Research Article

Non- Neurological Complications after Traumatic Brain Injury: A Prospective Observational Study

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Abstract

Introduction and Aims: Recognizing and treating nonneurological complications occurring in traumatic brain injury (TBI) patients during intensive care unit (ICU) stay are challenging. The aim is to estimate various nonneurological complications in TBI patients. The secondary aim is to see the effect of these complications on ICU stay, disability, and mortality. **Materials and Methods:** This was a prospective observational study at the neuro-ICU of a Level-I trauma center. A total of 154 TBI patients were enrolled. The period of the study was from admission to discharge from ICU or demise. Inclusion criteria were patients aged >16 years and patients with severe TBI (Glasgow coma score [GCS] ≤8). Nonneurological complications were frequent in TBI patients. **Results:** We observed respiratory complications to be the most common (61%). Other complications, in the decreasing order, included dyselectrolytemia (46.1%), cardiovascular (34.4%), coagulopathy (33.1%), sepsis (26%), abdominal complications (17.5%), and acute kidney injury (AKI, 3.9%). The presence of systemic complications except AKI was found to be significantly associated with increased ICU stay. Most of the patients of AKI died early in ICU. Respiratory dysfunction was found to be independently associated with 3.05 times higher risk of worsening clinical condition (disability) ($P < 0.018$). The presence of cardiovascular complications during ICU stay (4.2 times, $P < 0.005$), AKI (24.7 times, $P < 0.02$), coagulopathy (3.13 times, $P < 0.047$), and GCS <6 (4.2 times, $P < 0.006$) of TBI was independently associated with significantly increased risk of ICU mortality. **Conclusion:** TBI patients tend to have poor outcome due to concomitant nonneurological complications. These have significant bearing on ICU stay, disability, and mortality.

Keywords: Complications, neurocritical care, nonneurological complications, outcome, systemic complications, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death, disability, and economic burden to our society. Globally, the number of TBI patients every year is estimated to be 1.5–2 million; half of them succumb to death. Unlike in high-income group countries, middle- to low-income countries still have children and young adults as the most vulnerable group.[1] TBI has been predicted to become the third leading cause of death and disability in the world by 2020.[2] Gururaj calculated the economic losses resulting from TBI alone in India to the tune of 3% of gross domestic product.[3] Despite increasing facilities for TBI patients,[4,5] the mortality and morbidity still remains significantly high.[6]

Nonneurological complications involving either single or multiple organ system have been shown to have a negative impact on the outcome of these patients.[7] Whether these complications are due to pathophysiological changes brought about by the primary injury or as a result of brain-directed therapy in intensive care unit (ICU) is yet to be elucidated. Literature is scarce in highlighting the role of nonneurological complications as an important prognosticating factor in TBI patients.[7-11]

The primary objective of this prospective observational study was to assess the incidence of various nonneurological complications in TBI patients during their ICU stay. The secondary objective was to assess the effect of these complications on ICU stay, disability, and mortality of these patients.

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Materials and Methods

This was a prospective observational study of 154 TBI patients admitted to the neurosurgical ICU of a Level-I trauma center in India over a period of 6 months. Approval from the Institutional Ethics Committee for conducting this study and informed consent from the patients or relatives were taken. The patients were managed and treated as per the standard institutional protocol. The patients with TBI aged >16 years and Glasgow coma score (GCS) ≤8 were enrolled. Pregnant and nonconsenting patients were excluded from the study.

The predefined nonneurological complications are observed in Table 1. Variables pertaining to neurological conditions such as initial GCS at the time of admission to ICU, presence of hypoxia (PaO_2 <60 mmHg) or hypotension (systolic blood pressure <90 mmHg), computed tomography (CT) scan findings, and intracranial pressure (ICP) monitoring were recorded.

The study period ranged from the time of admission to discharge from ICU or death, whichever was earlier. Patient's neurological status during ICU stay was monitored and any added neurological deterioration was recorded. The criteria for neurological deterioration included deterioration of motor response in the component of GCS during ICU stay with respect to ICU admission.

Statistical analysis

Data were analyzed using statistical software STATA 14.0 (StataCorp LLC. College Station, Texas, USA). Quantitative data (age, weight, etc.) were expressed as mean ± standard deviation. ICU stay was expressed as median (range). Categorical data (qualitative) were expressed as frequency (percentage). Chi-square/Fisher's exact test was used to check the association between the variables. Univariate and multivariate logistic regression analyses were used to estimate the odds ratio. $P < 0.05$ was considered statistically significant.

