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Plasma cortisol as a noninvasive biomarker to assess severity and prognosis of patients with craniocerebral injury

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Abstract. – OBJECTIVE: The aim of this work is to evaluate the usefulness of plasma cortisol levels in determining the severity and prognosis in patients with a craniocerebral injury.

PATIENTS AND METHODS: About 90 patients with craniocerebral injury and 40 control subjects were selected prospectively for the study. The plasma cortisol level was measured on 1st, 3rd, 7th and 21st day after admission into the hospital. The patients with craniocerebral injury were divided into two groups according to the Glasgow Coma Scale (GCS 3-5 and GCS 6-8), and within each group sub-groups namely Death and Survival were made based on survival status of patients.

RESULTS: The plasma cortisol levels during the 1st and 3rd days were significantly increased in both GCS 3-5 and GCS 6-8 groups in comparison with control ($p < 0.01$); further, the GCS 3-5 group had higher plasma cortisol levels than GCS 6-8 ($p < 0.05$). The plasma cortisol level during the 1st and 3rd days in Death and Survival groups were significantly higher than the control ($p < 0.05$). Further, during the 7th day, plasma cortisol level was significantly elevated in the Death group than Survival group ($p < 0.05$).

CONCLUSIONS: Since we found a significant association between plasma cortisol level and severity (Glasgow Coma Scale) and prognosis in patients with craniocerebral injury, the plasma cortisol level can be used as a non-invasive biomarker to assess the severity and prognosis in craniocerebral injury patients.

Key Words:
Craniocerebral injury, Glasgow coma score, Cortisol, Brain injury.

Introduction

Head injury is a non-specific term indicating external injuries to the face, scalp, and calvarium. The craniocerebral injury is one of the main causes of death and disability with consequences ranging from physical disabilities to long-term cognitive, behavioural, psychological and social defects. There are two types craniocerebral injuries, closed and open. In closed craniocerebral injuries, the brain is not exposed to the external environment while in the open type the brain is exposed to the external environment, and this is a critical surgical condition as there is a co-existing fracture of the skull. Physical stress and trauma can provoke an increase in the level of plasma cortisol. Head injury patients have usually higher levels of plasma cortisol compared to normal individuals. Head trauma patients may present different patterns of hormonal response to trauma when compared to other trauma patients.

Cortisol is a glucocorticoid with several physiological and psychological functions, and is synthesized through the Hypothalamic-Pituitary-Adrenal cortex axis (HPA). Hypophysiotropic neurons produce and secrete corticotropin-releasing factor (CRF), the mean regulator of the HPA axis. In response to stress, CRF is released into hypophysial portal vessels that access the anterior pituitary gland. Glucocorticoids are the downstream effectors of the HPA axis and regulate physiological changes through universally distributed intracellular receptors. In healthy individuals, the concentration of plasma cortisol is high in the morning, decreases during the day, and rises again during the night. Major trauma provokes a neuroendocrine response characterized by stimulation of the hypothalamus and results in altered secretion of pituitary hormones and activation of the sympathoadrenal system.

We in this study evaluated the usefulness of plasma cortisol levels in determining the severity and prognosis in patients with a craniocerebral injuries and obtained excellent results.

Patients and Methods

Patients

A total of 90 patients admitted to ICU from January 2009 to June 2013 with craniocerebral

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injury were recruited for this study. Of the 90 patients, 55 were males and 35 were females and their age ranged from 17 to 80 years with an average of 41 years. By looking into the medical history and laboratory data, it was found that no patients had a record of heart attack, liver or kidney dysfunction or diabetes mellitus but three patients had a history of chronic obstructive pulmonary disease (COPD) in the past. The GCS score of patients was ≤ 8 points when they were admitted. Of the 90 patients admitted, 63 suffered injuries were due to road accidents, 25 were due to fall or tumble accidents and two were due to contusions. ed injury. CT scan was performed for all patients and through which the following it was diagnosed: that, 60 had cerebral contusion and laceration with intracranial hematoma, 35 had epidural hematoma, 41 had subdural hematoma, 10 had intracranial hematoma, 55 had sub-arachnoid hemorrhage, 45 had skull fracture, two had subdural effusion, eight had complicated pulmonary complication, 30 and 10 patients had limb and pelvic fractures respectively. Surgical treatment was provided under general anesthesia for 60 patients and non-surgical treatment was offered for 30 patients. Of the 90 patients, three died within seven days and 33 were died between 8th and 21st days of admission. About 40 healthy individuals with no specific disease during the study or in the past were selected to serve as controls. Of the 40 controls, 25 were males and 15 were females with an average age of 41 years.

