Original Article

Acute Neuroendocrine Profile in Predicting Outcomes in Severe Traumatic Brain Injury: A Study from a Tertiary Care Center in South India

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Abstract

Background: Pituitary dysfunction following severe traumatic brain injury (sTBI) is significant and may be correlated with the outcomes. **Aims and Objectives:** This study aimed to evaluate the early changes in pituitary hormone levels after sTBI and to correlate with outcomes in terms of severity and mortality. **Methods:** This was a prospective, observational study, involving consecutive patients of 16–60 years, with sTBI (Glasgow Coma Scale GCS < 9) presenting to the hospital within 24 h of trauma. Demographic and clinical data were collected. Serum samples were collected in the morning (08–10 am) on day 1 and day 4 for cortisol, thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and prolactin (Chemiluminescence immunoassay). Outcome was assessed in terms of mortality (which included both immediate and at 3 months) and Glasgow outcome scale at 3 months. **Results:** 54 patients were studied. Mean cortisol on day 4 was 28.5 µg/dL in alive patients and 13.7 µg/dL in patients deceased at 3 months ($P < 0.001$). Patients who were deceased at 3 months had significantly lower T3 on day 4 (0.973 vs 1.4 ng/dL) and lower T4 (8.1 µg/L vs 6.1 µg/dL) as compared to patients who survived ($P = 0.049$ and 0.005, respectively). Acute phase TSH on day 4 levels were significantly lower in patients deceased at 3 months. There was no significant difference in the prolactin levels. **Conclusion:** Day 4 cortisol, T3, T4, and TSH correlated with the outcomes at 3 months and hence have predictive value post-sTBI.

Keywords: Hormonal profile, outcomes, predictors, traumatic brain injury

Introduction

Traumatic brain injury (TBI) has emerged as a major public health problem in the last two decades. Pituitary dysfunction following TBI is significant but rarely considered. In the last two decades, studies have reported around 30% incidence of acute post-TBI anterior pituitary dysfunction depending on the TBI severity and location.[1-3]

Possible mechanisms of hypothalamic-pituitary damage in TBI are direct mechanical/shearing injury to the pituitary stalk and the long hypophyseal vessels or vasospasm, leading to anterior lobe infarction or small infarctions due to a very localized cessation of the circulation.[4]

Although multiple hormonal changes have been observed in post-TBI patients, the most important in the acute phase are cortisol and thyroid hormonal insufficiency, which maybe secondary to insufficiency in the hypothalamus-pituitary-adrenal axis (HPA-axis) and hypothalamus-pituitary-thyroid axis (HPT-axis), respectively, due to the lesions affecting their secretion or part of the stress response.

Significant changes in thyroid hormones have been observed in critical illness.[5-8] The levels of serum cortisol and thyroid hormones were predictive of both severity and outcome in these situations.[9] Hyperprolactinemia was observed in the acute phase following TBI in more than 50% of patients and reflects the stalk injury or the hypothalamic damage.

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The main objectives of this prospective study were to investigate the prevalence and dynamics of very early pituitary-related hormonal dysfunction, and possible prognostic implications in patients with severe TBI (Glasgow coma scale, GCS <9) in Indian population.

Aims and Objectives

The aim of the study was to evaluate the early changes in pituitary hormone levels after severe traumatic brain injury (sTBI) and to ascertain if the hormonal changes were related to outcomes in terms of severity and mortality.

Materials and Methods

This was a prospective, observational study, involving consecutive patients of 16–60 years, with sTBI (GCS <9) presenting to the hospital within 24 h of trauma. The study was conducted between February 2019 to November 2020. The study was approved by the Institutional Ethics Committee (EC/NIMS/2389/2019 dated 21st August 2019).

Inclusion criteria

1. Age between 16 and 60 years.
2. Arrival in the department within 24 h of trauma.
3. Severe head injury with GCS at presentation is ≤8.

