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Correlation of serum cortisol level with severity and short-term prognosis in acute ischemic stroke patients

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Abstract

Introduction and objectives: Stroke is the second leading cause of death and third most common cause of disability-adjusted life years in the world. There is an early and massive activation of Hypothalamo-Pituitary-Adrenal axis seen in acute phase of stroke. Cortisol levels remains increased for some period and affect the outcome. The main objective of our study was to ascertain level of serum cortisol in cases and control, and its correlation with severity in term of NIHSS (National Institute of Health Stroke Scale) score on admission and short-term outcome in context of Early Neurological Deterioration (END) in acute ischemic stroke patients.

Material and Methods: The case control study was carried out in 50 patients of acute ischemic stroke patients admitted in various wards and ICUs of Govt. medical college, Kota & associated group of hospitals and age sex matched 50 healthy controls. Serum cortisol level was measured on two occasions; first sample at 8AM after admission and second sample at 8AM after 72 hours of stroke. Other investigations namely blood sugar, total cholesterol, CT head/MRI brain were done in all patients. Data was analyzed and various observations made in proper statistical perspective.

Observations and results: On both occasions serum cortisol was found to be significantly high in cases (659.03±136.64 & 677.24±136.03) as compared to controls (480.32±94.18 & 492.86±94.09) irrespective of age and sex. Serum cortisol levels were found to be significantly higher (764.14±80.47 & 795.00±82.79) in the patients those presented with severe form of stroke as per NIHSS and developed END when compared with the patients (535.60±66.65 & 535.69±66.00) who presented with milder form of stroke as per NIHSS and didn't developed END.

Conclusion: Our study establishes the fact that high serum cortisol level correlates significantly with severity

and END in terms of NIHSS score in acute ischemic stroke patients.

Keywords: Acute ischemic stroke, serum cortisol, NIHSS (National Institute of Health Stroke Scale), Early Neurological Deterioration (END).

Introduction

A stroke or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause.[1] Cerebrovascular diseases include some of the most common and devastating disorders: ischemic stroke and hemorrhagic stroke. Stroke is the second leading cause of death worldwide, with 6.2 million dying from stroke in 2015, an increase of 830,000 since the year 2000.[1] Stroke is no longer a disease of the developed world, low- and middle-income countries account for 85.5% of total stroke deaths worldwide and the disability adjusted life years in these countries was approximately seven times that in high income countries. [2]

Rapid socioeconomic changes leading changes in people's lifestyle, work related stress, altered food habits and risk of developing hypertension, diabetes, dyslipidemia has resulted in increase in the incidence of stroke in India. A number of factors which increase the risk for ischemic stroke may be classified as modifiable and non-modifiable.[3] Non modifiable risk factors for stroke include older age, male gender, ethnicity, family history, and prior history of stroke. Modifiable risk factors include lack of physical activity, cigarette smoking (risk of stroke is two or three times greater than in non-smokers), alcohol abuse, arterial hypertension, diabetes mellitus (DM), dyslipidemia, heart disease (coronary artery disease, atrial fibrillation, dilated cardiomyopathy, valvular lesion), carotid artery disease, oral contraceptive use.

Stroke is a major disabling health problem in developing countries like India. It is a major cause of long-term disability among patients and has enormous emotional and socioeconomic consequences. In 20-40 percent of patients with acute ischemic stroke, neurological symptoms progress during the initial hours, resulting in increased mortality.[4] Early neurological deterioration (END) is defined as the clinical worsening or recurrence during the first 72 hours after ischemic stroke indicated by an increase of two or more points in the National Institute of Health Stroke scale (NIHSS) score or death not attributed to other cause, within the first three days.[5] It is a common complication, although incidence is variable across studies due to difference in the population and in the definition of END. The incidence ranges between 13-37% of all ischemic strokes.[5]

