



# Prognostic Role of Catecholamine in Moderate-to-Severe Traumatic Brain Injury: A Prospective Observational Cohort Study

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## Abstract

**Objective** Traumatic brain injury leads to the activation of sympathetic nervous system and elevation in serum catecholamine levels. The aim of this study was to determine whether catecholamine level obtained within 24 hours of traumatic brain injury provides a reliable prognostic marker for outcome.

**Materials and Methods** This study was a prospective observational cohort study on 36 moderate-to-severe traumatic brain injury. Plasma epinephrine (E), norepinephrine (NE), and dopamine (DA) levels were measured by using computed tomography enzyme-linked immunosorbent assay test and compared with Glasgow coma scale (GCS) that was obtained concurrently. Neurological outcome was determined by GCS at day 7 of treatment and by Glasgow outcome scale at mean follow-up of  $9.73 \pm 2.26$  months.

**Results** Patients with GCS 3 to 4 had markedly increase in baseline mean E ( $771.5 \pm 126.0$ ), NE ( $2,225.0 \pm 215.4$ ), and DA ( $590.2 \pm 38.8$ ) levels as compared with control, while patients with better GCS (11–12) had mildly elevated levels. Patients with GCS 5 to 10 had intermediate values. Cases with markedly elevated baseline E, NE, and DA level were either died or remained in poor GCS (3 or 4) at day 7 of treatment and remained in persistent vegetative state at mean follow-up of  $9.73 \pm 2.26$  months. Cases with only mildly elevated E, NE, and DA level were improved to better GCS on treatment and had good recovery on follow-up.

**Conclusion** These data indicate that a markedly elevated catecholamine level was an excellent endogenous and readily quantifiable marker that appears to reflect the extent of brain injury and predict the likelihood of recovery.

## Keywords

- ▶ traumatic brain injury
- ▶ moderate-to-severe
- ▶ catecholamine
- ▶ Glasgow coma scale
- ▶ outcomes

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## Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide.<sup>1</sup> It results in major socioeconomic problems for patient, family, and society. Despite the relationship of many variables and outcomes, prognostications are difficult to make. Multivariate analysis had identified age, degree of coma, computed tomography (CT) finding, hypotension, hypoxia, and some laboratory studies as important factors for the prediction of outcomes in brain injury.<sup>2</sup>

TBI in particular leads to immediate and profound sympathetic nervous system activation with massive release of catecholamine.<sup>3</sup> While the adrenergic response is essential for survival, hypotension doubles mortality of patient with severe TBI.<sup>4</sup> Elevated catecholamine level after TBI leads to peripheral vasoconstriction that results in arterial hypertension and increase in cerebral blood flow and raised intracranial pressure.<sup>5</sup> It also increases oxygen demand by the heart and brain causing cardiovascular dysfunction and may lead to further brain damage. In addition, catecholamine's induces disturbance of cytokine release resulting in systemic organ damage.<sup>6</sup>

Some recent studies indicate that catecholamine levels are higher in patients with severe TBI, as determined by Glasgow coma scale (GCS) than in patients with moderate TBI.<sup>7</sup> However, the spectrum of catecholaminergic responses, their relationship to the extent of TBI and neurological impairment, and the prognostic value of these neurochemical indices as marker of TBI are still not clear. We conducted a prospective, observational, cohort study to evaluate the association between circulating catecholamine levels after moderate-to-severe TBI and their impact on neurological outcome.

## Materials and Methods

This study was a prospective observational cohort study, done at the Uttar Pradesh University of Medical Sciences (UPUMS), Saifai, Etawah, UP, India. It includes 36 cases of moderate-to-severe TBIs admitted to the neurosurgery department from period September 2020 to February 2021 and 36 volunteer as a control group.

### Ethical Consideration

Informed written consent was obtained from each participant of the patient at the time of their enrolment in the study. For those patients who were critically ill at the time of admission, their attendants were approached to provide the consent for study. Ethical clearance (number: 12/2020–21) was taken from the Institutional Ethics Committee of the university before the commencement of the study.

