

PREOPERATIVE CRP AS A PREDICTOR OF DURATION OF ICU STAY FOLLOWING ONPUMP CABG

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ABSTRACT

Aims: Elevated CRP is associated not only with an increased risk for cardiovascular disease but also for increased morbidity and mortality in patients with established coronary artery or cerebrovascular disease. Whether elevate CRP further increases the morbidity and mortality in patients undergoing coronary artery bypass grafting on cardiopulmonary bypass (CPB) remains unknown.

Methodology: We conducted a prospective observational study with pre-operative measurement of plasma CRP levels in consecutive patients undergoing coronary artery bypass grafting on CPB. Patients with preoperative CRP level more than 5mg/l were studied.

Results: The association of pre-operative plasma CRP levels with post-operative duration of ICU stay

and morbidity and mortality were evaluated. Elevated CRP levels (>5 mg/l) associated with a prolong ICU stay (OR 3.00 95%CI 1.3550-6.641), psychosis (OR2.73, 95%CI1.4-5.0) and acute renal failure (OR 3.58, 95%CI1.12-11.4).

Conclusion: Elevated pre-operative CRP level is independently associated with increased morbidity particularly in patients undergoing CABG.

Key words: CRP; C reactive protein; CABG; Coronary artery bypass grafting; ICU; Intensive care unit, OnPump, Cardiopulmonary bypass machine

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INTRODUCTION

Ischemic heart disease is caused by atherosclerosis of coronary arteries. Localized inflammatory response in the intimal layer of arteries have been shown to be responsible for most of the aspects of intimal thickening and plaque disruption leading to acute cardiovascular events like angina and myocardial infarction¹.

Coronary artery bypass grafting with cardiopulmonary bypass is one of treatment modality of coronary artery disease. Coronary

artery bypass grafting with cardiopulmonary bypass is associated with major systemic inflammatory reactions. It results in global ischemia of whole body; increases postoperative morbidity and mortality. Several postoperative adverse outcomes such as renal, myocardial, neurological, bleeding and multiple organ dysfunctions have been reported².

Several inflammatory markers can be found elevated in patients with ischemic heart disease. Of these, raised level of CRP is most significantly associated with coronary events like angina, myocardial infarction in healthy population³. Elevated serum CRP level at presentation in patients with unstable angina or non Q wave myocardial infarction is correlated with increased risk of 14-days mortality, even in patients with a negative rapid cardiac troponin T (cTnT) assay⁴.

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Published studies indicate that elevated CRP may be a greater risk factor than high cholesterol in predicting heart attack and especially stroke risk along with the adverse outcome in patients with coronary artery disease having pre event raised CRP^{4,5,6}.

There are few studies which have analyzed the effect of pre intervention inflammatory status on post intervention outcome. Patients with raised serum CRP level have high incidence of stent restenosis⁷. Preoperative raised serum CRP level increases risk of low output heart failure, myocardial damage, stroke, sepsis, atrial fibrillation and prolonged mechanical ventilation^{8,9,10}. Despite surgical correction of cardiac disease, a high preoperative CRP value is considered an independent risk factor for mid-term survival and hospitalization for cardiac causes. In our study we investigate whether raised preoperative CRP is associated with any adverse event prolonging the ICU stay.

METHODOLOGY

This prospective observational study was planned to evaluate the relation of preoperative raised serum CRP level on duration of ICU stay following elective on-pump CABG. Single parameter of ICU stay may help us to confirm the significance of raised CRP on outcome following on pump CABG.

Operational definitions

Preoperative raised CRP : >0.5mg/dl

Prolonged ICU stay: ICU stays longer than 72 hours considered prolonged.