Collection of Sample and Quantification of Plasma Cortisol

A volume of 5 mL of venous blood from patients was drawn aseptically into a vacutainer between 06:30 and 07:30 am on 1st, 3rd, 7th and 21st days and sent to central laboratory of our hospital to quantify plasma cortisol levels. Radioimmunoassay method was utilized to quantify the plasma cortisol level. The same amount of venous blood at the same time from control subjects was obtained to quantify plasma cortisol as described for patients.

Statistical Analysis

Statistical analysis was carried out using the statistical software SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Mean ± standard deviation was calculated for plasma cortisol in each group. A *t*-test was applied to compare groups with $p \leq 0.05$ as the criterion for statistical significance.

Results

The variables like age and gender of patients and control did not influence the plasma cortisol level ($p \geq 0.05$).

Relationship Between Plasma Cortisol and GCS Scale or Severity of Sickness

An elevated plasma cortisol level was observed in patients during the 1st and 3rd day when compared with control and this difference was highly significant ($p \leq 0.01$). When the plasma cortisol level between GCS (3-5) and GCS (6-8) groups was compared, GCS (3-5) group harbored higher plasma cortisol level ($p \leq 0.05$). However, the plasma cortisol levels in both GCS (3-5) and GCS (6-8) groups restored to normalcy during the 7th and 21st days after hospitalization though the results were statistically insignificant (Table I).

Relationship Between Plasma Cortisol and Patients' Prognosis

Since all the 36 patients in the Death subgroup were died before the 21 days of hospitalization, only plasma cortisol levels observed during the 1st, 3rd and 7th days were only compared

Table I. Plasma cortisol levels in patients and controls

	Death sub-group Plasma cortisol (µg/dL)	Survival sub-group Plasma cortisol (µg/dL)	Control Plasma cortisol (µg/dL)
1st day	40.2 ± 5.9*	34.5 ± 7.6	16.7 ± 4.2
3rd day	36.2 ± 7.9*	28.5 ± 6.6	16.7 ± 4.2
7th day	34.3 ± 7.3*	15.2 ± 5.9	16.7 ± 4.2

Compared with the control: *$p \leq 0.01$, ** $p \geq 0.05$.

with Survival sub-group. The levels of plasma cortisol in both Death and Survival sub-groups during the 1st and 3rd day were higher than the control group ($p \leq 0.05$). During the 7th day, plasma cortisol level of the Death sub-group was higher than the Survival sub-group ($p \leq 0.05$). However, plasma cortisol level in Survival sub-group returned to normalcy during the period (Table II).

We also found a decreased plasma cortisol level than control in patients with COPD.

Of the three COPD patients, two died during the study and one survived until the end of the study. The plasma cortisol level in the survived patient during the 7th and 21st day wereas 14.0 µg/dL and 13.1 µg/dL respectively. This patient had abdominal distension and other symptoms associated with COPD. However, cortisol hormone replacement therapy improved the condition of the patient.

Discussion

In this study, we observed elevated levels of plasma cortisol in patients with craniocerebral injury than in control subjects. When the plasma cortisol levels were compared between patients of GCS (3-5) and GCS (6-8) groups, the former had elevated levels than the later and controls. The plasma cortisol level in Death sub-group was higher in comparison with Survival sub-group. But, plasma cortisol level returned to normalcy after 7th day in Survival sub-group in contrast to Death sub-group patients where plasma cortisol level persisted to with higher concentrations.

