Pentoxifylline is better than ketamine in modulating the systemic inflammatory response in patients undergoing coronary artery bypass grafting

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Objective
The aim of this study was to evaluate the effect of using pentoxifylline (PTX) and ketamine on serum levels of interleukin (IL)-6, IL-10, and malondialdehyde (MDA) during coronary artery bypass grafting surgery.
Patients and methods
The study included 60 patients, 39 men and 21 women, with a mean age of 48.6 ± 9.1 years and a mean ejection fraction (EF) of 56.7 ± 3.8%. Patients were randomly allocated into three equal groups: the control group received placebo infusion; the ketamine group received 0.5 mg/kg ketamine as an intravenous bolus dose administered after induction of anesthesia, followed by continuous infusion with 1.25 μg/kg/min ketamine until weaning from cardiopulmonary bypass (CPB); and the PTX group received 5 mg/kg PTX as an intravenous bolus dose administered after induction of anesthesia, followed by continuous infusion with 1.5 mg/kg/h PTX until weaning from CPB. Blood samples were collected from the patients after induction of anesthesia (baseline; T_0) and 4 h (T_1), 24 h (T_2), and 48 h (T_3) after aortic declamping for estimation of serum IL-6, IL-10, and MDA levels using ELISA.
Results
All patients showed a steadily progressive increase in serum IL-6 levels; however, both ketamine and PTX had a blunting effect on IL-6 release, manifested as nonsignificantly (P_3 = 0.262 and 0.794, respectively) higher serum levels estimated at T_1 compared with T_0, with significantly (P_3 = 0.0006) lower levels compared with those in the control group. All patients showed significantly (P_3 = 0.001, 0.005, and 0.028 in control, ketamine, and PTX groups, respectively) higher serum IL-6 levels at T_3 compared with T_2, which were significantly (P_3 = 0.0004, 0.0006, and 0.001 in control, ketamine, and PTX groups, respectively) higher than those at T_1. The PTX group showed significantly lower IL-6 levels at T_2 compared with the ketamine group (P_2 = 0.018). Serum IL-10 levels were significantly (P_3 = 0.029, 0.0005, and 0.0007 in control, ketamine, and PTX groups, respectively) higher at T_1 compared with T_0, with significantly higher levels in the ketamine (P_1 = 0.031) and PTX (P_1 = 0.0009) groups compared with the control group. Serum IL-10 levels were significantly higher in the control (P_3 = 0.041), ketamine (P_3 = 0.001), and PTX (P_3 = 0.009) groups at T_2 compared with T_1, with significantly higher levels in the ketamine (P_1 = 0.0006) and PTX (P_1 = 0.0007) groups compared with the control group and significantly higher levels in the PTX (P_1 = 0.002) group compared with the ketamine group. Serum IL-10 levels were significantly lower in the control (P_3 = 0.001) and ketamine (P_3 = 0.0009) groups, with nonsignificantly lower (P_3 = 0.136) levels in the PTX group, at T_3 compared with T_2, with significantly higher levels in the ketamine (P_1 = 0.002) and PTX (P_1 = 0.0005) groups compared with the control group and significantly higher levels in the PTX (P_1 = 0.0007) group compared with the ketamine group. Serum MDA levels were significantly (P_3 = 0.0004, 0.0005, and 0.0004 in control, ketamine, and PTX groups, respectively) higher at T_1 compared with T_0, with significantly higher levels in the ketamine (P_1 = 0.021) and PTX (P_1 = 0.0009) groups compared with the control group and significantly higher levels in the ketamine group (P_2 = 0.001) compared with the PTX group. Serum MDA levels were significantly higher in the control (P_3 = 0.006) and ketamine (P_3 = 0.049) groups, but nonsignificantly higher in the PTX (P_3 = 0.681) group, at T_2 compared with T_1, with significantly lower levels in the PTX group (P_1 = 0.003) and nonsignificantly (P_1 = 0.219) lower levels in the ketamine group compared with the control group and significantly lower levels in the PTX (P_2 = 0.002) group compared with the ketamine group. Serum MDA levels were nonsignificantly lower in the control (P_3 = 0.732), ketamine (P_3 = 0.164), and PTX (P_3 = 0.128) groups at T_3 compared with T_2, with nonsignificantly (P_3 = 0.678) higher levels in the ketamine group but significantly higher (P_1 = 0.003) levels in the PTX group compared with the control group and significantly lower levels in the PTX (P_1 = 0.028) group compared with the ketamine group.
Conclusion
Using of PTX or ketamine could ameliorate the systemic inflammatory response, as well as oxidative stress response, in patients undergoing coronary artery bypass grafting with CPB and could shift the immune response to surgery toward the

anti-inflammatory side. However, such effects were more pronounced with PTX than with ketamine.