Exclusion criteria

1. Age <16 or >60 years.
2. Arrival in the department >24 h of trauma.
3. Mild and moderate head injury with GCS at presentation >8.
4. Penetrating head injury.
5. Medication with glucocorticoids/thyroid replacements/anti-thyroid drugs.
6. Pregnant or breastfeeding woman.
7. Chronic systemic illness like chronic kidney disease/chronic liver disease.

As the study subjects were patients with severe head injury and low GCS, consent was taken from first-degree relatives/care takers.

At the time of enrollment, the demographic data of the patients such as name, age, sex, occupation, address and details of trauma such as time, place, mode of injury, delay in presentation were documented. Presenting GCS, vital details, presence of other system injuries, Computed tomography (CT) findings were recorded.

CT findings were categorized into type of injury and bleed, that is, Epidural hematoma (EDH), Subdural hematoma (SDH), Contusion or Diffuse axonal injury (DAI).

Serum samples were collected in the morning (08–10 am) on day 1 and day 4 after sTBI for analysis of cortisol, thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and prolactin. We have used chemiluminescence immunoassay for estimation of hormones. Analysis was done using ADVIA Centaur XPT for thyroid hormones and Beckman DXI 600 for prolactin and cortisol. Hormone analysis was done on the same day of collection. The routine blood investigations like complete hemogram, serum creatinine and liver function tests were collected. The clinical course of the study patients in the hospital was recorded.

Outcome was assessed in terms of mortality (which included both immediate and at 3 months) and Glasgow outcome scale (GOS) at 3 months.

GOS 1 - Deaths

GOS 2 - Persistent vegetative state

GOS 3 - Severe disability which includes severe injury with permanent need for help with daily living

GOS 4 - Moderate disability meaning no need for assistance in everyday life, employment is possible but may require special equipment and finally

GOS 5 - Low disability meaning light damage with minor neurological and psychological deficits.

Statistical analysis

Hormonal values are described as mean ± standard deviation and when data was skewed with extreme deviation, median and range were used for analysis. IBM SPSS Statistics 26 was used for analysis of data. A two-tailed Student's *t*-test was applied for continuous data. Skewed data were transformed into logarithmic values and statistical tests were applied on the transformed data. Correlation analyses were made using Pearson test for continuous data and Spearman's rho test when at least one parameter was ordinal. Factors influencing outcome were explored using logistic regression. A value of $P \leq 0.05$ was considered statistically significant.

Results

A total of 54 cases of severe head injury were studied from February 2019 to September 2020, which included 50 males (93%) and 4 females (7%). The age group ranged from 18 to 60 years with mean of 38 years. Road traffic accidents constitute a major cause of head injury (87%) followed by falls (7%) and assaults (3.7%).

Majority of the patients (>90%) had their first institutional care between half an hour to 3 h of trauma and the mean time of presentation to our institute was 14 h after trauma. All the patients had loss of consciousness, vomiting was present in 46.3% of the patients, one-third of the patients had ear bleed, 30% had nasal bleeding and 17% had seizures. 24% of the patients presented with GCS of 3 to 5, 30% had presenting GCS between 6 to 7 and about 37% of them had GCS of 8.

CT brain without contrast was done in all patients and SDH was found to be the most common CT finding ($n = 16$). 17 patients had DAI. 10 patients had EDH.

Hormonal profile was obtained in 54 patients on Day 1 and 51 patients on Day 4 after trauma, because 3 subjects were deceased before obtaining second sample [Tables 1 and 2]. Outcome was assessed at 3 months. 33 patients were alive and 21 patients were deceased at the end of 3 months.

Serum cortisol

Overall, there was an increase in the mean cortisol from day 1 to day 4 but it was not statistically significant. There was a significant interindividual variation in level of cortisol on day 4 ranging from 0.7 to 62.6 μg/dL. Using the lower limit defined by the critical illness-related corticosteroid insufficiency (CIRCI) of total serum cortisol 10 μg/dL, day 1 cortisol was low in 15/54 (7 – Alive/8 - Deceased) (27.8%) patients and Day 4 cortisol was low in 7/51 (All Deceased) (13.7%). Of the 21 patients who were deceased at 3 months, 8 had decreased cortisol on day 1, and 7 had decreased cortisol on day 4.

