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Original Research

To Evaluate Serum Cortisol Level In Patients With Acute Cerebrovascular Accidents

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Abstract
Aim: To evaluate serum cortisol level in patients with acute cerebrovascular accidents.
Material and Methods: The present prospective, observational study was conducted in The Department of Medicine, Government Medical College& Associated hospitals, Jammu for a period of one year, w. e. f November 2020 to October 2021. The study population included in the trial were the patients of cerebrovascular accident (CVA) who were of more than 18 years of age, of either sex, presenting to medicine emergency or outpatient department. A detail history regarding the clinical profile of stroke including risk factors like hypertension, diabetes mellitus, dyslipidemia, history of cardiac disease and smoking was recorded. Severity assessment was done by using National Institute of Health Sciences Scale (NIHSS) at the time of admission.
Results: There were 27 subjects with NIHSS score ≤6 and 73 subjects had NIHSS score >6. Modified Rankin Scale (MRS) among the study subjects was also recorded. MRS ≤3 was in 33% subjects and >3 in 67% subjects. In 27 subjects with NIHSS score ≤6, all had normal serum cortisol level. In 73 subjects with NIHSS score >6, 15 subjects had normal serum cortisol level and 58 patients had high serum cortisol level. Of the 67 subjects with Modified Rankin Scale (MRS) >3, only 10 subjects had normal cortisol level, and 57 subject had high cortisol level.
Conclusion: Among the patients with cerebrovascular accident (CVA), high serum cortisol levels at the time of admission correlates with, Clinical severity which is assessed by National Institute of Health Stroke Scale and poor prognosis and functional outcome after 15 days which is assessed by Modified Rankin Scale, and they had a statistically significant correlation.
Keywords: CVA, NIHSS, MRS, Cortisol

Introduction:

WHO defined stroke as rapidly developing clinical signs of focal disturbance of cerebral function, lasting more than 24hours or leading to death, with no apparent cause other than vascular origin (Sacco RL *et al*., 2013).[1] The cerebrovascular diseases occur predominantly in the middle and late years of life and theincidence of stroke increases with age. Thus the disability affects many people in their golden years. Among all neurological diseases of adult life, the cerebrovascular disease clearly ranks first in frequency and importance. The mortality and morbidity with stroke is still high (Sacco RL *et al*., 2013).[1] There are 15 million people worldwide who suffer from stroke each year (Patne SV *et al*., 2016).[2] According to the World Health Organization, for elderly individuals (age more than 60) it is the second most common cause of mortality and for individuals below 60 it is the fifth most common cause of death (Patne SV *et al*., 2016).[2] The three main types of stroke are:

- Ischemic stroke.
- Hemorrhagic stroke.
- Transient ischemic attack (a warning or "mini-stroke").

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 (Sorrells S *et al*., 2007)[3]. More severe illness stimulates correspondingly higher cortisol concentrations. The HPA axis is entrained on 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 (Reincke M *et al*., 1995)[4].

In conditions other than stroke there is some evidence that prolonged exposure to high cortisol levels is neurotoxic. For example, brain atrophy and cognitive impairments are often found in Cushing's disease (ACTH-secreting adenoma resulting in sustained high cortisol). Similarly, patients taking long-term oral corticosteroids (for a variety of chronic conditions) have been shown to have smaller hippocampal volumes compared with

controls (Brown E *et al*., 2004)[5]. Prolonged activation of the HPA axis has also been associated with adverse clinical consequences including delirium (van Munster B *et al*., 2010)[6], dementia and death (Kumari M *et al*., 2011)[7].

Change in serum level of this hormone have been reported in patients with ischemic stroke and some studies suggested high levels ofthis hormone is independently associated with increase in ischemic lesion volume (Zi WJ *et al*., 2013)[89]. Also, some studies indicated that cortisol level in patients with ischemic stroke is associated with significantly increased mortality rate (Neidert S *et al*., 2011)[9]. Some studies reported a Correlation between cortisol level and post stroke physical and psychological disability (Kwon OJ *et al*., 2015)[10]. Some studies have demonstrated that, this association was not limited to ischemic stroke and there is a relation between cortisol level, morbidity and mortality ratesin patients with subarachnoid and intracerebral hemorrhage (Yang X *et al*., 2014)[11]. Despite above-mentioned studies, in a number of researches, no association was found between cortisol level and mortality in ischemic stroke patients (Laures-Gore JS, 2012)[12].