Several studies have focused on the search for predictors of END and with the result we have been able to acknowledge the influence of a number of variables such as the initial severity measured by NIHSS score, the stroke a etiology, metabolic factors such as hyper glycemia on admission, increased serum urea, markers of inflammation, excitotoxicity and oxidative stress, hemodynamic factors such as blood pressure at admission (both high and low), radiological data such as the extensive lesion (>1/3 area of MCA) and the presence of vascular occlusion in the neurovascular study.[6] There are many clinical variables like severity of symptoms 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 period that ensues after the event of acute stroke can be regarded as a reaction to a stressful event. This stress response causes the activation of the Hypothalamo–

pituitary–adrenal (HPA) axis[7] and sympathetic nervous system. In acute stroke, the first measurable alterations are the endocrine changes because of the alteration in HPA axis. One of the HPA axis related hormone is cortisol, which has a robust circadian rhythm, wherein the levels peak typically in the early hours of the day and decline later on. Although cortisol level has diurnal variations, it has been showed that the normal circadian rhythm of cortisol is suspended during acute stroke and there is no variation of cortisol level in serum throughout the day due to perturbations in the HPA axis. Cortisol has got a significant effect on the glucose, fat and protein metabolism and cardiovascular reactivity.

Various studies in past have shown that higher level of serum cortisol in patients of acute ischemic stroke at the time of admission correlates significantly with severity of stroke and subsequent sequelae. Hence measurement of serum cortisol level at the time of admission and subsequently during in hospital stay of such patients may be a cost effective and handy method of recognizing the severity of acute ischemic stroke and subsequent prognosis.

Objective

Main objective of our study was-(a) to compare the serum cortisol levels in acute ischemic stroke patients with normal healthy controls, (b) to correlate the serum cortisol levels with severity of stroke in terms of NIHSS score on admission and short-term prognosis in context of END in acute ischemic stroke patients.

Material and methods

The case control study was carried out in 50 patients of acute ischemic stroke patients admitted in various wards and ICUs of Govt. medical college, Kota & associated group of hospitals and age sex matched 50 healthy controls. We included the patients with acute ischemic stroke presenting within 48 hours and aged above 18 years after obtained written informed consent to participate in our study whereas patient with presentation to hospital more than 48 hours of symptoms, age below 18 years, evidence of haemorrhagic stroke or transient ischemic attack, pregnancy, liver disease, critical illness, consumption of immunosuppressants, steroids, rifampicin, phenytoin and unwillingness to participate in our study were excluded.

The diagnosis of acute stroke was made on the basis of temporal profile of clinical syndrome, clinical examination and CT scan / MRI of brain. A detailed history taking, clinical examination, and routine lab investigations were done to identify ischemic stroke risk factors (non-modifiable and modifiable). Severity of stroke was determined with the National Institute of Health Stroke Scale (NIHSS) score in all patients at the time of admission. Stroke severity was grouped in minor stroke (1-4), moderate stroke (5-15), moderate to severe stroke (16-20) and severe stroke (21-42). Short term prognosis after stroke is well assessed by the Early Neurological Deterioration (END). END is defined as the clinical worsening or recurrence or an increment of NIHSS score ≥2 points during the first 72 h after ischaemic stroke. Serum Cortisol levels were measured on two occasions, first at 8:00AM after admission and second at 8AM after 72 hours of stroke. Blood samples of patients and controls obtained and the serum cortisol was measured with a solid phase competitive chemiluminescent enzyme immuno assay (CLIA) method. Reference range for cotisol value depends on the time when blood sample drawn, we used 119-618 nmol /L for morning sample drawn at 8AM.

The data were compiled and analyzed using standard statistical methods and relevant conclusions were drawn

using a computer-based software SPSS version 16.0. Continuous data were expressed as mean ± standard deviation (SD) and were compared using student t test for normally distributed variables and Mann Whitney U test for non-parametric data. Categorical data were expressed as frequencies and percentages, and were compared using chi-square test and Fisher's Exact test, wherever applicable. Univariate and multi variable analyses were done by logistic regression to determine relation of serum cortisol to END and severity. Correlation between variables was ascertained using Pearson's correlation coefficient for normally distributed data and Spearman's coefficient for non-parametric data. A value of $p>0.05$ was considered as not significant and $p<0.05$ as statistically significant. The study protocol and consent forms were reviewed and approved by the ethics committee of Govt. Medical College and attached group of hospitals, KOTA. All participants had given written informed consent for the study and for subsequent medical research.

