

## Original Research Article

# Clinical evaluation of association between high sensitivity C-reactive protein and stroke

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**Received:** 03 August 2016

**Accepted:** 08 August 2016

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### ABSTRACT

**Background:** Stroke is a leading cause of morbidity and long term disability all over the world. In this scenario, the present hospital based study was undertaken to study the elevation of hsCRP level in cases of ischemic and hemorrhagic, as an inflammatory marker and to assess the association of hsCRP with stroke and its common risk factors like hypertension, diabetes mellitus and dyslipidemia.

**Methods:** The study was conducted for a period of one year from 2011 to 2012 in 50 cases of stroke from the OPD, emergency and indoor wards of the hospital. 50 controls were also taken for valid comparison. The plasma hsCRP level of all patients was measured using the immunoturbidimetric method. The statistical analysis was done by SPSS v12.0 and EPI-info version 6.0. The baseline comparability was assessed using Pearson's chi-square/t-test and the comparison between the groups was done by ANOVA.

**Results:** In the present study out of 50 stroke patients, 35 were of ischemic stroke and 15 were of hemorrhagic stroke. There was a significant ( $p < 0.05$ ) elevation in both the cases of stroke and the mean hsCRP level was found to be  $8.32 \pm 6.60$  mg/dl. Further, there was no significant association was found between level of hsCRP in stroke case and hypertension, dyslipidemia, diabetes respectively. Furthermore, the poor GCS score was  $< 8$  in both the cases of stroke with the high level of hsCRP and the hsCRP level was elevated in non survivors as that of the survivors in both the stroke cases.

**Conclusions:** Thus, from the study the hs-CRP level was increased in stroke ischemic as well as hemorrhagic, suggesting an inflammatory response in acute stroke.

**Keywords:** GCS score, hs-CRP, Inflammation, Stroke

### INTRODUCTION

Globally, stroke is the preeminent cause of morbidity and mortality in neurological patients and pondered as a life threatening state in the healthcare causality.<sup>1</sup> This neurological insult show up over a few hours, linger for more than a day and this clinical manifestation may be due to a destruction of the blood supply to one part of brain. Previous clinical studies explore that inflammation

orchestrate a predominant role in the pathogenesis of cerebrovascular diseases.<sup>2-4</sup> Thus, in the event of stroke, activation of innate immunity occurs which may overture to release of inflammatory cells and production of acute phase inflammatory molecule such as C-reactive protein (CRP) during its initial phase.<sup>5</sup>

CRP is a member of the pentraxin protein family and produced by liver hepatocytes in response to cytokines

such as interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$  triggered during inflammatory process.<sup>6-8</sup> At the onset of inflammation, CRP rises steeply within 6 h and thus confirms the inflammation.<sup>9</sup> Elevated CRP level does not reflect any specific disease but are highly level sensitive markers which are secreted in response to tissue injury, microbial agents, and inflammation. Clinically, two forms of CRP exists, first the standard CRP used to assess active inflammation in chronic diseases like arthritis; to diagnose any new infection; and to monitor response to treatment of these conditions. The second type is high-sensitivity CRP (hs-CRP) which is used to assess low-grade vascular inflammation. Further, it plays a pivotal role in the progression and rupture of atheromatous plaque. Early measurement of hsCRP level may be an independent predictor of the first ischemic stroke.<sup>10</sup> In this light, the present work was scrutinized to study the association between hsCRP level and ischemic as well as hemorrhagic stroke. Further, risk factor such as hypertension, diabetes mellitus and dyslipidemia associated with hsCRP level in stroke patients was also assessed.

## METHODS

This prospective study was conducted on 50 patients of acute stroke, admitted to the emergency and indoor department of post graduate department of medicine, Acharya Shri Chander of Medical Sciences and Hospital, Sidhra, Jammu, India.

Patients presenting with history of focal neurological deficit of acute onset in the form of hemiparesis, hemianaesthesia or aphasia, or having evidence of the presence of ischemic or hemorrhagic infarct in CT scan of the brain were included in this study. Further, patients with new onset of stroke including those with past history of hypertension, diabetes mellitus and dyslipidemia were also included in the study. The patients with infectious pathology, arthritis, cancer, history of recent MI or acute coronary syndrome, history of smoking, or those in hepatic failure were excluded from this study. Also, patients presenting with focal neurological deficit after 72 hours and on drugs, e.g. NSAIDs, statins, hormone replacement therapy were excluded from the study.

