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Original Research Paper

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C- REACTIVE PROTEIN - AN OUTCOME PREDICTOR IN ACUTE INTRA CEREBRAL HEMORRHAGE

Pankaj Kumar Gupta	D.M. (Neurology), Consultant Neurologist, Arogyadham hospital Gwalior, (M.P.) India
Arti Gupta*	M.D. (Pathology), Associate Professor, Department of Pathology, GR Medical College, Gwalior, Madhya Pradesh, India. *Corresponding Author
Pushpendra Kumar Gupta	M.S. (Ophthalmology), Ophthalmologist, Bhopal, (M.P.), India

ABSTRACT **Background** Inflammation is considered to play an important role in the pathogenesis of cerebrovascular disease. C-reactive protein (CRP) is a hallmark of acute inflammatory response. There are growing evidences that inflammations are involved in atherosclerosis, plaque formation and ischemic event. There are many studies showing that the levels of CRP (hsCRP) have been found to be raised in cerebral ischemia, but there are few studies about the association of CRP level and intracerebral hemorrhage. This study was done to observe the levels of CRP (hs-CRP) in patients with acute intracerebral hemorrage, and to assess the severity and outcome. **Methods** Study was conducted in 30 patients admitted in medical ward and medical ICU of LLR and associated hospitals, G.S.V.M. medical college Kanpur. All patients of acute intra cerebral hemorrhage fulfilling the Inclusion and exclusion criteria were enrolled in the study. Serum CRP (hs-CRP) was measured by Turbidimetric immunoassay. Statistical analysis was done by using T test and chi square test. **Results** Maximum numbers of our patients were in the age group of 40-79 years with mean age of 64 years. Intra cerebral hemorrhage was more prevalent in males. CRP level was found to be elevated statistically significant in intra cerebral hemorrhage patients as compared to controls. There was significant rise from first day to third day ($P<0.05$). Mean CRP level of expired patients was elevated as compared to whole study group ($P<0.05$). **Conclusions** We concluded that higher C reactive protein level may be associated with worse prognosis and poor outcome in intra cerebral hemorrhage patients and CRP level can be an important factor of prognostic significance in these patients.

KEYWORDS : Intra cerebral hemorrhage, hemorrhagic stroke, hsCRP, hypertensive bleed

INTRODUCTION:

Stroke is a leading cause of mortality and morbidity worldwide. According to WHO, about 15 million population is affected from stroke yearly and the overall disease burden of stroke is higher in the developing countries [1, 2]. Deaths from stroke are more common in developing and less developed countries [3]. Spontaneous intra cerebral hemorrhage (ICH) is a devastating type of stroke with high global rates of deaths and disability. ICH is accountable for more than half of all deaths caused by stroke. Up to one-third of patients with ICH may develop hematoma expansion , leading to a higher mortality rate and poor clinical outcomes [4].The overall rate of stroke-associated mortality is decreasing but the absolute number of people with stroke, stroke survivors, stroke-related deaths, and the global burden of stroke- related morbidity is increasing [5]

There are growing evidences that inflammations are involved in atherosclerosis and cerebrovascular accidents. Earlier studies have shown that an acute inflammatory reaction may arise within minutes of an intra cerebral hemorrhage, consequently triggering an inflammatory cascade that exacerbates secondary brain damage [4]. Levels of C-reactive protein (CRP), as an indicator of inflammation, tend to be elevated following stroke. Studies have established that levels of CRP are also related with hematoma volume and clinical outcomes after intra cerebral hemorrhage[4]. C-reactive protein is an acute phase protein of produced in liver that increases, following interleukin 6 secretions by macrophages & T cells [6]. Inflammation plays an important role in pathology of spontaneous intra cerebral hemorrhage. Inflammatory markers on admission are associated with worse clinical outcome. CRP level >10 mg/L is independent predictor of early hematoma growth and neurological worsening in ICH and associated with increased mortality [7]. Levels of CRP measured after ICH predicted complementary aspects of prognosis that suggests the possibility of elevated levels of CRP is directly related to extent of cerebral parenchymal injury. Currently non contrast CT scan head is a standard diagnostic test for ICH. This study was done to investigate the prognostic significance of C - reactive protein level in acute intra cerebral hemorrhage patients.

