High Sensitivity C- Reactive Protein Level in Acute Cerebrovascular Accident (Stroke) at a Tertiary Care Centre

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ABSTRACT

BACKGROUND

Stroke is the leading cause of death worldwide and one of the main causes of long term disability. According to WHO, 15 million suffer from stroke each year. Studies have shown that levels of hsCRP measured shortly after stroke predicted complimentary aspects of prognosis. There is possibility that elevated hsCRP levels has direct relation to extent of cerebral tissue injury. We wanted to measure the levels of hsCRP in acute cerebrovascular accident. To correlate the level of hsCRP with severity of stroke and outcome.

METHODS

Study was conducted in patients admitted in medical ward and medical ICU in tertiary care hospital (Grant Government Medical College and Sir JJ Group of Hospitals). It was a cross sectional study. A total of 150 patients who presented with stroke and fulfilled inclusion and exclusion criteria were enrolled in the study. In all patients hsCRP levels were measured within 48 hours of admission. Data was collected prospectively in a Microsoft Excel database. Statistical analysis was done using non-parametric ANOVA (Kruskal Wallis test) and Mann Whitney test.

RESULTS

Mean age of patients was 59 ± 12 years. hsCRP levels were raised in stroke patients. Also values were found to be more in haemorrhagic stroke (value) than in ischemic stroke (value) and the difference was found to be significant. Significant correlation was also found between hsCRP levels and GCS with lower GCS scores associated with higher hsCRP levels in both types of stroke. Mean hsCRP level in survivors was 21.83 ± 23.17 mg/L and in non survivors was 82.07 ± 25.83 mg/L and the difference was statistically significant ($p < 0.0001$)

CONCLUSIONS

We concluded that hsCRP level is increased in cases of stroke (both ischemic and haemorrhagic) suggesting an inflammatory response in acute stroke. Increased levels of hsCRP correlated with severity of neurological deficit and worse outcome.

KEY WORDS

hsCRP, Ischemic Stroke, Haemorrhagic Stroke, Prognostic Marker in Stroke

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BACKGROUND

Stroke is the leading cause of death worldwide and one of the main causes of long term disability. According to WHO, 15 million people suffer from stroke each year. About 87% of the strokes are due to ischemia. There has been evidence about inflammatory processes involved in cerebral ischemia.[1–3] Each year more than 5 million people die as a consequence of stroke and at least 1 in 6 patients who survive will suffer another stroke in the next 5 years.[4] Stroke is defined as sudden onset loss of global or focal cerebral function persisting for more than 24 hours.[5] Stroke is defined as an abrupt onset of neurological deficit that is attributable to a focal vascular cause. Thus, the definition of stroke is clinical and laboratory and imaging studies are used to support the diagnosis. When the blood flow is quickly restored, the brain tissue can recover fully and the patient's symptoms are only transient: this is called a transient ischemic attack (TIA). Inflammation has an important role in development of atherosclerosis and during ischemic event. Inflammatory markers such as fibrinogen and hsCRP have been reported as predictable marker for stroke severity and outcome.[6] C-Reactive Protein is a annular pentameric protein found in plasma whose circulating concentrations rise in response to inflammation. It is an acute phase protein of hepatic origin that increases following interleukin – 6 secretion by macrophages & T cells. CRP is synthesised in the liver[7] in response to factors released by macrophages and adipocytes.[8] HsCRP is an acute phase reactant produced by liver under the control of interleukin-6. A growing body of evidence supports the concept that local & systemic inflammation plays a role in initiation & progression of atherosclerosis & it's complications. Acute stroke develops as a result of sudden interruption of focal cerebral blood flow. The cause of stroke is embolic or thrombotic occlusion in 70-80% of the patients with severe symptoms.[9] Intracerebral haemorrhage causes about 10% of acute stroke but is more common in low income countries.[10] Increased CRP levels are accepted as a sensitive but not specific marker of acute inflammatory response. Increased risk of death in stroke is linked with elevated levels of CRP within 72 hours of stroke. However vascular inflammation is more related to high sensitivity CRP (hsCRP). Levels of hsCRP measured shortly after stroke predicted complementary aspects of prognosis. There is possibility that elevated levels of hsCRP has direct relation to extent of cerebral tissue injury. Clinical research indicated that expression of hsCRP can be used to predict mortality from as short as 3 months to as long as 5 years. Currently neuroimaging modalities such as non-contrast CT scan and diffusion weighted MRI as the standard clinical tools for diagnosis of stroke. Biomarkers can assist with patient care by helping to confirm the diagnosis and predicting prognosis. hsCRP is emerging as a prognostic marker in stroke. The prognostic importance of hsCRP may be related to the extent of necrosis in the brain parenchyma partly and partly to unknown determinants of intensity of acute phase reactants. The prognostic value of hsCRP with respect to neurologic deficits and death as outcomes of stroke helps clinician to offer realistic expectations to families of stroke victims. This study was done to assess the level of high sensitivity C- Reactive Protein in acute cerebrovascular accident (stroke) and determine the outcomes with regards to neurological deficits and survival.

