CORRELATION BETWEEN MEAN SERUM C-REACTIVE PROTEIN (CRP) LEVEL AND MEAN LESION VOLUME IN ACUTE ISCHEMIC STROKE

Muhammad Zahid Younis, Ejaz Ahmed Mian, Syed Onaiz Zulfiqar Anwar, Fatima Naseem

Combined Military Hospital, Dera Ismail Khan, Pakistan

ABSTRACT

Objective: To determine the correlation between mean serum C-reactive protein (CRP) level and mean lesion volume in acute ischemic stroke.

Study Design: Cross sectional study.

Place and Duration of Study: This study was conducted at Department of Neurology and General Medicine Combined Military Hospital, Quetta, Pakistan, from Jan 2016 to Jul 2016.

Methodology: A total of 50 patients of both genders fulfilling the inclusion criteria were included in the study using non-probability consecutive sampling technique after taking informed consent. All patients were subjected to CT scan and infarct volume was calculated. Meanwhile blood samples were collected for CRP levels.

Results: 21 (42%) were between 18-50 years of age while 29 (58%) were between 51-80 years of age. Mean age was 52.46 ± 13.33 years, 31 (62%) were male and 19 (38%) were females, mean serum CRP level of the patients was 37.56 ± 30.78 mg/L, mean lesion volume in acute ischemic stroke cases as 7.5 ± 3.59, Pearson correlation coefficient of mean lesion volume and serum CRP in acute ischemic stroke was calculated r=0.9162 (*p*-value 0.01).

Conclusion: Correlation between CRP levels and infarction volume on CT scan in Acute Ischemic Stroke was found to be positive, therefore it may be used as a routine screening tool for estimation of infarct volume.

Keywords: Acute ischemic stroke, Correlation, Serum C-reactive protein (CRP), Mean lesion volume.

INTRODUCTION

Stroke is one of the most frequent causes of death and disability[1] worldwide. It is the first leading cause of disability in the developing and developed countries[2]. Its worldwide incidence has been shown to be around 9 million with a prevalence of 30.7 million[3]. 795,000 new or recurrent strokes occur per year in the United States, accounting for approximately 1 in 18 deaths[4]. The risk of stroke has plumped by 100% or more in the past decade, especially in third world countries where it accounts for more than 85% of all stroke-related mortality[5]. No large-scale epidemiological studies are available to determine the true incidence of stroke in Pakistan, however, a trial showed the prevalence of stroke to be 6.41%[6].

The treatment of stroke depends on its type i.e, with the stroke being hemorrhagic or ische-

mic. Computerized axial tomography (CT) scan brain is the fastest and the most robust technique to detect intra-cerebral hemorrhage (ICH) in acute stroke patients[7]. Other radiological tests include CT angiography (CTA) and cranial magnetic resonance imaging (MRI). Involvement of these imaging techniques depends on their availability, general state of the patient and cost factors. Therefore, a number of biologic inflammatory markers such as leptin, high sensitivity C-reactive protein (hs-CRP), insulin, cortisol, fibrinogen, protein C, protein S, von Willebrand factor, D-dimer (DD), Antithrombin III and MMP-9 (Matrix Metalloproteinase-9) have been evaluated for their prognostic values and their relationship with lesion volume in stroke patients[8].

C-reactive protein (CRP) is synthesized by liver and then secreted in blood. It is released in response to acute inflammation as a preliminary part of acute phase response by the body. The acute phase response develops in a wide range of acute and chronic inflammatory conditions like bacterial, viral, or fungal infections, rheumatic

and other inflammatory diseases, malignancy and tissue injury or necrosis. CRP is significantly increased in first 3 hours in acute ischemic stroke patients[9].

Glickman *et al* found that when the levels of CRP were added to the National Institutes of Health Stroke Scale (NIHSS), the combination was highly predictive of stroke[10]. Similarly Jaydip Chaudry and his colleagues concluded that high hsCRP level is strongly associated with and is an independent predictor of acute ischemic stroke[11]. The association was found in all ischemic stroke subtypes. Youn *et al* suggested that CRP may serve as a helpful serologic marker in the evaluation of severity of acute ischemic stroke[12].

