

The Study of HsCRP (High-Sensitivity C-reactive Protein) to evaluate the prognosis of Ischaemic Stroke

Dr. Swapan Sarkar¹, Dr. Pankaj Taparia²

¹(Assistant Professor, Dept. of Medicine, Jagannath Gupta Institute of Medical Sciences & Hospital, Kolkata, India)

²(PGT DNB (Neuromedicine), Gangaram Hospital, New Delhi, India)
Corresponding Author: Dr. Swapan Sarkar

Abstract: Stroke or cerebrovascular accident is one of the most common Neurological diseases. It is the second leading cause of death worldwide. 85 percent of strokes are due to Ischaemic Stroke. Major risk factors of ischaemic strokes are hypertension, diabetes, and dyslipidaemia. Atherosclerotic narrowing of cerebral blood vessels, embolic occlusion from heart and great vessels are principal causes of ischaemic stroke. High-sensitivity C-reactive protein (HsCRP) is an inflammatory marker which appears to be a strong predictor of risk factor and prognostic marker of Ischaemic stroke. Our objectives are to find the acute course of HsCRP and its association with short term prognosis following Ischaemic stroke. This cross-sectional observational study was conducted at M.R. Bangur Hospital, Kolkata during the period of July 2012 - November 2013. A total of 100 patients of both sexes were randomly chosen from the Department of Medicine and their plasma high sensitivity C-reactive protein (HsCRP) level was measured within 48 hours of admission and on the 5th day after admission. The study showed that the level of HsCRP did not change significantly when measured within 48 hours of onset of Ischaemic stroke and on 5th day after stroke ($p=0.335$) - the prognosis and severity remained same when followed for 5 days. It, also, showed that the level of CRP ≥ 3 within 48 hours of admission is associated with increased severity and mortality of stroke ($Z=14.4$; $p<0.0001$).

Date of Submission: 30-04-2019

Date of acceptance: 14-05-2019

I. Introduction

The World Health Organisation (WHO) defines stroke as: 'Rapidly developing clinical signs of focal or global disturbances of cerebral function with symptoms lasting for 24 hours or longer with no apparent cause other than of vascular origin'. Stroke or Cerebrovascular accident is the second most leading cause of death worldwide. Ischaemic stroke comprises 85 percent of all strokes; rest are due to Haemorrhagic stroke (15 percent). Hypertension, Diabetes, Dyslipidaemia, and Smoking are major risk factors of Ischaemic stroke. Various biomarkers have been studied as risk-factors and prognostic-markers for acute Ischaemic Strokes. C-reactive protein (HsCRP) appears to be a strong predictor of Cardio vascular and Cerebrovascular risk factors. CRP is an acute phase reactant that is exclusively synthesized in the liver in response to inflammation. Studies have shown the role of CRP as a predictor of outcome, severity, and mortality in Stroke patients¹⁻⁷. In a study it has been found that high plasma CRP is associated with increased risk of stroke⁸. The Framingham study has shown that HsCRP is also used to predict future risk of stroke.

II. Material and Methods

Cross sectional observational study at M.R. BANGUR HOSPITAL, KOLKATA – 33. Total number of subjects in this study were 100 with power 80% (persons aged 40 years & above; both male and female). Subjects were randomly chosen from patients admitted at M.R. BANGUR HOSPITAL, during the period July 2012 – November 2013 as per study protocol.

Study Design: Cross sectional observational study.

Study Location: Emergency Department of Medicine, M.R. Bangur Hospital, Kolkata, West Bengal – 700033.

Study Duration: July 2012 – November 2013

Sample size: 100 patients

Sample size calculation: The subjects were randomly chosen from patients admitted at M.R. Bangur Hospital during the study period.

Inclusion criteria:

1. Patients with first ever Ischaemic stroke.
2. Age more than 40 years.
3. Patients attending Emergency Department of Medicine at M.R BANGUR Hospital, within 48 hours of onset of neurological symptoms.

Exclusion criteria:

1. Patients with hg, subarachnoid hg, or extradural hg.
2. Patients attended with neuropathic symptoms secondary to intracranial tumor, infection, head injury, subdural hematoma.
3. Patients attending with features of old stroke.
4. Patients attending after 48 hours of stroke.
5. Conditions associated with high CRP elevation: fever, information, peripheral vascular disease, acute myocardial infarction.
6. Patients attending with features of TIA transient cerebral ischemia

III. Results

Table1.Age distribution:The mean age(mean±s.d.)of the patients was 63.06±11.18years with range of 40-90years. The median age was65 years. Test proportion showed that the proportion of theagegroup 60-69years(34.0%) was significantly higher than other age groups (Z=2.06; p<0.05).