Cortisol is an important glucocorticoids in humans and has a variety of physiological and psychological effects including raising and maintaining blood glucose levels, inhibition of inflammatory response and, suppression of body's immune response. Cortisol is synthesized through the Hypothalamic-Pituitary-Adrenal cortex axis (HPA) which is involved in physiological homeostasis and stress response. Briefly perception of stress initiates a signal in hypothalamus, as a result of which corticotrophin-releasing hormone (CRH) is released which then binds to specific receptors in the pituitary gland. This, in turn, stimulates the synthesis and release of adrenocorticotrophic hormone (ACTH) into the blood. Eventually, ACTH triggers the synthesis and release of cortisol from adrenal cortex.

In our study, we observed elevated cortisol levels in patients with craniocerebral injury than control subjects. There are several possible mechanisms behind this increased cortisol level in patients including (1) ACTH release increase due to the stress response to craniocerebral injury, and this ACTH which then binds to melanocortin receptor 2 on the plasma membrane of adrenal cortex, which ultimately resulting s in activation of enzymes required for the biosynthesis of cortisol[1]; (2) cytokines especially Interleukin-6 (IL-6) and Tumor Necrosis Factor α (TNFα) released due to stress in response to craniocerebral injury stimulate HPA axis through direct (adrenal cortex hormone production) and indirect effects leading to increased cortisol levels[2]; (3) stress in response to brain injury, results in release of catecholamines from the sympathetic nerve terminals which causes hypothalamic neurosecretory cells to release corticotrophin releasing hormone. This, then, stimulates anterior pituitary to release an adrenocorticotrophic hormone which ultimately induces adrenal cortex to secrete cortisol into the blood[3].

In this work, patients always showed high plasma cortisol levels during the 1st day irrespective of GCS scale; this might be due to the acute craniocerebral injury which caused severe stress and the severity decreased with time. However, patients had high cortisol level event after 7th day.

Table II. Plasma cortisol level in Death and Survival subgroups.

	Death sub-group Plasma cortisol (µg/dL)	Survival sub-group Plasma cortisol (µg/dL)	Control Plasma cortisol (µg/dL)
1st day	40.2 ± 5.9*	34.5 ± 7.6	16.7 ± 4.2
3rd day	36.2 ± 7.9*	28.5 ± 6.6	16.7 ± 4.2
7th day	34.3 ± 7.3*	15.2 ± 5.9	16.7 ± 4.2

Compared with the Survival sub-group: *$p \leq 0.05$.

A possible reason is that persisting higher cortisol level after crossing acute phase may be due to the intensity of the stress or emergence of new stress response later after the acute phase. Our findings are consistent with the results of Srinivas et al[4] and Cernak et al[5].

We believe, that the various mechanisms resulting in the increased levels of cortisol in the body of craniocerebral injury patients are related to the insufficient cerebral blood flow caused by increased intracranial pressure to combat brain injury through raising blood pressure.

We also observed persisting high cortisol levels even after 7th day or during recovery in Death sub-group patients, whereas in the Survival subgroup, higher cortisol levels in the acute stress phase came down to normal or equal to control during recovery phase period. The physiological responses that are adaptive to acute stress become damaging due to chronic stress. For instance, prolonged exposure to cortisol causes muscle wasting and bone thinning, suppresses immune system thereby inviting es infection and causes disease and continuous constriction of blood vessels causinges hypertension with retention of salt and fluid when no blood is lost[3]. Since the patients in Death sub-group experienced only a small decline inof cortisol levels during the recovery phase period from acute stress phase in comparison with Survival subgroup, cortisol level can be used to evaluate the prognosis.

The death of two patients with COPD and a far decreased cortisol level in one survived patient with COPD compared to control may be due to cortisol dysfunction which was manifested as abdominal distension in those patients. COPD is associated with endocrine function disorder in which decreased pituitary function impairs adrenal cortex function which ultimately produces very small quantities of cortisol[6]. The death of COPD patients with very low cortisol level may be due to the poor ability to tolerate stress in response to craniocerebral injury and furthermore mortality during recovery in such persons is significantly higher than the corresponding rate in normal individuals[7].

Conclusions

Taking into account the significant association between plasma cortisol levels and prognosis in patients with craniocerebral injury, the plasma cortisol level can be used as a non-invasive biomarker for severity assessment and prognosis.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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