METHODS:

The study was conducted on 30 patients admitted in Medical wards, ICU and emergency ward of LLR and associated hospitals, GSVM medical college, Kanpur, Uttar Pradesh.

Inclusion criteria:

1. All the patients of acute intra cerebral hemorrhage of either sex without any history of head injury, recent anticoagulant treatment.
2. Patients of whom the symptoms of ICH have started within 72 hours.

Exclusion criteria:

1. Patients with any recent head injury.
2. Patients with recent anticoagulation treatment.
3. Patients of ICH due to any other causes i.e aneurysm, AV malformation, bleeding or coagulation disorders.

The patients and controls were subjected to detailed history, clinical examination and investigations as per the Performa. Neurological deficit was scored by using the Scandinavian stroke Scale. Serum CRP level was measured by Turbidimetric immunoassay. It is a method of quantitative estimation of CRP in serum. Statistical analysis was done by using tools like T test, chi square test to assess the significance or difference between study and control group and between the subgroups of study group.

RESULTS:

A total of 30 patients who fulfilled inclusion criteria were included in the study. Mean age of patients enrolled in the study was 64 years. 73.33 % of the patients were between the ages 40-79 years. In the current study, 18 patients were males

and 12 were females [Table I]. Male to female ratio was 1.5:1. Smoker comprised 36.66 % of the patients in the group. Hypertension was the most common risk factor with 83.33 % of the patients having it. The other comorbidities in their order of prevalence were dyslipidemias (33.33%), chronic alcoholism (26.66%), and diabetes (10%). Clinical presentations in patients included hemiparesis (90%), slurring of speech (73.33%) altered sensorium (70%), vomiting (66.66%), headache (40%), aphasia (10%) and seizures (3.33%) etc. Serum CRP level was measured on admission, third and seventh day. Three patients expired till seventh day [Table II]. The mean CRP levels in patients of intra cerebral haemorrhage was 14 mg/L on first day, 19.38 mg/L on third day and 19.03 mg/L on seventh day as compared to controls (6.6mg/L) [Table III]. We also studied the correlation of CT scan findings with CRP level. In our study 13 cases had lesion <2.5 cm in CT scan out of which 53.8% patients had CRP between 3-10 mg/L and 46.2% had CRP between 11-24 mg/L. 17 patients had size of lesion in CT scan more than 2.5cm out of which 23.53% had CRP between 3-10mg/L, 52.94% had CRP between 11-24 mg/L and 23.53% patients had the CRP more than 24mg/L. The above observations showed that CRP level increases with increase in size of lesion indicating more brain parenchyma damage. CRP level was found to be raised statistically significant in ICH as compared to controls. There was significant rise from first day to third day (P<0.05). There was no significant difference in CRP from third day to seventh day (P>0.05). Mean CRP of expired patients was significantly higher as compared to the mean CRP of whole study group (P<0.05).

Table-I Age and sex distribution

Age	Male	Female	Total	Percentage
10 - 19	0	0	0	0
20 - 29	0	0	0	0
30 - 39	1	1	2	6.66
40 - 49	1	1	2	6.66
50 - 59	3	2	5	16.66
60 - 69	5	3	8	26.66
70 - 79	4	3	7	23.33
80 - 89	4	2	6	20.00
90 - 99	0	0	0	0
Total	18	12	30	

Table II CRP level in intra cerebral hemorrhage patients (n=30)

CRP(mg/L)	On admission	III day	VII day
3-10	16 (53.33%)	09 (30%)	08 (26.66%)
11-24	11 (36.66%)	15 (50%)	11 (36.66%)
25-36	01 (3.33%)	04 (13.33%)	07 (23.33%)
37-48	02 (6.66%)	02 (6.66%)	01 (3.33%)