Results

Of 154 patients at presentation, 21% were hypotensive and 31% were hypoxic [Table 2]. Raised ICP was found in almost 70% of TBI patients at ICU admission and was measured by intraparenchymal monitor (Codman™, DepuySynthes, West Chester, PA, USA) as per the institutional protocol. Of those patients who were managed conservatively, half of them required surgical decompression for raised ICP. Long bone injuries, multiple rib fracture, and faciomaxillary injuries were commonly associated (17.5%).

Respiratory problems (61%) were the most common nonneurological complication [Table 3]. It was followed by electrolyte imbalances (46.1%), cardiovascular complications (e.g., hypotension requiring inotropes) (34.4%), and coagulopathy (33.1%). The presence of all the systemic complications was associated with prolonged ICU stay [Table 4], except acute kidney injury (AKI). Table 5 lists the complications that were observed in patients who had deterioration in their neurological status.

Table 1: Definition and categorization of various nonneurological complications after traumatic brain injury

Complications	Parameters observed
Respiratory	Lung infiltrates on chest X-ray
	PaO_2/FiO_2 <300
	PaO_2/FiO_2 <200
	PaO_2/FiO_2 <100
	Atelectasis on chest X-ray
Cardiovascular	Hypotension (SBP <90 mmHg) during ICU stay requiring inotropes
	Hypertension (SBP >160 mmHg)
	Arrhythmias
Infection	Sepsis (WBC count <4000/ml or >12,000/ml, temperature >38.0°C [100.4°F] or <36°C [96.8°F])
	Septic shock (features of sepsis with SBP <90 mmHg, HR >90 beats/min)
AKI	Increase in serum creatinine by >0.5 mg/dl or 50% from baseline or fall in creatinine clearance by >50% with or without dialysis
Gastrointestinal	Diarrhea
	Bilirubin levels >2 mg/dL
	AST >60U/L)
	Ileus (absent bowel sound)
Electrolytes	Hypernatremia (Na level >150 mmol/L)
	Diabetes insipidus
	Hypovolemia
	Hyponatremia: (Na level <130 mmol/L)
	SIADH
	CSWS
	Hyperkalemia (K level >5.0mmol/L)
	Hypokalemia (K level <3.5 mmol/L)
	Hypocalcemia (Ca level <8 mmol/L)
Bleeding/ coagulopathy	Hemorrhage needing blood transfusion (>4 packed cells) and/or
	PT, aPTT, INR >1.5 times the control values and platelets <100,000/mm^3 of blood

SBP: Systolic blood pressure; AST: Aspartate aminotransferase; SIADH: Syndrome of inappropriate antidiuretic hormone; CSWS: Cerebral salt wasting syndrome; ICU: Intensive Care Unit; WBC: White blood cell; HR: Heart rate; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; AKI: Acute kidney injury

Severe TBI patients having GCS <6 showed more deterioration in their clinical condition as compared to GCS ≥6. Overall, 30% of the patients had deterioration in GCS as compared to their admission score.

Univariate analysis suggested that the presence of systemic complications such as respiratory complications, sepsis, and gastrointestinal complications were associated with increased neurological worsening during ICU stay [Table 6]. Multiple regression analysis suggested that the respiratory complications were independently associated with worsening clinical condition at discharge from ICU.

Majority of those who died had GCS <6 (68.8%) at the time of ICU admission [Table 7]. Complications associated with mortality are listed in Table 7. The univariate analysis of the various nonneurological complications showed

Table 2: Demographic characteristics

Demographic characteristics	*n* (%) Median (range)
Number of patients	154
Age (years)	34.5 (18-85)
Gender (%)	
Male	129 (83.8)
Female	25 (16.2)
Weight (kg) (mean±SD)	62.2±11.3
Mode of injury (%)	
Road traffic accident	111 (72.1)
Fall from height	39 (25.3)
Assault and others	4 (2.6)
Multiple trauma (%)	27 (17.5)
Underwent surgery (%)	76 (49.4)
GCS (%)	
<6	65 (42.2)
≥6	89 (57.8)
Hypotension at admission (%)	33 (21.4)
Hypoxia at admission (%)	48 (31.2)
Raised ICP at admission (%)	107 (69.5)
ICU stay (days)	7 (1-45)
Disability (%)	43 (30)
Mortality (%)	32 (20.8)

