

Preoperative oral administration of pentoxifylline ameliorates respiratory index after cardiopulmonary bypass through decreased production of IL-6

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Abstract

Activation of inflammatory response during cardiopulmonary bypass (CPB) may lead to considerable post-operative mortality. Recently, pentoxifylline (PTX), a methylxanthine derivative, has been reported to be effective in inhibiting proinflammatory cytokine production. This study aimed to determine whether or not PTX prevented CPB-induced systemic inflammatory response syndrome (SIRS) in patients undergoing cardiovascular surgery. Thirty adult patients were randomly separated into 2 experimental groups and 1 control group of 10 patients each. The experimental group received peroral PTX administration (Group 1: 600 mg/day, Group 2: 900 mg/day), while the control group did not. In Group 1 and Group 2, PTX administration was started on preoperative day 5 and continued for 5 days. Serum levels of PTX and IL-6 were measured just before and at 4 h after CPB using HPLC and ELISA, respectively. Respiratory index (RI) before and at 4 h after CPB was calculated, and serum levels of C-reactive protein (CRP) and fibrinogen on postoperative day 1 were also determined. There were no significant differences in age, body weight, sex, surgical procedures, CPB time, haemodynamics or risk factors among the 3 groups. Serum IL-6 level and RI index after CPB in Group 2 were significantly decreased compared with those in Group 1 and the control group. These results, therefore, suggested that preoperative daily administration of 900 mg/day PTX contributed to the attenuation of CPB-induced SIRS and had a beneficial effect on the postoperative course after cardiovascular surgery.

KEYWORDS: pentoxifylline, CPB, IL-6, SIRS, respiratory index

Original Article

Preoperative Oral Administration of Pentoxifylline Ameliorates Respiratory Index after Cardiopulmonary Bypass Through Decreased Production of IL-6

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Activation of inflammatory response during cardiopulmonary bypass (CPB) may lead to considerable post-operative mortality. Recently, pentoxifylline (PTX), a methylxanthine derivative, has been reported to be effective in inhibiting proinflammatory cytokine production. This study aimed to determine whether or not PTX prevented CPB-induced systemic inflammatory response syndrome (SIRS) in patients undergoing cardiovascular surgery. Thirty adult patients were randomly separated into 2 experimental groups and 1 control group of 10 patients each. The experimental group received peroral PTX administration (Group 1: 600 mg/day, Group 2: 900 mg/day), while the control group did not. In Group 1 and Group 2, PTX administration was started on preoperative day 5 and continued for 5 days. Serum levels of PTX and IL-6 were measured just before and at 4 h after CPB using HPLC and ELISA, respectively. Respiratory index (RI) before and at 4 h after CPB was calculated, and serum levels of C-reactive protein (CRP) and fibrinogen on postoperative day 1 were also determined. There were no significant differences in age, body weight, sex, surgical procedures, CPB time, haemodynamics or risk factors among the 3 groups. Serum IL-6 level and RI index after CPB in Group 2 were significantly decreased compared with those in Group 1 and the control group. These results, therefore, suggested that preoperative daily administration of 900 mg/day PTX contributed to the attenuation of CPB-induced SIRS and had a beneficial effect on the postoperative course after cardiovascular surgery.

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Cardiac surgery and cardiopulmonary bypass (CPB) initiate a systemic inflammatory response syndrome (SIRS) that may lead to considerable post-operative mortality as well as complications such as

bleeding, thromboembolism, fluid retention and temporary organ dysfunction. This syndrome arises mainly due to contact between the blood and the artificial surfaces of the bypass circuit [1-3]. Attempts to prevent CPB-mediated inflammation by pharmacological means are warranted, because a reduction in the inflammatory response may contribute to organ function protection and hence to improved recovery from surgical revascularization procedures, particularly in critically ill patients. CPB-induced SIRS is characterized by the activation of complement, monocyte/macrophages and neutrophils, and the release of cytokines and vasoactive substances [4, 5]. Proinflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-6, can be induced by a wide variety of stimuli and act on a large number of effector cells [6, 7]. Thus, their concentrations may reflect the status of the inflammatory response when multiple initiating processes are involved.

