Preoperative oral pentoxifylline in case of coronary artery bypass grafting with left ventricular dysfunction (ejection fraction equal to/less than 30%)

Soheil Mansourian, Payvand Bina, Arezoo Fehri, Abbas Ali Karimi, Mohammad Ali Boroumand, Kyomars Abbasi

Department of Cardiac Surgery, Tehran Heart Center, Tehran University of Medical Sciences; Tehran-*Iran*

Abstract

Objective: Most coronary artery bypass grafts are done by applying cardiopulmonary bypass, which usually induces unwanted inflammatory reactions and impairs the outcomes. In order to minimize the perilous response of cardiopulmonary bypass, pentoxifylline was getting used orally.

Methods: In a prospective, placebo-controlled, randomized clinical trial, 178 coronary artery bypass graft candidates with ejection fraction lower/equal to 30%, divided into two equal groups (pentoxifylline and control), participated in the study. Pentoxifylline patients received 400 mg pentoxifylline 3 times a day for 3 days before operation. The outcomes were compared between groups using student's t-test, Mann-Whitney U-test, Pearson chi-square, or Fisher's exact test.

Results: Pentoxifylline administration did not significantly affect troponin-T (p=0.68), but it reduced tumor necrosis factor-α (p=0.01) and interleukin-6 (p=0.01). It improved left ventricular ejection fraction significantly (p=0.01). White blood cell and platelet counts, hemoglobin, and hematocrit were not influenced by pentoxifylline. The drug did not affect blood urea nitrogen and creatinine, occurrence of renal failure, cerebrovascular accidents, and in-hospital mortality rate. The need for an intra-aortic balloon pump, cardiopulmonary bypass, and aortic cross-clamp times were not affected, either. Pentoxifylline decreased the intensive care unit stay (p<0.001), ventilation time, 10.4 hours in the pentoxifylline group against 14.7 hours in the control group (p=0.01), and the requirement of inotropic agents (p=0.02) and blood transfusion (p=0.01).

Conclusion: Pentoxifylline has more beneficial potencies in reducing adverse events after coronary artery bypass graft using cardiopulmonary bypass, than what are known. *(Anatol J Cardiol 2015; 15: 1014-9)*

Key words: coronary artery bypass graft, cardiopulmonary bypass, pentoxifylline, low EF

Introduction

The inflammatory response produced by cardiopulmonary bypass has been well known for many years; it is due to exposure of blood to non-physiologic surfaces, and it occurs in cases in which cardiopulmonary bypass (CPB) is applied (1). Cardiac surgery and CPB are triggers for starting systemic inflammatory response syndrome (SIRS), which may eventuate to several post-operative complications (2). In operations involving CPB, a very common complication is pulmonary dysfunction (3) or even death. Various events are responsible for the intricate CPB-produced inflammatory reaction mechanism (2). It is described as resulting from activation of the complement system and leukocytes, with subsequent leuko-sequestration (4). During recent years, in order to subside the hazardous effects of lung injuries in patients undergoing cardiac surgery, many methods, like using particular pharmacologic agents, were applied (2). Pentoxifylline (Ptx) is one of the medications that are supposed to subside the unwanted effects of CPB usage; it has been the subject of many studies, where it has been administered intravenously or orally (5-8). Ptx is a xanthine derivative that increases interleukin-10 (IL-10), decreases interleukin-6 (IL-6), and inhibits C-reactive protein (CRP) release and peripheral blood cell activity (9). In humans, its primary action seems to be a

This study was held in the Department of Cardiac Surgery, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

Address for Correspondence: Dr. Kyomars Abbasi, Tehran Heart Center, Tehran University of Medical Sciences, North Kargar Street, Tehran-*Iran*
Phone: +98 21 88029600-69 Fax: +98 21 88029731 E-mail: kyomarsabbasi@gmail.com

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reduction in blood viscosity. Besides, it is reported that Ptx increases blood flow to ischemic tissues and improves tissue oxygenation in patients with peripheral vascular disease (10). Ptx inhibits in vitro neutrophil activation, including adhesion and chemotaxis, and oxidant release (11, 12). It also inhibits phosphodiesterase activity non-specifically, resulting in the accumulation of the intracellular signaling molecule cyclic adenosine monophosphate (cAMP) (13, 14), which, in turn, terminates the inhibition of the production and release of various cytokines, like tumor necrosis factor-α (TNF-α) (15). It has been suggested that in patients undergoing coronary artery bypass graft (CABG), Ptx administration prevents post-pump lung injury related to CABG surgery by 1) attenuating inflammatory cytokines (16) and 2) having a direct effect on pulmonary endothelial cells and their interactions (6). Furthermore, pre-operative administration of Ptx in patients undergoing cardiac surgery using CPB reduces potential complications and improves the outcomes (17). The purpose of this study was to evaluate the potential properties of oral Ptx on post-operative outcomes among low ejection fraction (EF) patients, who are prone to cardiac and postoperative complications, undergoing on-pump CABG.