Clinical examination included vitals, i.e., pulse, blood pressure, and detailed examination of the neurological system. Laboratory investigations encompasses complete hemogram, serum electrolytes, blood urea and serum creatinine, fasting and postprandial blood glucose, hepatic markers (serum total bilirubin, conjugated bilirubin, unconjugated bilirubin, SGOT, SGPT, ALP, total proteins and albumin), lipid profile (total cholesterol, LDL, HDL, VLDL, and triglycerides) were measured employing standard methods. CT scan of the head and ECG were done within 72 hours of presentation. High-sensitivity CRP (hsCRP) levels were measured using a particle enhanced immunoturbidimetric assay

(DiaSys Diagnostic Systems Co., Ltd, Shanghai, China) on Roche Hitachi cobas e 411 Chemistry Analyzer.

## Statistical analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 12.0 and EPI-info version 6.0. Baseline comparability was assessed using Pearson's chi-square/t-test. The levels of hsCRP were expressed as mean $\pm$ SD. Difference in mean values was evaluated using one way analysis of variance (ANOVA). Mann-Whitney U test was used where the data showed extreme of values. All p values were reported two tailed. P-value <0.05 was considered as statistically significant.

## RESULTS

On the basis of selection and exclusion criteria, 50 stroke patients were recruited for the study. In this, 22 (44%) were males and 28 were females (56%), The mean age group was between 30-90 years, however maximum number of patients were in 61-70 (32%) years age group. The study also encompasses 50 control subjects.

Out of 50 stroke subjects, 35 patients (16 male and 19 female) were diagnosed as ischemic stroke and 15 patients (6male and 9 female) were reported as hemorrhagic stroke.

In the present study, the risk factors associated with were hypertension (40%), diabetes mellitus (40%) and dyslipidemia (34%). However in ischemic stroke patients 9 were hypertensive, 11 were diabetic and dyslipidemia was found in 12 cases. Whilst, in the hemorrhagic stroke, 11 were hypertensive, 9 were diabetic and dyslipidemia was found in 5 cases.

At the time of admission the stroke patients displayed the following symptoms; (i) Altered sensorium with left sided weakness with facial palsy, (ii) Altered sensorium with right sided weakness with facial palsy, (iii) Right sided weakness with aphasia, (iv) Left sided weakness with no altered sensorium no facial palsy and (v) Right sided weakness with no altered sensorium no facial palsy.

Further, in stroke patients, 40 cases (80%) displayed elevated level (>0.5 mg/ml) of hsCRP whereas in 10 cases (20%) the level of hsCRP was found to be normal (<0.5 mg/ml). However, in control patients 39 cases (78%) reported normal hsCRP level.

In ischemic stroke patients (n=35), out of 16 males, 13 (81%) displayed elevated hsCRP level whilst in females, out of 19 cases, 16 (84%) elicited abnormal hsCRP level. The hsCRP level between 6-10 mg/dl was more prevalent in maximum number of patients.

In hemorrhagic stroke patients (n=15), out of 6 males, 5 (83%) displayed elevated hsCRP level whilst in females, out of 9 cases, 6 (66%) elicited abnormal hsCRP level.

The hsCRP range 0-5mg/dl was observed in maximum numbers of cases, however 3 cases displayed hsCRP level >20mg/dl and this scenario was not evident in the case of ischemic stroke.

In stroke patients the mean hsCRP level ( $8.32\pm 6.60$ ) was statistically significant ( $P < 0.001$ ) when compared to the control ( $0.48\pm 0.44$ ) subjects. However, the hemorrhagic stroke patients displayed a significant ( $p < 0.05$ ) elevation in hsCRP level ( $10.93\pm 8.92$ ) when compared to the ischemic stroke patients ( $7.20\pm 5.06$ ). In the case of hemorrhagic stroke 60% of patients elicited stage 2 hypertension ( $\geq 160$ mm of Hg), whereas in the ischemic stroke, 74 % of patients were found to normotensive /pre-hypertension. However, the hsCRP level of normotensive and hypertensive patients in both the hemorrhagic stroke and ischemic stroke was found to non-significant ( $p > 0.05$ ).

Similarly, the hsCRP level of diabetic and non-diabetic and dyslipidemia and non-dyslipidemia patients in both the hemorrhagic stroke and ischemic stroke was found to non-significant ( $p > 0.05$ ).

In the present study, the glasgow coma scale (GCS) score was poor ( $< 8$ ) in patients with elevated hsCRP level in both the hemorrhagic stroke and ischemic stroke (Table 1). The Mean hsCRP level was found to be  $18.4\pm 4.42$  in non-survivors of hemorrhagic and  $12.00\pm 4.10$  in ischemic stroke; these values were found to be statistically significant ( $p < 0.05$ ). On analysing the data, correlation was found between hsCRP level and mortality of patients with stroke.