### Inclusion Criteria

Following TBI cases were included in our study:

- (1) GCS  $\leq$  12
- (2) No other associated chest/abdomen/pelvis/long bone or spinal injuries

- (3) No history of comorbidities like diabetes mellitus, hypertension, coagulopathies, and tumor pathologies
- (4) Reaching hospital within 24 hours of time since injury
- (5) Minimum 6 months of follow-up

### Exclusion Criteria

We excluded following cases from our study

- (1) Patients with mild TBI (GCS: 13–15)
- (2) Time since injury > 24 hours
- (3) Penetrating head injuries
- (4) Post arrest patients
- (5) TBI in pregnant women

### Control Group

Following informed consent, peripheral venous blood sample was also collected once from 36 healthy volunteers blood donor (mean age:  $36.6 \pm 9.3$ ), using a 21-gauge needle following a resting period of 30 minutes. Their catecholamine levels were used as the control. Control participants having previous history of TBI or comorbidities were excluded.

### Data Collection

Patients clinical, laboratory, and imaging data were collected at the time of hospital admission and throughout the hospital stay. It included baseline demographic trauma information, mode of injury, time since injury to hospital admission, time interval between injuries to first sample collection, GCS at the time of admission, Marshall CT classification, and Glasgow outcome scale at mean follow-up of  $9.73 \pm 2.26$  months (range: 6.0–13.5 months).

### Sample Collection and Preservation

Venous blood sample were drawn into 10 mL K2EDTA vacutainers as soon as possible after admission to the emergency room (baseline) and again after 72 hours. Blood samples were immediately centrifuged at 4°C, the plasma separated into aliquots and frozen at –70°C until analyses. The team caring for the patients was blinded to the results of all research assays and consequently the results were not available for treatment decisions.

### Determination of Plasma Catecholamine Concentration

Plasma epinephrine, norepinephrine (NE), and dopamine concentration were determined from duplicate samples using a direct competitive enzyme immunoassay method according to the manufacturer's instructions (CT enzyme-linked immunosorbent assay, DLD Diagnostika, GMBH, Hamburg, Germany). Briefly, plasma epinephrine, NE, and dopamine were extracted by using a cis-diol-specific affinity gel and acylated to N-acyl epinephrine and N-acyl norepinephrine and N-acyl-dopamine and then converted enzymatically into N-acyl metanephrine, N-acyl-normetanephrine, and N-acyl-3-methoxytyramine, respectively. The antibody bound to the solid phase catecholamine was detected by an antirabbit immunoglobulin G/peroxidase conjugate using tetra methyl benzidine as a substrate. This colorimetric reaction was terminated by the addition of 0.25 MH<sub>2</sub>SO<sub>4</sub>

**Table 1** Baseline characteristics of the study participants

Sl. no.	Variables name	Cases N = 36 n (%)	Control N = 36 n (%)	Statistical interpretation p-Value
1.	Age groups Up to 19 years 20 to 59 years 60 and above Mean $\pm$ SD years	2 (5.6) 29 (80.6) 5 (13.8) 41.0 $\pm$ 15.8	0 (0.0) 36 (100.0) 0 (0.0) 36.6 $\pm$ 9.3	$\chi^2 = 7.74^a$ $p = 0.021^c$
2.	Gender Male Female	25 (69.4) 11 (30.6)	25 (69.4) 11 (30.6)	$\chi^2 = 0.0^a$ $p = 1.0$
3.	Systolic blood pressure Mean $\pm$ SD (mm Hg)	126.1 $\pm$ 13.6	118.9 $\pm$ 11.6	$t = 2.41^b$ $p < 0.019^c$
4.	Diastolic blood pressure Mean $\pm$ SD (mm Hg)	73.2 $\pm$ 8.9	79.9 $\pm$ 18.4	$t = -1.95^b$ $p < 0.055$
5.	Pulse rate (beats/minute) Mean $\pm$ SD	81.9 $\pm$ 14.4	76.3 $\pm$ 7.6	$t = 2.06^b$ $p < 0.043^c$

Abbreviation: SD, standard deviation.

<sup>a</sup>Chi-squared test.

<sup>b</sup>Student's unpaired *t*-test.