Keywords:
coronary artery bypass grafting, IL-10, IL-6, ketamine, malondialdehyde, pentoxifylline

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Introduction

Proinflammatory and anti-inflammatory cytokines such as interleukin (IL)-6, IL-8, and IL-10 play a dominant role as local or systemic regulators in the acute inflammatory response. Inhibition of IL-6 with monoclonal antibodies leads to a marked attenuation in the inflammatory response [1–3]. Tissue injury causes the release of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β, which are involved in many aspects of inflammation [4–6].

The produced TNF-α triggers the release of a cascade of cytokines that mediate the release of prostaglandins and sympathomimetic amines. Indeed, TNF-α stimulates the production of IL-1β and IL-6, which in turn stimulate the production of cyclooxygenase products and IL-8/neutrophil chemoattractant-1, thereby enhancing the production of sympathomimetic amines [7,8]. IL-6 is also able to promote Th2 phenotypic responses and its actions can be classified as both proinflammatory and anti-inflammatory. The local balance between IL-6 and IL-10 is an important determinant of subsequent immune responses [9].

The coronary artery bypass grafting (CABG) procedure is a strong inflammatory stimulus that causes a substantial rise in circulating C-reactive protein, fibrinogen, and IL-6 levels. High-plasma IL-6 concentrations were in turn significantly associated with postoperative fever, atrial fibrillation, prolonged endotracheal intubation time, and duration of intensive care stay [10–14].

The *N*-methyl-d-aspartate receptor antagonist, ketamine, has an anti-inflammatory role in low dose, causing a significant reduction in proinflammatory mediators such as C-reactive protein and IL-6 in cardiac surgery using cardiopulmonary bypass (CPB) [15–17].

Pentoxifylline (PTX) is a methylxanthine. It inhibits tumor necrosis factor synthesis through inhibition of phosphodiesterase and by increasing intracellular cyclic adenosine monophosphate levels. It depresses TNF production by macrophages at the transcription level and has a potential to attenuate the inflammatory responses that occur during CPB. PTX also decreases neutrophil activation, which plays a central role in the pathogenesis of adult respiratory distress syndrome and multiple organ failure [18–20].

The current comparative study aims to evaluate the effect of preoperative priming with a continuous intraoperative infusion of PTX and ketamine on the release of inflammatory and anti-inflammatory cytokines and on oxidative stress during CABG with CPB.

Patients and methods

The current prospective comparative study was conducted after approval of the study protocol by the local ethics committee and obtaining informed consent from the patients; it was carried out between September 2010 and December 2012. Sixty patients assigned for elective CABG with CPB were enrolled in the study. Patients with left main coronary artery disease, EF less than 50%, renal or hepatic dysfunction, known hypersensitivity to the studied drugs, scheduled for an emergency operation, and with chronic obstructive pulmonary disease were not enrolled in the study. In addition, patients with infections, inflammatory diseases, or maintained on immunosuppressant drugs or steroid therapy were excluded from the study.

All operations were performed by the same surgical team. The patients were divided into three groups: the control group (n = 20), which received placebo infusion; the ketamine group (n = 20); and the PTX group (n = 20). The ketamine group received an intravenous bolus of 0.5 mg/kg ketamine after induction, followed by 1.25 μg/kg/min ketamine till weaning from CPB, whereas the PTX group received an intravenous bolus dose of 5 mg PTX (Trental ampoule, 100 mg in 5 ml; Sanofi Aventis, Germany), followed by 1.5 mg/kg/h PTX for the same time period as ketamine.

Patients were premedicated with 0.03–0.05 mg/kg midazolam on arrival at the operating room. The radial artery was cannulated, standard monitors were attached, and anesthesia was induced using

3–5 mg/kg thiopental sodium with 3–5 μg/kg fentanyl and 0.1 mg/kg pancuronium. Controlled mechanical ventilation was applied to keep $PaCO_2$ levels between 35 and 45 mmHg. Anesthesia was maintained with sevoflurane, using a mixture of oxygen and air (1 : 1), boluses of pancuronium, and boluses of fentanyl when needed.

Heparin sulfate was administered at a dose of 4 mg/kg and supplemented as needed to keep the activated clotting time greater than 400 s before the start of CPB. CPB was established using a membrane oxygenator, a roller pump, and a nonpulsatile flow with a flow rate of 2.4 l/min/m^2. Anesthesia was maintained on CPB using 3–4 mg/kg/h propofol; systemic temperature was allowed to drift to 34–35°C. Blood cardioplegia was prepared from equal volumes of normal saline and blood (1 : 1). Its composition was 30 mEq/l potassium chloride, 120 mg/l lidocaine, and 26 mEq/l sodium bicarbonate. Cardioplegia was administered initially at a dose of 10 ml/kg, followed by 5 ml/kg every 20–30 min. When inotropic support was needed, 3–5 μg/kg/min dobutamine was used.

