Original Article

Preoperative High Sensitivity C-reactive Protein Level Predicts Early Outcome After Coronary Artery By-pass Surgery

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Abstract

Background: *Coronary artery bypass surgery (CABG) with cardioplegia has been considered the gold standard operation for coronary revascularization. Activation of compliments system after CABG surgery involves C-reactive protein (CRP). Patients with preoperative increased CRP levels have significantly higher CRP levels on postoperative days and are at increased risk of developing postoperative complications. High sensitivity CRP (hs-CRP) is lower concentration of CRP measured by the hs-CRP test. It is more sensitive and more useful in predicting the potential risk level for cardiovascular disease, heart attacks and strokes.* ***Objective:*** *To assess the association of preoperative hs-CRP level with the incidence of postoperative arrhythmia, low output syndrome and sternal wound infection following on pump CABG surgery.* ***Materials & Methods:*** *The study was cross sectional analytical study. A total of 70 patients were selected. For the purpose of analysis the study subjects were divided into two group; Group A patients with preoperative hs-CRP level <3mg/l (n=35) and Group B patients with preoperative hs-CRP level >3mg/l (n=35). The incidence of early outcome- arrhythmia, low output syndrome and sternal wound infection were observed within 30 days of surgical procedure.* ***Results:*** *The incidence of arrhythmia, low output syndrome and sternal wound infection were significantly less in group A than those in group B. Logistic regression analysis showing significant correlation of hs-CRP with arrhythmia, p value is 0.005; with low output syndrome, p value is 0.003 and with sternal wound infection, p value is 0.004.* ***Conclusion:*** *Preoperative hs- CRP is an important determinant of post operative outcome after CABG surgery and might be useful as predictive marker in risk stratification for postoperative complications in patients scheduled for on pump CABG surgery.*

Keywords: *CABG surgery, High sensitivity C-reactive protein, Early outcome.*

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Introduction

Atherosclerosis is considered a chronic low grade inflammatory disease. The degree of such an inflammatory process strongly correlates with the extent and severity of atherosclerotic disease.[1] Inflammation is characteristic in all phases of atherosclerosis and provides a link between early fatty-streak formation up to plaque rupture leading to occlusion and infarction. So from pathological point of view, all stages, i.e. initiation, growth and complications of the atherosclerotic plaque might be considered to be an inflammatory response to injury.[2] C-reactive protein (CRP) has emerged not only as a relevant marker of this inflammatory process underlying the development of atherosclerosis, but also as one of the engines of the inflammatory cascade.[3] CRP, an acute-phase protein, synthesized in the liver in response to the cytokine interleukin-6. It was initially believed to be only marker of vascular inflammation, but now it is established that it also plays an active role in atherogenesis.[4] The smooth muscle cells of the human coronary arteries may also produce CRP as a local response to inflammatory cytokines and this locally produced CRP may participate in the atherogenic process.[5] The level of CRP in blood can be measured by two different tests: the standard CRP test and hs-CRP test. Both tests measure the same molecule in the blood but different ranges of CRP levels in the blood. The standard test measures a much wider range of CRP levels (10 to 1000 mg/l) but is less sensitive in the lower ranges. The CRP test is ordered for patients at risk for bacterial or viral infection (such as following surgery) or patients with inflammatory diseases (such as rheumatoid arthritis). The hs-CRP test can more accurately detect lower concentrations of the CRP (it is more sensitive) than the stasndard CRP test.

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It measures CRP in the range from 0.5 to 10 mg/l. So the hs-CRP test is more useful than the CRP test in predicting the potential risk level for cardiovascular disease, heart attacks and strokes.[6]

A number of large prospective epidemiologic studies have indicated that hs-CRP is a strong independent predictor of future cardiovascular events including myocardial infarction (MI), ischemic stroke, peripheral vascular disease and sudden cardiac death among individuals without known cardiovascular disease and in patients with established cardiac disease, with or without a previous MI and in patients with acute coronary syndrome.[4] In January 2003, joint guidelines from the Centers for Disease Control and Prevention (CDC) and American Heart Association (AHA) named hs-CRP as the in inflammatory marker of choice to assess cardiovascular risk. The guidelines support the use of hs-CRP in primary prevention and set cut off points according to relative risk categories: Low risk <1.0 mg/l, intermediate risk 1.0-3.0 mg/l and High risk >3.0 mg/l.[7]