Previous clinical studies have demonstrated a marked increase in serum IL-6 postoperatively, but have been unable to detect a consistent rise in serum TNF- α and IL-1 β [8]. The failure to detect TNF- α and IL-1 β in serum may be due to the transient, local paracrine release of these agents and their rapid proteolytic degradation [9]. Alternatively, the assays may not be sufficiently sensitive, or may fail to detect receptor-bound or protein-bound cytokines [10]. These reports have suggested that the serum levels of IL-6 are the best parameter for assessing the status of the inflammatory response to surgical stress. IL-6 is a pleiotropic cytokine involved in the regulation of immune responses and also plays an important role during acute-phase responses, which include fever, corticosterone release and hepatic production of acute phase proteins. This cytokine is produced by a variety of cells after some form of stimulation, such as an infection, trauma or immunological challenge, which stimulates the release of immune-competent proteins, such as CRP from the liver and, together with TNF- α and IL-1 β , causes activation of T cells. High serum IL-6 concentrations have been reported to be directly associated with mortality in patients with endotoxic shock [11, 12].

Furthermore, proinflammatory cytokines appear to mediate many of the cellular events that contribute to injury after CPB. Leukocytes are the main type of

white blood cell involved in the inflammatory response, and their recruitment, activation and cytotoxic effects play a major role in the damage process. The induction of inducible nitric oxide synthase (iNOS) has also been demonstrated in cardiovascular surgery with CPB [13, 14]. Nitric oxide (NO) is known to have cytotoxic effects in various pathological conditions; its major cytoprotective effect is to inhibit leukocyte-endothelial cell adhesion [15, 16]. Endothelial dysfunction with decreased NO levels has been implicated in ischemic-reperfusion injury [17]. Intact endothelial function is essential to the maintenance of an adequate vascular tone in order to prevent platelet aggregation in the intimal surface of blood vessels and to prevent smooth muscle proliferation [18]. Localized inflammatory reactions in the myocardium are mainly caused by endothelial injury induced by ischemic reperfusion, and CPB may exacerbate the resulting injuries through proinflammatory cytokine production. Reducing proinflammatory cytokine release may help to limit the CPB-induced SIRS. Reducing the invasiveness of cardiovascular surgery with CPB is therefore an issue of ongoing concern.

Pentoxifylline (PTX), a methylxanthine derivative, known for many years for its hemorheological properties [19], has proven to be a potent inhibitor of TNF- α production by mononuclear cells [20, 21]. PTX acts mainly by inhibiting phosphodiesterase, resulting in increased levels of cAMP [22]. PTX also reduces the production of interleukin-2 (IL-2) after the administration of OKT3 or lipopolysaccharide (LPS) in mice [23]. More recently, it was shown that PTX preferentially suppressed murine TH1 cytokines without affecting TH2 cytokines, and that this molecule can efficiently suppress the development of autoimmune encephalomyelitis [24]. These reports suggested that PTX has the potential to attenuate the inflammatory responses that occur following CPB and that are associated with significant postoperative hypoxemia and systemic release of neutrophil elastase and IL-6 [25]. Iskesen I *et al.* indicated that PTX infusion during cardiac surgery inhibited the proinflammatory cytokine release caused by CPB [26]. In addition, Ustunsoy H *et al.* showed that the addition of PTX to cardioplegic solution might help to avoid myocardial inflammation and ischemic/reperfusion injury during open heart surgery [27]. Moreover, Boldt J *et al.* clearly demonstrated that the use of PTX just after the induction

of anesthesia and continuing after CPB resulted in a reduced inflammatory response in comparison to an untreated control group [28]. However, no reports have addressed whether or not prophylactic oral administration of PTX could attenuate CPB-induced SIRS. Also, no reports have clearly demonstrated a correlation between the anti-inflammatory effect of PTX and respiratory function.

Patients and Methods

Patients requiring first-time coronary artery bypass grafting (CABG) were enrolled in the study. Thirty patients were randomly separated into 2 experimental groups and one control group of 10 patients each. The experimental groups received peroral Pentoxifylline (PTX) administration (Group 1: 600 mg/day, Group 2: 900 mg/day), while the control group did not. In the experimental groups, PTX administration was started on preoperative day 5 and was continued for 5 days. The exclusion criteria included recent myocardial infarction, unstable angina, acute infection, known immunological disease, insulin-dependent diabetes, acute or chronic renal failure, redo surgery, respiratory impairment and coagulopathy. The study protocol was approved by the Iwakuni Medical Center Trust Ethics Committee. Written informed consent was obtained from all patients.

Blood samples were collected for serological assay just before the start of cardiopulmonary bypass (pre-CPB) and at 4 h after the completion of CPB (post-CPB). The samples (10 ml) were collected in bottles containing EDTA and immediately placed in ice. Each sample was then centrifuged at 1,500 *g* for 10 min, and the serum was collected into small Eppendorff vials and frozen to -70°C for later analysis. Serum levels of pentoxifylline (PTX) were determined by high-performance liquid chromatography (HPLC) with solid-phase extraction, and serum levels of IL-6 were quantified using an commercial enzyme-linked immunosorbent assay (ELISA) kit (Quantikine, R & D Systems, Minneapolis, MN, USA). Blood samples were also obtained on postoperative day 1, and serum levels of C-reactive protein (CRP) and fibrinogen were measured as appropriate. The respiratory index (RI) was also determined in each group before the start of CPB and at 4 h after the completion of CPB.