Table 1:Age Distribution

AgeGroup (in years)	Number	%
40-49	13	13.0%
50-59	21	21.0%
60-69	34	34.0%
70-79	21	21.0%
≥80	11	11.0%
Total	100	100.0%

Table2.Gender distribution: Test proportion showed that proportion of males(64%) was significantly higher than females (36%) (Z=3.96;p<0.001)

Table2:Gender Distribution

Gender	Number	%
Male	64	64.0%
Female	36	36.0%
Total	100	100.0%

Table 3. HighsensitivityCRP within 48hrs:The mean HsCRP within 48hours(mean±s.d.) of the patients was 2.69±2.66 with range 0.6 - 12.6 and median 1.55. 27%of the patients had higherHsCRP (≥3) which was not statistically significant (p>0.05).

Table3:HighsensitivityCRP within 48hours

HsCRP within 48 hours	Number	%
≥3	27	27.0%
< 3	73	73.0%
Total	100	100.0%

Table 4.High sensitivity CRP on5th day: The mean HsCRP on 5th day(mean±s.d.) was 2.65±2.70 with range of 0.6-12.3 and median was 1.60. 26% of the patients had higher HsCRP (≥3) which was not statistically significant(p>0.05).

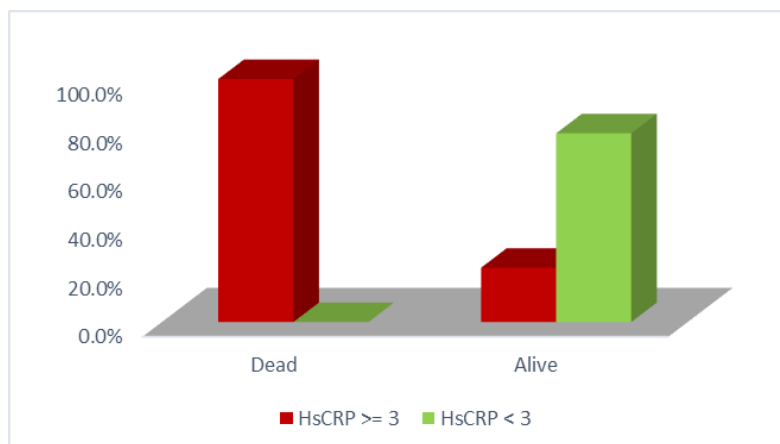
Table 4:Highly sensitiveCRP on 5th Day

HsCRP on 5 th Day	Number	%
≥3	26	26.0%
< 3	74	74.0%
Total	100	100.0%

Table 5.Outcome and level of HsCRP within 48 hours: Test of proportion showed that proportion of deaths were significantly higher for HsCRP≥ 3 as compared to HsCRP< 3 (Z = 14.14; p<0.0001).

Table 5: Outcome and level of HsCRP within 48 hours

Outcome	HsCRP ≥ 3 (n = 27)	HsCRP < 3 (n = 73)	Total
Dead	6	0	6
Row %	100.0%	0.0%	100.0%
Col %	22.2%	0.0%	6.0%
Alive	21	73	94
Row %	22.3%	77.7%	100.0%
Col %	77.8%	100.0%	94.0%
Total	27	73	100
Row %	27.0%	73.0%	100.0%
Col %	100.0%	100.0%	100.0%



IV. Discussion

Stroke is an abrupt onset neurologic deficit due to focal vascular cause. It is a major concern for the community regarding disability, social and mental burden. The prevalence of Ischaemic stroke has been increasing over the last decade. This may be attributed to increase in life expectancy and aging of population^{9,10}. Nevertheless, Ischaemic stroke is much less studied in terms of its prognosis. This study was conducted to elucidate relationship between high sensitivity C-reactive protein (HsCRP) and Ischaemic stroke. The aim of study was to find out acute course of C-reactive protein following an Ischaemic stroke and to find out the association of HsCRP with the short-term prognosis of Ischaemic stroke. All patients were selected strictly and carefully as per protocol (after satisfying inclusion and exclusion criteria) to avoid any confounding factor of increasing inflammatory markers (HsCRP).

Ischaemic stroke is caused mainly by atherosclerotic narrowing or occlusion of cerebral circulation. Studies have shown that atherosclerosis is an inflammatory condition¹¹. HsCRP is an indicator of inflammatory response to atherosclerosis. Indians have higher prevalence of hypertension and diabetes which puts more risk of atherosclerosis. The elevation of CRP following Ischaemic stroke suggests its role in inflammation. Some studies have shown the role of CRP as the predictor of outcome, severity and mortality in stroke patients¹. In a study it has been found that high plasma CRP concentrations are associated with increased risk of stroke^{8,12} and its recurrence¹³. The Framingham study has shown that HsCRP is also used to predict future risk of stroke¹⁴.

In this study we found that levels of acute phase proteins are stable after stroke for at least five days. There is no significant time trend in this period of time. Chi-square (χ^2) test showed that there was significant association between HsCRP within 48 hours and on 5th day after acute stroke ($p=0.000001$).