Mean cortisol on day 1 was 19.7 μg/dL in alive patients and 18.2 μg/dL in deceased patients, and the difference was not statistically significant. On the other hand, mean cortisol on day 4 was 28.5 μg/dL in alive patients and 13.7 μg/dL in patients deceased at 3 months which was statistically significant ($P < 0.001$).

There was a decreasing trend in morning cortisol levels from day 1 to day 4 in subjects presenting with GCS of 3 to 5 and those who were deceased at 3 months as compared with those who presented with GCS >6 and those who survived at 3 months [Figures 1 and 2]. From day 1 to day 4 the mean decrease among deceased patients was 6.6 μg/dL and mean increase among patients alive at 3 months was 8.75 μg/dL [Table 3].

T3

Mean T3 levels increased from day 1 to day 4. Serum T3 was below reference range (1.1–3.1 ng/L) in 32/54 (21 – Alive/11 - Deceased) (59.2%) patients on day 1 and in 26/51 (15 – Alive/11 - Deceased) (50.98%) patients on day 4 [Table 4].

Patients who were deceased at 3 months had significantly lower T3 on day 4 (0.973 ± 0.62 ng/L) as compared to patients who survived (1.4 ± 0.89 ng/L) ($P = 0.049$ when equal variances were not assumed).

There was a significant positive correlation between T3 at day 4 and GOS at 3 months. Mean T3 showed a decreasing trend in patients with presenting GCS of 3 to 5 and an increasing trend in patients presenting with presenting GCS of 6 or more [Figure 3]. From day 1 to day 4 the mean decrease among deceased patients was 0.3 ng/L and mean increase among patients alive at 3 months was 0.34 ng/L [Figure 4].

T4

Mean serum T4 levels also showed increasing trend from day 1 to day 4.

The level of T4 was below the reference range (5.0-14.0 μg/L) in 8/54 (14.8%) (6 – Alive/2 - Deceased) of the patients on day 1 and in 9/51 (17.65%) (2 – Alive/7 - Deceased) on day 4.

There was statistically significant difference in T4 levels on day 4 between the deceased and alive patients and those who presented with low GCS [Figure 5]. Mean T4 on day 4 was 8.1 μg/L in those patients survived at 3 months, whereas it was 6.1 μg/L in deceased patients and these differences were statistically significant. ($P = 0.005$) [Table 5, Figure 6]

TSH

Mean serum TSH showed a nonsignificant increase from day 1 to day 4. However, TSH showed a greater variability on day 4 than on day 1. On day 1, 4/54 (2 – Alive/2 - Deceased) (7.4%) of the patients showed TSH below and none above

Table 1: Hormone profile on day 1 post TBI

	Day 1 T3 (ng/L)	Day 1 T4 (μg/L)	Day 1 TSH (mIU/L)	Day 1 Cortisol (μg/dL)	Day 1 Prolactin (ng/ml)
Mean	1.1381	6.9152	1.1061	19.1335	11.7093
Median	0.9350	6.9000	0.7950	17.4600	11.7650
Std. Deviation	0.72659	2.06897	0.93272	12.01431	4.78547
Minimum	0.34	2.10	0.10	0.70	4.80
Maximum	3.80	13.80	3.80	62.60	25.80

Table 2: Hormone profile on day 4 post TBI

	Day 4 T3 (ng/L)	Day 4 T4 (μg/L)	Day 4 TSH (mIU/L)	Day 4 Cortisol (μg/dL)	Day 4 Prolactin (ng/ml)
Mean	1.2512	7.4231	1.2982	23.2653	15.1067
Median	1.0100	7.8900	0.8710	19.7000	14.7000
Std. Deviation	0.82559	2.31063	1.31275	13.17125	5.79646
Minimum	0.30	1.40	0.12	0.50	4.27
Maximum	3.80	12.60	7.12	55.87	25.80