<sup>c</sup>Statistically significant.

and the absorbance measured at 450 nanometers (nm) and 630 nm using a multidetection micro plate reader. Quantification of unknown samples was achieved by comparing their absorbance with a reference curve prepared with known standard concentration included in the kit. Detected antibody was inversely proportional to the catecholamine concentration of the sample.

### Outcome Measurements

The primary outcome was the association between circulating catecholamine levels measured at the time of hospital admission with mortality and functional outcomes assessed by GCS at day 7 of treatment and by Glasgow outcome scale at 6 months of follow-up.

### Statistical Analyses

The data thus collected was first entered on MS Excel spreadsheet and subsequently after being scrutinized for correctness, it was transferred and analyzed using statistical package for social sciences (SPSS) software, version 25 (IBM Corp., Chicago, Illinois, United States). Statistical significance was assessed using chi-squared test for qualitative parameters and unpaired student's *t*-test and analysis of variance test for comparing mean values of quantitative parameters of patients in the various groups and *p*-value less than 0.05 at 95% confidence interval was considered statistically significant. Bar and line diagrams were used to graphically represent the observations of the study.

### Results

Out of 576 TBI cases treated at our hospital, 36 cases follow our inclusion criteria and were enrolled in the study. The mean age of the cases and control were 41.0  $\pm$  15.8 and 36.6  $\pm$  9.3 years, respectively. Male-to-female ratio was

2.27:1 in both cases control. Age wise distribution of cases and control is given in **Table 1**. Other baseline characteristics were similar in both cases and control (**Table 1**).

Road traffic accident was the most common ( $n = 21$ , 58.3%) mode of injury. Majority of the cases ( $n = 19$ , 52.8%) were of severe TBI and admitted to the hospital within 6 to 12 hours of injury. Diffuse axonal injury ( $n = 17$ , 47.2%) constituted most common type of intracranial injury (**Table 2**).

Type V lesions were the most common type of lesion on Marshall CT classification. About 63.9% cases were managed conservatively and 36.1% by surgery. Out of 36 cases, 5 (13.9%) cases died, and 7 (19.4%) cases improved to mild GCS (13–15) after 7 days of treatment. Majority of the cases ( $n = 17$ , 47.2%) had good recovery at mean follow-up of 9.7361  $\pm$  2.2693 months (**Table 3**).

The baseline mean epinephrine level was approximately 5 times, NE 6 times, and DA 8 times higher in cases as compared with the control. Among catecholamine, baseline NE had the highest elevation as compared with epinephrine and dopamine. (**Table 4**) On repeat sample after 72 hours, there was significant reduction in the level of catecholamine ( $p < 0.001$ ; **Table 5**).

Critical GCS cases had approximately 2 times higher elevation of epinephrine and 3 times higher elevation of NE and dopamine as compared with moderate GCS cases. There were statistically significant differences ( $p < 0.001$ ) in catecholamine levels between critical, severe, and moderate GCS cases (**Table 6**).

TBI cases with poor GCS (3 or 4) had higher catecholamine levels and they gradually become lower in cases with higher GCS (**Fig. 1**). On repeat sample, catecholamine levels reduce significantly even in poor GCS patients ( $p < 0.001$ ; **Fig. 1**).

On day 7 of treatment, cases with higher level of baseline catecholamine either died or remained in critical GCS, while

**Table 2** Clinical profile of the cases (n = 36)

Sl. no.	Variables	n (%)
1.	Mode of injury	
	Road traffic accident	21 (58.3)
	Assault	10 (27.8)
	Fall from height	5 (13.9)
	Others	0 (0.0)
2.	Time gap since injury and admission	
	≤ 6 hours	7 (19.4)
	6 to 12 hours	19 (52.8)
	12 to 24 hours	10 (27.8)
	Mean ± SD	2.08 ± 0.69
3.	GCS at admission	
	Moderate (9–12)	6 (16.7)
	Severe (5–8)	19 (52.8)
	Critical (3–4)	11 (30.5)
4.	Type of intracranial injuries	
	Diffuse axonal injury	17 (47.2)
	Acute subdural hematoma	5 (13.9)
	Contusion	7 (19.4)
	Extradural hematoma	2 (5.6)
	Mixed lesion	5 (13.9)

Abbreviations: GCS, Glasgow coma scale; SD, standard deviation.

cases having lower level of catecholamine were improved in better GCS (→Fig. 2).

