Original Article

Is there a correlation between hs-CRP levels and functional outcome of Ischemic Stroke?

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ABSTRACT

Objective: C-reactive protein, a well known marker of inflammation is being investigated as a probable marker of predicting acute cardiovascular events and its severity. The aim of the present study was to assess the possible role of highly-sensitivity C-reactive protein (hs-CRP) in predicting short-term functional outcome of ischemic stroke.

Methodology: A prospective study was conducted on subjects admitted with first attack of confirmed ischemic stroke. It included 50 male and 52 female. Serum hs-CRP was measured in the 2nd (CRP-D2) and 5th days (CRP-D5) post-stroke. Modified Rankin scale (MRS) was measured in all subjects in the 2nd (MRS-D2), 5th days (MRS-D5) and also 3 month (MRS-M3) after stroke to assess the short-term functional outcome and mortality of subjects.

Results: The mean age of the patients was 71.75 ± 11.44 years. The mortality rate was 47.1% in the third months after stroke. There was no significant correlation between CRP-D2 and MRS-M3 and also between CRP-D5 and MRS-M3 ($P > 0.05$). However there was a significant association between high CRP-D2 (CRP>3) and MRS-M3 and also between high CRP-D5 and MRS-M3 ($P < 0.005$).

Conclusion: This study showed that the value of CRP by itself could not predict the severity of short-term functional disability and it might not be useful as a clinical tool for predicting outcome.

KEY WORDS: Atherosclerosis, C-reactive protein, Functional outcome, Inflammation, Ischemic stroke, Modified Rankin scale.

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INTRODUCTION

C-reactive protein (CRP) is an acute phase protein produced in response to inflammatory process and therefore it is regarded as a well-known marker of inflammation.[1] CRP is currently being investigated as a probable marker of generalized atherosclerosis. Atherosclerosis is considered a chronic inflammatory response by arterial endothelium.[2] Recently, the role of CRP as a reliable marker in predicting acute coronary syndrome and its outcome has been established.[3]

There are evidences that inflammatory response is a part of ischemic stroke course[4], therefore it might be hypothesized that a more severe stroke is associated with greater inflammatory response. Some studies have found evidence for CRP as a

predictor of future stroke attack and its severity[5,6], while others have not.[7] Some studies have evaluated the role of post-ischemic CRP in long-term mortality of patients suffering from stroke.[8-10] There has been only a few studies concerning the possible role of CRP as a predictor of functional outcome after stroke attack and there has been discrepancies regarding the results of these studies.[7,8,11-14] The aim of the present study was to assess the possible role of highly sensitivity CRP (hs-CRP) in predicting functional outcome of patients admitted with ischemic stroke.

METHODOLOGY

This study was a prospective study conducted in Neuroscience Research Center, Tabriz University of Medical Sciences, Iran from August 2009 to August 2010. It included 50 male and 52 female patients. The study was approved by local ethics committee at Tabriz University of Medical Sciences. After explaining the study process in detail to the patients, written informed consent was obtained from all of the participants. Patients of at least 40-year-old, who were admitted with first-time ischemic brain stroke, were chosen sequentially. Stroke was defined as developing clinical evidence of focal neurologic deficits lasting more than 24 hours. Full neurologic physical examination was performed in all subjects and the diagnosis was confirmed with either computed tomography (CT) scan or magnetic resonance imaging (MRI). Subjects in whom physical examination or imaging modality was not consistent with the diagnosis of ischemic stroke were not included in this study. Patients were excluded if they had any history of acute coronary syndrome or infectious disease within last month.

Furthermore, erythrocyte sedimentation rate (ESR) was measured in all subjects and those with abnormal ESR were not included in this study. Known risk factors of ischemic stroke were assessed and recorded in all patients. Serum total cholesterol concentration was measured while patients were under their regular regimens and subjects with hypercholesterolemia were identified. Blood pressure was measured in all subjects in a sitting position for three times and the average was taken as the reference. Subjects with a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg were defined as having hypertension. Fasting blood glucose (FBS) and random glucose was measured in all subjects who were not under treatment with glucose-lowering agents and those with a repeated FBS≥126 mg/dL or a repeated random blood glucose ≥200 mg/dL were considered as having diabetes mellitus.

Venous blood samples were obtained from all subjects two (CRP-D2) and five days (CRP-D5) after the beginning of the stroke attack. Within one hour of collection, the samples were centrifuged to separate the serum and were kept in -70°C. High-sensitivity CRP (hs-CRP) was measured using immunoturbidometric assays. CRP value of >3 was considered as high CRP.[15]

Modified Rankin scale (MRS) was used to evaluate short-term functional outcome of stroke. MRS was conducted in all subjects two days (MRS-D2), 5 days (MRS-D5) and 3 months (MRS-M3) after the stroke attack. The patients were subject to MRS scores from 0 to 6 (0 = no symptoms, 1 = no significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = dead).

