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Impact of Perioperative Pentoxifylline Treatment on Cardiopulmonary Bypass Induced Inflammatory Response: A Randomized Controlled Trial

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Abstract

Background: The frequent occurrence of bypass induced systemic inflammation after coronary artery bypass grafting (CABG) is a major concern for scientists. Various attempts in attenuating the inflammation have been tried. Recently few studies showed that pentoxifylline (PTF) treatment reduces inflammation from cardiopulmonary bypass (CPB). The perioperative use of PTF on inflammatory response was estimated by measuring biomarkers of inflammation. *Objectives:* To evaluate the effect of PTF on biomarker of inflammation in patients undergoing CABG using CPB. *Methods:* Sixty patients age between 40-65 years scheduled for CABG surgery using CPB were included in the study. The study group was administered PTF (Group I) 400 mg twice daily orally from the day of admission to 6th day after surgery. Whereas the control group was not administered PTF (Group II). Blood samples were collected perioperatively at 4 points of time; before induction of anaesthesia, after 1h of termination of CPB, 24h after surgery and 6thpost-operative day for interleukin-6 (IL6) and C- reactive protein (CRP) as inflammatory markers. The data was analyzed and P<0.05 was considered significant. *Results:* The IL-6 and CRP values were similarbefore induction of anaesthesia (p= 0.473 and p=0.315) between two groups. The PTF treated group had lesser rise in the level of IL-6 (51.38±30.04 vs 119.74±103.86. p<0.017; 69.70±23.60 vs 135.72±88.19, p<0.002; 12.11±5.65 vs 40.20±30.58; p< 0.000) and CRP (6.04±2.88 vs 8.83±2.9, p< 0.000; 158.79±42.37 vs 223.87±93.00, p<0.004; 92.70±33.07 vs 184.52±117.82, p< 0.000) compared to control group patients after 1h of termination of CPB, 24h after surgery and 6thpost-operative day. *Conclusions:* Pentoxifylline attenuates rise in level of IL6 and CRP due to cardiac surgery. Hence perioperative treatment of pentoxifylline will reduce inflammatory reaction in patients undergoing CABG with CPB.

Keywords: Coronary Artery Bypass Grafting; Cardiopulmonary Bypass; C- Reactive Protein; Interleukin-6; Pentoxifylline.

Introduction

Incidences of postoperative myocardial, pulmonary, renal, hepatic and neurocognitive dysfunctions are reported with coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB). [1] The major mechanism is systemic inflammatory response syndrome (SIRS) induced by CPB. Systemic inflammatory response syndrome leads to increased length of hospital stay, morbidity and mortality of the patients. [1, 2]

Many methods were tested to reduce the SIRS after CABG. The improvements in biomaterials, pharmacological, anaesthetic and surgical managements are continuously surfacing. [3] The complete reduction of SIRS from CPB is yet not

achieved. New effective pharmacological agents are needed to overcome the morbidities. Recently few studies show that pentoxifylline (PTF) administration reduces inflammation from CPB[4, 5]. Pentoxifylline with blood viscosity lowering and immunomodulatory property improves microcirculation and oxygenation of brain[6, 7]. Interleukin 6 (IL6) and highsensitivity (HS)-CRP are established markers for detecting inflammation[8].

The aim and objective of the study was to evaluate the effect of PTF on biomarkers of inflammation in patients undergoing CABG under CPB in a prospective randomized controlled trial.

Methods

Study Design

The prospective randomized controlled trial conducted in a tertiary care hospital. The study was conducted after ethical approval from the institutional ethics committee and written informed consent from all patients to participate in the study. The participants were free to withdraw at any time.

