] Shrestha *et al.* found the overall incidence of TIC to be 63% almost similar to our observation.[9] Greuters *et al.* too reported an incidence of TIC to be 54% while Epstein *et al*. found the incidence to be 35.2%.[10,11] The incidence of coagulopathy varies with the duration of the injury. Our study observed the maximum incidence of TIC during the first 24 h (21%) of injury, and then, it declined over 72 h to 12%. The cause of decline could be due to the intervention is done in ICU such as the transfusion of blood products, maintenance of temperature, and body pH within the physiological range. Greuter *et al*. and Lustenberger *et al*. also observed an increase in the incidence of coagulopathy in first 24 h[10,12] while Carrick *et al*. reported an increase in incidence by the 3rd postinjury day which is nearly double of the initial findings.[13]

We tried to analyze mortality in patients with TIC in iTBI. Coagulopathy was found in the majority (78.57%) (*n* = 22/28). Of the nonsurvivors during the hospital stay, which was statistically significant when compared to noncoagulopathy group (*P* = 0.041). Folkerson *et al*. have also reported a higher incidence of coagulopathy among nonsurvivors.[14] Coagulopathy has been suggested as an independent risk factor for mortality,[11,15] but Talving *et al*. after performing logistic regression to adjust for confounders have found no association.[16]

Among coagulation parameters, we observed that INR at admission (OR 4.38) and PTI at 24 h (OR 3.913) was strongly associated with in-hospital mortality. Initial abnormal PT and PTT increase the adjusted odds for death was observed by MacLeod *et al*.[17] Selladurai *et al*.[18] found that high fibrinogen degradation product (FDP) levels predict poor outcome independently and prognosis worsens as the level of FDP increases.

We had assessed the outcome of the patients based on the duration of ventilator days, ICU stays, and hospital stay. Talving *et al*. found that coagulopathy is associated with longer ICU lengths of stay.[16] Harhangi *et al*. and Wafaisade *et al*. showed an increase in hospital and ICU stay in patients with coagulopathy.[8,19] Sun *et al*. also reported an increase in ICU days and hospital stay in those with coagulopathy.[20] We observed longer ventilator days, ICU days, and hospital stays in patients who developed coagulopathy, but the difference was statistically not significant.

Neurological outcome was assessed by Glasgow Outcome Scale 1 and 3 months after discharge. The number of patients with poor GOS at 1 month were comparable between the groups having coagulopathy and those without it (88.9% vs. 87.09%). Similarly, on measuring GOS at 3 months after discharge, the percentage of patients having poor GOS was found to be less in both the groups (43.75% vs. 40.74%). However, no significant difference was found between the groups with or without coagulopathy during follow-up in 1 and 3 months after discharge. Harhangi found an overall odds ratio for the risk of a bad outcome (GOS 1-3) of 33.2 (95% CI: 15.9–69.1) after TBI and coagulopathy.[8] Sun *et al*. in their study assessed coagulation parameters and neurological outcome by GOS at 3 months after injury; they observed that abnormal PT,

fibrinogen (FIB), and D-dimer (D-DT) levels on admission were associated with increase patients' mortality and poor neurological outcome.[20] We found that INR at admission and PTI at 24 h was strongly associated with in-hospital mortality (OR 4.38 and 3.913, respectively.)

There are a few limitations in this study. We measured D-dimer and fibrinogen levels only in patients who had deranged coagulation parameters at admission and found it to be deranged in all the cases. We should have checked these parameters in all the cases included in the study. Viscoelastic method of assessing clotting mechanism (Sonoclot) could have given a better view of coagulopathy.

Conclusion

We have found an incidence of TIC in isolated moderate-to-severe TBI as 62%. Coagulopathy is more prevalent in severe head injury than in moderate head injury patients. Deranged INR at hospital admission and PTI at 24 h of hospital admission are highly predictive of mortality during the hospital course. Patients having TIC had increased incidence of death in 3 months compared to those who did not have coagulopathy, though the neurological outcome at 1 and 3 months after discharge was not different in between the groups.

This study alerts us to check for TIC and plan management accordingly to improve the outcome of the patients with TIC in isolated TBI.

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Conflicts of interest

There are no conflicts of interest.

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