Methods

The study was a single-center, prospective, placebo-controlled, randomized clinical trial that was carried out in Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran, between June 21, 2011 and July 21, 2012. The ethics committee of Tehran University of Medical Sciences approved the protocol. Because of the more frequent surgery complications and higher mortality rate in patients with low EF $\leq$30% than in other patients with higher EF and to detect the Ptx effects clearly, the inclusion criteria were isolated CABG candidates with EF $\leq$30%. During the study period, about 2956 cardiac surgeries were accomplished in Tehran Heart Center (THC), which comprised 2020 isolated CABGs. Also, 220 patients who had been proven to have poor left ventricular function with left ventricular ejection fraction (LVEF) lower/equal to 30% and candidates for on-pump surgery were selected for the study. After applying exclusion criteria, including previous renal failure (RF), recent myocardial infarction (MI) (less than 4 weeks ago), uncontrolled diabetes, and use of anti-inflammatory drugs, 178 patients entered the study and were divided in two groups (pentoxifylline group=89, control group=89). The study was blinded to the patient groups and surgeons. All patients signed written informed consent forms before enrollment. Randomization was done simply by using a random number table by one of the authors who was not involved in the data gathering and clinical investigations. Patients in the Ptx group received routine drugs plus 400 mg Ptx orally 3 times a day for 3 days before the operation. The control group received placebo plus routine drugs. The staff of the pre-operative ward prepared each medication (Ptx or placebo) based on the patient's random number from one responsible author. A blood sample was taken before entry into the operating room from all patients. All patients had on-pump CABG. After the operation, a second blood sample was taken immediately after arriving at the intensive care unit (ICU). Samples were analyzed for levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which were measured by enzyme-linked immunosorbent assay (ELISA), and cardiac troponin-T, which was measured by immunoassay method. Other laboratory tests, including previous and postoperative white blood cell (WBC), hemoglobin (Hgb), hematocrit (Hct), blood urea nitrogen (BUN), creatinine (Cr), and platelet (Plt) count, were rated. Patients were evaluated for the need for inotropes, transfusion, and intra-aortic balloon pump (IABP) in the ICU. The rates of post-operative cerebrovascular accident (CVA), RF, MI, ventilation dependency, ICU stay, and mortality were recorded. Post-operative LV function was checked by echocardiography during the hospital course. All of the patients who enrolled in the study were considered in the ultimate analysis.

Statistical analyses

Because of significant differences between the two groups in some pre-operative variables and in order to get higher confidence and accuracy, we not only considered the post-operation results in our analysis but also compared the changes in the pre- and post-operation variables in both groups. Results are presented as median (interquartile range), number (percent), and mean±standard deviation. Continuous variables were compared using the student's t-test or nonparametric Mann-Whitney U test whenever the data did not appear to have a normal distribution, and categorical variables were compared using Pearson chi-square or Fisher's exact test, as required. For the statistical analysis, the statistical software SPSS, version 19.0 for Windows (SPSS Inc., Chicago, IL, USA) was used. All p values are 2-tailed, with statistical significance defined by $p<0.05$.

Results

Table 1 shows the baseline characteristics of all patients of both randomized groups. There were no significant differences between the two groups of patients in our study according to their pre-operative characteristics, except for TNF-α and IL-6. There was no significant difference between the two groups of patients regarding age, either. The male/female ratio in the intervention group was 74/15 and 72/17 in the control group (p=0.69). Other preoperative laboratory tests results, including WBC, Hgb, Hct, BUN, Cr, and troponin-T, were the same. Also, there was no difference between the two groups among their history of CVA, RF, chronic obstructive pulmonary disease (COPD), and peripheral vascular disease (PVD). Levels of pre-operative TNF-α and IL-6 were higher in the Ptx group. Table 2 indicates the pre- and post-operative values and a comparison between post-operation levels in the two groups of study and between their changes. Post-operative rise of troponin-T was lower in the Ptx group, but the comparison of differences was not significant (p=0.68). The levels of both TNF-α and IL-6 decreased after surgery in the two

