

Effect of Morphine and Fentanyl on Inflammatory Biomarkers in Rheumatic Heart Patients Undergoing Valve Replacement Surgery

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Abstract

Background: Cardiopulmonary bypass (CPB) is well known to be associated with a complex physiological response that is clinically manifested as a systemic inflammatory response syndrome. The aim of the study is to compare between the effect of morphine and fentanyl as part of a balanced anesthetic technique on the inflammatory reaction that occurs in cardiac valve replacement surgeries after CPB.

Material and methods: Thirty patients undergoing cardiac surgery with cardiopulmonary bypass were randomized to receive either morphine or fentanyl as part of a standardized opioid-isoflurane anesthetic; Group 1 (15 patients received morphine, IV. Group 2 (15 patients received fentanyl. Hemodynamic data were recorded. Serum concentrations of interleukin [(IL)-6 and IL-10] and [(CD 11b, CD 11c, and CD 18)] were measured.

Results: There was a significant decrease in Heart Rate (HR) and Mean arterial pressure (MAP) in morphine group compared to fentanyl group. However, there were no significant differences between both groups in central venous pressure (CVP) and the incidence of intra operative arrhythmias. Serum levels of IL-6 and IL-8 concentrations increased in all patients after CPB. The increase in serum IL-6 levels was significantly attenuated in the morphine group compared to the fentanyl group at 3 and 24 hrs post CPB ($P < 0.05$). The increase in IL-6 and IL-10 concentrations was significantly attenuated in morphine group compared to the fentanyl group at 4hrs and 24hrs post-CPB ($P < 0.05$). The reduction in adhesion molecules expression (CD 11b, CD 11c and CD 18) were significantly more in the morphine group than in the fentanyl group at 4 hrs and 24 hrs post-CPB ($P < 0.05$).

Conclusion: There were perturbations in the release of circulating cytokines, adhesions molecules and postoperative hyperthermia which attenuated by the use of morphine.

Keywords: Cardiopulmonary bypass; Morphine; Fentanyl; Cytokines; Adhesion molecules

Introduction

Cardiac surgery aggravates an energetic inflammatory response that persists into the postoperative period [1]. The methods underlying ischemia-reperfusion injury are appropriate better appreciated but reactive oxygen species elaboration, free radical mediated membrane injury, mitochondrial dysfunction and organization of an inflammatory response are all central to the procedure [1,2]. The inflammatory responses that take places during cardiopulmonary Bypass (CPB) have been frequently referred to as a systemic inflammatory response syndrome (SIRS) similar to sepsis [2]. The property of an inflammatory response is the complex humoral and cellular communication with plentiful pathways including activation, generation, or expression of thrombin, complement, cytokines, neutrophils, adhesion molecules, and multiple inflammatory mediators [3]. Factors that set off the inflammatory response embrace surgical trauma, blood transfusion, and hypothermia.

Systemic interleukins (IL-6 and-8), that imitate myocardial reperfusion injury, are intricate by the injured myocardium and give out to drive systemic inflammation and upregulation of leukocyte adhesion molecules [4]. IL-10, unconfined primarily from the liver, acts as a counter-balance to these pro-inflammatory cytokines in addition, CPB may trigger the inflammatory response via contact activation of the immune system ensuing to revelation of blood to the foreign surfaces of the CPB circuit, via ischemia-reperfusion injury and via splanchnic hypoperfusion allowing gut translocation of endotoxin [4,5]. Of the cytokines measured in the inflammatory cascade in response to CPB, interleukins (IL-6 and IL-8) are the most consistently and significantly increased after CPB [6]. In addition IL-8 plays a chief role in neutrophil

activation, degranulation and upregulation of adhesion molecules (CD 11/CD 18) [5]. There is a crucial activation of the IL-10 pathway during the anti-inflammatory response to CPB [7]. The role of IL-10 as an anti-inflammatory cytokine has to be emphasized; it suppresses the production of pro-inflammatory cytokines and inhibits neutrophil endothelial interaction. It also exhibits an immunosuppressive function [8]. Drugs and techniques used to produce anesthesia and maintain postoperative sedation and analgesia have been thought to possess immunomodulatory effect [9]. Morphine may suppress expression of adhesion molecules on inflammatory cells and reduce binding of the cells to the endothelium. Some studies suggested that morphine may modify inflammatory processes and may be helpful to patients undergoing cardiac surgery [5]. These combined actions might be anticipated to attenuate the reperfusion injury. Thus we aimed to compare between the effect of morphine and fentanyl as part of a balanced anesthetic technique on the inflammatory reaction that occurs in cardiac valve replacement surgeries after CPB.