According to these controversies and lack of a final, this study was performed to evaluate serum cortisol level in patients with acute cerebrovascular accidents.

Material and Methods: The present prospective, observational study was conducted in The Department of Medicine, Government Medical College& Associated hospitals, Jammu for a period of one year, W .E .f November 2020 to October 2021. The study population included in the trial were the patients of cerebrovascular accident (CVA) who were of more than 18 years of age, of either sex, presenting to medicine emergency or outpatient department. Prior approval from The Institutional Research Committee and The Ethical committee was taken before the commencement of the study.

Inclusion Criteria:

- Patients admitted with acute stroke/ CVA within 72 hours of onset.
- Age >18 years

Exclusion Criteria

- Age < 18 years
- Liver disease
- Pregnancy
- Recurrent stroke
- Patients taking any of the following drugs – phenytoin, steroids, rifampicin, ketoconazole
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Methodology:

The eligible subjects/attendants were well informed about the study, the risks and benefits associated with the study, confidentiality and their freedom to refuse to participate in the study. The eligible patients/ attendants who agreed to participate in the study were recruited. The written informed consent for clinical examination & lab investigations was obtained either from patient or attendant. A detail history regarding the clinical profile of stroke including risk factors like hypertension, diabetes mellitus, dyslipidemia, history of cardiac disease and smoking was recorded.

Study Tools

a. Severity assessment by using National Institute of Health Sciences Scale (NIHSS) at the time of admission.
b. Blood investigation included Complete blood count, Renal function tests, liver function tests, Serum electrolytes, Coagulogram, Blood sugar levels, Serum cortisol, Lipid profile. Serum Cortisol levels measured on the next day early morning, using venous blood sample.
c. Non contrast Computed tomography (CT) of Brain.
d. Electrocardiogram
e. Cortisol levels were compared with NIHSS score and levels more than 690 nmol/L is considered to be elevated and severity defined by NIHSS score (score>6)at the time of admission.

Statistical analysis:

Statistical analysis was performed by SPSS 24 for Windows. Mean values of the parameters are calculated by Independent sample t test. Correlation between serum cortisol levels and stroke scales are assessed by Chi Square Test. A p value of less than 0.05 is considered to be statistically significant.

Results:

In the present trial, of the total 100 subjects, majority was of male (n=61) and rest of the subjects were females (n=39). The male to female ratio was 1.56:1. Of the total 100 subjects with cerebrovascular accident (CVA) most of the patients were in 61-70 years age group (41%), followed by 51-60 years age group (27%), 14 subjects were in 41-50 years age group, 11 subjects were in >70 years age group, 5 subjects were in 31-50 years age group and only 2 subjects were in 18-30 years age group. (Table 1)

Hypertension was the most common risk factor (n=55, 55%), followed by smoking (31%), diabetes mellitus (24%), Hyperlipidemia (18%). And only 12 % of subject gave history of previous stroke.

Table 1: Gender, age distribution among the study subjects

Gender	**N**	**%**
Male	61	61
Female	39	39
Age Group (in years)		
18-30	2	2
31-40	5	5
41-50	14	14
51-60	27	27
61-70	41	41
>70	11	11
Total	100	100

In present study, 42 subjects had normal cortisol level (≤ 690nmol/L) and 58 patient's cortisol level was high than normal range (>690nmol/L). The Mean±SD cortisol level was 669.23±171.76. (Table 2)

Table 2: Distribution of subjects according to serum cortisol

Serum Cortisol (nmol/L)	**N**	**%**
Normal (≤ 690nmol/L)	42	42
High (>690nmol/L)	58	58
Mean±SD	669.23±171.76	

Intracerebral hemorrhage and subarachnoid haemorrhage was reported among 79% and 21% of the subjects respectively. There were 27 subjects with NIHSS score ≤6 and 73 subjects had NIHSS score >6. Modified Rankin Scale (MRS) among the study subjects was also recorded. MRS ≤3 was in 33% subjects and >3 in 67% subjects. 14 subjects had infarct in Anterior cerebral artery territory (ACA), 82 subjects had infarct in middle cerebral artery territory (MCA) and only 4 subjects had infarct in the posterior cerebral artery territory (PCA). (Table 3)

