



A STUDY TO EVALUATE THE ROLE OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN CEREBROVASCULAR ACCIDENT IN THE DARBHANGA MEDICAL COLLEGE AND HOSPITAL

Medicine

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ABSTRACT

INTRODUCTION: Cerebrovascular accident (commonly called stroke) is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus, the diagnosis of stroke is clinical and laboratory studies including brain imaging are used to support the diagnosis

AIMS AND OBJECTIVES: To evaluate the serum levels of high sensitivity C-reactive protein (hsCRP) in different types of cerebrovascular accidents on admission.

MATERIALS AND METHODS: This study was an institution based cross-sectional study designed to investigate the association of hs-CRP levels with stroke and its types in Indian patients. The study was done in the Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Bihar from march 2019 to March 2020. 50 patients of either sex above 12 years of age admitted in Medicine Department of DMCH, Laheriasarai, Bihar with clinically or radiologically diagnosed stroke.

RESULT: The mean level of hsCRP (mean $\pm$ s.d.) of the cases in our study was 7.65 ± 7.01 with range 1.4 – 26 and the median was 3.7 and 58% of the cases were having level of hsCRP ≥ 3 ($p=0.023$). Mean level of hsCRP of cases was significantly higher than that of control ($t_{98}=7.25$; $p=0.001$).

CONCLUSION: We concluded that hs-CRP level is increased in cases of cerebrovascular accident- ischemic as well as haemorrhagic, suggesting an inflammatory response in acute cerebrovascular accident. hs-CRP level is increased in patients with ischemic cerebrovascular accident dramatically but not in haemorrhagic cerebrovascular accident which might be considered as useful adjunct method for determining type of stroke in patients with cerebrovascular problems.

KEYWORDS

High sensitivity C-reactive protein, Haemorrhagic cerebrovascular accident, Stroke.

INTRODUCTION

Cerebrovascular accident (commonly called stroke) is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus, the diagnosis of stroke is clinical and laboratory studies including brain imaging are used to support the diagnosis.

The clinical manifestation of stroke are highly variable because of the complex anatomy of the brain and its vasculature. Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds. Neurologic symptoms are manifest within seconds because neurons lack glycogen, so the signs of neurological deficit is rapid. If the cessation of flow lasts for more than a few minutes, infarction or death of brain tissue results. When brain perfusion quickly restored, brain tissue can recover full and the patient's symptoms are only transient this is called a transient ischemic attack (TIA). WHO defined cerebrovascular accident as 'rapidly developed clinical signs of focal (or global) disturbance of cerebral function; lasting for more than 24 hours or leading to death, with no apparent cause other than vascular origin'. This definition includes the stroke which is caused by a cerebral infarction, a Primary intracerebral hemorrhage (PICH), an intraventricular haemorrhage (IVH), a subarachnoid haemorrhage (SAH), while it excludes a subdural haemorrhage (SDH), epidural haemorrhage or an intracerebral haemorrhage (ICH) or infarction which is caused by an infection/tumor.

Cerebrovascular accident is the most common cause of adult disability and the second leading cause of death worldwide. Despite a decline in the stroke mortality, the incidence of stroke is not declining. The burden of stroke is likely to increase substantially in the future because of the aging population. It places a major effect on society in terms of death, disability and economic cost. Several population based survey on stroke were conducted from different parts of India. During the last decade the age -adjusted prevalence rate of stroke was 250-350 per 100000 populations in India.

The WHO has estimated 6.2 million deaths which were caused by stroke in 2015 worldwide, an increase of 830,000 since the year 2000, which was equivalent to 9.9 % of the total deaths. Over 85 % of these deaths occurred in people who were living in the low to the middle income countries. Approximately 33 % of these deaths occurred in people who are aged less than 70 years³⁴. Stroke accounts for 2 % of the hospital registrations, 1.5 % of the medical registrations and 9 - 30

% of the neurological admissions in the major hospitals¹.