Data were presented as mean ± standard deviation (SD). The statistical analysis was performed using SPSS for windows version 16.0 using Chi-square test and Mann-Whitney U test, whenever appropriate. A P value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 71.75±11.44 years (40-91 years). Only three patients died on the fifth day after stroke; however the mortality rate was 47.1% in the third months after stroke. The mean hs-CRP level at 2nd and 5th days was 11.61±9.45 mg/L (0.30-42) and 14.69±11.87 mg/L (1.1-49), respectively. There was no significant difference

Table-I: Patients' Demographic Data,
hs-CRP Levels and MRS Scores.

Variable	Total (n=102)
Gender (male:female)	50:52
Age (years)	71.75±11.44
hs-CRP (day 2)	11.61±9.45
hs-CRP (day 5)	14.69±11.87
High hs-CRP (day 2)	88 (86.27%)
High hs-CRP (day 2)	95 (93.14%)
MRS score (day 2)	3.83±0.72
MRS score (day 5)	3.92±1.06
MRS score (month 3)	4.17±1.97
Hypertension, n (%)	51 (50%)
Diabetes mellitus, n (%)	16 (15.7%)
Hyperlipidemia, n (%)	9 (8.8%)

Table-II: MRS Score at 3 Months between patients with Low and High CRP Levels.

		MRS-M3			P value
		0-1	2	3-6	
CRP-D2	Low (<3)	6	0	8	<0.005
	High (>3)	5	12	71	
CRP-D5	Low (<3)	2	1	4	<0.005
	High (>3)	9	11	75	

between the mean hs-CRP levels of day 2 and day 5 ($P>0.05$). Patients' demographic data, hs-CRP levels and MRS scores are shown in Table-I.

With regard to the MRS scores, MRS-M3 significantly correlated with MRS-D2 (r=0.44, $P<0.005$) and MRS-D5 (r=0.74, $P<0.005$). Furthermore, there was no significant correlation between CRP-D2 and MRS-M3 ($P=0.85$) and also between CRP-D5 and MRS-M3 ($P=0.59$). However there was a significant association between high CRP-D2 (CRP>3) and MRS-M3 ($P<0.005$, Table-II) and also between high CRP-D5 and MRS-M3 ($P<0.005$, Table-II). Furthermore, there were no significant differences between hypertension, diabetes mellitus, hyperlipidemia and hs-CRP levels and MRS scores at the studied times ($P>0.05$).

DISCUSSION

The present study did not find any correlation between hs-CRP levels and short-term (three months) functional outcome of ischemic stroke. Similar to the present study, Canova et al[8] and Modrego et al[12] failed to conclude any relationship between CRP and outcome of acute cerebrovascular events such as ischemic stroke. In contrast, CRP levels have been correlated positively with the size of the infarct and stroke severity.[11,16] Furthermore CRP elevation in ischemic stroke indicated a worse prognosis, as it has been associated with higher in-hospital mortality[17,18], higher mortality at six months[19], and more disability.[20]

The present study also revealed that high CRP (CRP>3) was associated with poor short-term (three months) functional outcome of ischemic stroke. Similarly, Idicula and colleagues found a crude association between on admission high CRP and short-term (7 days) functional outcome in patients with acute ischemic stroke. They used Barthel index and MRS to evaluate the stroke outcome.[7] Likewise, in a recent Korean study, Song et al[13] demonstrated that elevated hs-CRP levels on the seventh hospital day, rather than within 24 h after stroke onset, could strongly predict the prognosis of functional disability, assessed by MRS score, 12 months after stroke onset. Moreover, elevated CRP levels have been associated with poorer one-month functional outcome, evaluated with Barthel index, in Malaysian patients with acute ischemic stroke.[21] As CRP is produced as a response to brain tissue necrosis following ischemic stroke, it has been suggested as a valuable predictor of functional outcome.[11]

The clinical importance of possible relation between CRP and functional outcome of stroke is unclear. At present, it is believed that there is not enough evidence to recommend measurement of CRP in the usual evaluation of cerebrovascular disease risk in primary prevention. Nonetheless, in secondary prevention of stroke, elevated CRP adds to current prognostic markers, although it remains to be established whether specific therapeutic options can be derived from this.[22]

This study has several limitations. The prevalence of future vascular events was not assessed in this study and might be subject of other studies. Moreover, all the risk factors associated with ischemic stroke such as cigarette smoking and etc has not been studied in the present investigation. In addition, other functional outcome measurement scales such as Barthel index could have been applied in the present study. On the other hand, an advantage of the current study might be highlighted. Most of the studies evaluating the probable association of CRP and stroke outcome have based their results only on a sole measurement of CRP. CRP values might be affected by stress, infection or technical errors and therefore a once-measured high level cannot be trusted.[7] CRP level was measured twice in this study to avoid the error of overestimation.