Patient Selection

Eightyfive patients for elective CABG under CPB were eligible for the study. Twenty five patients were excluded after implementing allselection criteria. Remaining 60 patients were divided into 2 groups using a computer generated randomized list. Groups 1(n =30) received pentoxifylline (PTF) 400 mg twice daily orally from the day of admission to 6th day after surgery. Whereas the control group was not administered PTF (Group 2). Patients with neurological, kidney disease, liver disease, emergency surgery, recent myocardial infarction, redo-surgery, coagulation disorder, use of anti-inflammatory drugs and uncontrolled diabetes mellitus were excluded from the study.

Sample Calculation and Statistical Analysis

The sample size for the study was calculated based on the result of IL-6 values incontrol group 234±63 versus 99±43pg/ml in PTF group by Otani S et al[7]. Taking 5% as level of significance and 80% power, the estimated sample size of 30 in each group would be sufficientfor a two tailed study.

Statistical analysis was performed using STATA 11.2,Texas; USA was used for data analysis. Data was presented as mean and standard deviation (SD), percentage and frequency unless otherwise indicated. Demographic details, illness variables, anaesthesia and surgical details were recorded using a semi-structured proforma. All the quantitative baseline variables were compared using t-test or Mann Whitney, McNamara test between the two groups, whereas all the categorized variables will be compared using Chi-square or Fisher's exact test while change in groups was seen by paired t test or Wilcoxon Signed ranks or McNamara test as applicable. P value less than (<) 0.05 were considered significant results.

Anesthesia Technique

All patients were kept fasting 6 to 8 h for solid food and 3 to 4 h for liquid before surgery. They were premedicated with oral diazepam 5mg night before and on morning of surgery. All patients received injection morphine 0.1mg/kg and promethazine 0.5mg/kg intramuscular on the day of surgery 45 minutes prior to shifting operation room. Induction of anesthesia consisted of fentanyl, thiopentone sodium and rocuronium. Maintenance of anesthesia included intermittent doses of midazolam, fentanyl, pancuronium and oxygen in air and isoflurane. Monitoring included continuous 5 lead ECG, invasive arterial blood pressure, central venous pressure, pulmonary capillary wedge pressure (PCWP), transesophageal echocardiography, end tidal carbon dioxide, SpO_2, temperature, hourly urine output, intermittent arterial blood gases, electrolytes and blood glucose.

Surgical Technique and Cardiopulmonary Bypass

Standard mid-sternotomy, saphenous vein graft and left internal mammary artery graft harvestation were used. Coronary artery bypass with CPB involved heparin 400IU/kg, ascending aortic and two stage venous cannulation in the right atrium, a standard circuit primed with 1.5 liters of ringer's solution, 0.5mg/kg of mannitol and 5000IU of heparin, membrane oxygenator, non-pulsatile flow with perfusion 2.2 to 2.4L/min/m^2 with hypothermia up to 32^{0}C. The mean perfusion pressure was maintained in the range of 70-90mmHg. Cardiac asystole was achieved with multiple dose cold St. Thomas cardioplegia solution after application of aortic cross clamp. Hematocrit was maintained around 25% during CPB. Patients rewarmed to 36^{0}C and heparin was neutralized with protamine sulfate. All operations were performed by the same surgical team. The physicians working in the operating room and the ICU were blinded to treatment protocols. Duration of CPB, number of vessels grafted, any perioperative

use of blood, blood products, inotropes and use of IABP were noted. The decision for extubation and discharge in the ICU was made according to hospital protocol.

Blood Sampling

Blood samples were collected before induction of anaesthesia (T_1), after 1 hr. of termination of CPB (T_2), 24 h after surgery (T_3) and 6thpost-operative day (T_4) for estimation of IL6 and HS-CRP as a serologic marker of inflammation. The estimation of IL6 and HS-CRP were performed with ELISA immunoassay technique by a person blinded to the study.

Other Parameters

Any major cardiovascular, pulmonary, renal and neurological complications related to the procedure were recorded and those patients were excluded. Time of discharge from ICU and hospital were recorded.