CABG with cardioplegia has been considered the gold standard operation for coronary revascularization. This technique is linked to several side effects mostly due to aortic cross clamping, cardioplegia and use of cardio-pulmonary bypass (CPB).[8] Activation of compliments system after CABG surgery involves C-reactive protein. Fransen, et al. showed patients with preoperative increased CRP levels had significantly higher CRP levels on postoperative days 1 to 4, and 6 (p<0.001 at all time points). This findings indicate that preoperative CRP levels determine the increase in postoperative CRP levels.[9] Pre operative inflammatory status should be considered as a risk factors for postoperative inflammatory reaction, magnifying the effect of the intraoperative inflammatory stress of CPB, ischemia, endotoxemia and surgical trauma.[10]

Patients with preoperatively increased CRP levels who have cardiac operations, preexisting chronically activated immune cells or chronically activated inflammation might result in an inadequate response to the short term release of pro-inflammatory mediators induced by the operation. Consequently, in the perioperative period the immune system is deregulated and these patients are at increased risk of developing postoperative complications.[9]

This study had been done with an aim to assess the association of preoperative hs-CRP level with the incidence of postoperative Arrhythmia, Low output syndrome and sternal wound infection following on pump CABG surgery.

Materials and Methods

The study was cross sectional analytical study conducted at the Department of Cardiac surgery, National Institute of Cardiovascular Diseases, Dhaka from July 2010 to June 2012. Study population was patients with coronary artery disease (CAD) who were selected for on pump CABG surgery. A total of 70 patients were selected, fulfilled the inclusion and exclusion criteria. Sampling technique was purposive and convenient. Samples were selected according to inclusion and exclusion criteria. Inclusion criteria was patients with CAD selected for on pump CABG surgery. Exclusion criteria were chronic obstructive pulmonary disease, chronic renal disease, chronic liver disease, patients with history of MI within last 6 weeks, previous history of any form of Arrhythmia, emergency or redo CABG, combined CABG and valve or other congenital heart disease, carotid artery disease, previous history of cerebrovascular accident, active infection (Temperature >37.5c, WBC >12000/μL),history of chronic anti-inflammatory therapy or treatment with steroids or immuno suppressive drugs in the last 6 months, history of Tumour or Autoimmune disease. The study protocol was approved by the Institutional review board. Variables were:- Demographic variables: age and sex; Preoperative clinical variables: Diabetes Mellitus (DM), hypertension, dyslipidaemia and smoking;Preoperative Investigative variables: Echocardiogram-left ventricular ejection fraction (LVEF) and coronary artery angiogram (CAG); Peroperative variables: Total operation time and total number of grafts per patient; Postoperatve variables: Mechanical ventilation time (hr), inotropes, IABP, duration of ICU stay (day), duration of post opertative hospital stay; Postoperative complication variables: Arrhythmia, Low output syndrome (LOS), sternal wound infection. The hs-CRP level was measured day before surgery and report was recorded. For the purpose of analysis, the study subjects were divided into two group; Group A patients with preoperative hs-CRP level <3mg/l (n=35) and Group B patients with preoperative hs-CRP level ≥ 3mg/l (n=35). The incidence of early outcome- Arrhythmia, low output syndrome and sternal wound infection were observed within 30 days of surgical procedure. All instructed medications were continued except aspirin and clopidogrel, which were stopped 07 days before operation. Informed written consent was taken from all the patients. All patients received General anesthesia according to standard anesthetic protocol and I/V heparin, 300 iu/kg, immediately prior to cannulation for CPB with a target ACT 480 seconds.

Surgical Techniques

The operative technique was based on the complete revascularization in both groups. All patients were operated through a median sternotomy approach. Left internal mammary artery and Great saphenous vein were harvested simultaneously. Standard CPB technique (using an ascending aortic perfusion cannula, a two stage single venous cannula of right atrium and non pulsatile flow) was used. Standard CPB circuit, membrane oxygenator and roller pump heads were used for the CPB. Perfusion pressure was maintained within 50-70 mm of Hg. Systemic temperature was kept around 32ºC. All patients were operated under cardioplegic arrest using intermittent antegrade hyperkalaemic cold blood cardioplegia. In most cases surgical revascularization was started by distal anastomosis. Then proximal anastomosis was performed on partially clamped ascending aorta (after aortic cross clamp release) during re-warming. After completion of revascularization patients were gradually weaned from CPB. Protamine sulphate (1:1) was used to reverse the heparin effect at completion of the surgical procedure. In all cases hemodynamic optimization was attempted byvolume adjustment, inotropes administration and pacing etc as required. After completion of surgery patients were transferred to ICU and standard ICU management protocol was followed. They were shifted to ward and discharged in appropriate time according to consultant's assessment. Postoperative complications variable were followed up for 30days after operation.

