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Research Article

A STUDY ON THE CORRELATION BETWEEN SERUM CORTISONE LEVELS AND STROKE SEVERITY

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ABSTRACT

BACKGROUND:

There are many clinical variables like symptom severity and advanced age which are identified as potential predictors of outcome in patients with acute stroke. But there is an immense need to detect a biomarker for predicting the outcome of acute stroke. The stress response that occurs after the event of acute stroke causes the activation of the hypothalamic–pituitary–adrenal (HPA) axis. Certain studies have found that increased serum cortisol level in patients with acute stroke is related to larger infarct volume, greater stroke severity, and poor outcome, including death. The primary objective of this study dissertation is to test the hypothesis that an increased single serum cortisol level is associated with increased severity of acute ischemic stroke. Though cortisol level has diurnal variations it has been shown that the normal circadian rhythm of cortisol is suspended during the acute stroke and there is no variation of cortisol level in serum throughout the day due to perturbations in the HPA axis.

AIM: The aim of the study was to investigate if a single Serum cortisol level determination could predict the outcome of stroke. Whether Serum cortisol as well as stroke severity is related to any clinical or paraclinical parameters of known relevance in acute stroke.

MATERIAL AND METHOD:

The study was a Cross-sectional descriptive study has been conducted in the Department of General Medicine. A total of 50 patients were included in the study. The patients were recruited from the department of General Medicine Hospital. Written informed consent was taken from all the patients. All patients included in the study who was admitted within 6 hours in the hospital after the episode of stroke. Vital signs such as blood pressure, pulse rate, and body temperature were continuously monitored. The Scandinavian Stroke Scale (SSS)xx was monitored in all patients from admission. SSS was performed every 2 hours in the first 24 hours, every 4 hours in the next 48 hours, and then daily up to day 7.

RESULTS:

the mean age observed in the current series was 62.8 ± 10.48 years. There were 38 (73.1%) males and 12(27.9%) females. SSS was observed to be 35 (21-47) on admission. History of hypertension, History of stroke, Diabetes mellitus, and Atrial fibrillation was observed in 34(59.4%), 10(18.8%), 24(37.5%), and 9(17.2%) respectively. 44% with stroke were smokers (20 patients), 32% were alcoholics (14 patients)10 patients were both alcoholics and smokers (22%) Out of 50 patients, 16 patients had Hemorrhagic stroke& 34 patients had an ischemic stroke. The mean cortisol level was

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about 16.40 mg/dl with an SD of 8.87mg/dl Mean cortisol value was significantly higher in patients with hemorrhagic stroke than in patients with ischemic stroke.

CONCLUSION:

High serum cortisol correlated with the severity of stroke as evidenced by an inverse relation with SSS. As serum cortisol level increases SSS score decreases. High serum cortisol is also correlated with systolic blood pressure, diastolic blood pressure, total count, and admission blood sugar level. The highest correlation coefficient was observed with random blood sugar level at admission and the lowest was for diastolic blood pressure. This shows that admission blood sugar level correlates well with serum cortisol and hence with stroke severity.

KEYWORDS: Acute ischemic stroke, HPA axis, serum cortisol, clinical severity, Functional outcome and stroke scales

INTRODUCTION:

A stress response consisting of increased levels of serum cortisol, serum ACTH and catecholamines in the first weeks after acute stroke has been known since the 1950s.The serum cortisol and serum ACTH response has been identified in both cerebral infarction and intracerebral hemorrhage. High s-cortisol levels and s-ACTH have been related to poor outcomes. It is, however, not known whether this adrenal glucocorticoid stress response is beneficial or harmful to the damaged brain.[1] Activation of the hypothalamic–pituitary–adrenal (HPA) axis in the context of acute, severe illness generally results in elevated cortisol levels. This has physiological benefits, including the mobilization of glucose from the liver and adipose tissue and the potentiation of cardiovascular output.[2,3] More severe illness stimulates correspondingly higher cortisol concentrations.[4,5] The HPA axis is entrained in the circadian cycle, and exhibits diurnal variation, with a characteristic peak of cortisol being produced in the early morning and a nadir occurring in the late afternoon. Some studies have found that greater severity of illness is associated with the loss of diurnal variation in cortisol.[6]