Table 3: Distribution of subjects based on blood pressure, type of haemorrhage, NIHSS and MRS and type of infarct

Blood Pressure	**N**	**%**
Systolic Blood Pressure		
<140mmhg	77	77
≥140mmhg	23	23
Diastolic Blood Pressure		
<90mmhg	71	71
≥90mmhg	29	29
Haemorrhage		
Intracerebral Hemorrhage	79	79
Subarachnoid Hemorrhage	21	21
NIHSS Score		
≤6	27	27
>6	73	73
MRS	**N**	**%**
≤3	33	33
>3	67	67
Infarct		
ACA	14	14
MCA	82	82
PCA	4	4
Total	100	100

In 27 subjects with NIHSS score ≤6, all had normal serum cortisol level. In 73 subjects with NIHSS score >6, 15 subjects had normal serum cortisol level and 58 patients had high serum cortisol level. The p value was statistically significant ($p<0.01$). (Table 4)

Table 4: NIHSS score at admission among the study subjects

NIHSS Score	N	Serum Cortisol (nmol/L)				Chi Square	p value
		Normal		High			
		N=42	%	N=58	%		
≤6	27	27	64.29	0	0	67.02	<0.01*
>6	73	15	35.71	58	100		

*: statistically significant

Among 33 subjects with Modified Rankin Scale (MRS) ≤3, 32 subjects had normal cortisol level, and only 1 subject had high cortisol level. Of the 67 subjects with Modified Rankin Scale (MRS) >3, only 10 subjects had normal cortisol level, and 57 subject had high cortisol level. The p value was statistically significant (p<0.01). (Table 5)

Table 5: Modified Rankin Scale (MRS) at admission among the study subjects

MRS	N	Serum Cortisol (nmol/L)				Chi Square	p value
		Normal		High			
		N=42	%	N=58	%		
≤3	33	32	76.19	1	1.75	63.11	<0.01*
>3	67	10	23.81	57	98.25		

*: statistically significant

Discussion:

The cortisol response related positively to blood glucose, a parameter that increases after severe stroke possibly resulting from the stress response **(Christensen H et al., 2002)[13].** Cortisol has got a significant effect on the glucose, fat and protein metabolism and cardiovascular reactivity. There are studies which showed that high serum cortisol level associated with very much decreased physical function and impaired level of consciousness. In the present trial, of the total 100 subjects, majority was of male (n=61) and rest of the subjects were females (n=39). The male to female ratio was 1.56:1. The result of present study was in accordance with result of **Periyasamy R *et al*[14], 2019** who included 50 subjects of which 39 (78%) were male and only 11 (22%)were female. But in study done by **Agarwal A *et al*[15], 2020** of the total 64 subjects males were 34 (53.1%) and females were 30(46.9%). In study done by Christensen H*et al*., 2004 males were 54%. In present study, minimum age of patient recruited was 28 years and maximum was 86 years. Of the total 100 subjects with cerebrovascular accident (CVA) most of the patients were in 61-70 years age group (41%), followed by 51-60 years age group (27%), 14 subjects were in 41-50 years age group, 11 subjects were in >70 years age group, 5 subjects were in 31-50 years age group and only 2 subjects were in 18-30 years age group. These findings were same as result of **K.H Jnanendrappa[16], 2019,** who found that the minimum age of the patients enrolled in study was 30 years and the maximum age was 88 years. Among the 50 patients, 38 % of the acute ischemic stroke occurred in the age group of 61 to 70 years. According to findings of **Periyasamy R *et al*[14], 2019** mean age of presentation is 62 years. Out of 100 patients, subjects with Systolic Blood Pressure <140mmhg were 77 and with ≥140mmhg were 23. Diastolic Blood Pressure <90mmhg was present in 71 subjects and ≥90mmhg was in 29 patients. According to findings of **K.H Jnanendrappa[16], 2019**, of the 50 cases 13 had systolic BP less than 140 mm Hg , 37 had systolic BP more than or equal to 140mmHg.ie., 26 percent had normal systolic blood pressure and 74 percent had elevated systolic blood pressure. Also, 35 had diastolic BP less than 90 mmHg and 15 had diastolic BP more than or equal to 90 mmHg ie. 70 per cent had normal diastolic BP and 30 percent had elevated diastolic BP. In study done by **Periyasamy R *et al*[14], 2019,** Average SBP on admission was 162mmHg with SD of 21.75. Average DBP was 98mmHg with SD of 8.73.There were 27 subjects with NIHSS score ≤6. And 73 subjects had NIHSS score >6. In 27 subjects with NIHSS score ≤6, all had normal serum cortisol level. In 73 subjects with NIHSS score >6, 15 subjects had normal serum cortisol level and 58 patients had high serum cortisol level. The p value was statistically significant (p<0.01). As the NIHSS score of less than or equal to 6 is considered to be a minor stroke, it is obvious from the above findings that 27 subjects with normal cortisol level had minor stroke. According to findings of **K.H Jnanendrappa[16], 2019,** of the 50 cases, serum cortisol level of 23 cases were within normal limits (</=690nmol/L) of which 65.2% had NIHSS score of less than or equal to 6 and 34.8% of the cases had NIHSS score more than 6. According to study of **Zi WJ et al[8], 2013**, there was a positive correlation between the NIHSS and serum cortisol levels (P<0.0001).MRS ≤3 was in 33% subjects and >3 in 67% subjects. Among 33 subjects with Modified Rankin Scale (MRS) ≤3, 32 subjects had normal cortisol level, and only 1 subject had high cortisol level. Of the 67 subjects with Modified Rankin Scale (MRS) >3, only 10 subjects had normal cortisol level, and 57 subject had high cortisol level. The p value was statistically significant (p<0.01). Since MRS score is a measure of functional outcome and any score less than or equal to 3 is considered to have a favourable outcome, it is clear from the above findings that 32 cases with normal serum cortisol had a favourable outcome with minimal neurological impairment. Since MRS score more than 3 is

associated with bad outcome, most of the cases with elevated serum cortisol had a poor outcome with severe neurological impairment. According to findings of **K.H Jnanendrappa[16], 2019**, of the 50 cases, serum cortisol levels of 23 cases were within normal limits (/=690nmol/L) of which 78.3% had MRS score less than or equal to 3 and 21.7% had MRS score more than 3. And in the remaining 27 cases which had serum cortisol level more than 690 nmol/L, 3.7% had MRS score of less than or equal to 3 and 96.3% had MRS score of more than 3. With the p value of <0.001, this is statistically significant.14 (14%) subjects had infarct in Anterior cerebral artery territory (ACA), 82 subjects (82%) had infarct in middle cerebral artery territory (MCA) and only 4 subjects (4%) had infarct in the posterior cerebral artery territory (PCA). According to findings of **K.H Jnanendrappa[16], 2019,** 12 percent had ACA territory infarct, 84 percent had MCA territory infarct, 4 percent had PCA territory infarct. It is clear that majority of the cases had MCA territory infarct.

Limitations: There were some limitations of the present study. First, without serial measurement of the circulating cortisol levels, this study yielded no data regarding when and how long cortisol is elevated in these patients. Second, the effects of circulating cortisol on long-term clinical outcome were not included in the study protocol, so these relationships were not examined. Third, this was only a preliminary study; these results need to be replicated in more prospective studies with larger sample size to determine whether or not they are stable and valid.

Conclusion:

Among the patients with cerebrovascular accident (CVA), high serum cortisol levels at the time of admission correlates with, Clinical severity which is assessed by National Institute of Health Stroke Scale and poor prognosis and functional outcome after 15 days which is assessed by Modified Rankin Scale, and they had a statistically significant correlation. High serum cortisol also correlated with systolic blood pressure, diastolic blood pressure, and admission blood sugar level, but it was not statistically significant. In humans, the adrenal stress response causes increased blood glucose, catabolism, heart rate and potentiates ischemic neuronal damage. In cerebrovascular accident (CVA) these effects could induce secondary brain damage. Hypothalamo-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 CVA 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.

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