Table 3: Cortisol on day 1 and day 4 post TBI in patients alive vs deceased at 3 months

	D1 Cortisol of patients alive at 3 months (μg/dL)	D1 Cortisol of patients deceased at 3 months (μg/dL)	D4 Cortisol of patients alive at 3 months (μg/dL)	D4 Cortisol of patients deceased at 3 months (μg/dL)
Mean	19.7273	18.2005	28.4803	13.7044
Median	17.5600	17.0000	28.7000	12.4850
Std. Deviation	12.67882	11.12704	12.02433	9.40756
Minimum	0.70	0.70	11.30	0.50
Maximum	62.60	34.51	55.87	34.50
P value	0.643		< 0.001	

Table 4: T3 on day 1 and day 4 post TBI in patients alive vs deceased at 3 months

	D1 T3 of patients alive at 3 months (ng/dL)	D1 T3 of patients deceased at 3 months (ng/dL)	D4 T3 of patients alive at 3 months (ng/dL)	D4 T3 of patients deceased at 3 months (ng/dL)
Mean	1.0618	1.2581	1.4030	0.9728
Median	0.9000	0.9800	1.1000	0.8700
Std. Deviation	0.58854	0.90560	0.89096	0.61941
Minimum	0.34	0.38	0.31	0.30
Maximum	2.67	3.80	3.80	2.70
P value	0.381		0.049	

