

Preoperative Oral Pentoxifylline for Management of Cytokine Reactions in Cardiac Surgery

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ABSTRACT

Background: Cardiopulmonary bypass may lead to many inflammatory responses that may cause myocardial dysfunction after open heart surgery. We aimed to investigate the effect of preoperative pentoxifylline treatment to reduce the occurrence of cardiopulmonary bypass-induced inflammatory response.

Methods: In a prospective, randomized study, 40 patients undergoing coronary artery bypass graft surgery received either pentoxifylline (study group, $n = 21$) or not (control group, $n = 19$). Pretreatment with pentoxifylline (800 mg/day orally) was started 5 days before the operation. Blood samples for measurements of tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-8 from the arterial line, and venous blood samples for creatine kinase (CK) and CK isoenzyme fraction MB (CK-MB) were taken in both groups at 5 different time points. Hemodynamic parameters were measured with the thermodilution technique.

Results: TNF- α , IL-6, and IL-8 plasma levels increased in both groups after cardiopulmonary bypass, with a greater increase in the control group ($P < .05$). There were no significant differences between the groups for the values of CK-MB and hemodynamic parameters.

Conclusions: We conclude that pretreatment with oral pentoxifylline before cardiac surgery inhibits proinflammatory cytokine release caused by cardiopulmonary bypass and has some beneficial effects in protecting the myocardium during the cardioplegic arrest period in open-heart surgery, without affecting postoperative hemodynamics.

INTRODUCTION

The aim of this prospective, randomized, double-blinded study in patients undergoing coronary artery bypass graft (CABG) surgery was to investigate whether the preoperative use of pentoxifylline reduces cardiopulmonary bypass (CPB)-induced cytokine reaction and myocardial ischemia-reperfusion injury.

Cardiac surgery and CPB activate a systemic inflammatory response syndrome (SIRS) and cause some harmful changes

in cardiovascular and pulmonary function. This SIRS after CPB may be caused by contact of blood components with the extracorporeal circulation and activation of leukocytes. These mechanisms may be activated by operative trauma, ischemia-reperfusion injury, or body temperature changes [Czerny 2000]. Release of cytokines and oxygen-free radicals, activation of the complement system, expression of adhesion molecules with the activation of leukocytes, and presence of metabolites of arachidonic acid and of endothelin and platelet-activating factor all have major roles in systemic inflammatory response [Bittar 2006]. SIRS after CABG surgery is primarily associated with low blood pressure and increased heart rate, increased body temperature, leukocytosis, and tissue edema, and these factors contribute to prolonged hospital stays after surgery. Inflammation is an important factor in the pathogenesis of organ injury after CPB. Studies have investigated various protocols to reduce the inflammatory response and thereby improve myocardial and pulmonary function following CPB, such as administration of antiinflammatory drugs, steroids or some antioxidants [Larmann 2004].

The systemic inflammatory system produces proinflammatory cytokines such as interleukin (IL)-6 and IL-8 and antiinflammatory cytokines such as IL-10. Many factors such as ischemia-reperfusion events cause the release of cytokines. The release of cytokines also can be stimulated by other cytokines. These cytokines are intercellular messengers produced by tissues in response to different stimuli. They have been generally considered to be products of leukocytes.

Increased levels of the proinflammatory cytokines tumor necrosis factor α (TNF- α), IL-6, and IL-8, the role of the antiinflammatory cytokine IL-10, and the balance among these cytokines may be important in determining the level of the inflammatory response. This inflammatory reaction may contribute to the development of postoperative complications, including myocardial dysfunction, respiratory failure, renal and neurologic dysfunction, bleeding disorders, altered liver function, and sometimes even the occurrence of multiple organ failure.

Fortunately, significant morbidity is rare, and many patients can recover successfully from CPB, despite inflammatory reactions. However, inhibitory mechanisms may protect against inflammatory reactions and thereby prevent organ damage after heart operations. The balance of proinflammatory and antiinflammatory cytokines is important for the development of the inflammatory response and the patient's clinical features. The release of proinflammatory cytokines

Received December 23, 2008; accepted February 13, 2009.

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may contribute to the development of multiorgan failure [El Azab 2002]. On the other hand, the release of the anti-inflammatory cytokine IL-10 during CPB may play a protective role against inflammation by suppressing the production of proinflammatory cytokines [Giomarelli 2003].