**Table 1: Association between GCS score and hs-CRP level in ischemic and hemorrhagic stroke cases.**

GCS score	Ischemic stroke mean hs-CRP level (mg/dl)	Hemorrhagic stroke Mean hs-CRP Level (mg/dl)
13-15	$2.80\pm 1.00$	$3.40\pm 1.20$
9-12	$4.20\pm 1.20$	$5.10\pm 1.70$
<8	$9.00\pm 3.20$	$8.80\pm 2.80$

## DISCUSSION

Stroke is the third leading cause of mortality in the western world and also a major cause of disability. Recently, it was shown that elevated hsCRP levels independently predict the risk of future stroke and transient ischemic attack in the elderly.<sup>11</sup> The present study was undertaken to underscore the role of hsCRP in stroke. The study was conducted on 50 stroke patients, among them, 35 were cases of ischemic stroke and the other 15 were cases of hemorrhagic stroke. A control group having 50 persons, had been taken randomly from healthy subjects who were similarly evaluated as the stroke cases.

The age distribution of the stroke patients in this study was between 30 and 90 years and maximum number of patients were in 61-70 years of age. The risk of stroke increased with increasing age as was found in the present study which is in line with the earlier reports.<sup>12</sup> Besides old age, diabetes mellitus (40%) was the most common risk factor found in various study populations, followed by hypertension (40%) and dyslipidaemia (34%). Kannel reported that diabetes doubles the risk of stroke. Benson and Sacco observed that hypertension confers a relative risk for stroke of 3- to 5-fold.<sup>13,14</sup>

The most common presentation in the present study was altered sensorium with left-sided hemiparesis with facial palsy (50%). When the hsCRP levels were measured within 72 hours of admission, it was found to be high in cases of stroke. Similar observations have been reported by various other workers also. Napoli D et al in their study included 128 patients.<sup>15</sup> The CRP values within 24 hours and between 48 to 72 hours were 1.3 (0.5 to 3.3) and 1.0 (0.5 to 2.3) mg/ dl respectively. Arenillas et al, in their study showed that a hsCRP level above the receiver operating characteristic curve cut-off value of 1.41 mg/dl emerged as an independent predictor of new end-point events ( $P < 0.0001$ ).<sup>16</sup>

When hsCRP levels were compared in different types of stroke, the mean hsCRP level was more in haemorrhagic than ischaemic stroke. These results are different from those of Yoshiyuki W et al in the Hisayama study in which they observed no clear association between hsCRP levels and haemorrhagic stroke occurrence. This may be due to the presence of some confounding factors like obesity, elderly age, or due to large size of the bleed in our study secondarily leading to ischaemia, and thus increasing the hsCRP level. On comparing hsCRP levels with other risk factors, no significant correlation was found. Earlier reports in the available literature have not commented regarding correlation of hsCRP level with other risk factors.<sup>17</sup>

In both ischemic and hemorrhagic stroke, higher CRP concentration correlates with severe neurological deficit. This finding was similar to observations by Guo et al in which they had observed higher concentrations on admission correlated with leucocyte count and blood glucose level, larger infarct, severe neurological deficit and worse outcome.<sup>18</sup> Kerstin W et al observed that an increase in CRP level between 12 and 24 hours after the onset of symptoms, predicts an unfavourable outcome and is associated with an increase in the incidence of cerebrovascular and cardiovascular events.<sup>19</sup> It was also seen that patients who expired had high hsCRP levels than those who survived both types of stroke. Thus, there was a relation between the hsCRP level and mortality. Higher the hsCRP level, more is the chance of mortality. Elkind et al observes high-sensitivity CRP, but not Lp-lipoplysaccharide phospho lipase A2, was associated with stroke severity. After adjusting for confounders, hs-CRP was associated with the risk of death (adjusted

hazard ratio, 2.11; 95% confidence interval, 1.18 - 3.75).<sup>21</sup> From this study we concluded that hsCRP level is increased in cases of stroke ischemic as well as hemorrhagic, suggesting an inflammatory response in acute stroke. Furthermore, the increased levels were correlated with larger infarct and bleed, severe neurological deficit, and worse outcome.

## CONCLUSION

As we had a small sample size, a larger study is needed to endorse our observations, and to analyse further about association between hsCRP level and hemorrhagic stroke occurrence. A larger study should also focus on whether hsCRP level needs to be included as a health screening protocol.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the institutional ethics committee*

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**Cite this article as:** Gupta V, Gupta AK, Kakkar M, Mahajan N, Khosla S. Clinical evaluation of association between high sensitivity C-reactive protein and stroke. *Int J Adv Med* 2016;3:820-3.