Neurologic deficits;

- a. Permanent stroke: Neurologic deficit of abrupt onset caused by disturbance in blood supply to the brain persisting >24 hrs

- b. Transient ischemic attack: Loss of neurologic function that was abrupt in onset but with complete return of function within 24 hrs

Prolonged ventilation: Prolonged postoperative mechanical ventilatory support for >24 hrs

Renal failure: Acute or worsening renal function resulting in;

- a. Increase of serum creatinine to ≥ 2 mg/dL
- b. New requirement for dialysis

Delirium was defined according to Diagnostic and Statistical Manual for Mental Disorders (DSM IV) (7) criteria:

- (1) Disturbance in consciousness with reduced ability to focus, sustain or shift attention.
- (2) Change in cognition or the development of a perceptual disturbance.
- (3) Acute onset and fluctuating course.
- (4) Evidence of organic dysfunction.

Informed consent was obtained from all of the patients for enrollment in this study. A preoperative blood sample was drawn at night before surgery and sent for CRP level.

Patients with a CRP level > 0.5mg/dl were included in study. All patients irrespective of gender and age undergoing for elective on-pump coronary artery bypass grafting for multivessel disease at Cardiac Surgery Department at National Institute of Cardiovascular Diseases were included in study.

Following categories of patients were excluded from the study.

Patients having other inflammatory disorders, chronic obstructive airway disease, myocardial infarction within 30 days, requiring emergency surgery, combine valvular surgery, chronic renal failure, chronic liver disease, pulmonary

hypertension, ejection fraction <50%. Patients requiring preoperative treatment with positive inotropes and nitrates for cardiac support before surgery, repeat coronary artery bypass grafting for recurrent angina were also excluded. Similarly patients taking drugs those affect serum CRP level like steroids, hormonal replacement therapy, oral contraceptive pills were not included in study population.

Study design

Non-randomized, prospective case series study

Aims and objective

- Primary objective
 - Risk stratification
- Secondary objective
 - Association of preoperative inflammatory status with postoperative outcome

Preoperative echocardiographic and angiographic data was collected. In addition to routine hematological and biochemical investigations including hemoglobin, white blood cells count, bilirubin, random blood sugar, urea, creatinine, sample for CRP were collected at preoperative night.

Anesthesia and surgery: All the patients underwent general anesthesia with smooth induction with combination of intravenous and inhalational anesthetic agents. Tranexamic acid was used as an antifibrinolytic agent. Standard monitoring lines were placed e.g. an arterial line and central venous lines were maintained and pulse oxygen saturation and ECG monitoring was done.

Standard median sternotomy approach was used. Conduits were harvested. Patients were heparinized to ACT >480 sec. After palpation of aorta a two stage venous CPB was established with hypothermia at 30°C to 28°C. Perfusion pressure was maintains at 70 mmHg. Myocardial protection

was achieved by antegrade cold blood cardioplegia, microplegia or crystalloid cardioplegia depending upon the operating surgeon's choice. IMA was used to bypass LAD in majority of patients while great saphenous vein was used for rest of the vessels. Top ends were anastomosed with side biting clamp. Protamine was used to reverse the ACT. Adrenaline was used as first line ionotrope while noradrenaline was added to support adequate perfusion pressure if required. In ICU patients were planned for fast tract extubation. At the second postoperative day they were shifted to step down area.

Data collection: All the demographic and perioperative data were collected prospectively. Patients were followed from shifting to ICU to step down or 72 hours, whichever was earlier.

Statistical analysis: Data expressed as median with interquartile range for continuous variables and as number and percentage for binary categorical variables. Following perioperative variables were recorded: demographics; age, sex, weight and medical condition (hypertension, diabetes mellitus on medication, hemoglobin, any blood transfusion, preop atrial fibrillation. Operative variables considered were: CPB duration, aortic cross-clamping duration, myocardial protection (Table 1). The univariate association of raised CRP levels with the following outcome variables was also assessed: ICU stay, time on ventilator, and 72 hrs in-hospital mortality; acute renal failure, atrial fibrillation (new onset), ventricular arrhythmias, stroke, repeat operation for bleeding, need for allogeneic blood transfusions, low cardiac output syndrome (Table 1).