Data processing and Statistical Analysis

A structured questionnaire was used containing all the variables of interest. Data were collected from interview of the patients, clinical examination, laboratory investigations, preoperative findings and postoperative outcomes using the research instrument. Data were processed using software SPSS (version 16). The qulatative data was presented as frequency with corresponding percentage and compared between groups using Chi-square test and Fisher's exact test. The quantitative data was presented as mean and SD (standard deviation) and compared between groups using Students t test. For all analytical tests, the level of significance was set at 0.05 and a p value of <0.05 was considered significant. The summarized data was presented in the form of tables.

Results

The mean ages of the group A and the group B were almost identical (57.9 ± 6.4 vs 59.3 ± 6.4). There was no significant difference of age distribution, p-value 0.292. Male patients were predominant in both the groups (74.3% vs 80%, p=0.569). Distribution of risk factors of the groups demonstrated that diabetes mellitus, hypertension, dyslipidaemia and smoking were almost identically distributed between groups (p= 0.470, p= 0.607, p= 0.163 and p= 0.434 respectively). No significant difference was found, (Table I).

Table I: Comparison of risk factors

Risk factors	Group A n=35	Group B n=35	p-value
Diabetes	Yes 8(51.4)	21(60)	0.470 NS
	No 17(48.6)	14(40)	
Hypertension	Yes 25(71.4)	23(65.7)	0.607 NS
	No 10(28.6)	12(34.3)	
Dyslipidaemia	Yes 06(17.1)	11(31.4)	0.163 NS
	No 29(82.9)	24(68.6)	
Smoking	Yes 26(74.3)	23(65.7)	0.434 NS
	No 09(25.7)	12(34.3)	

Cardiac disease related variables revealed LVEF and number of diseased coronary artery were almost identical between groups (p= 0.135, p= 0.759 respectively) (Table II). Time required for completing the operation and number of graft per patient did not show statistically significant difference between the groups (Table III). Mechanical ventilation time and duration of ICU stay also did not show statistically significant difference. The need of postoperative inotropic support and duration of hospital stay were significantly less in group A than those in group B, (p=0.016, p=0.022 respectively), (Table IV). The incidence of arrhythmia, low output syndrome and sternal wound infection were significantly less in group A than those in group B 5.7 vs 28.6%, p= 0.023; 8.6% vs 28.6%, P=0.031; 8.6% vs 31.4%, p=0.034 respectively, (Table V).

Table II: Comparison of Cardiac disease related variables

Cardiac disease related variables	Group A n=35	Group B n=35	p-value
LVEF(%)	59.1±2.1	58±2.6	0.135 NS
DVD	07(20)	06(17.1)	
TVD	28(80)	29(82.9)	0.759 NS

Table III: Comparison of peroperative variables

Preoperative variables	Group A n=35	Group B n=35	p-value
Total operating time (minutes)	264.2±9.1	261.3±6.1	0.113 NS
Number of graft per patient	2.8±0.4	2.7 ±0.5	0.281 NS

Table IV: Comparison of postoperative outcome

postoperative outcome variables	Group A n=35	Group B n=35	p-value
Mechanical ventilation time(hrs)	7.6 ±1.1	7.8±0.9	0.359NS
Durationof ICU stay(days)	2.8±0.8	3.1±0.8	0.091NS
Hospital stay(days)	8.8±1.4	9.8±2.1	0.022S
Inotropi support	yes15(42.9)	25(71.4)	0.016S
	no20(57.1)	10(28.6)	
IABP required	yes 00	01(2.9)	0.314 NS
	no35(100)	34(97.1)	