Numerous reported studies have investigated myocardial protection during cardioplegic arrest. The main focus of these investigations was preservation of myocardial metabolism and thus protection of myocardial contractility. Some drugs added to cardioplegic solutions have prevented SIRS and improved myocardial protection. Steroids and some antiinflammatory drugs have been used for the prevention of deleterious effects of CPB for many years. Pentoxifylline, a methylxanthine derivative with rheologic effects, may be a useful agent to attenuate the negative effects of CPB on postoperative organ function. In a previous study we found that pentoxifylline infusion during cardiac surgery effectively suppressed cytokine increase in heart surgery [Iskesen 2006]. This drug can also be taken orally, and therefore we performed this double-blind, controlled, prospective randomized study to investigate the possible effects of the preoperative use of orally administered pentoxifylline on the biochemical markers of SIRS and myocardial injury during open heart surgery and to determine if it has any protective effects against systemic inflammation.

METHODS

A total of 40 patients undergoing elective CABG surgery were enrolled in this study. The study was approved by the local medical ethics committee. All patients gave their informed consent. Preoperatively, the patients were randomly divided into 2 groups. The study group (group PTX, $n = 21$) received pentoxifylline 400 mg twice a day (800 mg/day, orally) for the last 5 days preoperatively. Patients in the group PTX received their last dose in the morning of the day of surgery. The control group (group C, $n = 19$) had not received pentoxifylline preoperatively. The preoperative values did not differ statistically between the groups (Table 1). Exclusion criteria were severe left ventricular dysfunction (defined as a left ventricular ejection fraction of $<30\%$ or an end-diastolic pressure of >16 mm Hg); emergency or redo operation; recent myocardial infarction in the last 4 weeks; pulmonary disease; renal or hepatic dysfunction; insulin-dependent diabetes; age older than 80 years; white blood cell count higher than 10,000/mL; infection during the week preceding surgery; preoperative use of antibiotics, corticosteroids, nonsteroidal antiinflammatory drugs, and aspirin; or smoking in the last month. Patients using β -blockers were not included in the study because of possible interference with myocardial performance. Patients with hypertension continued to receive their medication until the operation. All operations were performed by the same surgical team. The surgical team and biochemical analysts were blinded with respect to the study medication.

All samples and parameters from the patients were obtained according to the following procedure, as in our previous study [Iskesen 2006].

Serial blood samples were collected from the radial artery for the measurement of TNF- α and IL-6 and -8. Values for the 2 groups were compared for samples collected at 5

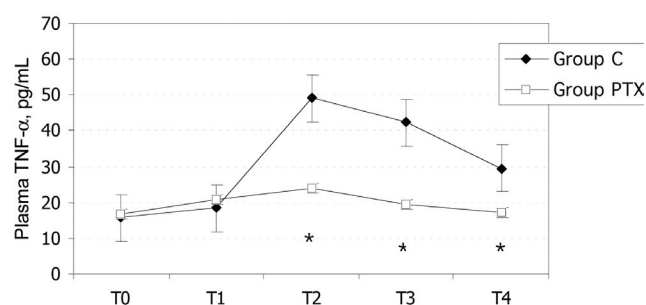


Figure 1. Comparison of plasma TNF- α levels between the pentoxifylline (PTX) and control (C) groups. * $P < .05$ versus control group.

different time points: before induction of anesthesia (T0), 10 minutes after placement of aortic cross-clamping (during the cross-clamp period) (T1), 10 minutes after the end of CPB (T2), 4 hours after skin closure (T3), and at the 24th hour postoperatively (T4) (Table 2).

Venous blood samples were also taken to determine the serum concentrations of creatine (CK) and CK isoenzyme fraction MB (CK-MB) preoperatively (T0) and postoperatively at the 2nd (T1) and the 18th hour (T2).

Standard radial arterial, central venous, and Swan-Ganz catheters were inserted preoperatively. Hemodynamic parameters such as heart rate, mean arterial pressure, central venous pressure, and pulmonary capillary wedge pressure were measured just before the CPB (H0), 10 minutes after removal of the aortic cannula (H1), at the 2nd hour in the intensive care unit (H2), and at the 18th hour postoperatively (H3). Calculated hemodynamic values from these findings were also recorded: cardiac output, cardiac index, systemic vascular resistance index, and left ventricle stroke work index. Total drainage amounts and the number of blood products used (units) in the postoperative period were also recorded.

The blood samples were immediately centrifuged after collection at 1000g, and the plasma was stored at -70°C until assays were performed. Plasma levels of TNF- α , IL-6, and IL-8 were measured with standard, commercially available enzyme-linked immunosorbent assay (ELISA) kits (BioSource Europe SA, Nivelles, Belgium). CK and CK-MB analysis was performed by use of an enzymatic method (Synchron Systems, Beckman Coulter, Galway, Ireland). Hemodynamic parameters were measured by using the thermodilution technique with cardiac monitors (Datascope-Ohmeda, Paramus, NJ, USA).