The predictive value of pre-operative raised CRP in determining the postoperative ICU stay was tested with a receiver operating characteristics (ROC) analysis, with assessment of the area under the curve (AUC) and standard error of the AUC. Cut-off values were searched from literature and tested for sensitivity and specificity (with 95% confidence interval) (Table 2).

TABLE 1: DEMOGRAPHIC, PREOPERATIVE, INTRAOPERATIVE AND POSTOPERATIVE DATA IN PATIENTS WITH RAISED CRP

Parameter	n(%)
Male	71(65%)
Female	39 (35%)
Age	63(median)
Weight	87kg(average)
Hypertension	81(74%)
Diabetes mellitus	61(55%)
Preop AF	7(6%)
Disease vessels	Left main=38(35%) ,3vd
Hb	10.9(average)
Old infarction	5
Cross clamp time	.65.24+/7.4
Total bypass time	100.48+/9.8
Myocardial protection	
Blood	107
Crystalloid	3
Whole blood	89
Microplegia	18
Blood transfusions	
>2	9
</2	101
Ionotrope	
2	56(51%)
IABP	7(6%)
Extubation	
>8	20(37%)

A P-value <0.05 was considered significant for all the statistical tests. All the statistical tests were two-sided. Statistical calculations were performed using a computerized statistical program.

RESULTS

Study population consisted of 110 patients with male to female ratio 65% to 35%. The primary end point of the study was to determine the number of patient with ICU stay more than 72 hrs. It was observed in 28 (25%) patients.

TABLE 2: POSTOPERATIVE MORBIDITY / MORTALITY IN PATIENTS WITH RAISED CRP

Morbidity/mortality	n(%)
Prolonged ventilation	14(13%)
Postop AF	43(39%)
Re-exploration	4
Renal dysfunction	14(13%)
Stroke	5(5%)
Psychosis	50(45%)
Mortality	6(5%)
Prolonged ICU stay	28(25%)

Demographic, preoperative, intraoperative and postoperative data in all patients with prolonged ICU stay is given in Table 2. Mechanical support with IABP was required in seven patients. Acute renal injury was observed in 14(13%) patients; two of them required renal replacement therapy. Stroke was observed in 5 patients, while psychosis had significantly high prevalence (45%). Atrial fibrillation was detected in 43 patients (7 had preoperative AF). However in 30 patients it was resolved by 72 hours.

DISCUSSION

Coronary artery disease (CAD) is one of the most important causes of morbidity and mortality in man. Coronary artery bypass grafting (CABG) is the most common cardiac surgery being performed and it has significant association with early and late postoperative complications compared to other surgical procedures. Preoperative risk stratification is an essential tool for risk assessment, analysis, and the study of therapy trends. Various score systems have been developed to predict mortality and morbidity after adult heart surgery. The evaluation of patient outcomes has become increasingly accepted as a first step to assess and improve quality of the patient care.

TABLE 2: DEMOGRAPHIC, PREOPERATIVE, INTRAOPERATIVE AND POSTOPERATIVE DATA IN ALL PATIENTS WITH PROLONG ICU STAY

Parameter	n(%)
Male	19(68%)
Female	9(32%)
Age	63(median)
Weight	85.3kg(average)
Hypertension	23(82%)
Diabetes mellitus	16(64%)
Preop AF	2(7%)
Diseased vessels Left main	4(14%)
Hb	10.8(average)
Old infarction	1
Cross clamp time	67.3min (average)
Total bypass time	103.48min (average)
Myocardial protection	
Blood	107
Crystalloid	3
Whole blood	19
Microplasma	9
Blood transfusion	
>2	3(11%)
</2	25
Inotrope	
2	17(68%)
IABP	7(28%)
Extubation	
>24h	14
Postop AF	12(43%)
Re-exploration	1
Renal dysfunctional	10(36%)
Stroke	5(6%)
Psychosis	21(75%)
Mortality	4(5%)
Prolonged ICU stay	28(25%)