Table 1. Baseline characteristics of all patients in the two groups

	Control (n=89)	Pentoxifylline (n=89)	*P*
Age, years[¥]	59.0 (53.0 to 69.0)	59.0 (53.0 to 69.0)	0.62
Male[†]	74 (83.0)	72 (80.9)	0.69
Previous CVA[†]	7 (7.9)	4 (4.5)	0.35
Previous RF[†]	2 (2.2)	3 (3.4)	0.65
Previous COPD[†]	4 (4.5)	7 (7.9)	0.35
Previous PVD[†]	1 (1.1)	1 (1.1)	0.99
Trop-T, ng/mL[¥]	20.9 (7.9 to 75.0)	15.4 (7.7 to 79.6)	0.56
TNF-a, pg/mL[¥]	139 (30.9 to 1117.5)	472 (115.6 to 1701)	0.02
IL-6, pg/mL[¥]	133.4 (38.2 to 246.0)	195.0 (92.0 to 256.0)	0.01
EF, %[¥]	30.0 (25.0 to 30.0)	30.0 (25.0 to 30.0)	0.91
WBC, $\times 10^3$/cmm[¥]	7.6 (6.2 to 9.3)	7.6 (6.5 to 9.1)	0.85
Hgb, mg/dL[¥]	13.3 (12.3 to 14.4)	13.7 (12.6 to 14.9)	0.06
Hct, %[¥]	40.8 (37.9 to 43.1)	41.5 (38.45 to 44.7)	0.10
Plt, $\times 10^3$/cmm[¥]	208.0 (171.5 to 246.5)	207.0 (168.5 to 257.0)	0.77
BUN, mg/dL[¥]	38.0 (31.0 to 46.7)	38.0 (30.0 to 43.3)	0.49
Cr, mg/dL[¥]	1.0 (0.90 to 1.25)	1 (0.8 to 1.2)	0.12

Values represent median (interquartile range): [¥]Number (%): [†]BUN - blood urea nitrogen; cmm - cubic millimeter; COPD - chronic obstructive pulmonary disease; Cr - creatinine; CVA - cerebrovascular accident; EF - ejection fraction; Hct - hematocrit; Hgb - hemoglobin; IL - interleukin; mg/dL - milligram/deciliter; ng/dL - nanogram/deciliter; pg/dL - picogram/deciliter; Plt - platelet; Pre-Op - pre-operative; PVD - peripheral vascular disease; RF - renal failure; TNF - tumor necrosis factor; Trop-T - troponin-T; WBC - white blood cell

Table 2. A comparison of post-op values between the two groups and the comparison of changes between them

	Control			Pentoxifylline			*Post-op*	*Change*
	Pre-op	Post-op	Change	Pre-op	Post-op	Change	*P*	*P*
Trop-T, ng/mL	20.9 (7.9 to 75.0)	304.6 (197.5 to 449.5)	255.2 (150.1 to 379.0)	15.4 (7.7 to 79.6)	308.2 (200.7 to 447.2)	242.4 (137.8 to 406.7)	0.94	0.68
TNF-a, pg/mL	139.0 (30.9 to 1117.5)	40.0 (3.6 to 135.0)	-83.1 (-977.5 to 0.4)	472.0 (115.6 to 1701.0)	18.0 (1.7 to 73.0)	-427.8 (-1518.3 to -57.8)	0.01	0.01
IL-6, pg/mL	133.4 (38.2 to 246.0)	40.00 (25.5. to 98.6)	-55.0 (-152.3 to 6.8)	195.0 (92.0 to 256.0)	32.0 (18.3 - 54.5)	-135.6 (-226.5 to -30.0)	0.08	0.01
EF , %	30.0 (25.0 to 30.0)	30.0 (25.0 to 35.0)	0.0 (0.0 to 5.0)	30.0 (25.0 to 30.0)	30.0 (27.5 to 35.0)	5.0 (0.0 to 5.0)	0.06	0.01
WBC, $\times 10^3$/cm	7.6 (6.2 to 9.3)	13.4 (99.0 to 18.4)	5.4 (2.0 to 9.5)	7.6 (6.5 to 9.1)	12.3 (10.4 to 15.1)	4.9 (2.8 to 7.5)	0.44	0.66
Hgb, mg/dL	13.3 (12.3 to 14.4)	9.6 (8.8 to 10.5)	-3.6 (-4.6 to -2.6)	13.7 (12.6 to 14.9)	10.0 (9.4 to 10.6)	-3.7 (-4.8 to -2.8)	0.03	0.77
Hct, %	40.8 (37.9 to 43.1)	29.3 (27.6 to 32.0)	-10.8 (-13.4 to -7.5)	41.5 (38.4 to 44.7)	30.6 (29.1 to 32.0)	-11.0 (-13.2 to -8.1)	0.02	0.93
Plt, $\times 10^3$/cm	208.0 (171.5 to 246.5)	152.0 (125.2.0 to 191.5.0)	-47.0 (-80.0 to -28.1)	207.0 (168.5 to 257.0)	146.2 (115.8 to 182.7)	-55.8 (-84.7 to -33.0)	0.29	0.25
BUN, mg/dL	38.0 (31.0 to 46.7)	32.9 (26.2 to 41.0)	-4.2 (-11.5 to 1.9)	38.0 (30.0 to 34.3)	33.0 (25.5 to 38.0)	-3.0 (-12.6 to -1.5)	0.56	0.89
Cr, mg/dL	1.0 (0.9 to 1.2)	1 (0.8 to 1.2)	0.0 (-0.2 to 0.1)	1.0 (0.8 to 1.2)	0.9 (0.7 to 1.1)	-0.1 (-0.2 to 0.1)	0.06	0.52