METHODS

This is cross sectional study conducted in 150 patients admitted in medical ward and medical ICU of tertiary care of hospital (Grant Government Medical College and Sir JJ Group of Hospitals). Sample size as per calculator for sample size was 380. But as recurrent strokes are excluded from the study the sample size of 150 was chosen. The study period was from March 2018 to September 2019. IEC clearance was taken from the institutional ethics committee at JJ Hospital. After IEC clearance and informed consent patients with both ischemic and haemorrhagic stroke admitted to the hospital within 72 hours of onset of stroke were included in the study. Patients with transient ischemic attack (TIA), recurrent stroke or with signs of active infection like fever, cough, burning micturition at the time of admission or with rheumatological conditions and on immunosuppressive therapy were excluded from the study. Detailed history and Serum samples were taken for hsCRP estimation within 48 hours of admission. Standard guidelines for treatment of ischemic and haemorrhagic stroke were followed. Patients' GCS score was reviewed on admission and at discharge and outcome was assessed in terms of GCS score at discharge or death. hsCRP was measured by fully automated Latex Agglutination with Beckman Coulter.

Statistical Analysis

The statistical tests that were used for analysis were ANOVA and Mann Whitney test. Nonparametric ANOVA (Kruskal Wallis test) has been used to find significance of difference between hsCRP levels in ischemic vs haemorrhagic stroke.

RESULTS

A total of 150 subjects who fulfilled inclusion criteria were included in the study. Mean age of patients enrolled in the study was 59 ± 12 years. 90.66% of the patients were between the ages 40-80 years. (Table I). In the current study, 106 patients were males and 44 subjects were females. Male to female ratio was 2.4:1. Addiction pattern was studied which showed that the most common addiction was tobacco chewing. 60.66% patients had no addiction. (Table II) Hypertension was the most prevalent comorbid condition with 68% of the study subjects having hypertension. The other comorbidities in their order of prevalence were diabetes (22%), ischemic heart disease (10%) and CKD (2%). Ischemic stroke was present in 59.33% of the patients, 36% of the patients had haemorrhagic stroke and 4.67% patients had both ischemic and haemorrhagic stroke.

Average hsCRP level in the current study was 45.12±38.07 mg/L with a median hsCRP value of 30.87 mg/L. The mean hsCRP levels in ischemic stroke patients was 31.68±31.79 mg/L. and the mean hsCRP levels in patients with haemorrhagic stroke was 62.82±27.42 mg/L. The mean hsCRP levels in haemorrhagic stroke was more than that in ischemic stroke and the difference was found to be

statistically significant (p<0.0001). It was also seen that patients with low GCS scores had higher hsCRP levels and the difference between hsCRP levels in patients with GCS <8 and patients with GCS ≥8 was statistically significant (p<0.0001). Mean hsCRP levels in was 21.83 ± 23.17 mg/L in survivors and 82.07 ± 25.83 mg/L in non survivors. These values were found to be statistically significant as shown in table V.

Age (Years)	No. of Patients	Percentage
20-40	9	6
41-60	76	50.66
61-80	60	40
>80	5	3.33
Average age (year)	59 ±12	

Table I. Age Distribution of Subjects

Addiction	No. of Patients	Percentage
None	91	60.66
Smoking	11	7.33
Alcohol	30	20
Tobacco Chewing	33	22

Table II. Addiction Pattern in Study Subjects

HsCRP (mg/L)	No. of Patients	Percentage
≤ 3	9	6
>3 -10	22	14.67
>10-40	55	36.67
>40	64	46.67
Average	45.12±38.07	
Median	30.87 (0.2 to 163)	

Table III. hsCRP Levels

GCS	Average HsCRP	p Value
<8	80.94±27.02	<0.0001
≥8	21.90±23.29	Mann-Whitney Test

Table IV. Correlation between hsCRP and GCS

	HsCRP (mg/L)	p Value
Survivor (92)	21.83±23.17	<0.0001
Non survivor (58)	82.07±25.83	Mann Whitney test

Table V. hsCRP Levels among Survivors and Non Survivors

DISCUSSION

The present study was a cross sectional study conducted at a tertiary care hospital among 150 IPD patients diagnosed with stroke. The correlation between hsCRP levels measured within 48 hours of admission to that of neurologic outcome in terms of discharge or death was carried out in the present study. The average age of patients enrolled in the study was 59 ±12 years with 90% of the patients within the ages of 40-80 years. Age is generally considered as a non-modifiable or fixed risk factor for stroke.[10] Similar results were obtained in studies conducted by Pinky Talreja Mishra et al,[11] Jaydip Ray Chaudhuri et al,[12] Sujit Kumar et al,[13] Davinder Rana et al,[14] Jayachandra et al,[15] the Mumbai Stroke Registry[16] and Yoshiyuki Wakugawa in the Hisayama Study.[17]

