A Prospective Analysis of Derangement of Coagulation Profile in Adult and Pediatric Age Group in Moderate-to-Severe Traumatic Brain Injury

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Abstract

Background and Aim of Study Coagulopathy is a common occurrence following traumatic brain injury (TBI). Various studies have reported the incidence and risk factors of coagulopathy and their correlation with poor outcome in adult as well as pediatric age group. In our study, we aim to analyze trauma-induced coagulopathy in adult and pediatric patients.

Methods Adult (> 18 years) and pediatric (< 18 years) patients of TBI admitted in the intensive care unit of a trauma center of a tertiary care center had been studied from August 2015 to March 2018. Patients were further subdivided into moderate and severe TBI based on Glasgow Coma Scale (GCS) of 9 to 12 and < 9, respectively. Coagulation profile (prothrombin time [PT], activated partial thromboplastin time [APTT], thrombin time, fibrinogen, and D-dimer) and arterial blood gas (ABG) analysis were done on day of admission and on days 3 and 7. Coagulation profiles were analyzed in both the age groups, and risk factors were studied and correlated with the mortality and morbidity based on the Glasgow outcome score.

Results Two hundred patients including 143 adults and 57 pediatric patients were included. Mean age among the adult and pediatric population was 31.51 ± 16.83 and 11.5 ± 5.90 years, respectively. In adults, 96 (83.62%) out of 116 in severe TBI group and 20 (74.07%) out of 27 in moderate TBI group developed coagulopathy, and in pediatric age group, 14 (70%) out of 20 in moderate TBI and 30 (81.08%) out of 37 in severe TBI developed coagulopathy. Midline shift was significantly associated with coagulopathy in both the age groups (p value < 0.039). Mortality was not significantly different in patients with coagulopathy between the age groups, but improved status as per the Glasgow outcome score was more in pediatric age group.

Conclusion The development of coagulopathy is a frequent complication in patients with moderate to severe TBI in both age groups. Even though it is not closely associated with death in this study, it may be regarded as a marker of injury severity.

Keywords
- coagulopathy
- traumatic brain injury (TBI)
- Glasgow Outcome Score

Introduction

Coagulation abnormalities frequently occur following traumatic brain injury (TBI), and the incidence of the disturbance in the coagulation parameters varies considerably.[1,2] Goodnight et al[3] first recognized that tissue thromboplastin, of which brain is a rich source, is released into the circulation resulting in uncontrolled activation of clotting factors leading to depletion of coagulation proteins, which may eventually result in disseminated intravascular coagulation

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(DIC) characterized by systemic coagulopathy, intravascular coagulation, and hemorrhage after the clotting factors are consumed.[3] Stein et al found a strong association between severity of coagulopathy and density of intravascular coagulation.[4] This insult to hemostatic system is further aggravated by the infusion of large number of colloids, crystalloids, and massive blood transfusion resulting in dilutional coagulopathy. Further, acidosis and hypothermia, which commonly follow traumatic injury, also add on to the hemostatic insult forming a vicious triad of coagulopathy, acidosis, and hypothermia. Coagulopathy has a significant impact on morbidity and mortality of patients with TBI.[5] Mortality in patients with severe head injury with coagulopathy is found to be four times higher than that in patients with head injury without any coagulopathy.[6] However, from the above literature, it is still unclear whether it is the development of coagulopathy or the severity of head injury, which predicts the poor survival for patients with TBI.

Aim of Study

In this study, we aim to assess the incidence of coagulopathy in pediatric and adult population with isolated TBI, the association of coagulopathy with prognostic outcome in addition to the correlation with mortality, and duration of hospitalization among survivors in pediatric and adult population and to identify the probable risk factors for development of coagulopathy and the reasons for poor outcome following head trauma by estimating the median survival time in these cases.

Materials and Methods

A total of 200 patients diagnosed with isolated head injury, admitted in an intensive care unit of neurosurgery at a tertiary care trauma center from August 2015 to March 2018 were enrolled in this prospective cohort study. Isolated TBI was defined as patient presenting with moderate to severe TBI (Glasgow Coma Scale [GCS] ≤ 12) without injury to chest, or abdomen, or limbs. Exclusion criteria were a known history of any hemorrhagic disorder, patient on anticoagulant medications, patient with poly-trauma or associated long bone fractures, clinical evidence of brain death at the time of admission, any other severe comorbidity, such as liver disease, diabetes mellitus, and a known history of hypertension, which is likely to influence outcome.