Intraoperative hemodynamic data including heart rate, systolic blood pressure and diastolic blood pressure, and central venous pressure changes were determined at the time of induction of anesthesia, after CPB weaning, and every 2 h thereafter. The number of grafted vessels, aortic cross-clamping time, CPB time, and total operative time were also recorded.

Blood samples were collected from patients after induction of anesthesia (baseline; T_0) and 4 h (T_1), 24 h (T_2), and 48 h (T_3) after aortic declamping. Temperature, heart rate, partial pressure of oxygen (PaO_2) levels, white blood cell counts, and neutrophil counts were recorded during the period of collection of blood samples. Blood samples were allowed to clot and then centrifuged at 3000 rpm for 10 min; the supernatant was separated, transferred into pyrogen-free Eppendorf tubes, and stored at -80°C until ELISA was carried out.

Measurement of IL-6 [21] and IL-10 [22] levels by ELISA

Commercial kits (Boehringer GmbH, Mannheim, Germany) were used for all ELISA assays. Immunoreagent solution was prepared by adding 50 μl of peroxidase-conjugated detection antibody to 0.9 ml of incubation buffer, and 50 μl of biotin antibody was added to this mixture. Twenty microliters of each supernatant was added into the microtiter plate provided, and 200 μl of immunoreagent was pipetted into all wells containing the test samples. The microtiter plate was then covered tightly with adhesive foil and incubated for 2 h at room temperature on a shaker at 250 rpm. The incubation buffer was removed by tapping, and the wells were rinsed three times with washing buffer. The washing solution was removed and 200 μl of substrate solution was added to the wells. The microtiter plate was covered again with the adhesive foil and incubated in the same manner for another 20–30 min at room temperature. Fifty microliters of stop solution was added to each well, and after incubation for 1 min the plate was read at 450 nm using a spectrophotometer; the optical density was read from the standard curve.

Measurement of serum MDA levels [23] by ELISA assay

Commercial kits (Boehringer GmbH) were used for all ELISA assays. Seven wells were prepared for standard and one well for blank; 100 μl each of dilutions of standard, blank, and samples were added into the appropriate wells. Thereafter, the plate was covered and incubated for 2 h at 37°C. The liquid of each well was removed without washing and 100 μl of detection reagent and working solution were added to each well; the plate was then covered and incubated for 1 h at 37°C. The solution was aspirated, the wells were washed, and the remaining liquid was removed from all wells completely by snapping the plate on to absorbent paper; the wash was repeated three times and after the last wash the plate was inverted and blotted against absorbent paper. Detection reagent B working solution was added to each well and the plate was incubated for 30 min at 37°C after covering it with the plate sealer. The aspiration/wash process was repeated five times; 90 μl of substrate solution was added to each well and the plate was covered and incubated for 15–25 min at 37°C. The plate was protected from light; substrate solution was added and the liquid turned blue; 50 μl of stop solution was added to each well, causing the liquid to turn yellow. A microplate reader was used to measure optical density at 450 nm immediately.

Statistical analysis

Obtained data are presented as mean ± SD, ranges, numbers, and ratios. Results were analyzed using the Wilcoxon rank test for unrelated data (*Z*-test) and the χ^2-test. Statistical analysis was carried out using SPSS (version 15, 2006; SPSS Inc., Chicago, Illinois, USA) for Windows statistical package. *P*-value less than 0.05 was considered statistically significant.

Power analysis

If the true serum IL-6 mean difference between the PTX-treated and ketamine-treated populations is similar to our calculated difference at T_1, T_2, and T_3, which is 3.6, 7.4, and 7.7 ng/ml, respectively, we will be able to reject the null hypothesis with 13.2, 28.9, and 8.7% power.

If the true serum IL-10 mean difference between the PTX-treated and ketamine-treated populations is similar to our calculated difference at T_1, T_2, and T_3, which is 7.6, 10.8, and 12.5 ng/ml, respectively, we will be able to reject the null hypothesis with 89.4, 72.5, and 96.9% power.

If the true MDA mean difference between the PTX-treated and ketamine-treated populations is similar to our calculated difference at T_1, T_2, and T_3, which is 0.126, 0.095, and 0.125 nmol/ml, respectively, we will be able to reject the null hypothesis with 97.1, 83.3, and 96.6% power. Student's *t*-test was used in the analysis with a type I error probability of 0.05. Calculations were performed using PS Power and Sample Size Calculations Software, version 2.1.30 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

Results

This study included 60 patients, 39 men and 21 women, with a mean age of 48.6 ± 9.1 years (range: 32–67 years). The mean BMI of enrolled patients was 30.6 ± 2.1 kg/m^2. The mean EF was 56.7 ± 3.8% (range: 51–65%); 25 patients (41.6%) had an EF of less than 55%, 19 patients (31.7%) had EF in range of 55–60%, and 16 patients (26.7%) had an EF of greater than 60%. There was nonsignificant difference between studied groups as regards patient demographics and clinical profile (Table 1).