Unless stated otherwise, all data are expressed as

the mean \pm standard error of the mean (SEM). Normally distributed parameters were analyzed using Student's *t* test, and *p*-values of 0.05 or less were considered statistically significant.

Results

Baseline patient demographics and clinical characteristics. Patient profiles and pre-, peri- and post-operative clinical data for each group of patients are listed in Table 1. There were no significant differences in age, weight and sex among the groups. In addition, no statistically significant differences were found among the groups in the pre- and peri-operative haemodynamic data nor in the number of risk factors for cardiovascular surgery. No statistically significant differences were observed among the groups in the post-operative CRP, LDH and GPT values, although all the values in Group 2 tended to be lower than those in the control group and Group 1. The peri-operative course and post-operative recovery periods were uneventful for patients in all 3 groups.

Serum PTX and IL-6 levels and RI index. The serum PTX levels at pre-CPB in the control group, Group 1 and Group 2 were 0, 351 ± 68 and 1255 ± 153 ng/dl, respectively. The serum PTX levels at post-CPB in the control group, Group 1 and Group 2 were 0, 125 ± 73 , and 813 ± 179 ng/dl, respectively.

The serum IL-6 levels at pre-CPB in the control group, Group 1 and Group 2 were 1.9 ± 1.1 , 3.3 ± 1.0 and 2.2 ± 1.2 pg/ml, respectively, and no statistical significances were found in the IL-6 levels at pre-CPB among the groups. The serum IL-6 levels at post-CPB in the control group, Group 1 and Group 2 were 234 ± 63 , 181 ± 96 , and 99 ± 43 pg/dl, respectively. The IL-6 level in Group 2 was significantly lower than that in the control group ($p < 0.01$); however, no statistically significant differences were found in the IL-6 levels at post-CPB between the control group and Group 1, and between Group 1 and Group 2.

The values of the RI index at pre-CPB in the control group, Group 1 and Group 2 were 0.67 ± 0.28 , 0.67 ± 0.32 and 0.51 ± 0.27 pg/ml, respectively, and no statistically significant differences were found in the RI index at pre-CPB among the groups. The values of the RI index at post-CPB in the control group, Group

Table 1 Patient profiles

	Control	Group 1	Group 2
Patients	10	10	10
Age (y)	67.9 ± 5.9	61.7 ± 5.9	64.7 ± 11.4
Weight (kg)	57.4 ± 7.1	63.1 ± 6.1	59.1 ± 10.3
Sex (% male)	90.0	80.0	90.0
Pre-operative data			
Pp/Ps	0.21 ± 0.04	0.17 ± 0.04	0.22 ± 0.07
%VC	88.5 ± 19.7	97.1 ± 21.4	95.7 ± 11.3
FEV _{1.0}	81.0 ± 9.1	80.5 ± 8.0	75.4 ± 10.8
Fibrinogen (mg/dl)	212.0 ± 16.0	298.0 ± 15.0	242.0 ± 11.8
Peri-operative data			
No. of grafts (1/2/3/4/5)	2.9 ± 1.2 (0/5/3/2/0)	3.1 ± 0.9 (3/4/3/0/0)	3.2 ± 1.4 (3/1/2/3/1)
CPB time (min)	96.7 ± 32.3	91.8 ± 23.7	119.0 ± 13.9
Post-operative data (POD 1)			
CRP (mg/dl)	5.2 ± 1.0	4.5 ± 0.6	4.4 ± 0.8
LDH (IU/l)	831.0 ± 98.0	965.0 ± 127.5	834.0 ± 92.0
GPT (IU/l)	23.0 ± 3.2	27.6 ± 5.7	20.1 ± 7.3

P-values were considered not significant.

CPB, cardiopulmonary bypass; CRP, C-reactive protein; FEV, Forced expiratory volume; Pp/Ps, ratio of pulmonary artery pressure and systemic (systolic) pressure; VC, vital capacity.

Unless stated otherwise, all data are expressed as mean ± SD.

No statistical significances were observed between the groups.

1 and Group 2 were 1.19 ± 0.26 , 0.71 ± 0.40 , and 0.57 ± 0.33 pg/dl, respectively. The value of the RI index level in Group 2 was significantly lower than that in the control group ($p < 0.05$); however, no statistically significant differences were found in the RI index levels at post-CPB between the control group and Group 1, and between Group 1 and Group 2 (Table 2).