Surgical Procedure

All operations were routinely done in our clinic. The patients were anesthetized with sufentanil and surgery was performed through a median sternotomy under with the patient in moderate hypothermia. Aortic cannulae and 2-stage venous cannulae were used for perfusion. A retrograde cardioplegia cannula was placed into the coronary sinus via the right atrium. The same anesthetic and cardioplegic protocols were used in all patients. The combination of ante- and retrograde blood cardioplegia was used in all patients. CBP was performed by use of a membrane oxygenator and a roller pump. Heparin was given before cannulation of the aorta

Table 1. Perioperative Characteristics of the Groups*

	Group PTX†	Group C
No. of patients (M/F)	21 (17/4)	19 (16/3)
Age, y	63 ± 5.2	61 ± 7.4
Weight, kg	85.2 ± 10.2	82.4 ± 7.5
No. of grafts per patient, n	2.85	2.60
Duration of CPB, min	75.5 ± 6	81.1 ± 5
Cross-clamp time, min	42.5 ± 3	49.5 ± 3
Use of blood products, units	3.5 ± 0.5	3.2 ± 0.7
Blood drainage, mL	725 ± 25	650 ± 55

*CPB indicates cardiopulmonary bypass.

† $P > .05$ versus control group

(3 mg/kg). Activated clotting time was higher than 400 seconds in all patients. Patient temperature was reduced to 32°C–34°C. Mean flow rate was approximately 2.4 L/min per m². The left internal thoracic artery was used as a graft for the left anterior descending artery and the greater saphenous vein for the other coronary vessels.

Statistical Analysis

Results are expressed as mean ± SEM. The significance in the difference for these results in the 2 groups was determined using the unpaired Student *t*-test. A difference was considered statistically significant for $P < .05$.

RESULTS

The clinical and demographic characteristics of 40 patients undergoing CPB are summarized in Table 1. There were no significant differences between the 2 groups of patients. The following biochemical values were obtained:

Preoperative values (T0) (as u/L) for CK were 61.3 ± 4.3 vs 63.1 ± 2.5 ($P > .05$) and for CK-MB were 16.4 ± 3.2 vs 18.2 ± 2.3 ($P > .05$) in the PTX and C groups, respectively.

Serum CK activity in the PTX group was lower at the 2nd postoperative hour (T1) (385.4 ± 9.7 u/L) than in the control group (435.4 ± 17.4 u/L) ($P > .05$). At the 18th postoperative hour (T2) the CK values in the PTX group were again not significantly lower (557.6 ± 5.5 u/L) than those in the control group (586.8 ± 18.4 u/L) ($P > .05$).

The difference in average CK-MB values on the first postoperative day did not reach statistical significance between the groups. Serum CK-MB values (T1) were lower in group PTX (44.2 ± 3.7 u/L) than in the control group (51.7 ± 7.8 u/L) at the 2nd postoperative hour ($P > .05$). At the 18th hour CK-MB values (T2) in the PTX group (37.7 ± 4.2 u/L) were also lower than those of the control group (41 ± 5.3 u/L) but not significantly ($P > .05$).

In the post-CPB period, the difference in the TNF-α, IL-6, and IL-8 levels of the 2 groups were found to be statistically significant ($P < .05$). The time course of blood cytokine levels is shown in Table 2.

TNF-α plasma levels increased to a peak level after CPB in the control group. At 24 hours postsurgery (T4), TNF-α

was down to the baseline level in the PTX-treated group (17.3 ± 0.5 pg/mL), but it was significantly greater in the control group (29.5 ± 1.5 pg/mL) ($P < .05$) (Figure 1).

IL-6 levels reached a peak level just after the completion of surgery (T2). The peak of IL-6 in the control group was significantly higher than in the PTX group ($P < .05$). At the 4th postoperative hour (T3), IL-6 was elevated in both groups, with a significantly higher level in the control group (287.7 ± 4.2 pg/mL) than in the pentoxifylline group (211.5 ± 12.4 pg/mL, $P < .05$); 24 hours after the termination of CPB, IL-6 levels (T4) were still significantly higher in the control group (227.3 ± 3.5 vs 171.4 ± 3.7 pg/mL, $P < .05$) (Figure 2).

IL-8 plasma levels were normal at baseline (T0) but increased after surgery until the first postoperative day. This increase was significantly higher in the control group (T2) (from 27.3 ± 5.4 pg/mL at baseline to 185.6 ± 13.4 pg/mL at the end of surgery) than in group PTX (from 25.5 ± 7.1 pg/mL at baseline to 125.3 ± 4.2 pg/mL at the end of surgery) (Figure 2).