GCS: Glasgow coma score; ICP: Intracranial pressure; ICU: Intensive Care Unit; SD: Standard deviation

that complications such as cardiovascular, sepsis, AKI, dyselectrolytemia, coagulopathy, and GCS <6 during ICU stay were the risk factors of poor outcome in relation to ICU mortality in TBI patients. On multivariate regression analysis, mortality during ICU stay was independently associated with AKI, cardiovascular complications, coagulopathy, and GCS <6 [Table 8]. Multiple trauma and surgical intervention did not seem to significantly influence death, disability, and ICU stay. Of six patients who developed AKI, 5 (83.3%) died in the ICU. The presence of AKI regardless of any factor multiplied the risk of ICU death by 24.7 times with 95% confidence interval of 1.5 to 400 ($P < 0.02$). The ICU mortality risk was multiplied 4.2 times ($P < 0.005$) by cardiovascular complications and 3.13 times ($P < 0.047$) by the presence of coagulopathy. GCS <6 multiplied the risk of death in TBI patients during ICU stay by 4.2 times ($P < 0.006$).

Discussion

Nonneurological complications are a common occurrence in neurotrauma ICU. Corral *et al*.[7] observed sepsis (75%) while Piek *et al*. found dyselectrolytemia as the most common complication (59%) followed by pulmonary infections (41%) and shock (29%).[12] In this study, respiratory complications was the most common observation. The difference in observation may be due to differences in interpreting the overlapping conditions, such as respiratory complications (decreasing PaO_2/FiO_2), pneumonia, and sepsis. Most of our patients presented with new infiltrates on chest

Table 3: Nonneurological complications after traumatic brain injury

Nonneurological complications*	*n* (%)
Respiratory	94 (61)
Infiltrates	54 (35)
FiO_2/PaO_2 <300	20 (13)
FiO_2/PaO_2 <200	15 (9.7)
FiO_2/PaO_2 <100	2 (1.3)
Atelectasis	3 (1.9)
Cardiovascular	53 (34.4)
Hypotension requiring inotropes	42 (27.3)
Hypertension	10 (6.4)
Arrhythmia	1 (0.64)
Infection	40 (26)
Sepsis	31 (20.1)
Septic shock	9 (5.8)
Abdominal	27 (17.5)
Diarrhea	20 (13)
Bilirubin (2 mg/dL)	3 (1.9)
Increase AST (60 U/L)	2 (1.3)
Ileus	2 (1.3)
AKI	6 (3.9)
Requiring dialysis	3 (2)
Electrolyte imbalance	71 (46.1)
Hypernatremia	52 (33.8)
Diabetes insipidus	12 (7.8)
Hypovolemia	40 (26)
Hyponatremia	10 (6.5)
SIADH	2 (1.3)
Cerebral salt wasting	1 (0.65)
Hypokalemia	5 (3.3)
Hyperkalmia	2 (1.3)
Hypocalcemia	2 (1.3)
Bleeding complications/coagulopathy	51 (33.1)

*Patients may have more than one complication at a time. AST: Aspartate aminotransferase; AKI: Acute kidney injury; SIADH: Syndrome of inappropriate antidiuretic hormone

X-ray suggestive of evolving pneumonia. These infiltrates could be due to ventilation-related causes such as secretions, inadequate cough, and natural barriers being compromised and poor GCS.[13] Decrease in FiO_2/PaO_2 ratio may also be secondary to associated pleural effusion, collapse, and probable deep vein thrombosis due to immobility.[14,15] The presence of respiratory complications was independently associated with neurological worsening.($P < 0.018$). ICU stay was significantly ($P < 0.0002$) increased in these patients, but mortality rate was not affected ($P < 0.74$). Our findings are consistent with previous other studies.[7,16-18] Few studies showed that acute lung injury resulted in doubling of mortality after TBI[14,19] and moderate and severe respiratory failure were the poor prognostic factors.[14,19,20] Other similar studies did not find any association with mortality.[7,21] Very few of our patients had severe respiratory failure which could be life-threatening.

Cardiovascular complications were present as an independent risk factor for ICU mortality ($P < 0.005$) as also evident

Table 4: Effect of the systemic complications on intensive care unit stay

Complications	ICU stay (days) Median (range)	*P*
Respiratory		
Yes	8 (1-45)	**0.0002**
No	4 (1-14)	
Cardiovascular		
Yes	9 (2-45)	**0.01**
No	6 (1-25)	
Infection		
Yes	11 (1-45)	**0.00**
No	5 (1-26)	
AKI		
Yes	3 (2-18)	0.84
No	7 (1-45)	
Abdominal		
Yes	12 (2-45)	**0.00**
No	6 (1-22)	
Dyselectrolytemia		
Yes	9 (1-45)	**0.00**
No	4 (1-22)	
Bleeding and coagulopathy		
Yes	10 (1-45)	**0.00**
No	6 (1-22)	