To examine the effect of HsCRP level, we divided the patients into two groups: low HsCRP group (HsCRP < 3mg/L) and high HsCRP group (≥ 3 mg/L). The risk of HsCRP ≥ 3 on 5th day was 134.16 times more among patients with HsCRP ≥ 3 within 48 hours and the risk was significant. This means patients with high HsCRP on 48hrs of onset of stroke remained high on 5th day when followed. As per Wilcoxon Signed Rank Test, there was no significant difference between level of HsCRP within 48 hours and on 5th day ($p=0.335$). This means level of HsCRP remained stable over short-term course followed for 5 days. This result is supported by a study by Mitchell SV Elkind et al in 2006¹⁵.

Association of HsCRP with the short-term prognosis following Ischaemic stroke:

This study showed CRP within 48 hours of onset of Ischaemic stroke is associated with severity and mortality. There is a crude association between high CRP and short-term outcome which is likely secondary to stroke severity as seen by NIHSS and marker of inflammation HsCRP. Mechanism of CRP elevation is not

completely defined in patients with Ischaemic stroke. Possible theory includes hyperfusion and congestion in the nervous tissue influence secretion of IL_6 thereby promoting CRP production by the liver tissue. It has been found that high CRP value within 48 hours of admission, the severity of neurological impairment was also high. As per Pearson correlation co-efficient in this study, significant correlation was observed between HsCRP within 48hours ($r=0.616$; $p=0.0001$), NIHSS on 5th day ($r=0.566$; $p=0.0001$) and NIHSS on 90th day ($r=0.616$; $p=0.0001$). So, the patients having higher CRP within 48 hours were significantly correlated with severity of stroke over time followed till 90 days. Also, deaths were significantly higher in HsCRP more than 3 times within 48 hours ($Z=14.4$; $p<0.0001$).

This has been shown previously in Bergen stroke study by Titto T. Idicula et al as Admission CRP is an independent predictor of Stroke severity and mortality³.

Demographic trends:

The study showed that males are predominantly affected. The age range was 40-90years with a mean of 63.06 years. According to data obtained from Framingham study, incidents of stroke increase steeply with age becoming double in each successive decade from 55years onwards. In this study, the risk of HsCRP ≥ 3 was 11.21 times more among the patients having ≥ 55 years of age as compared to patients having <55 years of age.

Risk factors:

The association of HsCRP and Ischaemic stroke in this study may be attributed to high prevalence of patients with hypertension and diabetes. Previously many studies have demonstrated association between CRP and hypertension and also with diabetes¹⁶.

In our study 44% of patients had hypertension, 47% had diabetes, 23% had heart disease. Systolic blood pressure if maintained <130 is favourable to reduce the risk of stroke.

In the Honolulu heart programme, subjects with known diabetes and asymptomatic hyperglycemia showed an increased risk of Ischaemic stroke and these associations were independent of age and other vascular risk factors¹⁷. Atrial fibrillation is the most common cause of embolic stroke. Artery to artery embolization from large arteries (carotid), prosthetic valve, myocardial infarction are other causes of Ischaemic stroke.

Mogensen UB et al had shown in 2013 that smoking and alcohol consumption were not associated with severity of stroke¹⁸. Same results are obtained from this study. We have shown that CRP level is associated with severity of stroke, but no association was found between habit of smoking and level of HsCRP ($p=0.08$).

The mean CBG (mean \pm s.d) of the patients was 160.94mg% with a range of 66.422mg% and the median was 120mg%. 43% patients had CBG >200 . In previous studies it was found that high blood glucose within 24hours is associated with poor outcome¹⁹. In our study, we found that patients who died due to Ischaemic stroke had significantly higher blood glucose at the time of admission (212.83 ± 137.86) than who survived (157.37 ± 183.85).

V. Conclusion

HsCRP level provides rapid and reliable information regarding severity & prognosis in patients with Ischaemic stroke. The level of HsCRP does not change significantly when measured within 48 hours of onset of Ischaemic stroke and on 5th day after stroke. Levels are not influenced by the site of infarction as seen by CT Scan of brain. Level of CRP ≥ 3 within 48 hours of admission is associated with increased severity and mortality of stroke. Also, the level of CRP on 5th day was same as within 48 hours of stroke - the prognosis and severity remained same. If confirmed by larger, longitudinal studies this association may be used as a tool to assess the severity and prognosis in a patient with Ischaemic strokes.