Discussion

PTX has been reported to be effective in inhibiting TNF- α production by mononuclear cells [20, 21]. Recently, various studies have demonstrated that the modulation of cytokine release induced by PTX is not restricted solely to TNF- α . *In vitro* studies showed that interleukin (IL)-1 β , IL-6, IL-2 and interferon- γ (IFN- γ) production could also be affected by PTX [29]. In fact, the present research clearly demonstrated that preoperative oral administration of PTX (900 mg/day) yielded a significant reduction in the CPB-induced induction of proinflammatory cytokine

IL-6, which was consistent with the previous *in vitro* studies [20, 21].

As described above, IL-6 plays an important role in the acute phase responses and the hepatic production of acute phase proteins, many of which are protease inhibitors [30]. IL-6 stimulates the release of immune-competent proteins, such as CRP, from the liver and, together with TNF- α and IL-1 β , causes the activation of T cells. High serum IL-6 concentrations have been reported to be directly associated with mortality in patients with endotoxic shock or trauma. Various *in vivo* studies using antibodies against IL-6 have shown conflicting results regarding whether it plays a direct functional role in mediating tissue injury [31].

A previous study found IL-6 concentration to be correlated strongly with the concentration of CK-MB (an isoenzyme of creatine kinase with muscle and brain subunits) [32]. Our previous study also showed that the change in IL-6 concentration was significantly correlated with that in leukocyte elastase in patients undergoing coronary artery bypass grafting [33],

Table 2 Comparison of serum levels of PTX, IL-6 and RI index before and after CPB

	Control	Group 1	Group 2
PTX (ng/dl)			
pre-CPB	0	351 ± 68	1255 ± 153
post-CPB	0	125 ± 73	813 ± 179
IL-6 (pg/ml)			
pre-CPB	1.9 ± 1.1	3.3 ± 1.0	2.2 ± 1.2
post-CPB	234 ± 63	181 ± 96	99 ± 43 ^a
RI index			
pre-CPB	0.67 ± 0.28	0.67 ± 0.32	0.51 ± 0.27
post-CPB	1.19 ± 0.26	0.71 ± 0.40	0.57 ± 0.33 ^b

PTX, pentoxifylline; RI, respiratory index

Unless stated otherwise, all data are expressed as mean ± SD.

^a*p* < 0.01 versus Control. ^b*p* < 0.05 versus Control.

indicating that IL-6 is a critical mediator in inducing myocardial injury. Neutrophil activation is an important early step in ischemic-reperfusion injury, and a greater degree of myocardial injury is seen after procedures associated with the increased production of IL-6, suggesting that proinflammatory cytokine IL-6 contributes to myocardial injury, possibly by activating neutrophils [34, 35].

Our study showed no significant differences in CRP concentration among the patients in the three groups, although the postoperative CRP level in patients receiving PTX administration tended to be lower than that in the control group. The IL-6 level at post-CPB in patients receiving PTX (900 mg/day) was significantly lower than that in the control group, which was consistent with the fact that the RI index level in Group 2 at post-CPB was significantly lower than that in the control group. These results suggested that preoperative oral administration of PTX yielded a significant reduction in CPB-induced IL-6 induction, resulting in a decrease in postoperative CRP levels, followed by beneficial effects on postoperative lung function.

Cytokines can act both individually and within a complex network of interrelated and interacting signals. PTX, which is highly active in the production of TNF- α [20, 21], a cytokine fundamental to the induction of the cytokine cascade, is also obviously active in the synthesis of other cytokines, particularly those with late expression, such as IL-6, which was

also reconfirmed in this clinical trial. The same may be true for IFN- γ , whose synthesis is stimulated by IL-2 which, in turn, is strongly inhibited by PTX [21, 27]. In addition, PTX, when administered to recipient animals, attenuates reperfusion injury to a degree similar to that seen with leukocyte-depleted reperfusion [23], suggesting that PTX could also decrease the systemic release of leukocyte elastase.

The neutrophil-mediated endothelium injury caused by ischemic reperfusion results in an increase in endothelium permeability, which leads to deterioration of gas exchange function in the lung, and in a dysfunction in the production of the endothelium-dependent relaxant factor NO, which contributes to an increase in pulmonary vascular resistance after reperfusion [36]. In conclusion, PTX prevented ischemic-reperfusion lung endothelium injury and improved post-ischemic-reperfusion lung function by decreasing neutrophil lung sequestration. This agent might be useful in preventing lung injury in cardiac surgery using CPB.

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