In India, after several population based survey, cerebrovascular accident is leading cause of disability adjusted life years (DALY). It is a worldwide health problem. It makes an important contribution to morbidity, mortality and disability in developed as well as developing countries. Stroke is one of the leading causes of death after heart disease and malignant diseases.²

C-Reactive Protein (CRP), an Acute Phase Reactant synthesized in liver in response to cytokine interleukin-6, is also a factor in development of atherosclerotic plaque. High sensitivity C-Reactive Protein (hs-CRP) is emerging as a new marker for coronary artery disease and associated cerebrovascular disorders. Although hs-CRP was initially believed to be a marker of vascular inflammation only, but recent researches indicate that it also plays an active role in atherogenesis.³

Inflammation theory of atherosclerosis suggests – CRP is not only a marker of inflammation but also proinflammatory, proatherosclerotic and prothrombotic in nature. It enhances production of MCP-1 (Monocyte chemoattractant protein) recruiting more monocytes, promoting uptake of LDL by macrophages and activation and thus plaque formation leading to atherosclerosis and subsequently stroke⁴.

To evaluate the serum levels of high sensitivity C-reactive protein (hsCRP) in different types of cerebrovascular accidents on admission.

MATERIALS & METHODS

STUDY AREA: Both rural and urban catchment areas of around Darbhanga Districts of Bihar.

INCLUSION CRITERIA: Patients of either sex above 12 years of age with clinically or radiologically diagnosed cerebrovascular accident, Primary intracerebral hemorrhage, Interventricular hemorrhage, Subarachnoid hemorrhage, Acute ischemic infarct of brain.

CONTROL: 50 age and sex matched controls were selected from the general population for comparison of hs-CRP levels.

EXCLUSION CRITERIA:

1. Patient with recent clinical infection, chronic inflammatory

- condition or neoplastic disease
2. Patient with surgery or major trauma in the previous month
3. Patient with major renal or hepatic disease
4. Patient on antioxidant medication
5. Individuals who are chronic smoker or chronic alcoholic
6. Past history of cerebrovascular accident, Transient ischemic attack.

STUDY POPULATION: Cases of cerebrovascular accident admitted in indoor of Medicine Department of Darbhanga Medical College and Hospital, Laheriasarai, Bihar.

STUDY PERIOD: March 2019 to December 2020.

SAMPLE SIZE: 50 patients.

SAMPLE DESIGN: Simple random selection amongst patients satisfying inclusion criteria.

STUDY DESIGN: A hospital based cross sectional study.

METHODOLOGY:

On admission cerebrovascular accident was confirmed by history, clinical examination and radiological evidences, 5 ml of venous blood was drawn from subject (from large peripheral vein) under aseptic precaution in a sterile container and sent for hs-CRP within 72 hours of onset of symptoms.

RESULT AND DISCUSSION

This study was done in the Department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Bihar from March 2019 to March 2020. 50 patients of either sex above 12 years of age admitted in Medicine Department of DMCH, Laheriasarai, Bihar with clinically or radiologically diagnosed as cerebrovascular accident through simple random selection. 50 age and sex matched controls were selected from the general population. Patients with recent clinical infection, chronic inflammatory condition or neoplastic disease, patients with surgery or major trauma in the previous month, past history of stroke, patients with major renal or hepatic disease, patients on antioxidant medication ,individuals who were chronic smoker or chronic alcoholic were excluded from the study.

On admission stroke was confirmed by history, clinical examination and radiological evidences, 5 ml of venous blood was drawn from subject (from large peripheral vein) under aseptic precaution in a sterile container and sent for hs- CRP within 72 hours of onset of symptoms. Apart from this all other routine investigations were sent to evaluate comorbidities and necessary exclusions.

Serum hs-CRP was done by sensitive Immunoturbidimetry Test (Rocheanalyser). hs-CRP level $\geq 3\text{mg/dl}$ was taken as high value. The hs-CRP levels are now becoming universally standardised and most centres accept a value above 3 mg/dl as high.⁵

This was a hospital based cross sectional study and the findings and inference derived from the study are discussed below.

The mean age (mean $\pm$ s.d.) of the cases was 60.70 ± 10.71 years with range 33 - 82 years and the median age was 64.5 years. The proportion of the patients with age ≥ 60 years (58.0%) was significantly higher ($p=0.023$). In this study, 70% patients were between 50-69 years of age. This observation was similar to the studies from South East Asia and western literature⁶. Among the studied patients 4% were below 40 years of age. The Indian studies have shown that about 10- 15% of the strokes occurred in patients who were below the age of 40 years, which was high as compared to that in other countries. This discrepancy can be explained due to a small sample size and study being done at a tertiary care centre which mostly receives referred cases.