CONCLUSION

In conclusion, this study showed that the value of CRP by itself could not predict the severity of short-term functional disability and it might not be useful as a clinical tool for predicting outcome.

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REFERENCES

1. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA. 2005;293(13):1609-1616.

2. Elias-Smale SE, Kardys I, Oudkerk M, Hofman A, Witteman JC. C-reactive protein is related to extent and progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study. Atherosclerosis. 2007;195:e195-e202.

3. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 1999;99(2):237-242.

4. Becker KJ. Inflammation and acute stroke. Curr Opin Neurol. 1998;11:45-49.

5. Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. Stroke. 2001;32:2575-2579.

6. Arenillas JF, Alvarez-Sabín J, Molina CA, Chacón P, Montaner J, Rovira A, et al. C-reactive protein predicts further ischemic events in first-ever transient ischemic attack or stroke patients with intracranial large-artery occlusive disease. Stroke. 2003;34:2463-2468.

7. Idicula TT, Brogger J, Naess H, Waje-Andreassen U, Thomassen L. Admission C-reactive protein after acute ischemic stroke is associated with stroke severity and mortality: the 'Bergen stroke study'. BMC Neurol. 2009;9:18.

8. Canova CR, Courtin C, Reinhart WH. C-reactive protein (CRP) in cerebro-vascular events. Atherosclerosis. 1999;147:49-53.

9. Muir KW, Weir CJ, Alwan W, Squire IB, Lees KR. C-reactive protein and outcome after ischemic stroke. Stroke. 1999;30:981-985.

10. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. Arch Intern Med. 2006;166:2073-2080.

11. Audebert HJ, Rott MM, Eck T, Haberl RL. Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. Stroke. 2004;35:2128-2133.

12. Modrego PJ, Boned B, Berlanga JJ, Serrano M. Plasmatic B-type natriuretic peptide and C-reactive protein in hyperacute stroke as markers of CT-evidence of brain edema. Int J Med Sci. 2008;5:18-23.

13. Song IU, Kim JS, Kim YI, Lee KS, Jeong DS, Chung SW. Relationship between high-sensitivity C-reactive protein and clinical functional outcome after acute ischemic stroke in a Korean population. Cerebrovasc Dis. 2009;28(6):545-550.

14. Ryu SR, Choi IS, Bian RX, Kim JH, Han JY, Lee SG. The effect of C-reactive protein on functional outcome in ischemic stroke patients. Int J Neurosci. 2009;119:336-344.

15. Scirica BM, Morrow DA. Is C-reactive protein an innocent bystander or proatherogenic culprit? The verdict is still out. Circulation. 2006;113(17):2128-2134.

16. Marquardt L, Ruf A, Mansmann U, Winter R, Buggle F, Kallenberg K, et al. Inflammatory response after acute ischemic stroke. J Neurol Sci. 2005;236:65-71.

17. Campbell DJ, Woodward M, Chalmers JP, Colman SA, Jenkins AJ, Kemp BE, et al. Soluble vascular cell adhesion molecule 1 and N-terminal pro-B-type natriuretic peptide in predicting ischemic stroke in patients with cerebrovascular disease. Arch Neurol. 2006;63(1):60-65.

18. Rallidis LS, Vikelis M, Panagiotakos DB, Rizos I, Zolindaki MG, Kaliva K, et al. Inflammatory markers and in-hospital mortality in acute ischaemic stroke. Atherosclerosis. 2006;189:193-197.

19. Kocer A, Canbulat C, Gozke E, Ilhan A. C-reactive protein is an indicator for fatal outcomes in first-time stroke patients. Med Sci Monit. 2005;11(11):CR540-CR544.

20. Arévalo-Lorido JC, Carretero-Gómez J, Calvo-Romero JM, Romero-Requena JM, Pérez-Alonso JL, Gutiérrez-Montaño C, et al. C-reactive protein in the acute phase of ischemic stroke. Med Clin (Barc). 2005;125:766-769.

21. Hamidon BB, Sapiah S, Nawawi H, Raymond AA. The prognostic value of C-reactive protein (CRP) levels in patients with acute ischaemic stroke. Med J Malaysia. 2004;59:631-637.

22. Di Napoli M, Schwaninger M, Cappelli R, Ceccarelli E, Di Gianfilippo G, Donati C, et al. Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care professionals from the CRP Pooling Project members. Stroke. 2005;36:1316-1329.

Authors' contribution:

AT and AP hypothesized and designed the study. SA preformed acquisition of the data. SA, RR, and KG analyzed and interpreted the data. SA, RR, and KG drafted the article and all the authors approved the final version of the article.