Hemodynamic data of all patients showed a nonsignificant difference between studied groups (Table 2). The mean ischemia time was 56.5 ± 10.8 min (range: 35–75 min), the mean CPB time was 74 ± 10 min (range: 50–90 min), and the mean total operative time was 177.3 ± 18.3 min (range: 140–210 min). The mean number of grafted vessels was 4 ± 0.8 vessels (range: three to five vessels). There was a nonsignificant difference between the studied groups as regards operative and postoperative data. No postoperative fever, new Q-wave in postoperative ECG, or mortality was reported. No postoperative dysfunction of the lungs, kidney, or liver was reported. Only four patients (6.7%) required reoperation, all of which were uneventful. The mean duration of postoperative mechanical ventilation was 4.9 ± 0.8 h (range: 3–6 h) and the mean duration of intensive care unit stay was 64 h. The mean amount of chest tube drainage was 1167.7 ± 142.5 ml (range: 900–1450 ml; Table 3).

Throughout the study period, all patients showed nonsignificant changes in temperature (Table 4) and total leukocytic count, with nonsignificant differences in neutrophil percentage (Table 5). In addition, the ratio of partial pressure of oxygen to the faction of inspired oxygen (PaO_2/FiO_2) showed a nonsignificant difference among the studied groups throughout the study period (Table 6).

No difference was observed in the baseline level of IL-6, IL-10, and MDA among the three groups. In both the ketamine and PTX groups, serum IL-6 levels were significantly ($P<0.05$) lower than that in the control group, with nonsignificantly ($P > 0.05$) higher levels at T_1 compared with T_0. IL-6 levels estimated at T_2 and T_3 were significantly higher compared with those at T_0 and T_1, with significantly higher T_3 levels compared with T_2 levels. The mean serum IL-6 levels were significantly higher at T_2, but nonsignificantly higher at T_1 and T_3, in the ketamine group compared with the PTX group (Table 7).

Serum IL-10 levels were significantly ($P<0.05$) higher in the PTX group compared with the control and ketamine groups. All patients showed a peak level of IL-10 at T_2, which declined at T_3, with significantly ($P < 0.05$) lower serum IL-10 levels at T_3 compared with T_2 in the control and ketamine groups; however, the difference was nonsignificant ($P > 0.05$) with PTX (Table 8).

PTX showed significant control of MDA levels. The levels of MDA were significantly lower in the PTX group compared with the control and ketamine groups at T_1, T_2, and T_3, whereas they were significantly lower at T_1,

Table 1 Demographics and clinical profile

	Control	Ketamine	PTX	*P*-value
Age (years)	49.2 ± 8.6	46.5 ± 9.7	50.2 ± 9	$P_1 = 0.287$ $P_2 = 0.777$ $P_3 = 0.225$
Sex (M:F)	13 : 7	12 : 8	14 : 6	$P_1 = 0.327$ $P_2 = 0.403$ $P_3 = 0.298$
Weight (kg)	88.2 ± 5.2	89 ± 5.5	89.2 ± 3.8	$P_1 = 0.736$ $P_2 = 0.519$ $P_3 = 0.779$
Height (cm)	169.5 ± 3.7	170.8 ± 3.5	170.4 ± 2.6	$P_1 = 0.202$ $P_2 = 0.212$ $P_3 = 0.630$
Ejection fraction [*n* (%)]				
<55	9 (45)	8 (40)	8 (40)	$P_1 = 0.824$ $P_2 = 0.783$ $P_3 = 0.912$
55–60	5 (25)	7 (35)	7 (35)	
>60	6 (30)	5 (25)	5 (25)	
Mean value	57.2 ± 4.5	56.2 ± 3.4	56.6 ± 3.6	$P_1 = 0.263$ $P_2 = 0.657$ $P_3 = 0.760$

Data are presented as mean ± SD; numbers and ratios; percentages are in parentheses. P_1, significance of difference between the control and ketamine groups; P_2, significance of difference between the control and PTX groups; P_3, significance of difference between the ketamine and PTX groups; PTX, pentoxifylline.