We observed no significant difference between the groups for any serial hemodynamic determinations ($P > .05$) (Table 3).

Total drainage amounts and the number of blood products used (units) were not different between the 2 groups ($P > .05$) (Table 1).

No adverse effects of the drug were detected in any patient. There were no electrocardiogram changes attributable to myocardial infarction and no deaths in the perioperative period. There were no significant differences between the groups in requirements for inotropic agents or in the use of defibrillation after removal of the cross-clamp. There were no significant differences in clinical outcomes between the group that received pentoxifylline and the group that did not.

DISCUSSION

CPB causes leukocyte and complement activation, the release of some cytokines and inflammatory mediators, and an increase in the release of oxygen free radicals [Larmann 2004]. Proinflammatory cytokines (TNF-α, IL-1, IL-6, and IL-8) can affect myocardial function and damage some organs [Edmunds 1999; Laffey 2002; Gessler 2003]. These factors interact with each other and affect one another so that they

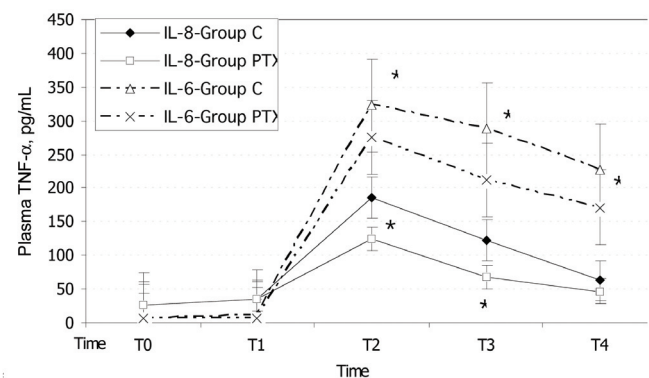


Figure 2. Comparison of plasma IL-6 and IL-8 levels between the pentoxifylline (PTX) and control (C) groups. * $P < .05$ versus control group.

Table 2. Biochemical Results of the Groups*

	T0	T1	T2	T3	T4
Group PTX					
TNF- α	16.7 $\pm$ 2.4	20.6 $\pm$ 3.1	24.1 $\pm$ 0.8†	19.5 $\pm$ 4.2†	17.3 $\pm$ 3.3†
IL-6	6.1 $\pm$ 2.1	7.2 $\pm$ 3.8	275.5 $\pm$ 6.5†	211.5 $\pm$ 12.4†	171.4 $\pm$ 3.7†
IL-8	25.5 $\pm$ 1.9	35.6 $\pm$ 2.8	125.3 $\pm$ 7.5†	67.4 $\pm$ 3.8†	46.8 $\pm$ 5.6
CK-MB	16.4 $\pm$ 3.2	44.2 $\pm$ 3.7	37.7 $\pm$ 4.2	—	—
Group C					
TNF- α	15.6 $\pm$ 0.5	18.3 $\pm$ 2.7	49.2 $\pm$ 4.2	42.3 $\pm$ 5.1	29.5 $\pm$ 3.4
IL-6	5.7 $\pm$ 0.3	10.2 $\pm$ 2.3	322.6 $\pm$ 4.6	287.7 $\pm$ 4.2	227.3 $\pm$ 3.5
IL-8	27.3 $\pm$ 2.1	34.5 $\pm$ 3.2	185.6 $\pm$ 8.8	122.6 $\pm$ 6.5	82.3 $\pm$ 5.3
CK-MB	18.2 $\pm$ 2.3	51.7 $\pm$ 7.8	41 $\pm$ 5.3	—	—

*T time points are detailed in the text. TNF indicates tumor necrosis factor; IL, interleukin; CK, creatine kinase; CK-MB, CK isoenzyme fraction MB.

† $P < .05$ versus control group

increase each other's potential for causing injury. Inflammation and ischemic changes occur at the beginning of CPB and arrive at peak level within 20 minutes. Blood levels of IL-1, IL-6, IL-8, and TNF- α increase during CPB, and the recovery time starts as soon as the cross-clamp is released [Edmunds 1997].