Stroke is a common neurological disorder causing death in developing as well as developed countries. A stroke is defined as an acute neurological injury occurring due to a vascular pathological process that manifests either as brain infarction or hemorrhage. Stress response after stroke can increase levels of cortisol and catecholamine.[7] This cortisol response to stroke is identified in both cerebral infarctions as well as ICH. High Serum cortisol levels have been related to the severity and adverse clinical and functional outcome of stroke. The cortisol response is related positively to blood glucose, WBC count, fibrinogen levels, and other markers of the inflammatory and immune response. Insular damage results in increased catecholamine levels. Normal circadian rhythm of cortisol secretion is lost. It is uncertain whether this stress response to stroke is just an epiphenomenon to stroke severity or it independently contributes to prognosis and functional outcome.[8] Cortisol, an important hormone in the hypothalamic–pituitary–adrenal axis, has important effects on the metabolism of glucose, protein, and lipid.[9] Change in serum level of this hormone has been reported in patients with ischemic stroke and some studies suggested high levels of this hormone are independently associated with an increase in ischemic lesion volume.[9] Also, some studies indicated that cortisol level in patients with ischemic stroke is associated with a significantly increased mortality rate.[10,11,12] Some studies reported a Correlation between cortisol levels and post-stroke physical and psychological disability.[13,14] Some studies have demonstrated that this association was not limited to ischemic stroke and there is a relation between cortisol level, morbidity, and mortality rates in patients with subarachnoid and intracerebral hemorrhage.[15,16] A stress response consists of increased levels of cortisol and catecholamines in the 1st weeks after acute stroke.[17,18] Activation of the hypothalamic-pituitary-adrenal (HPA) axis in acute, severe

illness results in elevated cortisol levels. This causes the mobilization of glucose from the liver and adipose tissue and the potentiation of cardiovascular output.[19] Also, severe illness correspondingly stimulates higher cortisol concentrations.[20] Authors have observed that there is an association between greater severity of illness with the loss of diurnal variation in cortisol.[21] It is observed that aging is associated with the dysregulation of the HPA axis. [1] The primary objective of this study dissertation is to test the hypothesis that an increased single serum cortisol level is associated with increased severity of acute ischemic stroke. Though cortisol level has diurnal variations it has been shown that the normal circadian rhythm of cortisol is suspended during the acute stroke and there is no variation of cortisol level in serum throughout the day due to perturbations in the HPA axis. So this study was designed to study the correlation of serum cortisol on stroke severity.

MATERIAL AND METHODS

The study was a Cross-sectional descriptive study has been conducted in the Department of General Medicine. A total of 50 patients were included in the study. The patients were recruited from the department of General Medicine Hospital. Written informed consent was taken from all the patients. All patients included in the study who was admitted within 6 hours in the hospital after the episode of stroke. Vital signs such as blood pressure, pulse rate, and body temperature were continuously monitored. The Scandinavian Stroke Scale (SSS)xx was monitored in all patients from admission. SSS was performed every 2 hours in the first 24 hours, every 4 hours in the next 48 hours, and then daily up to day 7.

Inclusion Criteria

- Patients with a history of Acute Stroke presenting within 24 hours will be taken as study subjects.
- 50 patients were admitted with acute stroke within 24 hours of onset. Patients recruited from medical wards and IMCU.

Exclusion criteria:

- Age< 18 years
- Pregnancy
- Liver disease
- Patients who are taking the following drugs: Immuno-suppressant, Steroids, Rifampicin, and Phenytoin.
- H/o malignancy
- Hemorrhagic stroke
- Acute febrile illness
- Major Surgery within 3 weeks

Diagnosis of ischemic stroke was based on CT-scan and MRI (DWI, T1, and T2) findings. A cardiologist visited all patients and the patients underwent transthoracic echocardiography and ECG monitoring for 24 hours. In the case of clinical suspicion, a trans-esophageal echo was done and cardioembolic stroke was excluded. Lacunar infarctions are also excluded. Patients with any underlying diseases other than diabetes and hypertension were excluded from the study. At follow-up of 3 months SSS, blood pressure and pulse rate were assessed. Cerebral infarction or intracerebral hemorrhage was diagnosed on the basis of clinical findings and CT-scan in all patients. Atrial fibrillation was diagnosed by 12-lead ECG on admission or by continuous ECG monitors. CT scan of each patient was performed and a follow-up CT scan at 7-8 days. Blood samples were obtained for routine investigation and estimation of serum cortisol. No patients had blood samples drawn for cortisol determination between 01:00 and 07:00 am. Blood samples were taken on the next day morning after admission and serum cortisol levels were measured. The serum cortisol is measured quantitatively using Enzyme Immuno-Assay.