Values represent median (interquartile range). BUN - blood urea nitrogen; cmm - cubic millimeter; Cr - creatinine; CVA - cerebrovascular accident; EF - ejection fraction; Hct - hematocrit; Hgb - hemoglobin; IL - interleukin; mg/dL - milligram/deciliter; ng/dL - nanogram/deciliter; pg/dL - picogram/deciliter; Plt - platelet; Post-Op - post-operative; Pre-Op - pre-operative; TNF - tumor necrosis factor; Trop-T - troponin-T; WBC - white blood cell

groups of the study. Comparison of post-operative levels of TNF-α in the Ptx and control groups showed a significant difference (p=0.01), which still existed when we compared their changes (p=<0.01), but the results were different for IL-6; there was no significant difference between post-operative levels of IL-6 (p=0.08), but the difference between changes in the two groups was statistically significant (p=<0.01).

We detected a significant difference between the pre- and post-operative rise of LVEF in the two groups (Ptx=4.1%, control=2.3%; p=<0.01). According to the laboratory tests, like WBC, Plt count, BUN, and Cr, there were no significant differences between the two groups in the pre- and post-operative periods. The levels of Hgb and Hct were significantly different in each group when comparing pre- and post-operative values (p=0.02 and 0.02, for Hgb and Hct, respectively), but when their changes were compared between the two groups, the difference disappeared (p=0.78 and 0.93 for Hgb and Hct, respectively). The post-operative findings are represented in Table 3. CPB time, cross-clamp time, post-operative CVA, RF, and mortality were the same between the two groups, and their differences were not statisti-

Table 3. Post-operative results and their comparison between the two groups

	Control (n=89)	Pentoxifylline (n=89)	*P*
CPB time, min‡	77.76±28.20	80.9±25.97	0.50
Cross-clamp time, min‡	43.89±17.50	44.83±15.45	0.71
ICU stay, day‡	4.4±1.9	2.6±1.6	<0.001
Ventilation time, hours‡	14.7±4.5	10.4±5.0	0.01
Post-op CVA†	1 (1.1)	0 (0.0)	0.99
Post-op RF†	2 (2.2)	3 (3.4)	0.99
Post-op IABP†	8 (9.0)	5 (5.6)	0.39
Post-op inotrope(s)†	54 (60.7)	39 (43.8)	0.02
Post-op transfusion†	43 (48.3)	26 (29.2)	0.01
Post-op mortality†	5 (5.6)	3 (3.4)	0.72

Values represent mean±standard deviation: †Number (%): ‡CPB - cardiopulmonary bypass; CVA - cerebrovascular accident; ICU - intensive care unit; IABP - intra-aortic balloon pump; Post-op - post-operative; RF - renal failure

cally significant. The need for IABP was decreased in the Ptx group, but the difference was not significant (Ptx=5.6%, control=9.0%, p=0.38). Mean ICU stay was decreased significantly in the intervention group (Ptx=2.6 days, control=4.4 days; p=0.01). Mean ventilation dependency time was 10 hours and 14 hours in the Ptx and control groups, respectively (p=0.01). The need for inotrope use was decreased in the Ptx group (Ptx=56.2%, control=43.8%; p=0.02). The transfusion rate decreased significantly, too (Ptx=23.6%, control=47.7%; p=0.01). Considering that among all cases of the two groups of the study, post-operative MI occurred in only 1 patient in the control group, we did not count it for the statistical comparison.