Proportion of males 29(58%) was significantly higher than that of females 21(42%). Male is to female ratio was found to be 1.4 : 1. Evidently, males outnumbered females in this study in synchrony with a similar study from India by Nayak et al⁷. However such a preponderance of stroke in male in hospital based studies from developing countries like India could be attributed to referral bias.

The mean age (mean $\pm$ s.d.) of the males was 62.51 ± 11.31 years with range 33 – 82 years and the median age was 65 years. The mean age

(mean $\pm$ s.d.) of the females was 58.19 ± 9.52 years with range 34 – 70 years and the median age was 58 years. There was no significant difference in the mean age of males and females ($p=0.16$). Thus subjects of both sexes were equally distributed over age.

We found that 56% of the patients had Hemorrhagic stroke and rest 44% had Ischemic stroke. Higher rate of haemorrhagic stroke in this study does not represent the actual proportions in the general population or community. This is due to the fact that, this study was not conducted at the community level. Majority of the patients with stroke, especially of ischemic stroke are not complicated and so are not referred to the higher centers for better management. They are managed at local health centers; mostly the complicated patients are referred to the higher centers. Nevertheless, the local patients from darbhanga also had higher rate of haemorrhagic contrary to the other studies (e.g. Indian Collaborative Acute Stroke Study- ICASS)⁸. Again, this may be due to the fact that, even in case of the local patients from darbhanga, most patients do not present to the hospitals within the time interval when they could be candidate for thrombolytic therapy (which is mostly due to lack of awareness and health education); so, the uncomplicated low- risk patients either due to apparently less dangerous symptom are unwilling to be admitted to trolley or floor (this is the actual scenario in our extremely overburdened hospital, where most of the patients have to be admitted on trolley and occasionally on floor, initially) or they were not admitted due to actual low-risk as assessed by the physician who attended them at OPD or at the Emergency Department. It should also be noted that incidence of haemorrhagic stroke in India is actually higher (31-35%) than that seen in western countries⁹.

In this study there was no significant association between age groups and stroke ($p=0.83$). We found that the risk of stroke was 1.08 times more among the patients having age ≥ 60 years as compared to the patients having age < 60 years [OR-1.08(0.49, 2.39); $p=0.83$] but the risk was not significant. Though most of the available literature shows an increase in incidence of stroke with increasing age, this result in our study can be explained by a small sample size where most of the cases were between 50-70 years of age.

There was no significant association between gender and stroke ($p=0.68$) in present study and the risk of stroke was 1.18 times more among male patients as compared to female patients [OR-1.18(0.53, 2.63); $p=0.68$] but the risk was not significant

The mean level of hsCRP (mean $\pm$ s.d.) of the cases in our study was 7.65 ± 7.01 with range 1.4 – 26 and the median was 3.7 and 58% of the cases were having level of hsCRP ≥ 3 ($p=0.023$). Mean level of hsCRP of cases was significantly higher than that of control ($t=7.25$; $p=0.001$). This finding was similar to the results of a study done by Jaydip Ray Chaudhary and others in Hyderabad in 2011. They found that the mean hsCRP was significantly higher in stroke patients (3.8 ± 2.5) than controls (1.8 ± 1.5) ($P < 0.001$). High hsCRP had higher frequency in stroke patients 130 (61.9%) compared to controls 10 (6.6%), $P < 0.001$.¹⁰

In this study proportion of patients with level of hsCRP ≥ 3 (58%) was significantly higher than that of patients with level of hsCRP < 3 (42%) ($p=0.0001$). Pinky Talreja Mishra and others in year 2010 conducted a study in Kanpur titled 'High Sensitivity C-reactive Protein (hsCRP) Level in Cerebrovascular Accident (Stroke) and found that hsCRP levels were found to be increased in stroke patients and on comparison with controls, the values were found to be significant ($p < 0.001$).¹¹

There was significant association between type of stroke and level of hsCRP ($p=0.00003$) in this study. The risk of hsCRP ≥ 3 was 6.236 times more among patients having Ischemic stroke as compared to patients having Hemorrhagic [OR-6.23(2.11, 45.53); $p=0.00003$] and the risk was significant. The mean level of hsCRP was significantly higher for the patients with Ischemic stroke ($t=8.99$; $p=0.0001$).