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Patients and Methods

After approval by the local ethics committee of Assiut University with written informed consent from all patients, 30 adult patients undergoing elective open-heart surgery for valve replacement were included. Patients were randomly allocated into two equal groups, morphine group (n=15), fentanyl group (n=15).

Anesthetic and operative techniques

All patients have been premedicated with IV midazolam (0.05 mg/kg) 30 min before the operation. After placement of electrocardiographic leads and pulse-oximeter, a peripheral IV and arterial access were inserted using local anesthesia. Central venous catheter also inserted in the internal jugular vein under local anesthesia. Anesthesia was induced with thiopental sodium (2-4 mg/kg) and cis-atracurium (0.15 mg/kg) intravenously, then either (0.1 mg/kg) of morphine or (5 µg/kg) of fentanyl was administered. The infusion pump was then programmed to deliver either morphine at a rate of (1-2 mg/h) or fentanyl at a rate of (1 µg/kg/h), (Dosing of fentanyl reflected the lower range of equipotence of fentanyl to morphine (40-50:1) [10] and the infusion was continued until the end of surgery and the arrival to the ICU. Anesthesia was maintained pre- and post-CPB using isoflurane and cis-atracurium (0.03 mg/kg). Patient was ventilated with a mixture of oxygen and air.

Cardiopulmonary bypass technique

All patients had a median sternotomy. An initial dose of 400 U/kg of heparin was used to obtain an activated clotting time (ACT) >450 s before CPB. CPB was instituted with a non-pulsatile heart-lung machine. Mean blood pressures of 50-70 mm Hg and blood flows of 2-2.4 L min⁻¹ m⁻² was maintained during CPB. The prime volume contains mannitol, non-glucose containing solutions and heparin. Moderate hypothermic CPB (28-32°C) was used in all patients. Cardiac arrest was achieved and maintained using cold cardioplegic solution at 4°C.

Data collections

Patient characteristics as age, weight, height, sex were recorded. Operative data including the operation type, bypass time, cross-clamping time, duration of surgery, fluid transfusion (ml), blood transfusion and plasma transfusion (units) were all recorded. Hemodynamic data were collected at several times in the perioperative period: immediately preinduction (T_{baseline}); 30 min postinduction (T₁); 30 min post-bypass (T₂); 1 hr post-bypass (T₃); 2 hrs post-bypass (T₄); upon ICU admission; (T₅) 3 hrs (T₆) and 6 hrs (T₇) after ICU admission. Hemodynamic data included heart rate, mean arterial blood pressure, and central venous pressure. The incidence of intraoperative arrhythmias was also recorded. Temperature was measured at the end of surgery (Temp_{baseline}), on arrival to the ICU (Temp₁), and every 2hrs for the next 12 hrs in the ICU (Temp₂-Temp₇). Duration of tracheal intubation and the length of ICU and postoperative ward stay were also recorded.

Cytokine determinations

Inflammatory markers: blood samples for cytokines (IL-6 and IL-10). At each time-point blood was drawn into an endotoxin-free heparinized vacutainer tube (Chromogenix, Moelndal, Sweden). Immediately after sampling blood was centrifuged at 2000 g at 4°C for 10min. Plasma was separated and aliquots were frozen at -70°C until analysis. Cytokines were measured by the use of commercially available ELISA kits (Bender MedSystem, Vienna, Austria).