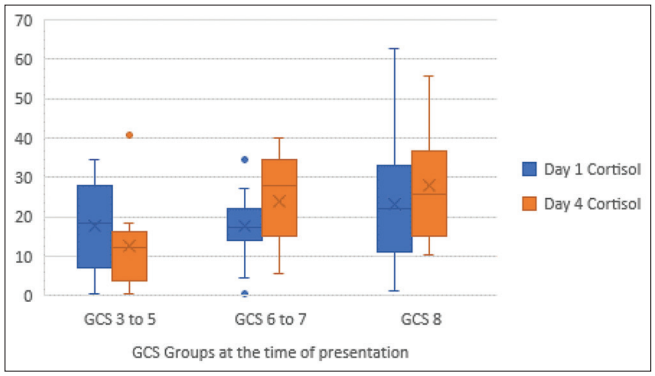

Figure 1: GCS at presentation vs serum cortisol

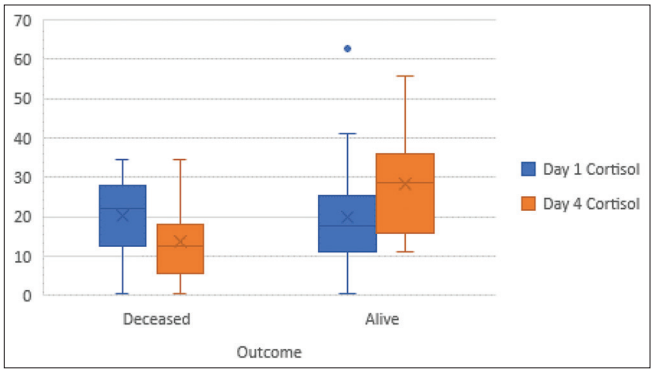

Figure 2: Outcome at 3 months vs serum cortisol

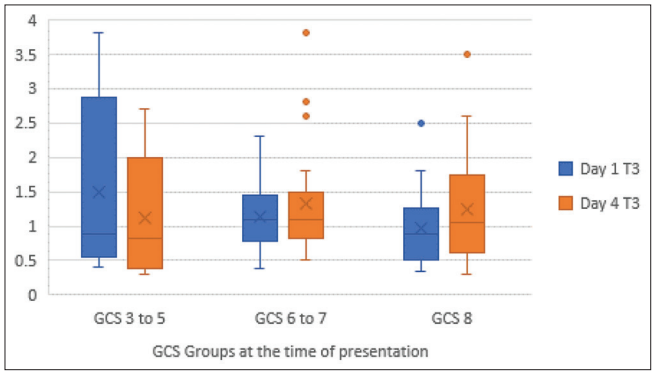

Figure 3: GCS at presentation vs serum T3

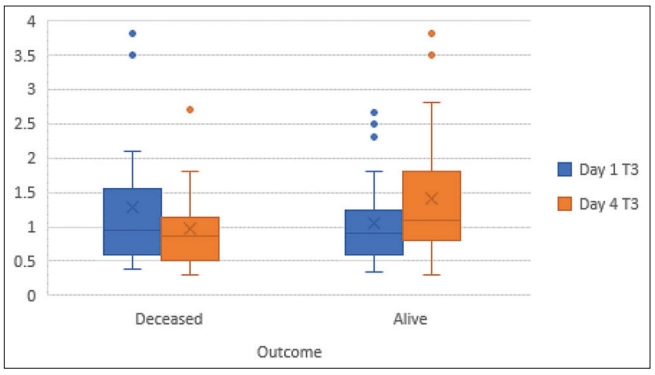

Figure 4: Outcome at 3 months vs serum T3

reference values (0.2-4.0 mIU/L), whereas TSH was low in 4/51 (1 – Alive/3 - Deceased) (7.84%) and high in 2/51 (Both Alive) (3.92%) at day 4.

Acute phase TSH on day 4 levels were significantly lower in patients deceased at 3 months after sTBI as compared to survivors, (0.816 ± 0.896 vs. 1.561 ± 1.437 mIU/L; $P < 0.02$ when equal variance was not assumed). The significant increase of TSH from day 1 to day 4 was only found in survivors ($P < 0.03$) whereas TSH in non-survivors showed a significant decrease [Table 6].

Prolactin

Mean serum prolactin was found to be within the normal range on both day 1 and day 4. There was no statistically significant difference in the prolactin levels between deceased/alive subjects and the levels were not correlated to GCS [Table 7].

Posterior pituitary hormones

In the study, although posterior pituitary hormones were not formally assessed, none of the patients had persistent deranged sodium levels along with clinical features suggestive of Diabetes insipidus or Syndrome of inappropriate antidiuretic hormone secretion.

Co-relation and prediction Analysis

Hormonal factors that were significantly correlated with outcome were T3, T4, and cortisol on Day 4. Moderate correlation was found for T3 (r = 0.38, P = 0.006), T4 (r = 0.333, P = 0.017) and strong correlation

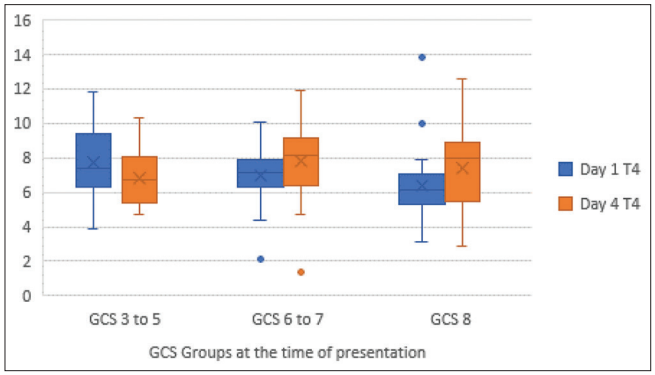

Figure 5: GCS at presentation V/s T4

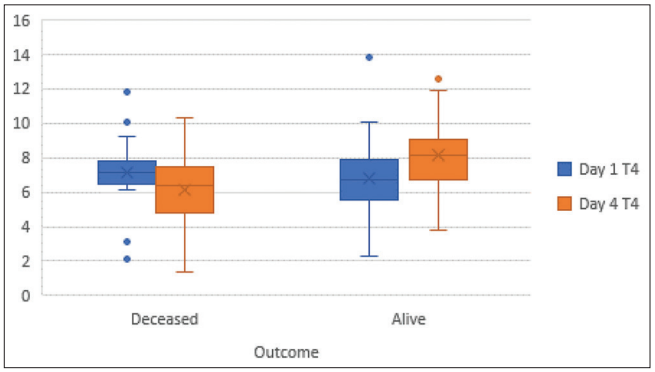

Figure 6: Outcome at 3 months V/s T4

Table 5: T4 on day 1 and day 4 post TBI in patients alive V/s deceased at 3 months