CRP is a powerful independent predictor of cardiovascular events in patients with coronary artery disease. Raised serum CRP level is associated with 2.3 fold increase risk of mortality compared to other inflammatory markers like fibrinogen, von Willebrand factor and leukocyte count¹¹. Same trend observed in patients with unstable angina when short term survival is observed¹². In stable coronary artery disease, an elevated serum CRP level even >1 mg/l is a significant predictor of adverse cardiovascular events independently of baseline characteristics and treatments¹³. Contrary to these reports there are other studies suggestive of no role of serum CRP level in predicting adverse outcome following on pump CABG^{14,15}. Recent years have shown significant improvement in mortality outcome in patients undergoing bypass grafting but morbidity is still an issue. Postoperative duration of ICU stay can be considered a marker of postoperative morbidity. Longer intensive care unit (ICU) stay is associated with worse long and short term outcome. Incidence of prolonged ICU stay in on pump coronary artery bypass grafting patients is 10%^{16,17}.

This prospective study was conducted to evaluate the relation between raised CRP and postoperative outcome in patients who underwent coronary artery bypass grafting. Primary objective of this study to evaluate whether CRP is a predictor of adverse outcome and preoperative inflammation has synergistic effect with global systemic inflammatory response associated with cardiopulmonary bypass. It was tried to enroll a

TABLE 3: RELATIONSHIP BETWEEN CRP AND EARLY OUTCOME

Complications	Study Population	Sts Data / Literature	P Value	Prolonged ICU stay
Prolonged Ventilation	14(13%)	(9.7%)	P=.5	14(50%)
Renal Failure	14(13%)	(3.6%)	P=.03	10(36%)
CNS event	14(13%)	(1.4%)	P=.01	5(5%)
Mortality	6(5%)	(2.3%)	P=.2	4(5%)
Prolonged ICU stay	28(25%)	(10%)	P=.0067	
Psychosis	50(45%)	8% to 23%	P=<.0001	21(75%)
Atrial fibrillation	43(39%)	20% to 40%	P=.18	12(43%)

population with minimum comorbidities influencing postoperative outcome. Study was carried out over a period of twelve months to collect a sample of 110 patients as per inclusion criteria.

Our data on pump CABG population suggest heightened risk of postoperative morbidity with elevated serum CRP level. Significant association was observed with raised preoperative CRP value and duration of ICU stay. Prolong ICU stay was observed in 28 (25%) of patients. Psychosis was detected in 45% of patients compare to other series showing 8% to 23%^{18,19}. Postoperative psychosis is due to extracorporeal circulation thought to lead to brain damage, partially due to SIRS and partly due hemodynamic fluctuations and air or debris micro emboli²⁰. Postoperative delirium was the main reason for prolonged ICU stay observed in our series. Similarly increased incidence of renal dysfunction 14(13%) patients developed renal dysfunction, two of them requiring renal replacement therapy initially with peritoneal dialysis. There were 6 mortalities, two of them caused by perioperative MI and ventricular fibrillation, while 4 patients died secondary to low output failure.

Elevated preoperative CRP is an independent predictor of prolong ICU stay. It has shown strong association with postoperative psychosis and renal dysfunction. CRP can be considered a tool of risk stratification. This study suggestive of synergistic effect of preoperative inflammation with pump associated systemic inflammatory response responsible for adverse organ function after CABG.

Limitations

This observational study should be regarded as a hypothesis generating exercise and caution should be exerted while inferring causation. This single tertiary centre study needs validation in future prospective investigation involving large number of patients undergoing CABG on CPB.

We have not assess the influence of elevated CRP levels on intermediate and long-term outcomes.

CONCLUSION

We conclude that raised preoperative CRP (preoperative inflammatory status) is a significant predictor of adverse postoperative outcome in patients undergoing on pump CABG. We also suggest that CRP may be considered a tool for risk stratification.

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