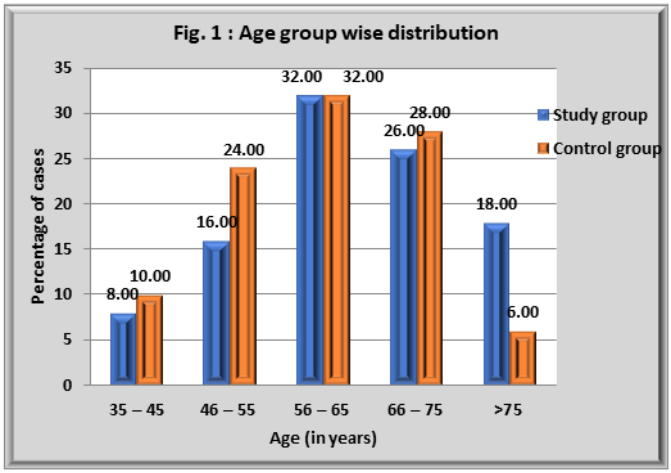
Observations and result

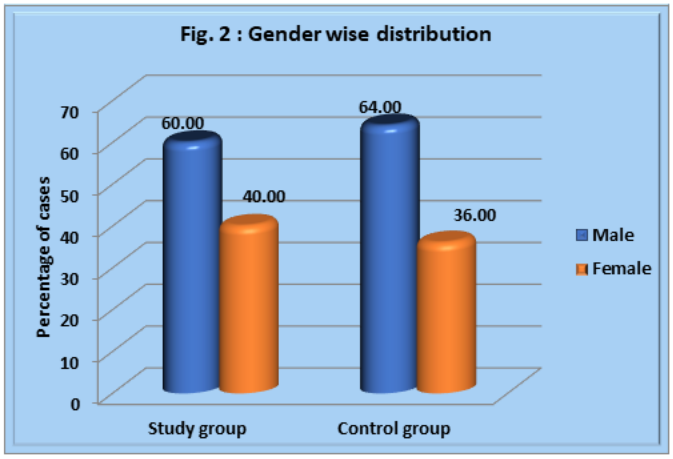
In our study, cases had mean age of 64.88±11.89 years which was comparable with the mean age of control group i.e., 61.68±11.02 years and both groups had maximum subjects in the range of 56-65 years i.e. 32% and 32% respectively. Males outnumbered females with a ratio of 1.5:1 in cases and 1.7:1 in control group. Table 1 and figure 1&2 depicts the age and gender wise distribution of subjects in case and control group.

In territory wise distribution of stroke, MCA territory infarctions were in 78% patients followed by PCA (20%) and ACA (02%) territory stroke. In our study, hypertension was the most common risk factor (60%) followed by smoking (42%), ischemic heart disease (34%), diabetes mellitus (34%). Distribution of acute ischemic stroke patients in different NIHSS score shows that maximum cases were present in NIHSS score group 5-15 (moderate stroke) both at the time of admission and after 72 hours of stroke. Mean NIHSS score in acute ischemic stroke patients at admission was 11.66±5.84 as compared to 12.88±6.91 after 72 hours of stroke.

Table 1: Age and sex distribution of cases in both groups

Age (in years)	Study group (n=50)		Percentage	Control group (n=50)		Percentage
	Male	Female		Male	Female	
36 – 45	02	02	8%	04	01	10%
46 – 55	04	04	16%	09	03	24%
56 – 65	10	06	32%	07	09	32%
66 – 75	09	04	26%	10	04	28%
>75	05	04	18%	02	01	6%
Total	30(60%)	20(40%)	100%	32(64%)	18(36%)	100%
Mean age	65.83±11.63	63.45±12.42		61.18±11.74	62.55±9.87	
	64.88±11.89			61.68±11.02		