All patients underwent detailed clinical evaluation followed by categorization into moderate and severe head injury group on the basis of GCS. Subsequent relevant laboratory investigations were performed such as prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (APTT), thrombin time (TT), fibrin degradation products (FDP), D-dimer level, platelet count, arterial blood gas (ABG), analysis and hemoglobin concentration on the day of admission, day third, and day seven. Coagulopathy in this study was defined as PT > 18.0 seconds or/and APTT > 48 seconds (> 1.5 times of the laboratory control). Laboratory control was calculated using 50 healthy individuals (equal numbers of males and females of different age groups). Control PT was 13.7 seconds, and APTT was 32 seconds. Acidosis was defined as arterial blood pH < 7.3 and arterial blood HCO_3 < 20 mEq/L. The patients had been kept under a constant follow-up for the period of their hospital stay to assess the outcome, whether discharged after recovery or died. The study was approved by the ethical committee of Sawai Man Singh Medical College and Hospital, Jaipur (SMS). Data entry was done using Microsoft Excel 2007 (Microsoft Corp.).

Statistical analysis was performed with the SPSS, trial version 23 for Windows statistical software package (SPSS Inc.) and Primer for the generation of descriptive and inferential statistics. Categorical data were presented as numbers (percent) and were compared using chi-square. The quantitative data were presented as mean and standard deviation, and appropriate test will be used. Probability p value < 0.05 was considered statistically significant.

Results

A total of 200 patients of isolated head injury presenting to the SMS trauma center were included in the study and were further categorized into moderate and severe head injury on the basis of GCS. The patients with GCS 3 to 8 were categorized as severe head injury (n = 153), and patients with GCS 9 to 12 were categorized as moderate head injury (n = 47). The patients were further categorized in adult (> 18 years; n = 143) and pediatric (< 18 years; n = 57). Males comprised 84% of the total study population, and the mean age of the study population was 31.51 ± 16.83 years. Coagulopathy as defined in the methodology above was present in 117 (81.82%) in adult and in 44 (77.19%) in pediatric TBI patients, irrespective of the severity of head trauma. Among severe TBI (GCS: 3–8), 96 (83.62%) out of 116 developed coagulopathy, and in moderate TBI group, 20 (74.07%) out of 27 developed coagulopathy, respectively in the adult age group. In pediatric age group, 14 (70%) out of 20 in moderate TBI and 30 (81.08%) out of 37 in severe TBI, respectively developed coagulopathy (base line parameters of two group shown in ►**Tables 1** and **2**)

Out of total 200 cases, 84% were males, and the rest 16% were females. Most common mode of injury was road-traffic accidents (RTA; 82%) followed by fall from height. On admission, severe TBI were 76.5%, and 23.5% were moderate TBI. Most of the cases had reactive pupillary reaction (74.5%) on admission. Respiratory distress on admission was present in 52.5% cases. No significant difference was observed according to sex, pupillary reaction, and respiratory distress on admission. As mode of injury, RTA were significantly associated with the > 18 years of age group as compared with ≤18 years of age group (91.61 vs 57.89%, respectively) (p < 0.001S), while fall from height was significantly less in > 18 years of age groups as compared with ≤18 years of age groups (6.99 vs 38.60%, respectively) (p < 0.001S). According to the GCS score on admission, cases were more in severe category as compared to moderate category in both age groups (p = 0.024S). No significant difference was observed according to findings and outcome, except in midline shift, was significantly associated with > 18 years of age groups as

Table 1 Association of demographic parameters in adult and pediatric age group

	> 18 years (n = 143) adults		≤18 Years (n = 57) pediatric		Total (n = 200)		p value LS
	No.	%	No.	%	No.	%	
Gender							
F	22	15.38	10	17.54	32	16	0.871
M	121	84.62	47	82.46	168	84	
Mode of injury							
RTA	131	91.61	33	57.89	164	82	0.001S
FFH	10	6.99	22	38.60	32	16	0.001S
gun shot	1	0.70		0.00	1	0.5	0.663
GCS on admission							
Moderate	27	18.88	20	35.09	47	23.5	0.024
Severe	116	81.12	37	64.91	153	76.5	
Pupillary reaction							
Nonreactive	42	29.37	9	15.79	51	25.5	0.07NS
Reactive	101	70.63	48	84.21	149	74.5	

Abbreviations: F, female; FFH, fall from height; GCS; M, male; RTA, road traffic accident.

compared with ≤ 18 years of age groups (36.36 vs 19.30%, respectively) (p < 0.03S). Mortality were significantly more in > 18 years of age groups as compared with ≤18 years of age groups (41.96 vs 22.81%, respectively) (p < 0.017S).