Table- III Statistical analysis of CRP level in Intra cerebral hemorrhage

GROUP	MEAN CRP(mg/L)	S.D.	STATISTICAL VALUES
Control (n=20)	6.6	1.795	t=3.23
Cases (n=30) On admission	14	9.92	P<0.005
Cases (n=30) On admission	14	9.92	t=1.85
Cases(n=30) on III day	19.38	12.02	P<0.05
Cases(n=30) on III day	19.38	12.02	t=0.10
Cases(n=27) on VII day	19.03	11.72	P>0.05
Cases(n=30) on admission	14	9.92	t=1.72
Cases(n=27) on VII day	19.03	11.72	P<0.05

DISCUSSION:

The study was a conducted in Medicine department of LLR and associated hospitals, GSVM medical college Kanpur in 30 patients diagnosed with acute intracerebral hemorrhage (hemorrhagic stroke). Stroke is the third major cause of death in India according to CDC 2012 and leading cause of morbidity [1]. The CRP level was measured on admission, third day and seventh day in all hemorrhagic stroke patients fulfilling inclusion criteria. Correlation between serum CRP level and neurological outcome in terms of improvement, morbidity and mortality was observed. The age distribution of patients was from 10-19 years to 90-99 years age groups with mean age of 64 years and maximum numbers of patients were of 40-79 years age group. Age is generally considered as a non-modifiable risk factor for stroke [8]. Similar results were observed in studies done by SD Bhaisare et al [1], PT Mishra et al [9] Jayachandra et al, [10] the Mumbai Stroke Registry [11] and Y Wakugawa in the Hisayama Study [12]. In this study there was male preponderance with 60% cases being males and 40% were females. Male to female ratio in the current study was 1.50:1. Male sex is also considered as a non modifiable risk factor for stroke [8]. The most common modifiable risk factor in the study was hypertension (83.33%) followed by dyslipidemias (33.33%). The most common addiction seen in study group was tobacco smoking with a prevalence of 36.66%. The mean CRP levels in patients of intra cerebral haemorrhage was 14 mg/L on first day, 19.38 mg/L on third day and 19.03 mg/L on seventh day as compared to controls (6.6mg/L). This shows that hsCRP levels are increased in case of acute hemorrhagic stroke. In the study by Yoshiyuki Wakugawa et al, [12] high hsCRP levels were observed as an independent risk factor for ischemic stroke in males but not for haemorrhagic stroke in either men or women but it differs from study by PT Mishra et al [9] which showed higher hsCRP in hemorrhagic stroke. This suggests that higher hsCRP levels are associated with severe neurological deficit and thus poor outcome. ICH patients were classified on the basis of Scandinavian Stroke Scale into minor, moderate and severe stroke. Patients with minor stroke had lower CRP values as compared to patients with severe stroke. Thus, higher CRP levels were associated with poor prognosis. In this study, the CRP levels were correlated with outcomes in terms of death. Mean CRP of expired patients was significantly higher as compared to the mean CRP of whole study group (P<0.05). Similar observations were found in study by Jayachandra et al [10]. Thus there was a relation between high CRP and mortality. We also studied the correlation of CT scan findings with CRP level. Our observations showed that CRP level increases with increase in size of lesion in CT scan head. The prognostic significance of hsCRP may be related to the extent of necrosis in the brain parenchyma and somewhat unknown determinants of intensity and concentration of acute phase reactants. Mario Di Napoli et al observed that CRP>10 mg/L is independently predictive of early hematoma growth (EHG) and early neurological worsening (ENW), both of which are related with increased mortality [7]. The prognostic significance of CRP regarding neurological deficits and mortality as outcomes of intra cerebral hemorrhage may help clinician to suggest realistic expectations to families of ICH sufferers. Thus CRP and other inflammatory markers can be measured in routine for all intra cerebral hemorrhage patients to assess the probability of hematoma expansion, neurological worsening and to provide expected prognostic information.

CONCLUSIONS:

In this study CRP level was elevated in intra cerebral hemorrhage patients. CRP was significantly higher in expired patients and in patients with severe neurological deficit and large lesion. Higher CRP level had poor prognosis as compared to patients with lower CRP. Results in this study suggest the role of inflammation and inflammatory markers

such as CRP in severity of intra cerebral hemorrhage. Increased risk of early hematoma growth (EHG) can be assessed by measurement of CRP in the first few hours after symptom onset. This may contribute to improve patient care and deliver prognostic information.

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