A Study of prognostic value of Hs-CRP and fibrinogen in patients of unstable angina

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ABSTRACT

Background: *Unstable angina constitutes a clinical syndrome that is usually caused by atherosclerotic coronary artery disease and is associated with an increased risk of cardiac death and myocardial infarction.*

Material and methods: *An open, prospective, observational, comparative study was conducted. The study included 50 cases in age group 20-80 years admitted in Government Medical College, Amritsar diagnosed as unstable angina ruled out by Trop T and CPK-MB at admission. Hs-CRP and Fibrinogen levels were estimated at time of admission and repeated after 48 hours.*

Results: *There was significant difference in the mean value of Hs-CRP between favourable and unfavourable group at the time of admission (0.807 ± 0.37mg/l v/s 3.57 ± 1.70mg/l, $p<0.001$). A significant difference in the mean value of Hs-CRP was found between favourable and unfavourable group after 48 hours (0.51 ± 0.22mg/l v/s 4.03 ± 1.84mg/l, $p<0.001$) There was significant difference in the mean value of fibrinogen between favourable and unfavourable group at the time of admission (356.94 ± 72.50mg/dl v/s 588.60 ± 94.89mg/dl, $p<0.001$). A significant difference in the mean value of fibrinogen was found between favourable and unfavourable group after 48 hours (309.11 ± 75.25mg/dl v/s 622.60 ± 133.42mg/dl, $p<0.001$).*

Conclusion: *It is concluded that in patients with unstable angina, elevated levels of Hs-CRP and Fibrinogen at admission indicate an adverse hospital outcome.*

Keywords: *Hs-CRP, unstable angina, fibrinogen, myocardial infarction, coronary artery disease*

Introduction

Acute coronary syndrome can be sub divided into ST segment elevation myocardial infarction (STEMI), Non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina (UA). Unstable Angina / NSTEMI is characterised by an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of the epicardial coronary arteries. Unstable angina is one of the most common serious cardiovascular disorder.[1] Coronary artery disease (CAD) causes more deaths, disability and economic costs than any other diseases.

Unstable angina is defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of three features.[2] Occuring at rest (or minimal exertion) and usually lasting >10 minutes (if not interrupted by the administration of a nitrate or an analgesic),

Relative recent onset (within prior 2 weeks) and Occurring with a crescendo pattern (i.e. pain awakens the patient from sleep or that is more severe, prolonged or frequent than previously) Risk factors for unstable angina[3] includes: Unmodifiable - Hereditary, Age, Race and Sex. Modifiable - Smoking, Hypertension, Dyslipidemia, Diabetes, Obesity, metabolic syndrome and physical inactivity.

Newer- Inflammation and infectious agents, [4] Hyperhomocystinemia, Lipoprotein(a), [5] Psychosocial factors, Genetic polymorphisms and Socioeconomic status.

In this study the prognostic role of two inflammatory biomarkers in unstable angina has been studied. Inflammation has a very important role in the natural history of atherosclerotic lesions. C-reactive protein is an acute phase reactant. CRP can induce the expression of the

adhesion molecules such as ICAM-1, VCAM and E-selectin in human endothelial cells.[6] The CRP induced increase in expression of adhesion molecules resulted in elevated adhesion of monocytoid U937 cells to endothelial cells in vitro.[7] C-reactive protein reduces the expression and bioactivity of endothelial nitric oxide synthase (eNOS) in human aorticendothelial cells,[8] C-reactive protein also affects vascular smooth muscle cells by up-regulating the angiotensin type 1 receptor (AT1-R), which mediates the majority of the proinflammatory effects of angiotensin II.[9] C-reactive protein promotes MCP-1-mediated chemotaxis through up-regulation of chemokine receptor 2 expression in human monocytes.[10] C- reactive protein is able to activate the classical route of complement activation and it colocalizes with the terminal complement complex in the intima of early atherosclerotic lesions.[11] On the basis of data obtained from population based studies, the AHA/CDC (American Heart Association/Centres For Disease Control) working group on markers of inflammation in CVD has classified serum Hs-CRP levels as:[12]