Table 2 Hemodynamic data

Data	Control	Ketamine	PTX
Heartrate(beat/min)			
Afterinductionofanesthesia			
Value	76.4 ± 5	75.7 ± 5.4	76.2 ± 5.8
P-value		P_1 = 0.475	P_2 = 0.747 P_3 = 0.983
AfterCPBweaning			
Value	80.1 ± 6.6	80.8 ± 7.8	79.8 ± 5.2
P-value		P_1 = 0.711	P_2 = 0.888 P_3 = 0.573
2hafterCPBweaning			
Value	80.9 ± 7	81.4 ± 7.6	80.1 ± 5.3
P-value		P_1 = 0.810	P_2 = 0.727 P_3 = 0.456
SBP(mmHg)			
Afterinductionofanesthesia			
Value	110.3 ± 5.8	109.9 ± 7.6	108.4 ± 7.9
P-value		P_1 = 0.920	P_2 = 0.169 P_3 = 0.601
AfterCPBweaning			
Value	112.9 ± 5.1	110.2 ± 7	111.9 ± 8.1
P-value		P_1 = 0.214	P_2 = 0.601 P_3 = 0.556
2-hafterCPBweaning			
Value	113.7 ± 4.5	111.3 ± 5.7	112.1 ± 7.1
P-value		P_1 = 0.142	P_2 = 0.499 P_3 = 0.850
DBP(mmHg)			
Afterinductionofanesthesia			
Value	66.8 ± 3.2	66.7 ± 3	67.4 ± 4.1
P-value		P_1 = 0.815	P_2 = 0.628 P_3 = 0.585
AfterCPBweaning			
Value	73.1 ± 4.3	71.8 ± 6	72.1 ± 5.4
P-value		P_1 = 0.631	P_2 = 0.297 P_3 = 0.962
2hafterCPBweaning			
Value	74.5 ± 4.1	72.4 ± 6	72.7 ± 5.2
P-value		P_1 = 0.184	P_2 = 0.206 P_3 = 0.986
CVP(mmHg)			
Afterinductionofanesthesia			
Value	8.7 ± 1.9	8.6 ± 1.3	8.7 ± 1.9
P-value		P_1 = 0.537	P_2 = 0.707 P_3 = 0.944
AfterCPBweaning			
Value	10.3 ± 1.2	10.5 ± 1.3	10.4 ± 1.6
P-value		P_1 = 0.638	P_2 = 0.874 P_3 = 0.877
2hafterCPBweaning			
Value	10.8 ± 1.4	10.7 ± 1.4	10.8 ± 1.2
P-value		P_1 = 0.942	P_2 = 0.834 P_3 = 0.773

Data are presented as mean ± SD. CPB, cardiopulmonary bypass; CVP, central venous pressure; DBP, diastolic blood pressure; P_1, significance of difference between the control and ketamine groups; P_2, significance of difference between the control and PTX groups; P_3, significance of difference between the ketamine and PTX groups; PTX, pentoxifylline; SBP, systolic blood pressure.

but nonsignificantly lower at T_2 and T_3, in the ketamine group compared with the control group (Table 9).

Discussion

The current study showed a blunting effect of PTX and ketamine on the release of inflammatory cytokines with concomitant pronounced release of anti-inflammatory cytokines, an effect that was manifested more with PTX than with ketamine. These data indicate a modulatory effect of PTX on the immune response to surgery, which is more pronounced than that of ketamine.

These data illustrate the effect of both bolus dose and PTX infusion on cytokine release associated with surgical interference and are in accordance with the results of multiple previous clinical trials. Coimbra *et al*. [24] reported that PTX downregulates neutrophil activation and proinflammatory mediator synthesis with markedly decreased TNF-α production in patients with hemorrhagic shock treated with PTX added to resuscitation fluid. Izadpanah *et al*. [25] reported that intravenous infusion with PTX, administered preoperatively, induced significantly lower postoperative plasma levels of TNF-α and IL-6 compared with placebo, and PTX could be

Table 3 Operative and postoperative data of studied patients

Data	Control	Ketamine	PTX
Aorticcross-clampingtime(min)			
Value	55.6 ± 10.2	56.9 ± 11.8	57.1 ± 11.7
P-value		P_1 = 0.397	P_2 = 0.779 P_3 = 0.955
CPBtime(min)			
Value	73.9 ± 10.5	75.3 ± 8.1	72.7 ± 11.4
P-value		P_1 = 0.868	P_2 = 0.657 P_3 = 0.190
Durationofsurgery(min)			
Value	177.8 ± 14.7	175 ± 16.7	179.5 ± 23.5
P-value		P_1 = 0.468	P_2 = 0.856 P_3 = 0.535
Numberofgraftedvessels			
Value	4 ± 0.9	3.9 ± 0.8	4.1 ± 0.9
P-value		P_1 = 0.686	P_2 = 0.712 P_3 = 0.225
Resumptionofsinusrhythm	17 (85)	18 (90)	19 (95)
Postoperativeatrialfibrillation	2 (10)	1 (5)	1 (5)
Defibrillation	3 (15)	2 (10)	1 (5)
Inotropicsupport	3 (15)	2 (10)	2 (10)
Reoperation	2 (10)	1 (5)	1 (5)
Durationofmechanicalventilation(h)			
Value	5 ± 0.8	5.1 ± 0.8	4.5 ± 0.7
P-value		P_1 = 0.425	P_2 = 0.069 P_3 = 0.129
Amountofchesttubedrainage(ml)			
Value	1181.5 ± 168.1	1118 ± 127.6	1203.5 ± 120
P-value		P_1 = 0.070	P_2 = 0.687 P_3 = 0.061