Results

All 60 patients, 30 patients in study or pentoxifylline group (group 1) and 30 patients in control group (group 2) completed the study and qualified for statistical analysis. The mean age of the control group (58.1±6.7) was slightly higher than the study group (56.4±7.7) however the difference was not statistically significant. Higher percentages of patients were male in both the groups, (Table 1). Group 2 patients had more number of patients with diabetes ($p<0.03$).

The levels of IL-6 between group-1 and group-2 had significant difference except at the base line time T_1 (Table 2, Figure 1). The results from IL6 levels proved that the control group patients had higher inflammation in comparison to PTF treated group.

The levels of CRP between group-1 and Group-2 had significant difference except at the base line time T_1 (Table 3, Figure2). The results from CRP levels proved that the control group patients had higher inflammation in comparison to PTF treated group.

Table 1: Demographic data

Parameters	Group 1(Study) n=30	Group2(Control) n=30	P value
Age (mean±SD)	56.4±7.7	58.1±6.7	0.36
Weight	69.6±10.3	64.6±8.1	0.04
Gender			
Male	26 (86.7%)	27 (90%)	0.89
Female	4 (13.3%)	3 (10%)	0.54
Diabetes mellitus	6 (20%)	14 (46.6%)	0.03*
CPB time	48.6±11.1	47.38±14.5	0.66
Number of grafts	3.2±0.6	3.18±0.6	0.6
No of PRBC used	2.3±0.9	2.2±0.7	0.5
ICU discharge time (hours)	28.2±4.9	32.4±7.0	0.01*
Hospital discharge time (days)	7.9±0.7	8.0±0.8	0.82
IABP and high inotropes support	7 (23.3%)	7 (23.3%)	1

Abbreviations: CPB- Cardiopulmonary Bypass, ICU- Intensive Care Unit, IABP- Intra aortic Balloon Pump, PRBC- Packed Red Blood Cells, SD- Standard Deviation.

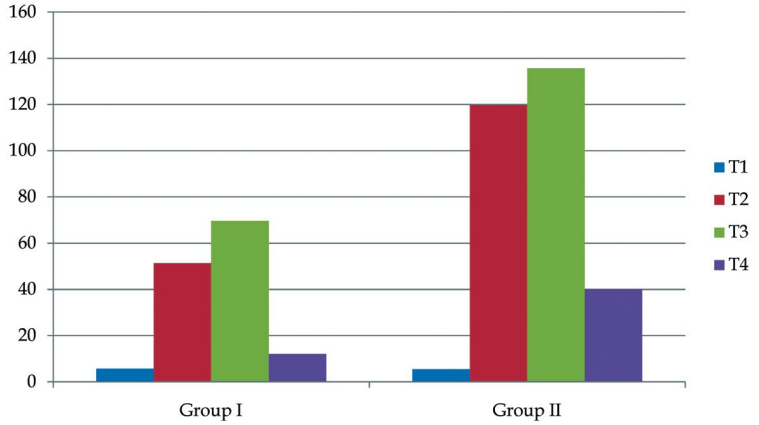

Fig. 1: Chart diagram showing the levels of IL-6 (pg/mL) between two groups at four time points

Table 2: Levels of IL-6 (pg/ml) at different time points of both groups

Time points	Group-1 (n=30)	Group-2 (n=30)	P value
T1	5.76±7.58	5.55±8.00	0.473
T2	51.38±30.04	119.74±103.86	0.017
T3	69.70±23.60	135.72±88.19	0.002
T4	12.11±5.65	40.20±30.58	0.000

Table 3: Levels of CRP (mg/L) at different time points of both groups

Time points	Group-1 (n=30)	Group-2 (n=30)	P value
T1	1.93±2.13	2.68±2.96	0.315
T2	6.04±2.88	8.83±2.91	0.000
T3	158.79±42.37	223.87±93.00	0.004
T4	92.70±33.07	184.52±117.82	0.000