Table V: Postoperative complications encountered between groups

postoperative outcome variables	Group A n=35	Group B n=35	p-value
Arrhythmia	yes 02(5.7)	10(28.6)	0.023S
	no 33(94.3)	25(71 .4)	
Low output syndrome	Yes 03 (8.6)	10(28.6)	0.031S
	No 32(91.4)	25(71.4)	
Sternal wound infection	Yes 03(8.6)	11(31.4)	0.034S
	no 32 (91.4)	24(68.6)	

Table VI: Logistic regression analysis-Arrhythmia as dependent variable

Independent variable	Standardized Coefficients (β)	P Value	Exp (β)	95% Confidence interval for β	
				Lower bound	Upper bound
Constant	-14.003	0.717	0.000		
Diseased vessel	0.637	0.769	1.890	0.027	131.754
Graft number	-1.278	0.633	0.279	0.001	53.020
Operation time	0.009	0.950	1.009	0.757	1.345
Inotropic support	0.542	0.831	1.720	0.012	247.936
hs-CRP	2.805	**0.005**	16.534	2.353	116.170

Table VII: Logistic regression analysis-Low output syndrome as dependent variable

Independent variable	Standardized Coefficients (β)	P Value	Exp (β)	95% Confidence interval for β	
				Lower bound	Lower bound
Constant	-6.264	0.814	0.002		
Ejection fraction	0.034	0.811	1.034	0.783	1.366
Number of graft	-0.824	0.532	0.439	0.033	5.811
Operation time	-0.014	0.879	0.986	0.818	1.188
hs-CRP	1.971	0.003	7.176	1.922	26.796

Logistic regression analysis was done considering Arrhythmia as dependent variable and diseased vessels, number of graft, operation time, inotropic support and hs-CRP as independent variable. There was significant correlation of hs-CRP with arrhythmia; p value is 0.005, (Table VI). Logistic regression analysis done considering Low output syndrome as dependent variable and ejection fraction, number of graft, operation time and hs-CRP as independent variable. There was significant correlation of hs- CRP with low output syndrome, p value is 0.003, (Table VII).

Table VIII. Logistic regression analysis-Sternal wound infection as dependent variable

Independent variable	Standardized Coefficients (β)	P Value	Exp β	95% Confidence interval for β	
				Lower bound	Lower bound
Constant	-16.726	0.358	0.000		
Diabetes Mellitus	-0.556	0.467	0.574	0.128	2.564
Operation time	0.030	0.669	1.030	0.899	1.180
Hospital Stay	0.086	0.640	1.089	0.761	1.559
hs-CRP	2.014	0.004	7.446	1.927	29.162

Logistic regression analysis done considering sternal wound infection as dependent variable and diabetes mellitus, operation time, hospital stay and hs-CRP as independent variable. There was significant correlation of hs- CRP with sternal wound infection, p value is 0.004, (Table VIII).

Discussion

The mean ages of the group A and the group B were almost identical 57.9±6.4 years and 59.3±6.4 years respectively, p=0.292. There was no significant difference of age distribution between two groups. Biancari, et al.(2003) reported a study of preoperative C-reactive protein and outcome after CABG surgery, showed mean age was 63.7±9.1 years in group A and 65.1±9.6 years in group B p=0.15,[11] which was similar to our study.

Sex distribution of the patients demonstrates that 74.3% of the subjects of group A and 80% of the subjects of group B were male patients. There was no significant difference in the age distribution between the two groups. Biancari, et al. (2003) reported male predominance with 76.4% male in group A and 70.2% male in group B,[11] which was similar to our study.

Comparison of risk factors between groups demonstrate that diabetes mellitus, hypertension, dyslipidaemia and smoking habit were almost identically distributed between groups (p= 0.470, p= 0.607, p= 0.163 and p= 0.434 respectively), (Table I). No significant difference was found. Bernad Lo., et al. (2005) reported a study of C reactive Protein is a risk indicator for atrial fibrillation after myocardial revascularization showed 13% were diabetic, 42% hypertensive, 68% dyslipidaemia and 73% had smoking habit among group A patients compared to 5% were diabetic, 55% hypertensive, 80% dyslipidaemia and 80% had smoking habit among group B patients,13 which was similar to our study.