	D1 T4 of patients alive at 3 months (μg/L)	D1 T4 of patients deceased at 3 months (μg/L)	D4 T4 of patients alive at 3 months (μg/L)	D4 T4 of patients deceased at 3 months (μg/L)
Mean	6.7867	7.1171	8.1127	6.1589
Median	6.7500	7.1000	8.1000	6.3500
Std. Deviation	2.12628	2.00994	2.05132	2.27304
Minimum	2.30	2.10	3.78	1.40
Maximum	13.80	11.80	12.60	10.31
P	0.568		0.005	

Table 6: TSH on day 1 and day 4 post TBI in patients alive V/s deceased at 3 months

	D1 TSH of patients alive at 3 months (mIU/L)	D1 TSH of patients deceased at 3 months (mIU/L)	D4 TSH of patients alive at 3 months (mIU/L)	D4 TSH of patients deceased at 3 months (mIU/L)
Mean	1.0602	1.1782	1.5611	0.8161
Median	0.7900	0.8000	1.0210	0.4745
Std. Deviation	0.84848	1.06988	1.43674	0.89597
Minimum	0.10	0.14	0.12	0.12
Maximum	3.20	3.80	7.12	3.46
P value	0.672		0.027	

Table 7: Prolactin on day 1 and day 4 post TBI in patients alive V/s deceased at 3 months

	D1 Prolactin of patients alive at 3 months (ng/ml)	D1 Prolactin of patients deceased at 3 months (ng/ml)	D4 Prolactin of patients alive at 3 months (ng/ml)	D4 Prolactin of patients deceased at 3 months (ng/ml)
Mean	11.8867	11.4305	15.5527	14.2890
Median	11.8600	11.7000	14.1800	15.2850
Std. Deviation	4.84655	4.79278	5.26837	6.74391
Minimum	4.80	5.70	6.53	4.27
Maximum	24.15	25.80	25.80	24.50
P value	0.734		0.498	

was found for cortisol with co-relation coefficient 0.592 ($P < 0.001$) [Figure 7] [Table 8].

A rising trend of cortisol and thyroid hormones from day 1 to day 4 was associated with better outcome. Positive predictive value of rising trend was 92.3% for serum cortisol whereas it was 85.2%, 86.7%, 86.2% for T3, T4, TSH, respectively.

Table 8: Individual variation in various hormones on day 1 and day 4 post TBI in patients alive V/s deceased at 3 months

			Normal	Below normal	Above normal
Cortisol	Day 1	Alive	21	7	5
	(*n*=54)	Deceased	10	8	3
	Day 4	Alive	20	0	13
	(*n*=51)	Deceased	10	7	1
T3	Day 1	Alive	12	21	0
	(*n*=54)	Deceased	8	11	2
	Day 4	Alive	16	15	2
	(*n*=51)	Deceased	7	11	0
T4	Day 1	Alive	27	6	0
	(*n*=54)	Deceased	19	2	0
	Day 4	Alive	31	2	0
	(*n*=51)	Deceased	11	7	0
TSH	Day 1	Alive	31	2	0
	(*n*=54)	Deceased	19	2	0
	Day 4	Alive	30	1	2
	(*n*=51)	Deceased	15	3	0

There was no significant difference in CT findings between alive and deceased patients and no significant co-relation between CT findings and hormone levels.

Discussion

In this prospective study of patients with sTBI with follow-up of 3 months, we have described the alterations in the pituitary-adrenal and thyroid axes along with the prolactin levels in the acute phase and their importance in predicting outcomes. Our study has revealed the following important findings in the study population.