Inflammation plays a pivotal role in the progression of acute ischemic stroke. Heidi Ormstard and his colleagues studied the correlation of different inflammatory markers (serum C-reactive protein (CRP), glucose, and hemoglobin) in acute ischemic stroke patients. They also studied the relationship of these inflammatory markers with stroke lateralization, type, and infarct volume. It was found that, in acute ischemic stroke, infarct volume was significantly positively correlated with CRP level ($r=0.47$, $p=0.005$)[13].

Pakistan is a developing country and health care resources are very limited. Basic neuro-imaging studies like CT scan and MRI (diagnostic tools to diagnose acute ischemic stroke and determine its volume) are not available in many parts of the country. On the other hand, CRP is an easily available and cost effective parameter. The purpose of this study was to determine the local correlation between CRP levels and infarction volume on CT scan in acute ischemic stroke. On the basis of CRP levels, it may be recommended as a routine screening tool for estimation of infarct volume on CT scan.

METHODOLOGY

This cross-sectional study was carried out at Department of Neurology and General Medicine, Combined Military Hospital (CMH), Quetta Pakistan from 31st July 2015 to 31st January 2016. This study was conducted after approval from the hospital ethical and research committee. Sample size was calculated by WHO sample size calculator keeping significance level of 5%, Correlation coefficient (r) = 0.47. A total number of 50 patients were selected after taking informed written consent by using non-probability consecutive sampling technique.

Patients aged between 18 to 80 years of both genders with acute ischemic stroke confirmed on CT scan which was done within 7 days of development of symptoms of stroke were included in the study. Patients with concomitant acute or chronic inflammatory conditions (bacte-rial, viral, or fungal infections), rheumatic or other inflammatory diseases, malignancy and patients with tissue injury or necrosis were excluded from the study as these conditions act as confounders and if included would have introduced bias in the study results. All indoor patients meeting the inclusion criteria were included in the study.

Informed consent was obtained from the patient or his next of kin, after explaining the purpose and benefits of study. Data was collected on a specially designed proforma. All patients were subjected to detailed history and examination. Infarct was confirmed on CT scan brain. The lesion volume was calculated on CT scan by the radiologist. Within 24 hours of admission, blood sample was drawn under strict aseptic technique and sent to specified laboratory of the hospital on the same day. CRP levels were measured under the supervision of an experienced pathologist with CRP Latex Test Kit using latex agglutination method.

Data collected was entered in SPSS (16.0). Continuous variables were expressed as mean ± SD. Categorical variable were expressed as frequencies and percentages. The Pearson correlation coefficient was used to correlate mean serum CRP level and mean infarct volume on CT scan. The *p*-value of ≤0.05 was significant.

RESULTS

A total of 50 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the correlation between mean serum C-reactive

protein (CRP) level and mean lesion volume in acute ischemic stroke. Age distribution of the patients was done showing that 21 (42%) were between 18-50 years of age while 29 (58%) were between 51-80 years of age, mean age 52.46 ± 13.33 years (table-I). 31 (62%) patients were male and 19 (38%) were females (table-II). Mean serum CRP level of the patients was 37.56 ± 30.78 mg/L. Mean lesion volume in acute ischemic stroke

Table-I: Age distribution (n=50).

Age (in years)	No. of patients	Percentage (%)
18-50	21	42
51-80	29	58
Mean ± SD	52.46 ± 13.33	

Table-II: Gender distribution (n=50).

Gender	No. of patients	Percentage (%)
Male	21	42
Female	29	58

Table-III: Mean serum CRP levels of the patients and mean lesion volume (n=50).

CRP	Mean ± SD
	37.56 ± 30.78
Lesion volume	7.5 ± 3.59

Table-IV: Pearson correlation coefficient of mean lesion volume and serum CRP in acute ischemic stroke (n=50).

Lesion volume	Mean ± SD
	7.5 ± 3.59
Serum CRP levels	37.56 ± 30.78

r value=0.7971, p-value=0.01

cases found 7.5 ± 3.59 (table-III).