Left ventricular ejection fraction (LVEF) were almost identical in the both groups (59.1 ± 2.1 vs 58.2 ± 2.6 %, p=0.135) (Table II). In the study conducted by Biancari, et al. (2003), LVEF was 68.2±15.2% in group A and 62.1±16.6% in group B, p=0.7,[11] which was similar to our study. In our study, 80% of patients in group A presented with triple vessel disease (TVD) compared to 82.9% in group B. No significant difference was found between the groups (p=0.759), (Table II). Balciunas, et al. (2009) reported TVD 82% in group A and 88% in group B (p=0.5),[12] which was similar to our study.

Preoperative data revealed both the groups were matched with no statistically significant difference of preoperative patients' characteristics. So these features had no influence on peroperative and postoperative clinical outcome. Time required for completing the operation was in group

A 264.2±9.1 minutes and in group B 261.3±6.1 minutes, p=0.113, (table III). Balciunas, et al. (2009) reported that mean operation time was 227.1 ±51.4 in group A and 242.9 ±62.8 in group B (p=0.4),[12] which was similar to our study. Number of graft per patient was in group A 2.8±0.4 and in group B 2.7±0.5, p=0.281, (Table III) Cappabianaca, et al. (2006) reported number of graft per patient were 293± 0.98 in group A and 2.97 ±0.97 in group B (p=0.44),[10] which was similar to our study.

Postoperative outcomes variables showed that duration of hospital stay were significantly shorter in group A compared to those in patients of group B (8.8±1.4 vs 9.8± 2.1 days, p=0.022), (Table IV). Cappabianca, et al. (2006) reported that duration of hospital stay was 7± 3 vs 7± 3day, p=0.11,[10] which was similar to our study. Inotropic support was significantly less in group A than those in group B (42.9% vs 71.4%, p=0.016), (Table IV). Bernard Lo., et al. (2005) reported the need of postoperative inotropic support was 12% vs 26%, p=0.10.[13]

Postoperative complication variables were studied upto 30 days of operation. The incidence of arrhythmia, low output syndrome and sternal wound infection were significantly less in group A than those in group B (p= 0.023, p= 0.031, p= 0.034 respectively), (Table V). Bernard Lo. et al. (2005) reported incidences of arrhythmia was significantly less in group A than those in group B (21% vs 55% , p=0.01).[13] Biancari, et al. (2003), reported incidences of low output syndrome was significantly less in group A than those in group B (3.7% vs 8.8%, p< 0.05).[11] Cappabianca, et al. (2006) reported incidences of sternal wound infection was significantly less in group A than those in group B (2.8% vs 10.7%, p<0.0001).[10] Results were consistent to our study.

Logistic regression analysis showed significant correlation of hs-CRP with arrhythmia, p value is 0.005; with low output syndrome , p value is 0.003; with sternal wound infection, p value is 0.004, (Table VI), (Table VII) and (Table VIII).

So like most of the studies, we are able to demonstrate that preoperative serum concentration of hs-CRP in patients undergoing on-pump CABG surgery is an important determinant of early postoperative outcome. The hs-CRP estimation is simple, affordable and widely available test like other routine investigation such as TC, DC, ESR and HB%, it can be easily done in each and every patient admitted to hospital and should be included as a part of routine screening. A high hs-CRP should be treated by aggressive risk factor reducing strategies. These include lifestyle changes, such as: eaing a heart healthy diet, reducing high cholesterol levels, maintaining a healthy weight, exercise regularly, managing diabetes and high blood pressure, stopping smoking or tobacco use and drinking less alcohol. Cholesterol lowering statin drugs both reduce CRP and LDL and lower cardiac risk. Antithrombotic medications such as low dose aspirin or clopidogrel may provide protection as well.

Conclusion

This cross-sectional analytical study had shown the incidence of post operative complications arrhythmia, low output syndrome and sternal wound infection following CABG surgery occurred significantly in the patients of preoperative high level of hs-CRP. So we conclude that preoperative inflammatory state as measured by hs- CRP is an important determinant of post operative outcome after CABG surgery and might be useful as predictive marker in risk stratification for post operative complications in patients scheduled for on pump CABG surgery. This study help us in preoperative patients selection and optimization of patients condition before surgery. It also help us to find out the better methods for reduction of early postoperative complications after CABG surgery. The hs-CRP level estimation is simple and affordable like other routine investigation. Thus hs-CRP can be used as a new and even simpler tool for risk stratification in early surgical outcome after CABG surgery.

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