- Hs-CRP level <1 mg/l-low risk for developing CVD
- Hs-CRP level 1-3 mg/l-average risk for developing CVD
- Hs-CRP level >3mg/l-high risk for developing CVD

As a clotting factor, fibrinogen is an essential component of the blood coagulation system being the precursor of fibrin. Fibrinogen binding to endothelial cell (EC) receptors (ICAM-1) causes the release of vasoactive mediators.[13] Elevated plasma fibrinogen levels increase the velocity of platelet aggregation and also increase platelet reactivity.[14] Elevated fibrinogen levels lead to larger thrombi and formation of tight and rigid network structures, decrease the deformability of the clot and render it less amenable to endogenous fibrinolysis.[15] Recent data also show that high fibrinogen levels interfere with the binding of plasminogen to its receptor, thus leading to impaired fibrinolysis.[16]

The present work is aimed to estimate the level of high sensitivity C-reactive protein and fibrinogen in patients of unstable angina and to assess whether raised levels of high sensitivity C-reactive protein and fibrinogen in patients with unstable angina is related to the development of complications and whether they can be used as a prognostic marker in unstable angina.

Material and methods

An open, prospective, observational, comparative study was conducted in Department of Medicine, Guru Nanak Dev Hospital, Amritsar after taking approval from institutional thesis and ethical committee. The study included 50 cases in age group 20-80 years admitted in Government Medical College, Amritsar diagnosed as unstable angina ruled out by Trop T and CPK-MB at admission. Hs-CRP and Fibrinogen levels were estimated at time of admission and repeated after 48 hours. All patients were enrolled after taking informed consent from the patients/relatives in their vernacular language.

Inclusion criteria: Angina occurring at rest (or minimal exertion) and usually last >10 minutes (if not interrupted by the administration of a nitrate or an analgesic), relative recent onset (within prior 2 weeks), angina occurring with a crescendo pattern (i.e. pain awakens the patient from sleep or that is more severe, prolonged or frequent than previously)

Exclusion criteria: Elevated serum SGOT, CPK-MB, Troponin T, patients with recent myocardial infarction (<4 week), patients with valvular heart disease, patients with concomitant inflammatory or neoplastic condition.

All patients were evaluated with a detailed history, clinical examination and important investigations. History was taken in detail pertaining to chest pain whether it satisfies the criteria of unstable angina. History regarding risk factors like smoking, diabetes, hypertension, alcohol consumption, activity and life style was obtained. Past history of angina or myocardial infarction was acquired. Family history was also taken into account. Detailed history of previous treatment was also taken. All patients were subjected to a detailed general and systemic physical examination prior to study. All the selected patients were admitted and were treated with aspirin, clopidogrel, heparin, nitrates, beta blockers, ACE inhibitors, etc as

required. They were observed for 48 hours. Clinical monitoring for pulse, respiration, blood pressure, urine output, etc was done regularly for 48 hours and improvement with treatment was assessed. Based up on the result, the patients were divided into two groups: Favourable group-which include those patients who recovered and Unfavourable group- which include those patients who were referred to higher cardiac centre for refractory unstable angina and those who expired.

Plasma fibrinogen and high sensitivity C-reactive protein were estimated at the time of admission and tabulated. These serum markers were again estimated at the end of 48 hours.Plasma fibrinogen and high sensitivity C-reactive protein were compared amongst themselves to ascertain whether plasma fibrinogen and high sensitivity C-reactive protein levels were rising or returning to baseline. The level of plasma fibrinogen and high sensitivity C-reactive protein in both the group were compared statistically with the prognosis of unstable angina.