At mean follow-up of  $9.73 \pm 2.26$  months, patients with higher level of catecholamine either died or remained in persistent vegetative state, while patients with lower values of catecholamine had good recovery (→Fig. 3).

## Discussion

Autonomic nervous system (ANS) activation is a well-known phenomenon after traumatic or nontraumatic causes.<sup>8–10</sup> Twenty-five to thirty percent of patients of severe TBI exhibit periodic tachypnea (> 30/m), tachycardia (> 120/m), hypertension (systolic blood pressure > 160 mm Hg), and rise in

**Table 3** Management and outcomes

1.	Marshall CT classification of TBI	
	Type I	3 (8.33)
	Type II	5 (13.9)
	Type III	9 (25.0)
	Type IV	6 (16.7)
	Type V	10 (27.8)
	Type VI	3 (8.33)
2.	Type of management	
	Conservative	23 (63.9)
	Operative	13 (36.1)
3.	GCS/Outcome at day 7 of treatment	
	Death	5(13.9)
	GCS 3–4	4(11.1)
	GCS 5–8	7(19.4)
	GCS 9–12	13(36.1)
	GCS 13–15	7(19.4)
4.	Glasgow outcome scale at mean follow-up of $9.73 \pm 2.26$ months	
	Death	5 (13.9)
	Persistent vegetative state	3 (8.3)
	Severe disability	4 (11.1)
	Moderate disability	7 (19.4)
	Good recovery	17 (47.2)

Abbreviations: CT, computed tomography; GCS, Glasgow coma scale; TBI, traumatic brain injury.

the temperature (> 39°C).<sup>9</sup> It also results in increase in cardiac output, pulmonary shunting, and oxygen delivery that are essential for survival.<sup>11</sup> Therefore, while ANS activation is essential adoptive response after TBI, when excessive or prolonged, that hyperadrenergic state may have a negative impact on outcome. Factors influencing the patient outcome in severe TBI are age, depth, and duration of coma, GCS, papillary response to light, eye movements, abnormalities on CT, and evoked potential.<sup>12–14</sup> The responsiveness of the sympathetic nervous system is an important biochemical

**Table 4** Comparison of baseline catecholamine levels in cases and controls

Sl. no.	Variables name	Cases (mean ± SD)	Controls (mean ± SD)	Statistical interpretation <sup>a</sup> p-Value
1.	Epinephrine	521.1 ± 177.3	106.4 ± 29.5	t = 13.84 p < 0.001 <sup>b</sup>
2.	Norepinephrine (NE)	1,294.9 ± 558.6	192.5 ± 36.2	t = 11.82 p < 0.001 <sup>b</sup>
3.	Dopamine	345.0 ± 155.1	42.3 ± 8.3	t = 11.7 p < 0.001 <sup>b</sup>

Abbreviation: SD, standard deviation.

<sup>a</sup>Unpaired t-test.

<sup>b</sup>Statistically significant at 5% level of significance.

**Table 5** Comparison of baseline (at the time of admission) and repeat (after 72 hours of treatment) catecholamine

Sl. no.	Variables	At the time of admission (mean ± SD)	After 72 hours of treatment (mean ± SD)	Statistical interpretation <sup>a</sup> p-Value	Correlation coefficient (r)
1.	Epinephrine	521.1 ± 177.3	138.6 ± 53.8	t = 15.27 p < 0.001 <sup>b</sup>	0.615
2.	Norepinephrine	1,294.9 ± 558.6	494.3 ± 130.7	t = 10.16 p < 0.001 <sup>b</sup>	0.722
3.	Dopamine	345.0 ± 155.1	76.36 ± 32.59	t = 11.54 p < 0.001 <sup>b</sup>	0.554

Abbreviation: SD, standard deviation.

<sup>a</sup>Paired t-test.

<sup>b</sup>Statistically significant at 5% level of significance.