Discussion

Consistent with previous studies, our results showed that Ptx inhibits TNF-α release significantly (p=0.01), and it also affects levels of the other effective mediator, IL-6. The IL-6 level in post-CABG patients receiving Ptx was significantly lower than in the control group (p=0.08). These results remained unchanged when we compared the difference values instead of post-operation crude values (p=0.01 and 0.01 for TNF-α and IL-6, respectively). In fact, several inflammatory pathways are involved in the complex inflammatory response derived from applying CPB in cardiac surgery. Intensified post-operative morbidity may eventuate from the systemic inflammatory reaction produced by various pro-inflammatory cytokines that are released from different types of activated cells (1). TNF-α is one of the mediators that are supposed to be responsible for dysfunction and instability following the application of CPB (18). Our findings suggested that pre-operative oral administration of Ptx significantly reduces CPB-produced TNF-α and IL-6 induction, resulting in desirable impacts on post-operative pulmonary function. The indicative decline of ventilation time in our patients (p=0.01) confirms improvement of lung function. One of the most affected systems in this process is the respiratory system, which its dysfunction varies from least to most (3). In fact, deteriorating oxygen supply after cardiac surgery may be a prominent impediment, for which patients need prolonged mechanical ventilation (6). Involvement of the lungs in the inflammatory process after using CPB results from leukocyte activation, produced by pro-inflammatory mediators, like TNF-α and IL-6 (19). Inhibition of TNF-α release is a probable mechanism by which Ptx abates the inflammatory response after cardiac surgery (14). One of the most prominent points in some previous studies is that Ptx was administered orally (6).

Inhibition of the inflammatory action of TNF-α on leukocyte function by Ptx protects WBCs from sequestration in the lungs; therefore, it decreases leukocyte-dependent lung dysfunction (6).

In this study, patients who received Ptx pre-operatively had a significantly shorter ICU stay than the others; they had been transferred from the ICU 1.8 days before other patients. A very remarkable part of the overall disbursement of any cardiac surgery is the ICU stay (20). As post-operative care phase in the ICU extends, the complications will rise, and furthermore, occupation of ICU beds may restrict the number of surgeries (21). Many attempts have been made to reduce the ICU length of stay (22). Decreased ventilation time and ICU length of stay, both of which occurred in this study, can decrease the total hospital length of stay, costs, and complications by shortening the post-operative recovery period and earlier patient movement induction (23).

Furthermore, ejection fraction, as an indicator of cardiac function (24), showed a small but significant improvement among patients who received Ptx before surgery, compared with the control group. We could claim that the intervention drug may improve myocardial function among the receivers. Previous studies represented that although Ptx affected the activity of many blood cells and changed their inflammatory functions, it did not alter their counts (25). In accordance with this research, our findings indicated that Ptx did not change leukocyte and platelet counts, and also, it did not affect Hgb and Hct levels after the operation.

However, Boldt et al. (7) have shown that prescribing intravenous Ptx in patients over 80 who underwent CABG improved

renal function (8), but more studies are required to confirm the drug competence and generalize the results to patients in all age groups. Although our patients' average age was 20 years lower than those in the Boldt et al. (7) study, our results showed a larger decrease in BUN and Cr levels among patients who received Ptx compared to those in the control group, but the differences were not significant in comparison with pre-operation BUN and Cr, as shown in other study (19).

In former studies, it has not been indicated that Ptx can improve CPB and cross-clamp (6, 19) time during CABG. In agreement with this research, our findings did not signify expressive influence on cardiopulmonary pump and cross-clamp time by Ptx.

In our study, Ptx administration did not alter post-operation outcomes, like RF, CVA, and the need for IABP.

Although there is a study in 1996 in which the authors claimed that Ptx did not affect the requirement for blood products and inotrope (6), our results depicted a significantly lower need for inotropic agents and blood transfusion in patients who received Ptx in comparison with those in the control group.

We used the oral form of Ptx because of its easy administration, low adverse effects, and low cost.

Study limitations

In spite of the randomization and allocation of the patients between the two groups, some pre-operative values between groups were significantly different, which made us consider it in the statistical analysis and compare the change in values between the two groups.

The study was not designed to investigate the effects of Ptx on long-term mortality, but considering in-hospital mortality, we did not detect significant differences in the Ptx and control groups.

Conclusion

Considering Ptx impacts on improvement of pulmonary function (6, 16), its role on reducing ventilation time, Probable positive effect of the drug on myocardial performance (EF enhancement), and also, lack of significant differences in changes of Hgb and Hct levels between two groups of investigation. The results of our study represent profitable properties of oral Ptx in reducing inflammatory factors after CABG and present some beneficial effects. We could reach the novel results which (mention) some of which did not report in previous studies about oral Ptx. Ptx reduced TNF-α, IL-6, ventilation time, inotrope, and blood transfusion requirements, and also, it shortened the ICU length of stay-valuable outcomes that should be confirmed in future studies.

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