Results

The mean age distribution in our study was 56.02±9.51 years. In the favourable group maximum patients were in the age group 40 – 50 years while in the unfavourable group maximum patients were in the age group 51 – 60 years. The mean age in the favourable group was 54.91 ±10.26 years while the mean age in the unfavourable group was 58.60±7.55 years (p=0.217) The Male to Female ratio in our study was 1.27(28 males and 22 females). The majority of patients in both groups were males (57.14% infavourablegroup and 53.33% in unfavourable group). Females constituted 42.86% infavourablegroup while unfavourable group had 46.67% females.

The majority of patients with favourable outcome had Hs-CRP level < 1 mg/l while the majority of patients with unfavourable outcome had Hs-CRP level >3 mg/l.The majority of patients with favourable outcome had fibrinogen level between 301-400 mg/dl while the majority of patients with unfavourable outcome had fibrinogen level >600 mg/dl.

Table:1 Trend of hs-CRP and fibrinogen in patients of favourable group (n=35) and unfavourable group (n=15) at the time of admission and 48 hrs

|	Hs-CRP (mg/l)			Fibrinogen (mg/dl)		
	Favourable group	Unfavourable group		Favourable group	Unfavourable group	
	Mean±SD	Mean±SD	p=value	Mean±SD	Mean±SD	p=value
At admission	0.807±0.372	3.57±1.7	<0.001	356.94±72.5	588.66±98.44	<0.001
After 48 hours	0.510±0.22	4.30±1.84	<0.001	309.11±75.25	622.60±133.42	<0.001
P=value	<0.001	<0.005		<0.001	<0.01	
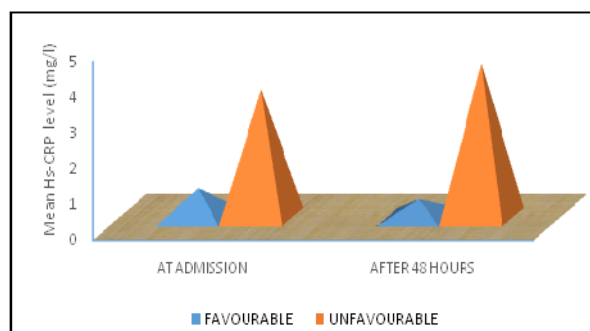
Fig.1 Trend of hs-CRP in patients of favourable group (n=35) and unfavourable group (n=15) at the time of admission and 48 hrs
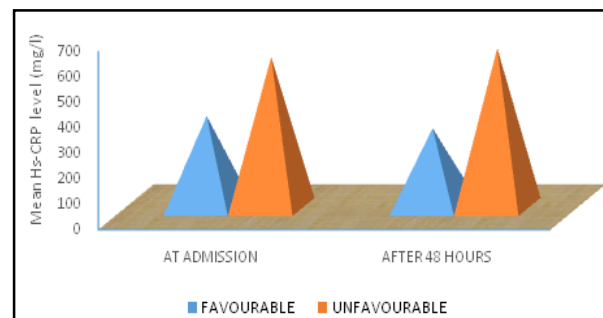
Fig.2 Trend of Fibrinogen in patients of favourable group (n=35) and unfavourable group (n=15) at the time of admission and 48 hrs
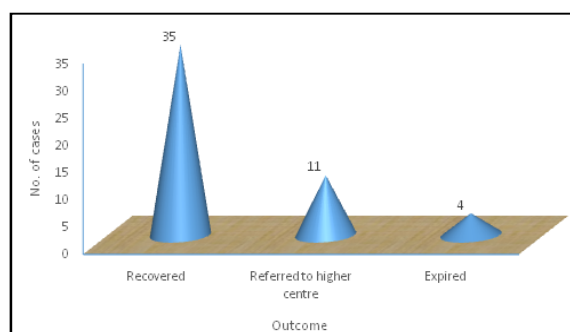
Fig.3 Overall outcome of the patients