Pearson correlation coefficient of mean lesion volume and serum CRP in acute ischemic stroke was calculated r=0.9162 (p-value 0.01). This was a strong positive correlation.

DISCUSSION

Acute ischemic stroke may trigger an inflammatory response that leads to increased levels of C-reactive protein (CRP). High levels of CRP may be associated with poor outcome because they reflect either an inflammatory reaction or tissue damage. CRP is an easily available and cost effective parameter. We aimed to determine the local correlation between CRP levels and infarction volume on CT scan in acute ischemic stroke. On the basis of CRP levels, it

may be recommended as a routine screening tool for estimation of infarct volume on CT scan.

In our study, mean serum CRP level of the patients was 37.56 ± 30.78 mg/L, mean lesion volume in acute ischemic stroke cases was 7.5 ± 3.59, pearson correlation coefficient of mean lesion volume and serum CRP in acute ischemic stroke was r=0.9162 (p-value 0.001). This was a strong positive correlation, which that high CRP levels go with high Lesion volume.

Inflammation plays a pivotal role in the progression of acute ischemic stroke. Heidi Ormstard and his colleagues studied the correlation of different inflammatory markers (serum C-reactive protein (CRP), glucose, and hemoglobin) in acute ischemic stroke patients. They also studied the relationship of these inflammatory markers with stroke lateralization, type, and infarct volume. It was found that, in acute ischemic stroke, infarct volume was significantly positively correlated with CRP level (r=0.47, p=0.005)[13]. These findings were in agreement with our findings.

Many investigators have demonstrated that a high CRP level after ischemic stroke is a predictive factor of poor outcome[14,15] Therefore, testing the CRP level would not only identify patients being at high risk, but would also provide an opportunity for intervention. In one study[16], poor discharge outcome was assessed in patients of acute ischemic stroke at discharge using the Modified Rankin Scale (MRS >2). Multivariate logistic regression analysis was performed to determine the risk factors of poor outcome at discharge after adjusting for potential confounders. They found CRP level measured at admission to be one of the independent predictors of poor outcome at discharge. Results of another study[17] indicated a significant association between elevated baseline high sensitivity CRP and unfavorable long-term functional outcome. Similarly High-sensitivity C-reactive protein was also shown to be an independent predictor of short-term outcome and mortality after AIS in patients with acute ischemic stroke[18]. Elevated

baseline hs-CRP level is independently associated with ischemic stroke risk but exhibit no clear effect on hemorrhagic type of stroke[19]. However; being the limitation of the study we could not follow the patients for their outcome.

Adnan Khan *et al*[20] found out the frequency of raised C-reactive protein (CRP) levels in patients with first-ever acute ischemic stroke and recorded that thirty one (46.27%) patients had hs-CRP level of >3.0 mg/L having a high risk of ischemic stroke while 22/67 (32.8%) with hs-CRP level of 1.0-3.0 mg/L had an average risk of ischemic stroke. Fourteen (20.89%) patients had hs-CRP level of <1.0 mg/L and had low risk of ischemic stroke. Mean serum level of hs-CRP in ischemic stroke patients was 23 ± 11.24 mg/L, which was near to our recorded CRP levels.

In summary, as Pakistan is a developing country and health care sources are very limited where basic neuroimaging studies like CT scan and MRI (diagnostic tools to diagnose acute ischemic stroke and determine its volume) are not easily available in many parts of the country. CRP is an easily available and cost effective parameter. The local correlation between CRP levels and infarction volume on CT scan in acute ischemic stroke On the basis of CRP levels is found to be positive, so, it is recommended that it may be used as a routine screening tool for estimation of infarct volume.