Reperfusion of the heart and lungs may be the main factor for emergence of the systemic inflammatory response. Neutrophils, macrophages, and endothelial cells release cytokines in response to injury [Frangogiannis 2002]. TNF- α , which is produced by macrophages and monocytes, is a proinflammatory cytokine and an activator of neutrophil and endothelial cells. IL-6 has proinflammatory and some antiinflammatory properties. Endothelial cells, monocytes, and T cells release IL-8, which is recognized as a mediator of organ dysfunction because of its role in leukocyte activation. The levels of IL-8 correlate with myocardial injury after cardiac surgery. IL-10 is a potent antiinflammatory cytokine that reduces neutrophil adhesion and so has an important effect in the reduction of ischemia/reperfusion injury. The myocardium is a major source of TNF- α , IL-6, and IL-8, whereas IL-10 emerges from the liver [Wan 1997]. The levels of these proinflammatory cytokines have been correlated with the duration of cardiac ischemia during CPB [Wan 1997], but we did not find any reports about the association of levels of these markers with CPB time.

Our IL-6 results are similar to the results of previous studies [Miller 1997]. IL-6 is responsible for morbidity associated with the inflammatory response to CPB. It increases after initiation of CPB, peaks at 4 hours, and, as in our study, is still elevated 24 hours after the end of CPB. IL-6 may cause a depression in myocardial contractility, so its level may be a sensitive indicator of myocardial damage [El Azab 2002]. In our study the maximum level of IL-6 was significantly reduced in the PTX group. TNF- α affects the release of IL-6, and the reduction of IL-6 levels may be the result of an inhibition of TNF- α release. This finding suggests that there is an effect of pentoxifylline on TNF- α . IL-8 also plays a major role in bridging the humoral mediators with the cellular mediators

of inflammation, and in our study the same marker level pattern was obtained as in previous other studies [Miller 1997].

The balance of the proinflammatory and antiinflammatory cytokines may affect the degree of the whole-body inflammatory reaction and its possible damages [Aleshin 2004]. According to the results of some studies, the inhibition of IL-6 release may also be explained by increase of the release of IL-10 [Giomarelli 2003]. We were unable to draw any conclusion on this subject in our previous study [Iskesen 2006], and we did not perform any IL-10 measurement in this study because of our laboratory limitations and financial restrictions.

Many different strategies to reduce the inflammatory reaction have been studied, such as the administration of corticosteroids and other agents and methods such as leukocyte depletion. The effects of pentoxifylline on the production of IL-6, IL-8, and TNF- α have been studied previously [Ji 2004]. We studied the effect on the release of proinflammatory cytokines of pretreatment of patients undergoing CABG surgery. Our results suggest that pentoxifylline decreases the production of proinflammatory cytokines during CPB and therefore may alleviate tissue damage. On the other hand, postoperative CK and CK-MB levels were not found to be statistically different between the 2 groups. However, this study may be considered a preliminary one for the evaluation of the effects of oral pretreatment with this agent, and further studies with more patients and more sensible markers may be necessary to clarify this point.

Pentoxifylline, a methylxanthine derivate, nonspecifically inhibits phosphodiesterase activity, resulting in an accumulation of the intracellular signaling molecule cyclic AMP

Table 3. Hemodynamic Results of the Groups

Hemodynamic values, CI = L/min per m ²	H0	H1	H2	H3
Group PTX	1.9 $\pm$ 0.3	2.32 $\pm$ 0.4	2.6 $\pm$ 0.5	2.4 $\pm$ 0.2
Group C	2.0 $\pm$ 0.2	2.4 $\pm$ 0.2	2.5 $\pm$ 0.3	2.5 $\pm$ 0.5

*H time points are detailed in the text. CI indicates cardiac index.

[Heinze 2007], which leads to the inhibition of production and release of various cytokines. Pentoxifylline is a rheologic agent that increases red cell deformation and may cause bleeding. To investigate these possible effects, we measured total drainage amounts and the number of blood products used (units). These were not different between groups, suggesting, as in our previous study and other reported investigations, that pentoxifylline does not increase the risk of bleeding and that it also does not change the coagulation or the bleeding times [Szefer 1995].

We used 800 mg oral (400 mg twice a day) pentoxifylline for 5 preoperative days in each patient undergoing an operation. In other studies an infusion of pentoxifylline is used during surgery [Iskesen 2006; Ustunsoy 2006]. Timing of pentoxifylline administration may be important, according to other studies. Prophylactic and continuous administration of pentoxifylline is also important and beneficial for preventing inflammatory injuries. Early use of pentoxifylline before cardiac surgery also has been reported to attenuate endothelial injury occurring in CPB [Tsang 1996].

CONCLUSIONS

This study indicates that pentoxifylline pretreatment before cardiac surgery with CPB in human subjects has significant effects on the release of several inflammatory markers but does not affect hemodynamic parameters. The systemic proinflammatory cytokine response in patients undergoing CPB can be reduced to a certain level with oral preoperative pentoxifylline use.

ACKNOWLEDGMENT

This study was supported by a grant from the "Celal Bayar University Scientific Investigation Fund."

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