In this study, those patients undergoing drug therapy or having a systolic blood pressure higher than 140 or diastolic higher than 90 mm/Hg were considered as having hypertension. Patients were also treated as diabetic who was under drug therapy or had fasting blood glucose greater than 126 mg/mL or random blood sugar over 200 mg/dL with the symptoms of diabetes. Those who inhaled five cigarettes per day were regarded as smokers.[22] Serum cortisol level was measured at 8 AM on the day after admission by radioimmunoassay method. Serum cortisol level higher than 25µg/dL was considered abnormal.[9] For every

patient, a questionnaire containing demographic information and NIHSS, (which is a criterion with a maximum score of 44 for evaluation of the clinical condition of patients with stroke) on admission was provided.

STATISTICAL ANALYSIS

Statistical analysis was performed by SPSS 21.0 for Windows. Normal distribution was assessed. Student's t-test was used in comparing means of independent, normally distributed, continuous variables. Stratifications were based on the median of the SSS score. Multivariate logistic regression was performed after assessing the normal distribution. A significance level of 0.05 was selected.

RESULT: -

Out of the 50 patients, 38 were male, and 12 were female. The mean age of presentation is 62 years

Table 1: Patients characteristics

N=50	value
Age (mean ± SD)	62.8 ± 10.48
Male (%)	38 (73.1%)
Female (%)	12(27.9%)
SSS (mean / range)	35 (21-47)
History of hypertension (%)	34(59.4%)
History of stroke (%)	10(18.8%)
Diabetes mellitus (%)	20(37.5%)
Atrial fibrillation (%)	9(17.2%)
Smokers	44%
Alcoholics	32%

As described in table 1, the mean age observed in the current series was 62.8 ± 10.48 years. There were 38 (73.1%) males and 12(27.9%) females. SSS was observed to be 35 (21-47) on admission. History of hypertension, History of stroke, Diabetes mellitus, and Atrial fibrillation was observed in 34(59.4%), 10(18.8%), 24(37.5%), and 9(17.2%) respectively. 44% with stroke were smokers (20 patients), 32% were alcoholics (14 patients)10 patients were both alcoholics and smokers (22%) Out of 50 patients, 16 patients had Hemorrhagic stroke& 34 patients had an ischemic stroke.

Table 2: Show the Mean Value of the Indicator of Patients

Indicators	Mean	SD
SBP	162mmHg	20.55
DBP	98mmHg	7.62
TC	10,205	3220
Blood Sugar	123	25
Serum cortisol	16.40	8.87

Middle cerebral artery territory Average SBP on admission was 162mmHg with SD of 20.55. All 50 had SBP > 130mmHg. The average DBP was 98mmHg with an SD of 7.62.TC revealed 10,205 cells on average with an SD of 3220 cells. Blood sugar revealed an average random blood sugar of 123 mg/dl. Serum cortisol measured ranged between 2.36-4.23 mg/dl. The mean cortisol level was about 16.40 mg/dl with an SD of 8.87mg/dl Mean cortisol value was significantly higher in patients with hemorrhagic stroke than in patients with ischemic stroke.

Table 3: Rankin Score of the stroke patients

Rankin score		Mean	SD
At discharge		3.98	0.714
At end of 3 months		2.40	1.16

Scandinavian stroke scale assessment, which is a measure of the severity of stroke ranged from 4 to 50 in our patients for a total of 60 at the of admission with a mean of 25.5 and SD of 10.05. Ranges from 3 to 6 out of a total of 6 with a mean of 3.98 and SD of 1.16 Correlation between serum cortisol and the Scandinavian stroke scale (SSS) score was found to be statistically significant with a p-value of <0.001. A similar significant correlation was found between serum cortisol and indices of functional outcome like Barthel index and Modified Rankin score at the end of 3 months, the functional outcome showed a high correlation with the admission day cortisol level.