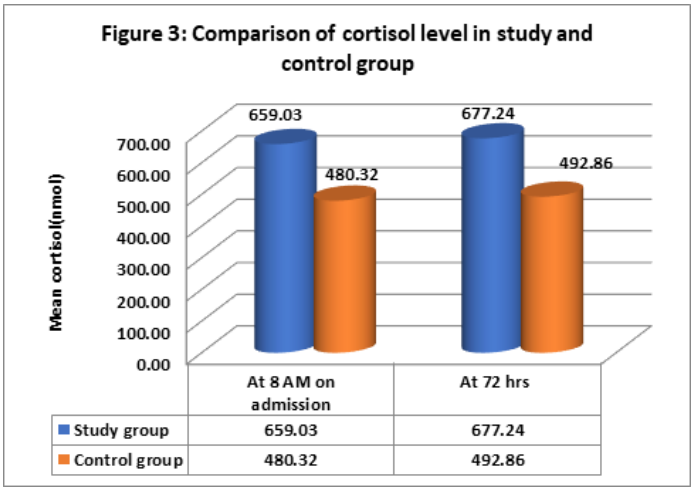
The serum cortisol levels were compared in study and control group, first time at 8AM after admission and second time at 8AM after 72 hours of stroke onset, on both occasion serum cortisol levels were higher in cases (659.03±136.64 & 677.24±136.03) as compared to control (480.32±94.18 & 492.86±94.09) which was statistically significant with p value<0.0001(table 2 & figure 3). The serum cortisol levels were found to be higher in males when compared to female counterpart in study and control groups (table 3)

Table 2: Comparison of cortisol level in study and control group

Cortisol	Study group (n=50)	Control group (n=50)	P value
First sample (after admission)	659.03±136.64	480.32±94.18	<0.0001
Second sample (after 72 hours)	677.24±136.03	492.86±94.09	<0.0001

Table 3: Gender wise difference in cortisol level at 8AM after admission in both groups

Sex	Number (50)	Study group	Number (50)	Control group
Male	30 (60.0%)	661.13±140.49	32 (64.0%)	482.62±92.75
Female	20 (40.0%)	655.85±134.18	18 (36.0%)	476.22±99.25

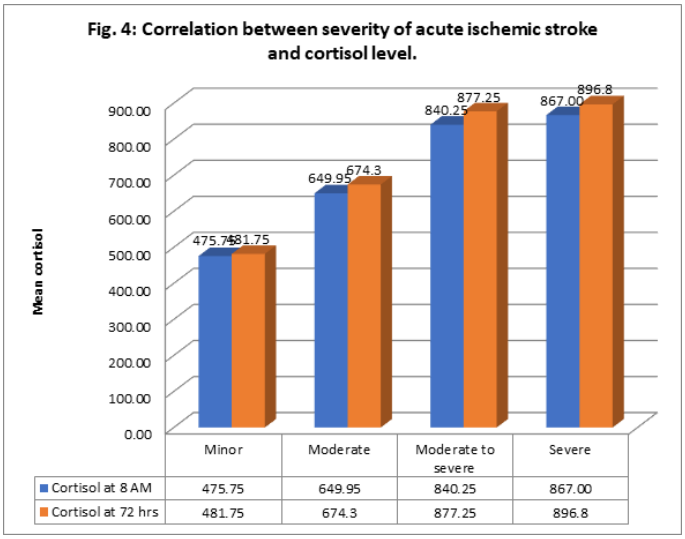


The serum cortisol levels were compared in different severity groups of acute ischemic stroke, the levels were minimum in minor group (475.75±58.88 & 481.75±62.31) and were maximum (867.00±75.49 & 896.8±76.57) in severe group of the acute ischemic stroke on both the occasions respectively. The serum cortisol levels were increased as severity of stroke progressed (table 4 & figure 4)

Table 4: Correlation between severity of acute ischemic stroke and cortisol level.

Severity	Total	First cortisol sample (after admission)	Second cortisol sample (after 72 hours)
Minor	08 (16.0%)	475.75±58.88	481.75±62.31