Data are presented as mean ± SD and numbers; percentages are in parentheses. CPB, cardiopulmonary bypass; P_1, significance of difference between the control and ketamine groups; P_2, significance of difference between the control and PTX groups; P_3, significance of difference between the ketamine and PTX groups; PTX, pentoxifylline.

Table 4 Body temperature estimated at different time points

	Control	Ketamine	PTX
T_0			
Level	37 ± 0.26	36.9 ± 0.28	36.8 ± 0.32
P-value		P_1 = 0.295	P_1 = 0.063 P_2 = 0.392
T_1			
Level	37.1 ± 0.29	37 ± 0.33	37 ± 0.36
P-value		P_1 = 0.445	P_1 = 0.202 P_2 = 0.717
T_2			
Level	37.1 ± 0.22	37 ± 0.26	36.9 ± 0.34
P-value		P_1 = 0.384	P_1 = 0.084 P_2 = 0.114
T_3			
Level	37.2 ± 0.17	37.1 ± 0.25	37 ± 0.39
P-value		P_1 = 0.534	P_1 = 0.073 P_2 = 0.089

Data are presented as mean ± SD. T_0, after induction of anesthesia; T_1, 4 h after aortic declamping; T_2, 24 h after aortic declamping; T_3, 48 h after aortic declamping; P_1, significance versus the control group; P_2, significance versus the ketamine group; PTX, pentoxifylline.

administered to reduce inflammatory changes. Gupta *et al.* [26] found PTX significantly reduced circulating levels of vascular cell adhesion molecule-1 and interferon-γ-induced protein, significantly improved endothelial function during the 8-week trial, and may reverse HIV-related endothelial dysfunction by directly inhibiting the endothelial leukocyte adhesion pathway.

In terms of the applicability of PTX in patients undergoing cardiac surgery, Groesdonk *et al.* [27] reported that the use of PTX may blunt the inflammatory response induced by cardiac surgery using CPB, and it has been shown that perioperative application of PTX may improve postoperative function of organs at risk, such as the kidney and liver. Iskesen *et al.* [28] reported a significant increase in plasma levels of TNF-α, IL-6, and IL-8 in both the control and study groups after CPB, with a greater increase in controls compared with patients who received preoperative PTX, and concluded that pretreatment with oral PTX before cardiac surgery inhibits proinflammatory cytokine release caused by CPB and has some beneficial effects in protecting the myocardium during the cardioplegic arrest period in open-heart surgery, without affecting postoperative hemodynamics. Barkhordari *et al.* [29] found that PTX could reduce the occurrence of acute kidney injury, as determined by attenuation of serum creatinine rise with concomitant reduction in urinary neutrophil gelatinase-associated lipocalin levels, without causing hemodynamic instability or increased bleeding.

As regards the reported attenuating effect of ketamine on inflammatory response, Bartoc *et al.* [17] reported that low-dose ketamine (0.5 mg/kg) attenuates increases in C-reactive protein and IL-6 levels, whereas decreases vasodilatation after CPB. Welters *et al.* [30] found that the levels of all cytokines increased during and after CPB; however, the increase in the levels of proinflammatory cytokines IL-6 and IL-8 at 6 h