1. Mean cortisol on day 4 predicted outcome at 3 months. A decreasing trend in cortisol levels from day 1 to day 4 was observed in those with worse GCS at presentation and in those deceased at 3 months.
2. There was a significant positive correlation between T3 at day 4 and GOS at 3 months. Mean T3 showed a decreasing trend in patients with presenting GCS of 3 to 5 and an increasing trend in patients presenting with presenting GCS of 6 or more. An increasing trend in T3 from day 1 to day 4 was correlated with better outcomes at 3 months.
3. Similarly, a lower T4 on day 4 was seen in patients with lower GCS at presentation and a decreasing trend was associated with poorer outcomes.
4. A significant increase of TSH from day 1 to day 4 was associated with better survival at 3 months.
5. Serum prolactin on day 1 or day 4 did not predict survival or outcomes.

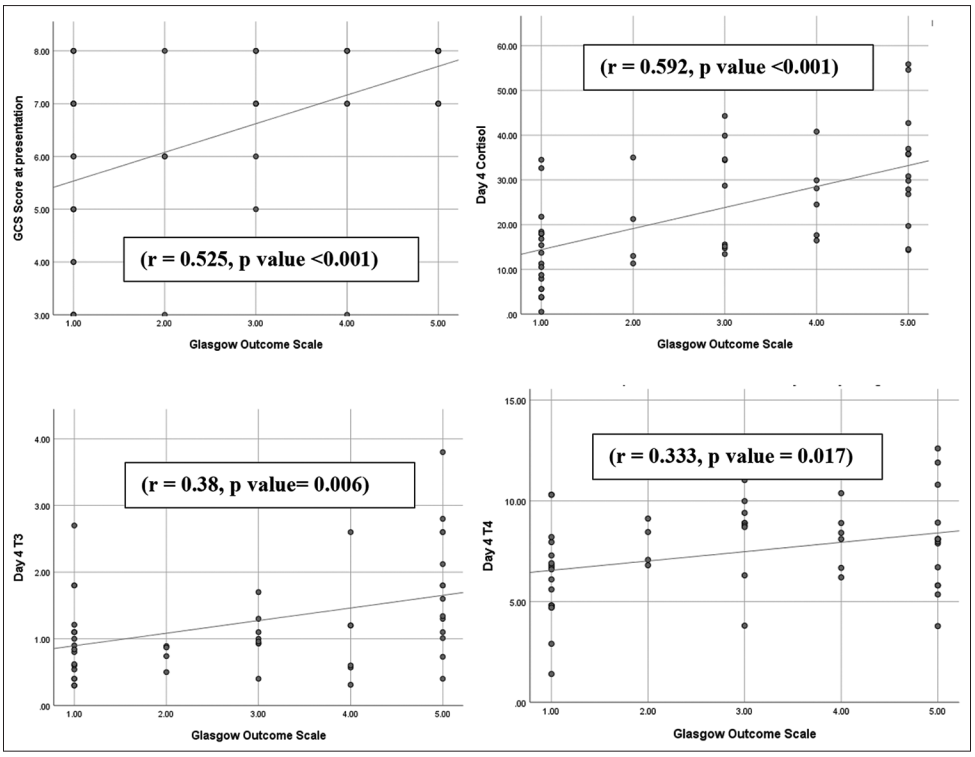

Figure 7: Corelation between various hormones and outcome

Although interpretation of serum hormones in the acute phase of TBI is complex owing to the acute changes in critical illness, we have tried to ascertain the importance of these changes in predicting outcome. Previous studies on this subject have shown that acute hypothalamo-pituitary injury may lead to single or multiple hormone deficits following TBI.[10]