CONCLUSION

There was a positive correlation between serum C-reactive protein and mean infarct volume in acute ischemic stroke. On the basis of our findings, serum CRP may be used as a routine test to estimate infarct volume if CT scan is either not available or not affordable to a patient.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Sahan M , Sebe A, Acikalin A, Akpinar O, Koc F, Ay MO et al. Acute-phase reactants and cytokines in ischemic stroke: do they have any relationship with short-term mortality? Eur Rev Med Pharmacol Sci 2013; 17(20): 2773-7.
2. Hashmi M, Khan M, Wasay M. Growing burden of stroke in Pakistan: A review of progress and limitations. Int J Stroke 2013; 8(7): 575-81.
3. Fischer M, Norrving B. The international agenda for stroke. In: Ist Global Conference on Healthy Lifestyles and Non-communicable Disease Control Moscow 2011; 1-29.
4. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM. Heart disease and stroke statistics 2011 update: A report from the American Heart Association. Circulation 2011; 123(1): e18-e209.
5. Nomani A, Nabi S, Badshah M, Ahmed S. Review of acute ischemic stroke in Pakistan: Progress in management and future perspectives. Stroke Vasc Neurol 2017; 2(1): 30-39.
6. Khealani BA, Hameed B, Mapari UU. Stroke in Pakistan. J Pak Med Assoc 2008; 58(1): 400-03.
7. Knauer C, Knauer K, Müller S, Ludolph1 AC, Benge D. A biochemical marker panel in MRI-proven hyperacute ischemic stroke-a prospective study. Bio Med Central Neurol 2012; 12(1): 14-20.
8. Sanchez P, Fernandez M, Fuentes B, Masjuan J, Cases M, Novillo-Lopez M et al. Biochemical and inflammatory biomarkers in ischemic stroke: translational study between humans and two experimental rat models. J Transl Med 2014; 12(1): 220-32.
9. Camerlingo M, Valente L, Tognozzi M, Beretta GL, Moschini L, Cesana BM. C-Reactive protein levels in the first three hours after acute cerebral infarction. Int J Neurosci 2011; 121(2): 65-72.
10. Glickman SW, Phillips S, Anstrom KJ, Laskowitz DT, Cairns CB. Discriminative capacity of biomarkers for acute stroke in the emergency department. J Emerg Med 2011; 41(3): 333-39.
11. Chaudhuri J, Mridula K, Umamahesh M, Swathi A, Balaraju B, Bandaru V. 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.
12. Youn CS, Choi SP, Kim SH, Oh SH, Jeong WJ, Kim HJ. 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): 124-28.
13. Ormstad H , Aass HCD, Sorensen NL, Amthor KF, Sandvik L. Serum levels of cytokines and C-reactive protein in acute ischemic stroke patients, and their relationship to stroke lateralization, type, and infarct volume. J Neurol 2011; 258(1): 677-85.
14. Guo J, Yu L, Zhang J, Chen N, Zhou M, He L. CRP gene polymorphism predicts post-stroke functional outcome in Han Chinese. Acta Neurol Scand 2014; 129(4): 263-68.
15. Abubakar SA, Okubadejo NU, Ojo OO, Oladipo O, Ojini FI, Danesi MA. Relationship between admission serum C-reactive protein and short term outcome following acute ischaemic stroke at a tertiary health institution in Nigeria. Niger J Clin Pract 2013; 16(3): 320-24.
16. Geng H, Wang X, Fu R, Jing M, Huang L, Zhang Q et al. The relationship between C-Reactive protein level and discharge outcome in patients with acute ischemic stroke. Int J Environ Res Public Health 2016; 13(7): 636-46.
17. VanGilder R, Davidov D, Stinehart K, Huber J, Turner R, Wilson K, et al. C-reactive protein and long-term ischemic stroke prognosis. J Clin Neurosci. 2014; 21(4): 547-53.
18. Tu W, Zhao S, Liu T, Yang D, Chen H. Combination of high-sensitivity C-reactive protein and homocysteine predicts the short-term outcomes of Chinese patients with acute ischemic stroke. Neurol Res 2013; 35(9): 912-21.
19. Zhou Y, Han W, Gong D, Man C, Fan Y. Hs-CRP in stroke: A meta-analysis. Clin Chim Acta 2016; 453(1): 21-7.
20. Khan A, Ali Z. Frequency of raised C - reactive protein in acute ischemic stroke. Khyber Med Univ J 2012; 4(2): 45-8.

....