ICU: Intensive Care Unit; AKI: Acute kidney injury

Table 5: Factors affecting the disability

Demographic characteristics	*n* (%)
Total (*n*)	43
Gender	
Male	38 (88.4)
Female	5 (11.6)
Mode of injury	
Road traffic accident	33 (76.7)
Fall from height	10 (23.3)
Underwent surgery	27 (62.8)
GCS	
<6	23 (53.5)
>6	20 (46.5)
Complications	
Respiratory	35 (81.4)
Cardiovascular	14 (32.6)
Infection	18 (41.9)
Gastrointestinal	14 (32.6)
Dyselectrolytemia	25 (58.1)
Bleeding/coagulopathy	19 (44.2)

GCS: Glasgow coma score

in other studies.[7,9,12] Among these, hypotension requiring ionotropic support was common. When required, dopamine and noradrenaline were used.

Paiva *et al*. reported the incidence to be 45% that is comparable to our results.[22] Hypernatremia was the most common electrolyte disorder observed (86.5%) and has been attributed to inadequate volume status of patients after overzealous administration of mannitol and diuretics.[23] Transient diabetes insipidus requiring desmopressin was found in four patients.

Reported incidence of coagulopathy in TBI patients ranges from 10% to 97%.[24-30] Our study suggests 33%. The wide variation is due to different criteria used by different authors. Chhabra *et al*. utilized similar criteria and observed the incidence to be 46%.[30] In our study, development of coagulopathy was associated with longer ICU stay; it correlates with the literature.[31] The presence of TBI coagulopathy in our study was associated with 3.13-fold increased risk of mortality which is contrary to the results by Affonseca *et al*.[32] In TBI, coagulopathy may be because of hypoperfusion,[33] hypothermia,[34] and release of brain thromboplastin.[35]

Sepsis was more prevalent in postoperative patients. Positive cultures from blood, tracheal, urine, cerebrospinal fluid, central venous catheter, and wound sites were common. Different studies have shown very high (75%) incidence.[7] However, in our study, the incidence was relatively less probably due to the overlapping with the respiratory complication. Sepsis was associated with increased ICU stay, but on multivariate analysis, it did not influence the neurological deterioration and mortality.

Incidence of abdominal complications was comparable to other studies.[7] Frequent gastrointestinal complications that we encountered included bowel incontinence, ileus, stress ulcers, and liver dysfunction. Diarrhea was mostly due to high osmotic load of initial enteral feed, antibiotic-induced, and rarely infective. This had significant influence on ICU stay. On univariate analysis, gastrointestinal complications were found to be significantly associated with disability; however, it was not found to be an independent predictor of disability.

The incidence of AKI following trauma is reported from 0.098% to 17.3%.[7,36-40] The incidence of AKI in our study was 3.5%, while in Corral *et al.*'s study, it was 8%.[7] This difference was probably due to the fact that our study period was restricted to ICU stay only. In this study, a more comprehensive AKI definition was utilized that included either a single creatinine cut-off value or patients requiring dialysis.[39-44] TBI triggers a series of catabolic processes that lead to reduced glomerular filtration and developing AKI that is further worsened by reduced renal perfusion pressure secondary to hypovolemia and shock.[42,45] Seventy-six percent deaths have been reported in these patients in TBI,[37,41] which is almost similar to our results (83.3% deaths). In our study, the risk of mortality increased by 24.7 times in TBI patients who developed AKI. This was much higher as compared to the study by Corral *et al*., who observed an increase of 6.17-fold risk of death in TBI patients who develop severe AKI.[7] The length of ICU stay in TBI patients did not correlate with AKI because of early deaths in ICU in these patients.

In our study, on subgrouping of severe TBI patients, GCS <6 was independently associated with poor outcome in ICU,

Table 6: Multivariate analysis and correlation of predictors of disability in traumatic brain injury patients

Variables	Nondisabled	Disabled	95% CI unadjusted	*P*	95% CI adjusted	*P*
Respiratory						
0	52	8	3.85 (1.64-9)	**0.002**	3.05 (1.20-7.7)	**0.018**
1	59	35				
Cardiovascular						
0	72	29	0.89 (0.42-1.88)	0.763	0.45 (0.17-1.16)	0.099
1	39	14				
Infection						
0	89	25	2.91 (1.35-6.2)	**0.006**	1.89 (0.70-5.07)	0.205
1	22	18				
AKI						
0	105	43	-	-	-	-
1	6	0				
Gastrointestinal						
0	98	29	3.64 (1.53-8.6)	**0.003**	2.12 (0.71-6.31)	0.177
1	13	14				
Dyselectrolytemia						
0	65	18	1.96 (0.96-4)	0.064	0.95 (0.38-2.39)	0.924
1	46	25				
Bleeding and coagulopathy						
0	79	24	1.95 (0.94-4)	0.07	1.99 (0.76-5.18)	0.160
1	32	19				
GCS <6						
0	69	20	1.88 (0.93-3.85)	0.08	1.91 (0.85-4.3)	0.115
1	42	23				