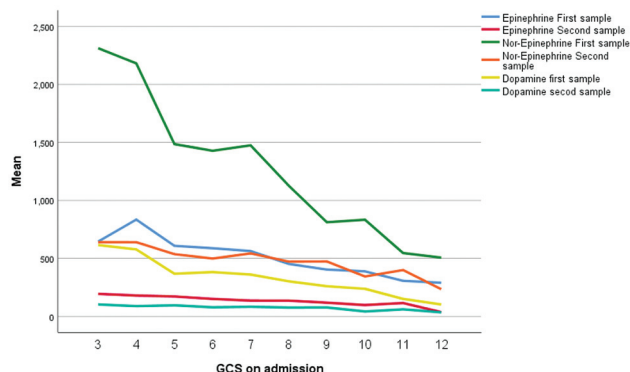
**Table 6** Comparison of baseline (at admission) mean catecholamine levels according to GCS score

Catecholamine	GCS score		
	Critical (3–4)	Severe (5–8)	Moderate (9–12)
Number of cases	11	19	6
Epinephrine <sup>a</sup>	771.5 ± 126.0	533.7 ± 133.9	362.8 ± 65.5
Norepinephrine <sup>a</sup>	2,225.0 ± 215.4	1,335.4 ± 243.1	717.6 ± 271.2
Dopamine <sup>a</sup>	590.2 ± 38.8	345.7 ± 112.7	210.0 ± 66.6

Abbreviations: ANOVA, analysis of variance; GCS, Glasgow coma scale.

ANOVA test applied to compare means between groups.

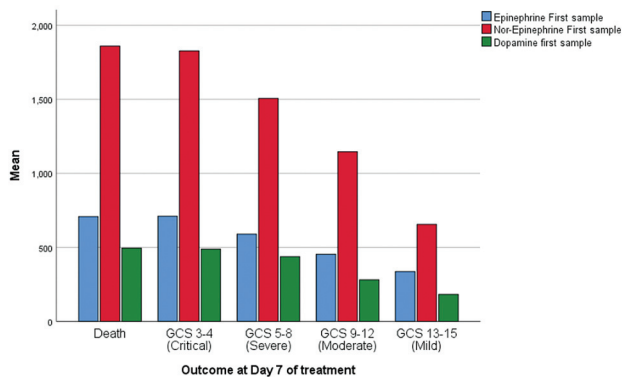
<sup>a</sup>Groups were statistically different with p < 0.001.



**Fig. 1** Polynomial line diagram showing changes in baseline mean catecholamine levels during the hospitalization with respect to Glasgow coma scale (GCS) at admission.

variable that may be used in predicting eventual recovery from severe TBI.

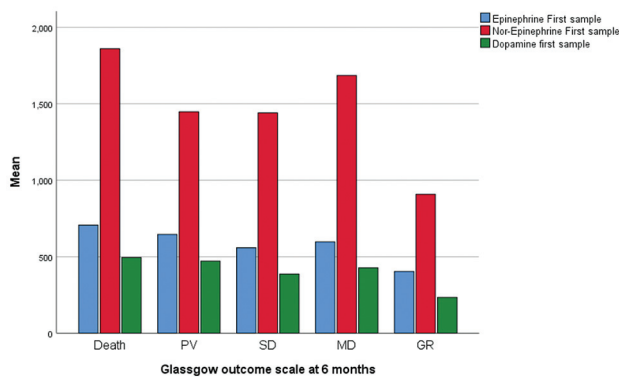
Some previous studies have already recognized the association between high catecholamine levels and severity of TBI.<sup>3,15,16</sup> Clifton et al<sup>15</sup> in his study stated that in patients with isolated TBI, baseline NE levels are proportional to the severity of the brain injury, measured by GCS on admission. They reported that patients with poor GCS (3–4) score have 7 times higher NE values and patients with better GCS (11–12) score have values closer to the normal range. Study done by Hamill et al<sup>17</sup> reported that patients with GCS 3 or 4 on admission have 4 to 5 times elevated epinephrine and NE



**Fig. 2** Correlation of baseline catecholamine level with outcome at day 7 of treatment. GCS, Glasgow coma scale.

value above normal level, while patients with GCS more than 11 have only slightly elevated catecholamine levels. Our results support and expand the concept that circulating catecholamine levels were proportional to the severity of the TBI. In our cohort, patients with poor GCS (3–4) had 6.7 times elevation of baseline NE, 5 times epinephrine, and 8 times dopamine level as compared with control, and patients with better GCS (11–12) had only slightly elevated epinephrine value. Disproportionally higher value of dopamine in our study may be due to variation in the timing since injury and sample collection.