No significant difference was observed between association of deranged profile and coagulopathy with age groups (►**Table 3**). Although the number of cases of deranged profile decreased with the time from 86.01% at day 1 (D1) to 30.77% at D7 in > 18 age group and from 78.95% at D1 to 24.56% at D7 in ≤ 18 age group. Similar observation and pattern were observed in coagulopathy profile.

In moderate TBI with coagulopathy, mean hospital stay was 8.68 days in adult, and in pediatric age group, it was 9.21 days, which was statistically insignificant (p = 0.74), while in severe TBI, mean hospital stay in adult and pediatric age group was 9.18 and 9.89 days, respectively, which was also insignificant (p = 0.32) (►**Table 4**).

In moderate TBI with coagulopathy, a total of two (10%) deaths out of 20 cases were reported in adult age group, and no deaths were reported in pediatric age group, which was insignificant (p = 0.63 NS). In severe TBI with coagulopathy, total death in adult age group was 56 (57.73%) out of 97, and in pediatric age group, it was 13 (43.33%) out of 30, which was also insignificant (p = 0.24 NS) (►**Table 5**).

Bivariate analysis was performed to identify the risk factors associated with the development of coagulopathy (►**Table 6**). On bivariate analysis, severity of TBI, effaced basal cisterns on CT scan, low hemoglobin level, and elevated D-dimer level at admission, was found to predict the development of coagulopathy. However, on multivariate logistic regression analysis, effaced basal cisterns on CT scan, hemoglobin < 10 g/dL, and D-dimer > 1 μg/dL were found to predict the development of coagulopathy independently.

No significant difference was observed according to the Glasgow outcome score for the first four age groups except in score 5, where cases were significantly less in > 18 years of age groups as compared with ≤18 years of age groups (25.17 vs 50.88%, respectively) (p < 0.001S). No significant difference was observed according of the Glasgow outcome score status in patients whose condition deteriorated while improved status was more in ≤ 18 years of age groups as compared with > 18 years of age groups (►**Table 7**).

Discussion

This is one of the large series of patients with isolated TBI, which has looked into the prognostic factors such as coagulopathy and severity of TBI in pediatric and adult age group. None of study has analyzed the adult and pediatric population with TBI with respect to the above-mentioned end points. In our study, we aim to analyze trauma-induced coagulopathy in adult and pediatric patients. Coagulopathy frequently occurs following head injury and is a well-recognized confounding phenomenon. If this coagulative derangement is severe, this coagulopathy may disseminate resulting in deposition of thrombi in microvasculature and activation of fibrinolysis leading to development of DIC and uncontrollable bleeding.[7–9]

In the present study, the prevalence of coagulopathy was found to be 81.82% in adult and 77.19% in pediatric age group, irrespective of the severity of brain injury. In literature, the incidence of coagulopathy varies considerably among different studies. The reported incidence ranges between 10 and 97%.[10–15] This wide variation in incidence among various studies could be attributed to different criteria used by different authors to define coagulopathy (as no standard definition is available so far), varying inclusion criteria, and varying severity of the head trauma among different studies.

Release of tissue factor from the injured brain cortex is implicated in development of coagulopathy following TBI. This tissue factor released from the brain activates the extrinsic

Table 2 Associated demographic parameters in adult and pediatric age group

	> 18 years (*n* = 143) adults		≤18 years (*n*= 57) pediatric		Total (*n* = 200)		*p* value LS
	No	%	No	%	No	%	
CT finding							
EDH	22	15.38	5	8.77	27	13.5	0.664
SDH	43	30.07	13	22.80	56	28	0.391
ICH/contusion lobar	113	79.02	45	78.94	158	79	
SAH	31	21.68	10	17.54	40	20	0.646
Fracture	27	18.88	18	31.58	45	22.5	0.079
Pneumocephalus	4	2.80	4	7.02	8	4	0.329
Miscellaneous (DAI)	31	21.68	12	21.05	43	21.5	0.926
Midline shift							
< 5 mm	52	36.36	11	19.30	63	68.5	0.03
> 5 mm	91	63.34	46	80.70	137	31.5	
Effaced cistern	109	67.70	19	48.14	128	64	0.042
pH							
≥7.4	83	58.04	31	54.39	114	57	0.754
< 7.4	60	41.96	26	45.61	86	43	
Management							
Conservative	92	64.34	42	73.68	134	67	
Operative	51	35.66	15	26.32	66	33	0.27
Duration of ventilatory support							
< 24 h	42	29.37	28	49.12	70	35	0.013
> 24 h	101	70.63	29	50.88	130	65	
Complications							
ARDS	30	20.98	9	15.79	39	19.5	0.523
ARDS with hypotension	48	33.56	22	38.60	70	35	0.611
Size of hematoma increases	2		1		2	1	
Normal	64	44.76	22	38.60	86	43	0.525
Patient's outcome							
Died	60	41.96	13	22.81	73	36.5	0.017
Discharged	83	58.04	44	77.19	127	63.5	