References

- [1]. Mario Di Napoli, Francesca Papa and Vittorio Bocola; C-Reactive Protein in Ischemic Stroke An Independent Prognostic Factor; Stroke 2001;32:917-924
- [2]. Di Napoli M, Di Gianfilippo G, Sollecito A et al., (2000); C-Reactive protein and outcome after first-ever Ischemic Stroke. Stroke; 31:231-233.
- [3]. Titto T Idicula, Jan Brogger, Halvor Naess, et al., (2009) Admission C-Reactive protein after acute ischemic stroke is associated with stroke severity and mortality: The 'Bergen stroke study' BMC Neurology, 9:18.
- [4]. Yue Huang Jing, Xing-Quan Zhao, Chun-Xue Wang, et al., (2012): High-Sensitivity C-Reactive Protein is a Strong Risk Factor for Death after Acute Ischemic Stroke among CNS Neuroscience TherapeuticsV 18, Issue 3, pp 261-266
- [5]. M.S.V. Elkind, MD, MS, J.M. Luna, MPH, Y.P. Moon, MS et al., (2009): High-sensitivity C-reactive protein (hs CRP) predict stroke, vascular events, and mortality in prospective cohort study. Neurology vol. 73 no. 16 1300-1307.
- [6]. Rodorf G, Koroshetz W, Efir JT, et al., (2000): Predictors of mortality in stroke patients admitted to an intensive care unit. Crit Care Med. 18:1301-5
- [7]. Den Hertog HM, van Rossum JA, van der Worp HB, et al (2009). C-reactive protein in the early phase of acute ischemic stroke: association with poor outcome and death. J Neurol. 256(12):2003-8.
- [8]. Makita S, Nakamura M, Satoh K, Tanaka F, Onoda T, Kawamura K, et al (2009). Serum C-Reactive Protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population. Atherosclerosis; 204:2348.
- [9]. Shyamal Kumar Das Banerjee TK.; Stroke: Indian Scenario, Circulation. 2008;118:2719-2724

The Study of HsCRP (High-Sensitivity C-reactive Protein) to evaluate the prognosis of Ischaemic

- [10]. Shyamal K. Das Banerjee TK, Biswas A, Roy T, Raut DK, Mukherjee CS, Chaudhuri A, Hazra A, Roy J; A Prospective Community-Based Study of Stroke in Kolkata, India ; Stroke. 2007; 38:906-910.
- [11]. R. Ross, "Atherosclerosis – an inflammatory disease," New England Journal of Medicine, vol. 340, no. 2, pp. 115-126, 1999.
- [12]. E. van Exel, J. Gussekloo, A.J.M. de Craen, A. Bootsma-van der Wiel, M. Frolich and R.G.J. Westendorp; Inflammation and Stroke: The Leiden 85-plus Study Stroke. 2002; 33:1135-1138;
- [13]. Whitely W, Jackson C, Lewis, et al: Association of circulating inflammatory markers with recurrent vascular events after stroke: a prospective cohort study. Stroke.; 42(1):10-6 British Journal of Science 30 April 2013, Vol. 8(2) 2013 British journals ISSN 2047-2745
- [14]. Natalia S. Rost, MA; Philip A. Wolf, MD; Carlos S. Kase, MD; Margaret Kelly-Hayes, EdD, RN; HalitSilbershatz, PhD; Joseph M. Massaro, PhD; Ralph B. D'Agostino, PhD; Carl Franzblau, PhD; Peter W.F. Wilson, MD; The Framingham Study Plasma Concentration of C-Reactive Protein and Risk of Ischemic Stroke and Transient Ischemic Attack; Stroke. 2001; 32:2575-2579.
- [15]. Elkind MS, Coates K, Tai W, Paik MC, Boden-Albala B, Sacco RL. Levels of acute phase proteins remain stable after ischemic stroke. BMC Neurol. 2006;6:37.
- [16]. Ghanshyam Palamaner Subash Shantha Anita Ashok Kumar Emmanuel Bhaskar Kamesh SivagnanamDevasena Srinivasan Manjunath SundaresanPreetam Arthur Georgi Abraham; Hypertensive retinal changes, a screening tool to predict microalbuminuria in hypertensive patients: a cross-sectional study; Nephrol Dial Transplant. 2010 Jun. 25(6):1839-1845.
- [17]. Rodriguez BL, Lau N, Burchfiel CM, Abbott RD, Sharp DS, Yano K, Curb JD; Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. Stroke 1994; 25:951-7.
- [18]. Mogensen UB1, Olsen TS, Andersen KK, Gerds TA; Cause-specific mortality after stroke: relation to age, sex, stroke severity, and risk factors in a 10-year follow-up study; J Stroke Cerebrovasc Disc. 2013 Oct. 22(7):e59-65.
- [19]. Bill O, Zufferey P, Faouzi M, Michel P; Severe stroke: patient profile and predictors of favorable outcome; J ThrombHaemost. 2013 Jan;11(1):92-9.

Dr. Swapan Sarkar. "The Study of HsCRP (High-Sensitivity C-reactive Protein) to evaluate the prognosis of Ischaemic Stroke." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 5, 2019, pp 37-41.