Flow cytometric analysis of (CD 11b, CD11c and CD18)

Instantaneously following venipuncture, whole blood were drawn directly away before the start of CPB (baseline), 4 hrs post-CPB, and 24 hrs after baseline then all blood were cooled to 4°C. Data acquired of (CD 11b, CD 11c and CD 18) were measured using flow cytometry. Summarized briefly; blood sample tubes were located on ice and flow cytometric analysis was carried out within 2 hrs from blood sampling. For study, blood samples were situated in 12x75 mm polystyrene tubes (Falcon, Becton Dickinson UK Ltd, Cowley, UK) using, per condition, 90 µL whole blood and 10 µL primary antibody (100 µg/mL). Foremost incubations were approved out on ice for 15 minutes. After labeling unbound antibody was removed, every antibody was corresponding at each time point to an extraneous isotypic control. After two washes with phosphate-buffered saline, fluorescein isothiocyanate-conjugated secondary antibodies were added at the manufacturer's recommended concentration (Sigma Chemical Co, Dorset, UK) and incubation was sustained for a further 15 minutes. Red blood cells were lysed for 60 seconds by the addition of 1 mL Coulter whole blood lysing reagent and fixed in 250 µL fixative solutions (Coulter Electronics Ltd, Luton, UK). Lysed samples were preserved in 5% formaldehyde and read on a flow cytometry (EPICS XL, Coulter Electronics Ltd) within 24 hrs. Neutrophil and monocyte cell populations were identified by their characteristic forward and side scatter profiles and confirmed by staining with anti-CD14 monoclonal antibody [11]

Statistical analysis and power of the study

All continuous variables are expressed as mean ± standard deviation, and discrete variables are presented as frequencies and percentages. Between groups analysis of categorical variables was performed with chi-square test while analysis of continuous variables was performed with a non-parametric Wilcoxon Signed-Rank test. Comparisons between times in the same group were performed using repeated measures of ANOVA test with least significant difference (LSD) as a post hoc test. P value of <0.05 was considered statistically significant.

Results

Demographic data of the patients

There were insignificant statistical differences between the two studied groups with respect to age, weight, height and sex as shown in Table 1.

Changes in operative data

There were insignificant statistical differences between the two studied groups as regarding type of the operation, bypass time (min), cross-clamping time (min), duration of surgery (min), fluid transfusion (ml), blood transfusion (units), and plasma transfusion (units) as shown in Table 2.

Changes in hemodynamic data

Hemodynamic data were collected at several times in the

	Morphine	Fentanyl	Significance
Age (years)	30.4 ± 11.2	30.47 ± 10.8	N.S
Weight (kg)	60.27 ± 9.88	57.07 ± 11.8	
Height (cm)	164.1 ± 8.5	160.4 ± 6.13	
Sex (male/female)	10/5	10/5	

Data presented as median (interquartile range). P value by Kruskal-Wallis (p<0.5). N.S: Non-Significant

Table 1: Demographic data in the two studied groups (mean ± SD).

		Morphine	Fentanyl	Significance
Type of the operation	Mitral Valve Replacement	11 (73%)	13 (87%)	N.S
	Aortic Valve Replacement	4 (27%)	2 (13%)	
Bypass time (min)		151 ± 38	148 ± 32	
Cross-Clamping time (min)		120.6 ± 38.2	123.8 ± 30.5	
Surgery duration (min)		396 ± 63.79	354.33 ± 52.3	
Fluid transfusion (ml)		3617 ± 489.8	3557 ± 425.4	
Blood transfusion (units)		2 (2-3)	2 (1-3)	
Plasma transfusion (units)		0 (0-3)	0 (0-2)	

Data presented as median (interquartile range), frequency (%). P value by Kruskal-Wallis. Intergroup differences (p<0.05) by Tukey's test after log transformation: (N.S=Non Significant)

Table 2: Operative data in the two studied groups.