Table 5 Leukocytic count at different time points

	Control	Ketamine	PTX
TLC($\times 10^3$ cell/ml)			
T_0			
Level	6.21 ± 1	6.22 ± 1.03	6.2 ± 1
P-value		P_1 = 0.955	P_1 = 0.793 P_2 = 0.317
T_1			
Level	6.37 ± 0.77	6.34 ± 0.88	6.33 ± 0.88
P-value		P_1 = 0.897	P_1 = 0.743 P_2 = 0.567
T_2			
Level	6.4 ± 0.74	6.36 ± 0.87	6.34 ± 0.9
P-value		P_1 = 0.940	P_1 = 0.911 P_2 = 0.715
T_3			
Level	6.36 ± 0.69	6.33 ± 0.88	6.28 ± 0.92
P-value		P_1 = 0.985	P_1 = 0.709 P_2 = 0.400
Neutrophilcount(%ofTLC)			
T_0			
Level	60 ± 4.15	59.1 ± 4	58.7 ± 3.7
P-value		P_1 = 0.485	P_1 = 0.248 P_2 = 0.344
T_1			
Level	60.6 ± 4.5	60.1 ± 5.6	59.1 ± 5.3
P-value		P_1 = 0.794	P_1 = 0.121 P_2 = 0.331
T_2			
Level	60.4 ± 3.2	60 ± 3.9	58.9 ± 3.4
P-value		P_1 = 0.602	P_1 = 0.203 P_2 = 0.131
T_3			
Level	60.1 ± 3.5	59.6 ± 5.3	58.7 ± 4.2
P-value		P_1 = 0.679	P_1 = 0.285 P_2 = 0.385

Data are presented as mean ± SD. T_0, after induction of anesthesia; T_1, 4 h after aortic declamping; T_2, 24 h after aortic declamping; T_3, 48 h after aortic declamping; P_1, significance versus the control group; P_2, significance versus the ketamine group; PTX, pentoxifylline; TLC, total leukocyte count.

Table 6 Ratio of partial pressure of oxygen to faction of inspired oxygen (PaO_2/FiO_2) estimated at different time points

	Control	Ketamine	PTX
T_0			
Level	461.5 ± 87.7	450.2 ± 70.6	452.8 ± 70.8
P-value		P_1 = 0.668	P_1 = 0.779 P_2 = 0.293
T_1			
Level	445.3 ± 47.6	462 ± 46	448.3 ± 38.6
P-value		P_1 = 0.365	P_1 = 0.906 P_2 = 0.370
T_2			
Level	427 ± 59.4	422 ± 57.7	430.3 ± 50
P-value		P_1 = 0.794	P_1 = 0.695 P_2 = 0.463
T_3			
Level	426.1 ± 55.9	424.9 ± 48.8	422.1 ± 49.3
P-value		P_1 = 0.537	P_1 = 0.640 P_2 = 0.180

Data are presented as mean ± SD. T_0, after induction of anesthesia; T_1, 4 h after aortic declamping; T_2, 24 h after aortic declamping; T_3, 48 h after aortic declamping; P_1, significance versus the control group; P_2, significance versus the ketamine group; PTX, pentoxifylline. The FiO_2 at T_0 is 0.5 and at T_1, T_2, and T_3 is 0.4.

after aortic unclamping was significantly lower with ketamine compared with sufentanil, whereas the anti-inflammatory cytokine IL-10 showed higher levels with ketamine compared with sufentanil 1 h after declamping. Du *et al*. [31] found that postoperative IL-6 and TNF-α concentrations in patients given ketamine were lower than those in control patients who did not receive ketamine.

In contrast to the obtained results, Cho *et al*. [32] found that low-dose ketamine administered during anesthesia induction did not exert any evident anti-inflammatory effect in terms of reducing the serum concentrations of proinflammatory markers in low-risk patients undergoing off-pump CABG. However, such discrepancies could be attributed to the dose difference in the current study, which relies on a bolus dose of 0.5 mg/kg ketamine, followed by continuous intravenous infusion of 1.25 μg/kg/min ketamine until weaning from CPB, whereas Cho *et al*. [32] used a bolus dose of 0.5 mg/kg without intraoperative infusion.

Both ketamine and PTX ameliorated the ischemia reperfusion injury manifested as a significant reduction in the level of MDA, a lipid peroxidation product that peaked at 4 h sample denoting release of oxidative products during aortic cross clamping. However, this ameliorative effect was more pronounced with PTX. These findings support those documented experimentally previously. Yu *et al*. [33] reported that ketamine shows potent protective effects against spinal cord ischemia/reperfusion injury in the rabbit model and

Table 7 Serum levels of interleukin-6 (ng/ml) at different time points

	Control	Ketamine	PTX
T_0			
Level	66.9 ± 15.3	66.1 ± 14.2	66.6 ± 11.7
P-value		P_1 = 0.852	P_1 = 0.926 P_2 = 0.920
T_1			
Level	110 ± 21.5	71.6 ± 13.7	68 ± 13.2
P-value	P_3 = 0.0006	P_3 = 0.262 P_1 = 0.0009	P_3 = 0.794 P_1 = 0.0006 P_2 = 0.396
T_2			
Level	137.9 ± 22.3	100.9 ± 15.5	93.5 ± 16.3
P-value	P_3 = 0.0004	P_3 = 0.0006 P_1 = 0.0008	P_3 = 0.001 P_1 = 0.0006 P_2 = 0.018
T_3			
Level	201.4 ± 50.5	130.2 ± 40.8	122.5 ± 37.2
P-value	P_3 = 0.001	P_3 = 0.005 P_1 = 0.001	P_3 = 0.028 P_1 = 0.0004 P_2 = 0.380

Data are presented as mean ± SD. T_0, after induction of anesthesia; T_1, 4 h after aortic declamping; T_2, 24 h after aortic declamping; T_3, 48 h after aortic declamping; P_1, significance versus the control group; P_2, significance versus the ketamine group; P_3, significance versus the preceding reading of the same group; PTX, pentoxifylline.