AKI: Acute kidney injury; GCS: Glasgow coma score; CI: Confidence interval

Table 7: Factors affecting mortality

Demographic and clinical characteristics	*n* (%)
Total	32
Gender	
Male	24 (75)
Female	8 (25)
Mode of injury	
Road traffic accident	22 (68.8)
Fall from height	9 (28.1)
Others	1 (3.1)
Underwent surgery	20 (62.5)
GCS	
<6	22 (68.8)
≥6	10 (31.3)
Complications	
Respiratory	22 (68.8)
Cardiovascular	23 (71.9)
Infection	13 (40.6)
Gastrointestinal	7 (21.9)
Dyselectrolytemia	23 (71.9)
Bleeding/coagulopathy	21 (65.6)
AKI	5 (15.6)

AKI: Acute kidney injury; GCS: Glasgow Coma Score

which correlated well with previous studies.[7-9] There was almost 4.2-fold increased risk of mortality in patients with GCS <6 ($P < 0.006$). This reemphasizes that severity of primary brain injury is independent predictor of poor outcome.

This study is one of the largest series from a Level-I trauma center in a developing country and one of the first in Southeast Asia. Literature in TBI patients has implicated various nonneurological complications such as hypotension, sepsis, pneumonia, and coagulopathy with poor outcome.[8,12,46-49] Corral *et al*. found AKI and hypotension in low GCS (GCS 3–5) patients as the independent prognosticating factors for deciding mortality.[7] Our study found ICU mortality independently associated with GCS <6, presence of AKI, cardiovascular complications, mostly hypotension and coagulopathy. This study is not without limitations. Complications related to blunt trauma, crush injury, and orthopedic morbidities, which have equal importance in trauma management and its final outcome, have not been individually studied. Serum levels of magnesium and phosphorus were not included, and thus, the impact of its fluctuating level on final outcome could not be known. Similarly, we did not take into consideration the nutritional status of the patients and their metabolic demand during ICU stay and hence on the outcome. Further studies are required with better inclusion criteria to highlight the importance of nonneurological complications in outcome of TBI patients.

Conclusion

Nonneurological complications are quite common following TBI. These complications had significant bearing on ICU stay, disability, and ICU mortality. Respiratory complications

Table 8: Univariate and multivariate analysis and correlation of predictors of mortality in traumatic brain injury patients

Variables	Survival	Mortality	95% CI unadjusted	*P*	95% CI adjusted	*P*
Respiratory						
0	50	10	1.52 (.66-3.5)	0.317	0.83 (0.27-2.48)	0.735
1	72	22				
Cardiovascular						
0	92	9	7.83 (3.2-18.8)	**0.00**	4.2 (1.5-11.6)	**0.005**
1	30	23				
Infection						
0	95	19	2.41 (1.1-5.5)	**0.04**	1.67 (0.52-5.4)	0.387
1	27	13				
AKI						
0	121	27	22.4 (2.5-199.7)	**0.00**	24.7 (1.5-400.6)	**0.024**
1	1	5				
Gastrointestinal						
0	102	25	1.43 (0.5-3.75)	0.47	0.25 (.06-1.1)	0.068
1	20	7				
Dyselectrolytemia						
0	74	9	3.94 (1.68-9.24)	**0.00**	2.1 (0.66-6.53)	0.216
1	48	23				
Bleeding/coagulopathy						
0	92	11	5.85 (2.53-13.5)	**0.00**	3.13 (1.02-9.7)	**0.047**
1	30	21				
GCS <6						
0	79	10	4.04 (1.75-9.3)	**0.00**	4.2 (1.5-11.74)	**0.006**
1	43	22				

AKI: Acute kidney injury; GCS: Glasgow coma score; CI: Confidence interval

were significantly associated with an increased ICU stay, and their presence was an independent predictor of worsening neurological condition. The presence of hypotension, AKI, coagulopathy, and GCS <6 were the independent risk factors of increased ICU mortality in TBI patients. Early management of systemic complications in TBI patients may have an impact on outcome.

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Conflicts of interest

There are no conflicts of interest.

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