In the current study there was male preponderance with 70.66% cases being male and 29.33% cases being female. Male to female ratio in the current study was 2.4:1. Male sex is also considered as a fixed risk factor for stroke.[10] Similar results were obtained in the studies conducted by Sujit Kumar et al,[13] Davinder Singh Rana et al[14] and Jayachandra et al[15] which had male preponderance. The most common comorbidity in the current study was hypertension (68%) followed by diabetes mellitus (22%). This is in line with other studies conducted by Jaydip Rai Chaudhuri et al,[12] Jayachandra et al[15] and Yoshiyuki Wakugawa et al.[17] However in the study conducted by Pinky Talreja Mishra et al,[11] diabetes mellitus was the most common comorbidity followed by hypertension. The most common addiction in patients enrolled in our study was tobacco (chewing and smoking) with a prevalence of 29.33%. This is corroborated by findings in studies conducted by Davinder Singh Rana et al[14] and Jaydip Rai Chaudhuri et al.[12] The average hsCRP level in the study population in the current study was 45.12±38.07 mg/L. This shows that hsCRP levels are increased in case of stroke.

The mean hsCRP value in patients with ischemic stroke was 31.68±31.79 mg/L and in patients with haemorrhagic stroke was 62.82±37.42 mg/L. Thus, hsCRP levels were higher in patients with haemorrhagic stroke than in patients with ischemic stroke and this difference was found to be statistically significant (p<0.0001). These findings are similar to the findings of Pinky Talreja Mishra et al[11] and Jayachandra et al.[15] Thus higher hsCRP levels in haemorrhagic stroke suggest a more severe inflammatory response. However, these findings are in contradiction to findings of Yoshiyuki Wakugawa et al in the Hisayama study[17] and Ritesh Lal et al.[18] In the study by Yoshiyuki Wakugawa et al,[17] high hsCRP levels were found to be an independent risk factor for ischemic stroke in men but not for haemorrhagic stroke in either men or women. In the study by Ritesh Lal et al,[18] mean hsCRP levels in ischemic stroke were higher than in haemorrhagic stroke. This may be due to presence of some confounding factors like obesity, elderly age or due to large size of bleed in our study secondarily leading to ischemia and increasing hsCRP.

The coefficient of correlation between hsCRP and GCS at discharge in our study was -0.85 which was significant (p<0.0001). Thus, higher hsCRP levels were associated with lower GCS scores. Patients with GCS of 8 and above had a mean hsCRP level of 21.90±23.29 mg/L which was significantly lower than patients with GCS <8 who had mean hsCRP level of 80.94±27.02 mg/L. This suggests that higher hsCRP levels are associated with severe neurological deficit and thus worse outcome. Similar findings were obtained in the study by Pinky Talreja Mishra,[11] Jayachandra et al,[15] Ritesh Lal et al[18] and Davinder Singh Rana et al,[14] In the study by Ritesh Lal et al,[18] stroke patients were classified on the basis of Scandinavian Stroke Scale into minor, moderate and severe stroke. Patients with minor stroke had lower hsCRP values as compared to patients with severe stroke. In the study by Davinder Singh Rana et al,[14] hsCRP levels were correlated with acute ischemic stroke. Patients were classified as per NIHSS stroke scale into mild, moderate and severe grades. Patients with mild stroke had lower hsCRP levels as compared to patients with severe stroke. Thus, higher hsCRP levels were associated with worse neurologic outcomes.

In the current study, the hsCRP levels were correlated with outcomes in terms of death. The mean hsCRP levels in survivors was 21.83±23.17 mg/L and in non survivors was 82.07±25.83 mg/L. The difference between mean hsCRP levels in survivors and non survivors was significant. The coefficient of correlation between hsCRP level and death was 0.75 which was statistically significant (p<0.0001). Thus higher hsCRP levels are associated with more mortality. Similar results were obtained in results by Jayachandra et al.[15] Patients who expired had high hsCRP levels than those who survived both types of strokes. Thus there was a relation between high hsCRP and mortality. Higher hsCRP

had high chance of mortality. In a study conducted by Yue Huang et al,[19] elevated hsCRP levels of acute ischemic stroke are independent prognostic factors for all cause death within 3 months in Chinese patients. Similar results were seen in a study conducted by Sujit Kumar et al,[13] which showed increased risk of morbidity and mortality in cases with elevated hsCRP levels within 72 hours of stroke. In a study conducted by Naess H, Waje-Andreassen U, Thomassen L, Titto I T, Jan B, titled the Bergen Stroke Study,[20] long term mortality was significantly associated with CRP even after adjusting for age, sex and stroke severity in ischemic stroke.