Table 8 Serum levels of interleukin-10 (ng/ml) at different time points

	Control	Ketamine	PTX
T_0			
Level	22.1 ± 6 (12–35)	23 ± 5.56 (10–32)	22.7 ± 4.5 (13–29)
P-value		P_1 = 0.508	P_1 = 0.604 P_2 = 0.824
T_1			
Level	26.6 ± 8.25 (13–41)	31.2 ± 4.1 (25–39)	38.8 ± 7.32 (29–53)
P-value	P_3 = 0.029	P_3 = 0.0005 P_1 = 0.031	P_3 = 0.0007 P_1 = 0.0009 P_2 = 0.001
T_2			
Level	30.6 ± 7.3 (20–46)	37.5 ± 6.1 (29–51)	48.3 ± 13 (30–75)
P-value	P_3 = 0.041	P_3 = 0.001 P_1 = 0.0006	P_3 = 0.009 P_1 = 0.0007 P_2 = 0.002
T_3			
Level	24.4 ± 3.66 (17–31)	29.6 ± 5.35 (20–38)	42.1 ± 10 (26–62)
P-value	P_3 = 0.001	P_3 = 0.0009 P_1 = 0.002	P_3 = 0.136 P_1 = 0.0005 P_2 = 0.0007

Data are presented as mean ± SD and ranges are in parentheses. T_0, after induction of anesthesia; T_1, 4 h after aortic declamping; T_2, 24 h after aortic declamping; T_3, 48 h after aortic declamping; P_1, significance versus the control group; P_2, significance versus the ketamine group; P_3, significance versus the preceding reading of the same group; PTX, pentoxifylline.

Table 9 Serum levels of malondialdehyde (nmol/ml) at different time points

	Control	Ketamine	PTX
T_0			
Level	0.62 ± 0.08	0.64 ± 0.07	0.62 ± 0.08
P-value		P_1 = 0.481	P_1 = 0.888 P_2 = 0.380
T_1			
Level	1.42 ± 0.13	1.31 ± 0.08	1.18 ± 0.08
P-value	P_3 = 0.0004	P_3 = 0.0005 P_1 = 0.021	P_3 = 0.0004 P_1 = 0.0009 P_2 = 0.001
T_2			
Level	1.28 ± 0.127	1.25 ± 0.09	1.154 ± 0.07
P-value	P_3 = 0.006	P_3 = 0.049 P_1 = 0.219	P_3 = 0.681 P_1 = 0.003 P_2 = 0.002
T_3			
Level	1.27 ± 0.15	1.21 ± 0.13	1.09 ± 0.11
P-value	P_3 = 0.732	P_3 = 0.164 P_1 > 0.05	P_3 = 0.128 P_1 = 0.003 P_2 = 0.028

Data are presented as mean ± SD. T_0, after induction of anesthesia; T_1, 4 h after aortic declamping; T_2, 24 h after aortic declamping; T_3, 48 h after aortic declamping; P_1, significance versus the control group; P_2, significance versus the ketamine group; P_3, significance versus the preceding reading of the same group; PTX, pentoxifylline.

protects against the loss of antioxidant activity in spinal cord tissues. Ergün *et al.* [34] they recommended that ketamine might be preferred in certain operations with the risk for ischemia/reperfusion injury. Le Campion *et al.* [35] reported significant reductions in serum TNF-α, IL-6, and MDA levels in pancreatic tissue, with a significantly found that in rats treated with subanesthetic doses of ketamine, elevated malondialdehyde levels in ischemia/reperfusion injury were reversed to control levels by each dose and recommended that ketamine

might be preferred in certain operations with the risk of ischemia/reperfusion injury. Ramallo *et al.* [36] detected burn-injury-induced oxidative stress in lung homogenates, with increased total protein, cytokine, and MDA levels on bronchoalveolar lavage, but all these parameters were decreased in animals treated with PTX.

Conclusion

In patients assigned for elective CABG surgery, bolus dose and continuous intraoperative infusion of either PTX or ketamine is safe and could ameliorate the oxidative stress secondary to ischemia/reperfusion, concomitant with aortic cross clamping and release, and shift the immune response to surgery towards the anti-inflammatory side. However, such effects were more pronounced with PTX than with ketamine.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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