	Morphine	Fentanyl	Significance
Pre-induction (T _{baseline})	89.93 ± 18.49	94.93 ± 11.34	N.S
30 min post-induction (T ₁)	83 ± 17.33	83 ± 17.33 ^{**}	N.S
30 min post-bypass (T ₂)	78.73 ± 8.92 ^{**}	83.73 ± 4.27 ^{**}	N.S
1 hour post-bypass (T ₃)	98.27 ± 3.63	113.4 ± 15.34 ^{***}	P<0.05
2 hours post-bypass (T ₄)	87.53 ± 9.57	93.73 ± 6.75	P<0.05
On ICU admission (T ₅)	81.47 ± 7.35	87.4 ± 3.44	P<0.05
3 hours after ICU admission (T ₆)	82.07 ± 15.25	89.87 ± 11.81	P<0.05
6 hours after ICU admission (T ₇)	83.07 ± 12.85	85.33 ± 6.63 ^{**}	N.S

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences (p<0.05) by Tukey's test after log transformation: N.S=Non Significant, **P<0.01 compared to T_{baseline}, ***P<0.001 compared to T_{baseline}

Table 3: Heart rate changes (beats/min) in the two studied groups.

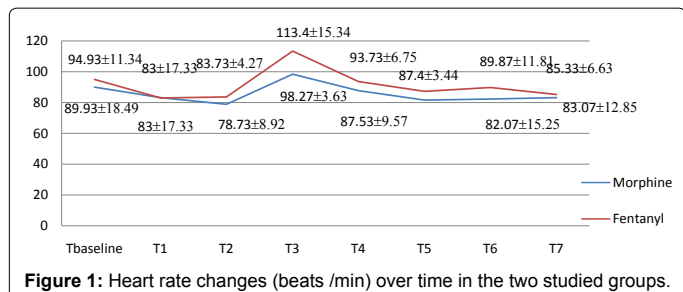


Figure 1: Heart rate changes (beats/min) over time in the two studied groups.

perioperative period: immediately pre-induction (T_{baseline}); 30 min post-induction (T₁); 30 min post-bypass (T₂); 1hrs post-bypass (T₃); 2 hrs post-bypass (T₄); upon ICU admission (T₅); and 3 hrs (T₆), 6 hrs (T₇) after ICU admission. Hemodynamic data included heart rate, mean arterial blood pressure and central venous pressure.

Heart rate (HR): In morphine group, there was significant decrease in HR from baseline reading only at 30 min post-bypass (P<0.01) while there were insignificant differences at the other times of the study (Table 3 and Figure 3).

In fentanyl group, compared with baseline reading there was significant decrease in HR at 30 min post-induction (P<0.003), 30 min post-bypass (P<0.005) and 6 hrs after ICU admission (P<0.01). A significant increase in HR from baseline reading at one hour post-bypass was reported (P<0.001). However, there were insignificant differences at 2 hrs post-bypass, on ICU admission and 3 hrs after ICU admission (Table 4 and Figure 1).

Between groups: there was significant decrease in HR value in morphine group from fentanyl group as shown in Table 3 and Figure 1.

Mean arterial blood pressure (MAP): In morphine group, there was significant decrease in MAP value. P value <0.001 as shown in Table 4 and Figure 2.

In fentanyl group, there was significantly decrease in MAP value from baseline reading at 30min post-induction (P<0.05), 30 min post-bypass (P<0.001), 1hour post-bypass (P<0.001) and 2hrs post-bypass (P<0.005). On ICU admission; 3 and 6hrs after ICU admission MAP increased gradually but still insignificantly decreased from baseline (Table 4 and Figure 2).

Between groups: there was significant decrease in MAP value in morphine group from fentanyl group on ICU admission and 3 hrs after ICU (p<0.001, p<0.01 respectively) as showin in Table 4 and Figure 2.

Central venous pressure (CVP): In morphine group, there was significant decrease in CVP value measured in cm H₂O from its baseline reading at 1hr and 2hrs post-bypass (P<0.001 and P<0.05 respectively) while there were insignificant differences at the other study times (Table 5 and Figure 3).