Abbreviations: ARDS, acute respiratory distress syndrome; CT, computed tomography; ICH, intracranial hemorrhage; DAI, diffuse axonal injury; EDH, epidural hemorrhage; SAH, subdural hemorrhage.

coagulation pathway leading to increased consumption of clotting factors and development of coagulopathy. Also, the exposure of negatively charged collagen vascular layer contributes to activation of coagulation pathway by stimulating the intrinsic pathway. This was evident in the present study from a significant increase in PT, INR, and APTT on days 1, 3, and 7 of admission among patients who developed coagulopathy in comparison to patients who did not develop coagulopathy following TBI. Findings of the present study are similar to as reported by Bayir et al who, in their study on 62 patients of isolated head trauma, found a prolonged mean PT and APTT within first 3 hours of head injury.[16] Similar findings were also reported by Stein et al. They reported that mean PT and PTT at admission were significantly longer in patients developing delayed brain injury.[17] A recent study by Talving et al[2] on 436 patients also supported the results of this study. Greuters et al in their study including 107 patients have reported significantly increased mean PT and APTT following head injury.[18] Neither are many studies available that assessed TT with TBI, nor has TT been found to be associated with development of coagulopathy. This study supports the findings of Vecht et al who also reported the prolongation of TT following head injury[19]; although Auer in his study on 30 patients did not find any significant changes in TT.[20]

D-dimer levels were significantly elevated in patients who developed coagulopathy indicating the activation of the fibrinolytic system. Olson et al[11] and Jovan et al[21] in their study also reported similar results.

Table 3 Association of deranged profile and coagulopathy with age groups

	> 18 years (*n* = 143)		≤ 18 years (*n* = 57)		Total	*p* value LS
	No	%	No	%	No	
Deranged profile						
D1	123	86.01	45	78.95	168	0.89NS
D3	79	55.24	26	45.61	105	0.28NS
D7	44	30.77	14	24.56	58	0.48NS
Coagulopathy						
D1	117	81.82	44	77.19	161	0.58NS
D3	49	34.27	13	22.81	62	0.16NS
D7	35	24.48	10	17.54	45	0.38NS

Table 4 Association of coagulopathy with hospital stay among the group

Hospital stay	Total	With coagulopathy			*p* value LS	Without coagulopathy			*p* value LS
		n	Mean	SD		*n*	Mean	SD	
Moderate	> 18	19	8.68	2.00	0.74NS	7	7.71	1.25	0.95NS
	≤18	14	9.21	6.65		6	7.67	1.21	
	Total	33	8.91	4.50		13	7.69	1.18	
Severe	> 18	66	9.32	4.07	0.32NS	15	10.33	2.50	0.65NS
	≤18	21	10.33	3.83		7	10.86	2.61	
	Total	87	9.56	4.02		22	10.50	2.48	
Total	> 18	85	9.18	3.71	0.39NS	22	9.50	2.48	0.89NS
	≤18	35	9.89	5.08		13	9.38	2.60	
	Total	120	9.38	4.15		35	9.46	2.49	

Abbreviation: SD; standard deviation.

Table 5 Association of demographic variable (death and gender) with GCS

		Coagulopathy			*p* value LS	Without coagulopathy			
		> 18	≤18	Total		> 18	≤18	Total	*p* value LS
Death									
Moderate	Died	2	0	2	0.63NS	0	0	0	NA
	Alive	18	14	32		7	6	13	
	Total	20	14	34		7	6	13	
Severe	Died	56	13	69	0.24NS	4		4	0.48NS
	Alive	41	17	58		15	7	22	
	Total	97	30	127		19	7	26	

Abbreviation: GCS; Glasgow Coma Scale.