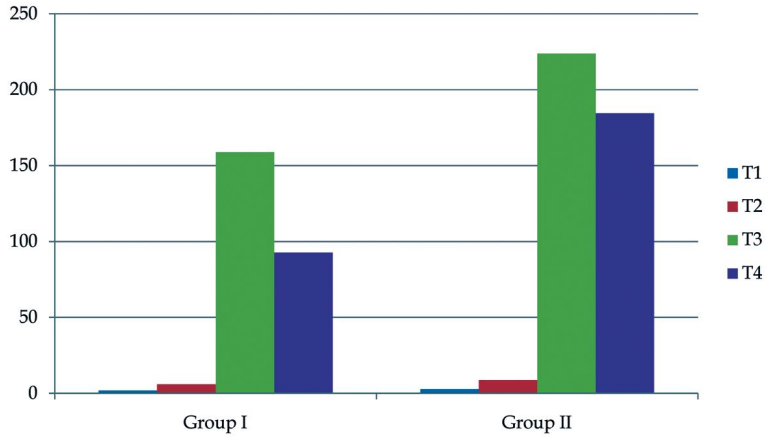

Fig. 2: Chart diagram showing the levels of HS-CRP (mg/L) between two groups at four time points

Discussion

The present study determined that perioperative PTF was effective in reducing the rise in level of inflammatory markers like IL6 and CRP in patients of CABG surgery with CPB. The reduction in inflammation was manifested by early discharge of patients from ICU. The levels of CRP and IL-6 were increased in both the groups from base line time. But the PTF treated group had markedly low rise of the biomarkers than control group patients in the subsequent periods of 1h after termination of CPB, 24h after surgery and 6thpost-operative day.The study also showed that the pro-inflammatory markers level continued to be high even after 6 days after cardiac surgery.

Pentoxifylline is methyl xanthine derivative with phosphodiesterase inhibiting property[6]. It releases the intracellular signaling molecules mainly the cyclic adenosine monophosphate (c-AMP)[7]. The accumulation of c-AMP prevents the release of inflammatory cytokines like tumor necrosis factor alpha (TNFá), IL-6 and CRP. Pentoxifylline has the vasodilatory and rheological property in blood[6]. This improves the microcirculation, reduction in inflammation and immune modulation during cardiac surgery under hypothermic CPB[7,9]. Pentoxifylline also prevents endothelial injury produced due to systemic inflammatory response[10]. All the mechanism of PTF helped in reducing the levels of inflammatory markers in PTF group patients.

Interleukin-6 and CRP are markers of tissue inflammation and complement activation[11]. The levels of IL6 and CRP are high in control group compared to PTF treated group. This suggested that PTF had anti-inflammatory effect. The anti-inflammatory effect of PTFis supported by the study of Otani S et al with the evidence of reduction in IL-6 level[7]. In a similar study with single dose administration of PTF by Heinze Het al detected a marked reduction in the level of inflammatory marker like TNF-á.[12]Tsang GMK et al detected insignificant reduction of IL-6 in PTF treated patients in comparison to placebo therapy in patients undergoing CPB for CABG[10].

The time of ICU discharge was short in PTF group compared to control group. The reason is the anti-inflammatory effect of PTF producing less pulmonary dysfunction related to CPB. Reduced inflammation might have facilitated for less tissue edema, early

extubation, and early stabilization of cardiac function in PTF group. This is supported by the study of Otani S et al and Heinze H et al [7, 12]. Otani S et al detected reduced respiratory index and better pulmonary function in PTF treated patients. Heinze H et al detected lower ventilation time and high dependence unit stay in cardiac surgical patients treated with PTF.Tsang GMK et al in a study found that PTF reduced endothelial injury and lung permeability as well as dysfunction [10].

Limitations**:** The present study had not included elderly patients of age more than 65 year. Patients were only coronary artery disease with less co-existing diseases. The patients were small in number; a larger population will strengthen the finding.

To conclude the perioperative pentoxifylline treatment reduces inflammation markers like interleukin-6 and C-reactive protein in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass support. Further study with enrollment of large number of patients will establish .the findings of the present study.

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