The prognostic importance of hsCRP may be related to the extent of necrosis in the brain parenchyma and partly unknown determinants of intensity of acute phase reactants. The prognostic value of hsCRP with respect to neurological deficits and deaths as outcomes of stroke helps clinician to offer realistic expectations to families of stroke victims. Thus hsCRP can be routinely measured for all stroke patients to provide a statistically significant level of prognostic information as to the outcome of stroke.

CONCLUSIONS

hsCRP levels were elevated in acute cerebrovascular accident. The rise in hsCRP level was more in haemorrhagic than in ischemic stroke. hsCRP was significantly higher in patients with severe neurological deficit and a GCS score of <8. Higher hsCRP level had poorer outcome as compared to patients with lower hsCRP. Thus, level of hsCRP can be used as a prognostic marker for assessing the outcome in stroke patients.

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REFERENCES

[1] Youn CS, Choi SP, Kim SH, et al. Serum highly selective C-reactive protein concentration is associated with the volume of ischemic tissue in acute ischemic stroke. Am J Emerg Med 2012;30(1):124-8.
[2] Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: an overview with emphasis on therapeutic significance beyond thrombolysis. Pathophysiology 2010;17(3):197-218.
[3] Whiteley W, Jackson C, Lewis S, et al. Association of circulating inflammatory markers with recurrent vascular events after stroke: a prospective cohort study. Stroke 2011;42(1):10-6.
[4] Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: Incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001;32(12):2735-40.
[5] Yip HK, Tsai TH, Lin HS, et al. Effect of erythropoietin on level of circulating endothelial progenitor cells and outcome in patients after acute ischemic stroke. Crit Care 2011;15(1):R40.
[6] Vibo R, Kõrv J, Roose M, et al. Acute phase proteins and oxidised low-density lipoprotein in association with ischemic stroke subtype, severity and outcome. Free Radic Res 2007;41(3):282-7.
[7] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. Journal of Clinical Investigation 2003;111(12):1805-12.
[8] Lau DCW, Dhillon B, Yan H, et al. Adipokines: molecular links between obesity and atheroslcerosis. American Journal of Physiology Heart and Circulatory Physiology 2005;288(5):H2031-41.
[9] Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. J Am Med Assoc 1999;282(21):2003-11.
[10] Langhorne P. Stroke medicine. In: Ralston SH, Penman ID, Strachan MWJ, et al. eds. Davidson's Principles and Practice of Medicine. 23rd edn. Elsevier 2018: p. 1147-62.
[11] Mishra PT, Chandra R, Saxena SK, et al. High Sensitivity C - reactive protein (hsCRP) level in cerebrovascular accident (Stroke). JIACM 2010;11(3):204-7.
[12] Chaudhuri JR, Mridula KR, Umamahesh M, et al. High sensitivity C-reactive protein levels in acute ischemic stroke and subtypes: a study from a tertiary care center. Iran J Neurol 2013;12(3):92-7.
[13] Kumar S, Kumar AG. Evaluation of the role of plasma high sensitivity C - reactive protein levels as a prognostic and diagnostic marker in acute ischemic stroke. Int J Sci Study 2016;4(2):148-53.
[14] Rana DS, Anand I, Batra A, et al. Serum levels of high-sensitivity C-reactive protein in acute ischemic stroke and its subtypes: a prospective case-control study. Asia Pacific J Clin Trials Nerv Syst Dis 2018;3(4):128.
[15] Jayachandra J, Mamatha TR, Veeranna GKM, et al. High sensitivity C - reactive protein as a prognostic marker in acute stroke. J Evol Med Dent Sci 2014;3(10):2675-9.
[16] Dalal PM, Bhattacharjee M, Vairale J, et al. Mumbai stroke Registry (2005-2006)- surveillance using WHO steps stroke instrument - challenges and opportunities. J Assoc Physicians India 2008;56:675-80.
[17] Wakugawa Y, Kiyohara Y, Tanizaki Y, et al. C-reactive protein and risk of first-ever ischemic and hemorrhagic stroke in a general Japanese population: The Hisayama study. Stroke 2006;37(1):27-32.
[18] Lal R, Gupta A, Virmani S, et al. High sensitivity C-reactive protein as a prognostic marker in ischaemic and haemorrhagic stroke. Int J Adv Med 2016;372-7.
[19] Huang Y, Jing J, Zhao XQ, et al. High-sensitivity C-reactive protein is a strong risk factor for death after acute ischemic stroke among Chinese. CNS Neurosci Ther 2012;18(3):261-6.
[20] Idicula TT, Brogger J, Naess H, et al. Admission C – reactive protein after acute ischemic stroke is associated with stroke severity and mortality: The 'Bergen stroke study'. BMC Neurol 2009;9(1):18.