There is activation of the HPA axis during acute illness which causes a rise in serum cortisol concentrations. This is an adaptive phenomenon, essential for survival as it changes the metabolism of macronutrients to increase the availability of energy and to maintain vital functions.[11] This rise in cortisol also causes retention of intravascular sodium and water. These responses may be impaired in TBI due to corticotropin-releasing hormone and adrenocorticotropic hormone deficiency and reduced adrenal cortisol synthesis and secretion. The latter may be due to the increased levels of cytokines which may also cause peripheral tissue resistance to corticosteroids.[12] The cutoff for this "functional/relative adrenal insufficiency" has been a subject of debate. Recent recommendations are to consider morning serum cortisol levels <10 μg/dL as highly suggestive of acute adrenal insufficiency.[13] Using these criteria, almost one-fourth of our patients had low cortisol on day 1. None of the patients had received glucocorticoids. In spite of this, we did not find any association between day 1 cortisol and the outcomes. Although, we did find that the day 4 cortisol predicted outcomes and there was a decreasing trend in those with poorer outcomes at 3 months. In contrast to our findings, the study by Olivecrona *et al*.[14] had shown higher serum cortisol in the acute phase in those deceased at 3 months compared with survivors. They had attributed these findings to the severity of the critical illness and correspondingly higher stress response. There have been inconsistent results with regards to the cortisol dynamics post-TBI and both high and low serum cortisol levels have been associated with poorer outcomes.[15] This inconsistency could be partially explained by the fact that some of these studies have measured both total and free cortisol whereas a few others including ours have looked at only the total cortisol. Nevertheless, the failure to mount an adequate stress response in terms of cortisol increase post-TBI could predict poor outcomes. Although specific cut-offs for serum cortisol are lacking in the acute setting of TBI for these reasons, our study highlights the importance of the dynamicity of cortisol in that a failure to increase the cortisol by 8.75 ± 3.04 μg/dL during the acute phase predicts poor outcomes.

With regards to the thyroid axis, the findings of our study are in line with most other studies that have shown a stronger suppression of the hypothalamic–thyroid axis to be correlated with poorer outcomes.[16,17] We observed that the T3 tends to decrease in patients presenting with lower GCS and there was an increasing trend from day 1 to day 4 in those with better outcomes at 3 months. The T4 followed similar patterns. A faster recovery from the axis suppression as reflected by an increasing TSH from day 1 to day 4 was associated with better survival at 3 months. In the study by Olivecrona *et al*.,[14] significantly lower free T4 on day 4 was seen in those with unfavorable outcomes and a significant increase of TSH from day 1 to day 4 was only found in survivors. In the setting of critical illness, it may be difficult to differentiate between sick euthyroid syndrome and central hypothyroidism.

It is still unclear whether this transient downregulation of the hypothalamo-pituitary-thyroid (HPT) axis in critical illness is an adaptive mechanism or whether it represents tissue hypothyroidism. Nevertheless, the findings from our study indicate that a prolonged suppression of the HPT axis portends worse prognosis.

The mean serum prolactin in our cohort of patients was found to be within normal range on both day 1 and day 4 but it had increased significantly from day 1 to day 4. These findings are in accordance with other studies which have reported a similar response in prolactin levels.[14,18] There was no statistically significant difference in the prolactin levels between deceased/alive subjects and the levels were not correlated to GCS. Hence, in our study, the prolactin was not a significant predictor of outcome.

Conclusion

In this prospective study of patients with severe TBI, we found that the day 4 cortisol, T3, T4, and TSH correlated with the outcomes at 3 months. Failure to mount an adequate stress response of cortisol on day 4 was shown to be the most significant factor for poor outcomes. Future research should focus on the therapeutic implications of these findings, if hormone supplementation in those not showing adequate response, could improve outcomes.

Limitations

1. This study did not assess growth hormone and gonadotrophins which were significantly affected in sTBI in other studies.
2. We have assessed only total cortisol in the morning, but it has diurnal variation and in stress there is less correlation between total, free, and tissue cortisol in view of altered cortisol binding globulin levels. Hence multiple samples and assessment of free cortisol would have added more light on this issue.
3. Though few patients were in acute cortisol deficiency, according to Brain Trauma Foundation guidelines[19] which is followed routinely in our institute no cortisol supplementation was given.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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