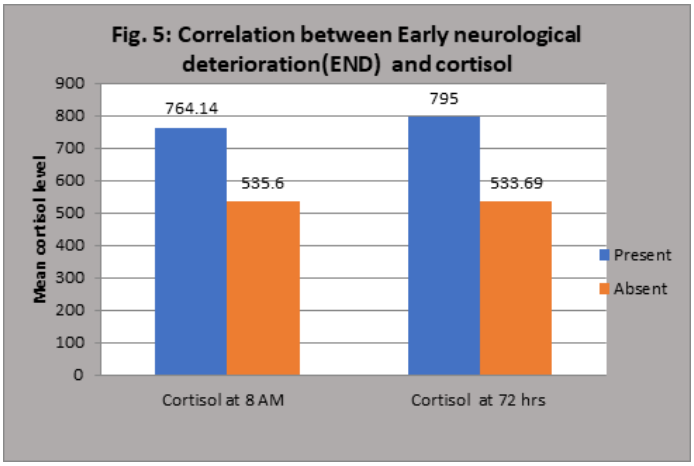
Moderate	33 (66.0%)	649.95±87.23	674.30±112.12
Moderate to severe	04 (8.0%)	840.25±41.62	877.25±32.32
Severe	05 (10.0%)	867.00±75.49	896.80±76.57
ANOVA p		<0.0001	<0.0001



The incidence of END was observed after the admission and the serum cortisol levels were compared in the patients who developed END with the patients who didn't developed END. Out of 50 cases 27 patients (54%) developed END with higher serum cortisol levels on both the occasions 764.14±80.47 & 795.00±82.79 respectively while 23 patients (46%) who didn't developed END had lower levels of the serum cortisol on both the occasions 535.60±66.65 & 533.69±66.00 respectively. The difference of the serum cortisol levels between these two groups was statistically significant with p value <0.0001.(table 5 & figure 5)

Table 5: Correlation between Early neurological deterioration (END) and cortisol level in study group

END	Total	First cortisol sample (after admission)	Second cortisol sample (after 72 hours)
Present	27 (54.0%)	764.14±80.47	795.00±82.79
Absent	23 (46.0%)	535.60±66.65	533.69±66.00
P value	50	<0.0001	<0.0001



Serum cortisol level was compared with classical risk factors of stroke in study and control groups. In study group we found high serum cortisol levels in hypertensives (725.63±116.31) as compared to normotensives (559.10±99.92) with p value<0.0001. Similar correlation also found in patients with IHD (738.35±133.69) compared to the patients didn't have IHD (618.15±120.77) with p value 0.002 while in control group no such correlation was found between serum cortisol level and these classical risk factors of stroke. (Table 6)

Table 6: Correlation of cortisol level with Hypertension and IHD in study and control groups

	Number (50)	Cortisol in study group	Number (50)	Cortisol in control group
HTN	Yes-30(60.0%)	725.63±116.31	Yes-14 (28.0%)	453.35±110.71
	No-20(40.0%)	559.10±99.92	No-36 (72.0%)	490.80±86.38
		p<0.0001		p-0.210
IHD	Yes-17(34.0%)	738.35±133.69	Yes-08(16%)	464.25±104.59
	No-33(66.0%)	618.15±120.77	No-42(84%)	483.38±93.12
		p-0.002		p-0.120

Similar comparison was done with other risk factors namely diabetes melitus, smoking, alcohol abuse but we didn't find any statistically significant correlation in our study.

Discussion

Cerebrovascular disease predominates in the old as well as young age groups. It is world-wide concern as it is causing morbidity, mortality and disability in developed and developing countries. Several studies have focused on the severity at the time of admission and search for predictors of Early Neurological Deterioration (END) in acute ischemic stroke patients.

In our study 50 acute ischemic stroke patients and 50 age sex matched healthy controls subjects were included. Levels of Serum cortisol were done at 8AM after admission and at 8AM after 72 hours of stroke and compared with age sex matched controls and correlated with NIHSS score to see the neurological outcome in stroke patients. Our study had male preponderance with male to female ratio of 1.5:1 which was similar to all other studies done by Kay Sin Tan et al[8] and R P Eapen et al[9] etc. The mean age of our study group was 64.88± 11.89 years with the maximum cases in the age range of 56 to 65 years. This is in accordance with various other studies done by Grau et al, [10] and Naik M, Rauniyar, Sharma U.K et al.[11] In our study hypertension was the most common risk factor detected in 60% of the patients followed by smoking (42%), ischemic heart disease (34%), diabetes mellitus (34%). This is similar to the recent studies by Grau et al, [10] Tallawy et al, Essa et al, El Sayed et al and Banerjee TK et al. [12]

Our study tried to evaluate the role of serum cortisol levels as an indicator of severity and poor prognosis in acute ischemic stroke patients on two different occasions. On both the occasions the serum cortisol levels were higher in study group (659.03±136.64 & 677.24±136.03) as compared to control group (480.32±94.18 & 492.86±94.09) which was statistically significant with p value<0.0001. Our study was concordant to other studies Szczudlik et al[13] which found mean serum cortisol level was significantly higher in acute ischemic stroke patients than in controls in each time point and Amanda Jayne Barugh et al, [14] conducted a systemic review in which Cortisol levels are high for at least 7 days after acute ischemic stroke and are within the normal range in the majority of people by 3 months.