Discussion

The study was aimed to determine the prognostic value of Hs-CRP and Fibrinogen in patients of Unstable Angina. Hs-CRP, Fibrinogen, ECG, CPK-MB, Trop-T and other basic and necessary investigations related to study were done at the time of admission and repeated at 48 hours. In our study, in favourable group the mean value of Hs-CRP was 0.807±0.372 mg/l at the time of admission while after 48 hours the mean value was 0.510±0.22 mg/l (p<0.001). In the study by Thompson et al,[17] mean value of Hs-CRP in favourable group was 1.61±1.38 mg/l. In our study, in favourable group the mean value of fibrinogen was 356.94±72.5 mg/dl at the time of admission while after 48 hours the mean value was 309.11±75.25 mg/dl (p<0.001).In the study by Gil et al,[18] the mean value of fibrinogen in favourable group was 326 + 65mg/dl. Thus in relation to Hs-CRP and fibrinogen in patients of favourable group it was found in our study that mean value of Hs-CRP was less and mean value of fibrinogen was more as compared to their counterparts in the earlier conducted study.

In unfavourable group the mean value of Hs-CRP was 3.57±1.70 mg/l at the time of admission while after 48 hours the mean value was 4.30±1.844 mg/l (p<0.005). In study by Koenig et al,[19] mean value of Hs-CRP in unfavourable group was 2.56 mg/l. In unfavourable group the mean value of fibrinogen was 588.66±98.44 mg/dl at the time of admission while after 48 hours the mean value was 622.60±133.42 mg/dl (p<0.01).In the study by Kumar and Sivakanesan,[20] the mean value of fibrinogen in unfavourable group was 357.88+ 23.18mg/dl. Thus in relation to Hs-CRP and fibrinogen in patients of unfavourable group it

was found in our study that both mean value of Hs-CRP and mean value of fibrinogen was high as compared to their counterparts in the earlier conducted study.

There was significant difference in the mean value of Hs-CRP between favourable and unfavourable group at the time of admission (0.807±0.37mg/l v/s 3.57±1.70mg/l, p<0.001). A significant difference in the mean value of Hs-CRP was found between favourable and unfavourable group after 48 hours (0.51±0.22mg/l v/s 4.03±1.84mg/l, p<0.001). In the study by Rana et al.[21] it was found that there was a significant difference in the mean value of Hs-CRP between favourable and unfavourable group (1.5 vs 2.2mg/l, p<0.001).

There was significant difference in the mean value of fibrinogen between favourable and unfavourable group at the time of admission (356.94±72.50mg/dl v/s 588.60±94.89mg/dl, p<0.001).Thus in relation to significance of difference of mean value of Hs-CRP between favourable and unfavourable groups it was found in our study that there was a significant difference in the mean value of Hs-CRP between favourable and unfavourable groups (p<0.001) which is same as compared to their counterparts in the earlier conducted study. A significant difference in the mean value of fibrinogen was found between favourable and unfavourable group after 48 hours (309.11±75.25mg/dl v/s 622.60±133.42mg/dl, p<0.001).). In the study by Kumar and Sivakanesan,[21] it was found that there was a significant difference in the mean value of fibrinogen between favourable and unfavourable group (237.55 + 17.40 vs 357.88 + 23.18mg/dl, p<0.001). Thus in relation to significance of difference of mean value of fibrinogen between favourable and unfavourable groups, it was found in our study that there was a significant difference in the mean value of fibrinogen between favourable and unfavourable groups (p<0.001) which is same as compared to their counterparts in the earlier conducted study. The main limitation in our study was small sample size (n=50) and the duration of follow up was small (48 hrs).

In our study out of 50 patients, 35 patients recovered, 11 patients were referred to

higher centre and 4 patients expired. Thus, it is concluded that in patients with unstable angina, elevated levels of Hs-CRP and Fibrinogen at admission indicate an adverse hospital outcome. The elevated levels of these easily measurable markers can therefore be useful in risk stratification of patients with unstable angina.

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