To add, to the best of our knowledge, very few studies have mentioned the risk factors associated with the development of coagulopathy. In this study, severity of head injury (GCS ≤ 8), D-dimer level of > 1 mg/dL, effaced cisterns, presence of midline shift on CT scan, and hemoglobin level < 10 g/dL strongly predicted the development of coagulopathy. Talving et al[2] had also reported GCS ≤ 8 and presence of cerebral edema, subarachnoid hemorrhage (SAH), systolic blood pressure (SB*p*) < 90 mm Hg, and midline shift as the factors, which independently predicted development of coagulopathy. Similar findings were also reported by Affonseca et al[22] in their study on pediatric patients where they found severity of head injury, presence of brain swelling, and injuries to chest and abdomen being associated with the development of coagulopathy.

In this study, the development of coagulopathy following severe isolated head injury was associated with a longer hospital stay, although coagulopathy did not bear any impact

Table 6 Risk factor for development of coagulopathy

	Coagulopathy (*n* = 161)					*p* Value LS
GCS	With (*n* = 161)		Without (*n* = 39)		Total	
	No	%	No	%		
Moderate	34	21.12	13	33.33	47	0.16NS
Severe	127	78.88	26	66.67	153	
Midline shift		0.00		0.00		
<5 mm	51	31.68	27	69.23	78	<0.001S
>5 mm	110	68.32	12	30.77	122	
Effaced cisterns		0.00		0.00		
e	109	67.70	19	48.72	128	0.042S
No	52	32.30	20	51.28	72	
		0.00		0.00		
HB < 10	116	72.05	11	28.21	127	<0.001S
	45	27.95	28	71.79	73	
		0.00		0.00		
D1 (D–dimer)	117	72.67	5	12.82	122	<0.001S
D3	92	57.14	1	2.56	93	<0.001S
D7	40	24.84	0	0.00	40	<0.001S

Abbreviation HB, hemoglobin.

Table 7 Association of Glasgow outcome score/status with age groups

Glasgow outcome score	> 18 years (*n* = 143)		≤18 years (*n* = 57)		Total (*n* = 200)		*p* value LS
	No	%	No	%	No	%	
GCS improved/same/deteriorated by							
1	44	30.77	11	19.30	55	27.5	0.143
2	9	6.29	2	3.51	11	5.5	0.663
3	32	22.38	11	19.30	43	21.5	0.773
4	4	2.80	2	3.51	6	3	0.847
5	36	25.17	29	50.88	65	32.5	<0.001S
Deteriorated	2		1.40	1 1.75	3	1.5	0.64NS
Improved	79		55.2	42 73.68	119	59.5	0.036S
Died	62		44.06	13 22.80	78	39	0.03S

Abbreviation: GCS; Glasgow Coma Scale.

on the length of the total hospital stay. Similar findings were reported by Talving et al.[2]

The overall mortality in the present study was 75 (37.5%). Patients with coagulopathy were found to be significantly associated with poor survival as compared with patients who did not develop coagulopathy. Development of coagulopathy and severity of head trauma (GCS ≤ 8) independently predicted poor outcome. The result is similar to the findings reported by Macleod et al who in 7,638 patients found presence of coagulopathy and GCS ≤ 8 as the predictors for poor outcome.[23] Olson et al[11] reported decreased GCS, elevated DIC score, and increased fibrin degradation product as independent predictors for poor outcome. Talving et al[2] also found coagulopathy to be independent risk factor for mortality. However the finding of our study was supported by findings of Affonseca et al[22] who found coagulopathy following TBI was not associated with increase in mortality. This difference in results may be probably attributed to the fact that our definition for coagulopathy was based on firm criteria, which very few studies comply with. Also we had controlled other factors such as severity of head trauma, presence or absence of other injuries, etc., which could affect the outcome.

In spite of the best efforts, our study has some limitations since we did not take into account the soft tissue injuries,

which could have also possibly triggered the coagulation cascade. Sepsis, which is commonly present in traumatic injury patients, is associated with decreased protein C levels, and this decreased protein C has also been implicated in the mechanism of coagulopathy.[14] The strength of present study is the large number of cases, extensive review of all the routine hemostatic parameters following head trauma, and analysis of several possible risk factors for the development of coagulopathy with identification of the factor predicting poor outcome following isolated TBI.

Conclusion

Present study leads to conclusion that coagulopathy occur frequently following TBI. But the role of coagulopathy in increased mortality of TBI patients remains questionable. According to the findings of the present study, coagulopathy is not a determining factor of mortality in both age group, but a marker of the severity of brain injury, which means that patients with coagulopathy should be more closely and intensively monitored in both age groups.

Source of Support
None.

Conflicts of Interest
None.

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