In the present study, baseline catecholamine level correlates with GCS on admission. As we had taken patients with



**Fig. 3** Correlation of baseline catecholamine level with Glasgow outcome scale at mean follow-up of  $9.73 \pm 2.26$  months. GR, good recovery; MD, moderate disability; PV, persistent vegetative state; SD, severe disability.

TBI only with no systemic injury, so the extent and character of brain injury were the etiological factor in the neurohumoral response. Woolf et al<sup>16</sup> analyzed the catecholamine response to multisystem trauma and reported that catecholamine levels were significantly correlated with severity of injury only if the injury involves the brain.

In this study, baseline catecholamine levels also correlated with outcomes at day 7 of injury. Patients with higher level of epinephrine, NE and dopamine were either died or remained in poor GCS (3 or 4). Thus, plasma level of catecholamine helps to predict clinical outcome and may represent a useful prognostic marker in patient with severe TBI. Woolf et al<sup>3</sup> had reported that patient with high level of NE (> 900 pg/mL) remained in poor clinical status or die, while patients with NE level less than 900 pg/mL improved within 1 week.

In our cohort, all three catecholamines correlated with comparable elevation in poor GCS (3 or 4) patients and outcomes at day 7 and at mean follow-up of  $9.73 \pm 2.26$  months. Rosner et al<sup>10</sup> in his experimental study showed that level of epinephrine, NE, and dopamine is comparable in patients with normal or measured elevation of intracranial pressure. Jennett et al<sup>18</sup> and Woolf et al<sup>3</sup> further emphasize that the predictive power of NE is superior to that of GCS score, since the later only predicts outcome with 97% accuracy only in 60% of patients with acute brain injury.

In present study, there was decrease in catecholamine concentration in repeat sample after 72 hours of first sample. We found this temporal change had no relation to outcome, rather it was the absolute level of catecholamine at baseline (admission) that was associated with outcome. Rizoli et al<sup>19</sup> stated that there is no relationship between the changes in epinephrine level over time and mortality or unfavorable outcome.

Given the present findings, adrenergic blockade may, therefore, be a potential therapeutic intervention worthy of further exploration. The electrocardiographic changes and cardiac arrhythmias associated with head trauma were believed to be due to autonomic imbalance or over reactivity,<sup>20</sup> and both myocardial lesions and cardiac arrhythmias are prevented by  $\alpha$ - and  $\beta$ -adrenergic blockade.<sup>21</sup> A recent meta-analysis had

demonstrated that exposure to  $\beta$ -blockers after TBI was associated with a profound reduction in hospital mortality by 65% (pooled adjusted odd ratio: 0.35; 95% confidence interval: 0.27–0.45).<sup>22,23</sup> Despite these results, the benefit of the use of  $\beta$ -blockers in the acute phase of TBI remains unproven and in need of a more robust evaluation in a randomized control trial. At present, it is unclear whether the sympathetic responses reflect a specific type of brain lesion such as diffuse axonal injury that is associated with “autonomic storm” or whether certain critical diencephalic and/or brain stem lesions are present.

## Conclusion

TBI cases reaching to the hospital with in poor clinical status (GCS: 3 or 4) had markedly elevated serum catecholamine levels as compared with cases with in better clinical status (GCS: 11 or 12). Patients with GCS 5 to 10 had intermediate values. TBI cases with markedly elevated catecholamine levels either died or remained in poor clinical status (GCS: 3 or 4) at day 7 of treatment or remained in permanent vegetative state at mean follow-up of  $9.73 \pm 2.26$  months. Cases with slightly elevated catecholamine level had good recovery. Thus, level of circulating catecholamine was excellent endogenous and readily quantifiable marker that appears to reflect the extent of brain injury and that may predict the likelihood of recovery. Their measurement in severe TBI might provide a guide for determining which patients might benefit from therapy with adrenergic blockade.

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## Conflict of Interest

None declared.

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