Stroke cases were categorised into different severity groups on the basis of NIHSS score: Minor (1-4), Moderate (5-15), Moderate to severe (16-20), Severe stroke (21-42). The serum cortisol levels were measured on both occasions(after admission and after 72 hours of stroke), 16% cases had minor stroke with mean cortisol levels 475.75±58.88 & 481.75±62.31 respectively, 66% cases had moderate stroke with mean cortisol level 649.95±87.23 & 674.30±112.12 respectively, 8% cases had moderate to severe stroke with mean cortisol level 840.25±41.62 & 877.25±32.32 respectively, 10% cases had severe stroke with mean cortisol level 867.00±75.49

& 896.8±76.57 respectively. The minor group had serum cortisol levels within normal range while rest all groups had elevated levels and the cortisol levels further increased as severity of stroke progressed thus severity of stroke showed positive correlation with the serum cortisol levels. Our study showed similar results with other studies i.e. K.H Jnanendrappa et al[15] conducted a study among the 50 patients with acute ischemic stroke, high serum cortisol levels at the time of admission correlates with Clinical severity which is assessed by National Institute of Health Stroke Scale, Wen Jie Zi et al[16] conducted a study in which acute ischemic stroke Patients with a poor outcome and no survivors had significantly increased serum cortisol levels on admission (P<0.0001, P<0.0001). There was a positive correlation between levels of cortisol and the NIHSS (r=0.298, P<0.0001).

In our study short term prognosis of acute ischemic stroke was determined by END which was defined as the clinical worsening or recurrence or an increment of NIHSS score ≥2 points during the first 72 h after ischemic stroke. Out of 50 cases 27 patients developed END and 23 patients didn't. The serum cortisol levels were significantly higher in patients who developed END on both the occasions i.e. 764.14±80.47 after admission and 795.00±82.79 after 72 hours of stroke compare to patients who didn't developed END i.e. 535.60±66.65 and 533.69±66.00 respectively. The difference between these two groups were statistically significant with p value<0.0001. Our study was concordant to other study N Marklund et al[17] in which initial cortisol levels were significantly higher in the patients with acute disorientation versus orientated patients (P < 0.05) in acute ischemic stroke.

In our study serum cortisol level was compared with classical risk factors of stroke. In study group we found high serum cortisol levels in hypertensives (725.63±116.3) as compared to normotensives (559.10±99.92) with p value<0.0001. Similar correlation also found in patients with IHD (738.35±133.69) compared to the patients didn't have IHD (618.15±120.77) with p value 0.002.

Summary and conclusion

1. Overall serum cortisol was found to be significantly high in cases as compared to controls irrespective of age and sex on both occasion at 8AM after admission and at 8AM after 72 hours of stroke.
2. Overall serum cortisol levels were found to be significantly higher in the patients who presented with severe form of occlusive stroke as per NIHSS score at the time of admission.
3. Overall serum cortisol levels were found to be significantly higher in all cases of occlusive stroke who developed Early Neurological Deterioration (END).
4. State of hypertension showed statistically significant correlation with higher serum cortisol levels as compared to normotensives and such patients had significantly higher incidence of severity of stroke on day 1 and END. Similar correlation was seen with IHD patients having stroke as compared to non IHD patients. In our study no such correlation was seen with other classical risk factors of stroke namely diabetes mellitus, smoking, hypercholesterolemia.

Finally, this study establishes the fact that high serum cortisol level correlates significantly with severity of occlusive stroke and END in term of NIHSS score more so, when hypertension and IHD coexist. Hence recognition of higher levels of serum cortisol may

predict severity of occlusive stroke and END related to it.

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