DISCUSSION

Here we evaluated the relationship between admission-day Serum cortisol and stroke severity as determined by the Scandinavian stroke scale (SSS) score and our Study showed a statistically significant correlation between serum cortisol and stroke severity. **Christensen H, Boysen G, et all 2004**[23] showed serum cortisol reflects severity and mortality. Also showed that serum cortisol correlated well with SSS, and PR, and our study showed a significant correlation between serum cortisol and various parameters like SBP, DBP, and TC admission blood sugar. **Theodoropulou et al.2006**[24] conducted a study in Greece on 17 patients with cerebral infarction and found no correlation between mortality and serum cortisol level. In another study in Germany, **Fassbender et al.1994**[25] found no association between cortisol level and the severity of stroke in patients with ischemic stroke. Another study in America also showed no relationship between cortisol and the severity of aphasia.[26] A study done by **Marklund N et al2004**[12] showed high cortisol levels predict poor stroke outcomes. This study showed patients with severe functional impairment (n=38, grade 3-4) had higher cortisol levels on day 1 when compared with the patients with mild symptoms. Also, 28-day mortality was significantly predicted by high levels of serum cortisol on day 1. Hence it was very clear that acute ischemic stroke was very severe in patients with high serum cortisol levels at the time of admission and also the outcome of the patients after 15 days was poor in patients with high serum cortisol levels.

Despite numerous studies in this field, disagreements on the effect of cortisol on the prognosis of stroke remain strong so that a systematic review which was published in 2014 showed that elevated cortisol after stroke is associated with dependency, morbidity, and mortality but, there is insufficient evidence to conclude that these relationships are independent of stroke severity.[27] Whether the increase in cortisol level is merely a result of the infarct severity or an independent factor, is still controversial. Some studies show that an increase in cortisol directly worsens the ischemic damaged area, especially in the hippocampus. Also, an increase in cortisol is associated with ischemic heart disease events and reduced resistance to infections in patients with a stroke so these factors increase the mortality rate.[9, 28] Some other studies indicated a correlation between cortisol and inflammatory markers such as fibrinogen, and white blood cells and the possible effects of cortisol on prognosis is more originated from inflammatory responses than stress-induced responses.[9]

The study also investigated the relationship between cortisol and blood pressure and found a positive correlation.[29] Studies also reported the relationship between cortisol and length of stay, that a higher cortisol level was associated with a longer length of intensive care unit stay.[30] The etiology of increased cortisol levels in ischemic stroke is not obvious and some studies claim that ischemic stroke acts like a stressor and activates pituitary - adrenal axis.[9,29] This finding is also seen in intracerebral hemorrhage.[30] Our study has several limitations,

including a relatively short follow-up period and a small sample size. Obviously, if the follow-up period becomes longer in future studies, the results will be more valuable. Our next limitation was the single measurement of cortisol on the first day. Measuring the serial of cortisol levels may affect the results and should be considered in future studies

In humans, the adrenal stress response causes increased blood glucose, catabolism, and heart rate, and potentiates ischemic neuronal damage. In acute ischemic stroke, these effects could induce secondary brain damage. Hypothalamic-Pituitary- adrenal axis alterations are one of the major stress-induced alterations after the event of cerebral ischemia. Cortisol is an independent short-term marker of prognosis of functional outcome and death in patients with acute ischemic stroke even after the correction of confounding factors. Elevated cortisol after the onset of stroke is clearly associated with morbidity, dependency, and mortality. A combined model can however add significant information to the clinical score. Our study has several limitations, including a relatively short follow-up period and a small sample size. Obviously, if the follow-up period becomes longer in future studies, the results will be more valuable. Our next limitation was the single measurement of cortisol on the first day. Measuring the serial of cortisol levels may affect the results and should be considered in future studies.

CONCLUSION:

High serum cortisol correlated with the severity of stroke as evidenced by an inverse relation with SSS. As serum cortisol level increases SSS score decreases. High serum cortisol is also correlated with systolic blood pressure, diastolic blood pressure, total count, and admission blood sugar level. The highest correlation coefficient was observed with random blood sugar level at admission and the lowest was for diastolic blood pressure. This shows that admission blood sugar level correlates well with serum cortisol and hence with stroke severity. Serum cortisol is a prognostic marker to predict functional outcomes and mortality in patients with stroke. From these findings, we concluded that adrenal glucocorticoid stress response in acute stroke is harmful.

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