These results were supported by a study by Jaydip Ray Chaudhary and others who found that high hsCRP level was more prevalent in the stroke subtypes of cardioembolic stroke (83.3%) and large artery atherosclerosis (72%) After adjustment of regression analysis it was observed that high level hsCRP is independently associated with acute ischemic stroke (Odds 4.5; 95% CI: 2.5-12.2); especially the stroke subtypes of cardioembolic stroke, (odds ratio 3.4, 95% CI: 1.9-10.5) and large artery atherosclerosis (odds ratio 2.1, 95% CI: 1.5-3.8).¹⁰

A study done by Seyed Ali et al in year 2010 shows that hs-CRP level increases in patients with Ischemic infarct dramatically but not in hemorrhagic stroke which might be considered as a usefully adjunct method for determining type of stroke in patients with cerebrovascular problems.¹²

Jitendra Ahuja and others in 2012 conducted a study in India titled 'Study of C-Reactive Protein Level in Patients of Acute Ischemic Stroke and Its Correlation With Serum Lipid Profile' and found that out of 100 patients of acute ischemic stroke, 70% of patients had raised CRP while 30% of patients had low level of CRP. The finding of this study clearly revealed that increased level of C-reactive protein is associated with increased risk of ischemic stroke.¹³

Roudbary SA et al assessed the concentration of hs-CRP in patients with documented ischemic and hemorrhagic stroke in the first 24 hours of the onset of symptom and found that serum level of hs-CRP in Ischemic patients were 18.92 ± 11.28 and in hemorrhagic group was 2.65 ± 1.7 . This relationship was statistically significant ($P < 0.0001$).¹⁴

After doing regression analysis we found that risk of stroke was 24.31 times for level of $hsCRP \geq 3$ [$OR=24.31(5.75, 102.68); p=0.0001$] and the risk was significant. The Hisayama study, a cohort follow up study in middle aged and elderly Japanese men & women found that elevated serum hs-CRP levels are an independent risk factor for future ischemic stroke in men and that the coexistence of another risk factor with high hs-CRP levels increased the risk further.¹⁵

Table-: Distribution of Type of Stroke, stroke patients with/without diabetes mellitus (DM) and level of HsCRP

		hsCRP ≥ 3 (n =29)	hsCRP <3 (n =21)	TOTAL	hsCRP (Mean $\pm$ s.d.)
Type of Stroke	Ischemic	21	1	22	13.85 $\pm$ 6.3
	Row %	95.5	4.5	100.0	1
	Col %	72.4	4.8	44.0	
	Hemorrhagic	8	20	28	2.78 $\pm$ 1.48
	Row %	28.6	71.4	100.0	
	Col %	27.6	95.2	56.0	
Stroke patients with/without diabetes mellitus (DM)	TOTAL	29	21	50	$t_{48}=8.99$; $p=0.0001$
	Row %	58.0	42.0	100.0	
	Col %	100.0	100.0	100.0	
	Stroke patients with DM	16	5	21	10.09 $\pm$ 8.5
	Row %	71.4	28.6	100.0	2
	Col %	51.7	28.6	42.0	
	Stroke patients without DM	13	16	29	5.89 $\pm$ 5.14
	Row %	48.3	51.7	100.0	
	Col %	48.3	71.4	58.0	
	TOTAL	29	21	50	$t_{48}=2.16$; $p=0.035$
	Row %	58.0	42.0	100.0	
	Col %	100.0	100.0	100.0	

CONCLUSION

From this study we concluded that hs-CRP level is increased in cases of cerebrovascular accident- ischemic as well as haemorrhagic, suggesting an inflammatory response in acute cerebrovascular accident. hs-CRP level is increased in patients with ischemic cerebrovascular accident dramatically but not in haemorrhagic cerebrovascular accident which might be considered as useful adjunct method for determining type of stroke in patients with cerebrovascular problems. As we had a small sample size a larger study is needed to endorse our observations and to analyse further about association between hs-CRP level and cerebrovascular accident. A larger study should also focus on whether hs-CRP level needs to be included as a health screening protocol.

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