	Morphine	Fentanyl	Significance
Pre-induction (T _{baseline})	88.27 ± 13.78	83.67 ± 6.6	N.S
30 min post-induction (T ₁)	71.87 ± 9.2 ^{**}	77.1 ± 14.67 ^{**}	N.S
30 min post-bypass (T ₂)	69.8 ± 8.9 ^{**}	69.13 ± 9.49 ^{**}	N.S
1 hour post-bypass (T ₃)	67 ± 10.64 ^{**}	71 ± 8.4 ^{**}	N.S
2 hours post-bypass (T ₄)	68.73 ± 8.2 ^{**}	74.87 ± 7.51 ^{**}	N.S
On ICU admission (T ₅)	70.13 ± 6.1 ^{**}	78.87 ± 6.1	P<0.001
3 hours after ICU admission (T ₆)	72.47 ± 5.05 ^{**}	79.9 ± 6	P<0.01
6 hours after ICU admission (T ₇)	76.4 ± 6 ^{**}	80.33 ± 5.3	N.S

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences (p<0.05) by Tukey's test after log transformation: N.S=Non Significant, **P<0.01 compared to T_{baseline}, *P<0.05 compared to T_{baseline}, ***P<0.001 compared to T_{baseline}

Table 4: Mean arterial blood pressure changes (mm Hg) in the two studied groups.

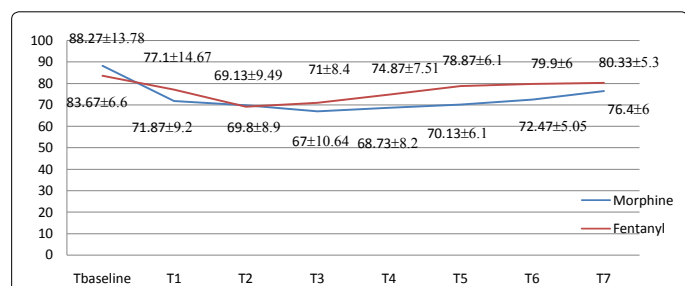


Figure 2: Mean arterial blood pressure changes (mm Hg) in the two studied groups.

	Morphine	Fentanyl	Significance
Pre-induction (T _{baseline})	9.6 ± 2.5	9.1 ± 2.7	N.S
30 min post-induction (T ₁)	8.9 ± 1.5	8.8 ± 2.1	
30 min post-bypass (T ₂)	9.9 ± 1.9	8.8 ± 2.1	
1 hour post-bypass (T ₃)	7.3 ± 2.7 ^{**}	6.5 ± 1.4 ^{**}	
2 hours post-bypass (T ₄)	8.1 ± 1.9 [*]	7.7 ± 1.1 ^{**}	
On ICU admission (T ₅)	8.6 ± 1.9	8.3 ± 1.2	
3 hours after ICU admission (T ₆)	8.8 ± 2.8	7.9 ± 2.2 [*]	
6 hours after ICU admission (T ₇)	8.3 ± 0.7	8.4 ± 0.9	

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences (p<0.05) by Tukey's test after log transformation: N.S=Non Significant, **P<0.01 compared to T_{baseline}, *P<0.05 compared to T_{baseline}, ***P<0.001 compared to T_{baseline}

Table 5: Central venous pressure changes (cm H₂O) in the two studied groups.

	Morphine	Fentanyl	Significance
On arrival to ICU (Temp _{baseline})	36.6 ± 0.8	36.7 ± 0.9	N.S
2 hrs post-arrival to ICU (Temp ₁)	36.8 ± 0.4	37.4 ± 0.4***	P<0.001
4 hrs post-arrival to ICU (Temp ₂)	37.1 ± 0.2***	37.5 ± 0.3***	P<0.001
6 hrs post-arrival to ICU (Temp ₃)	37.3 ± 0.4***	37.6 ± 0.3***	N.S
8 hrs post-arrival to ICU (Temp ₄)	37.2 ± 0.3***	37.5 ± 0.3***	P<0.05
10 hrs post-arrival to ICU (Temp ₅)	37.2 ± 0.2***	37.5 ± 0.3***	P<0.01
12 hrs post-arrival to ICU (Temp ₆)	37.1 ± 0.2***	37.5 ± 0.1***	P<0.05

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences (p<0.05) by Tukey's test after log transformation: N.S=N/A Significant ***P<0.001 compared to Temp_{baseline}

Table 6: Temperature changes (°C) in the two studied groups.

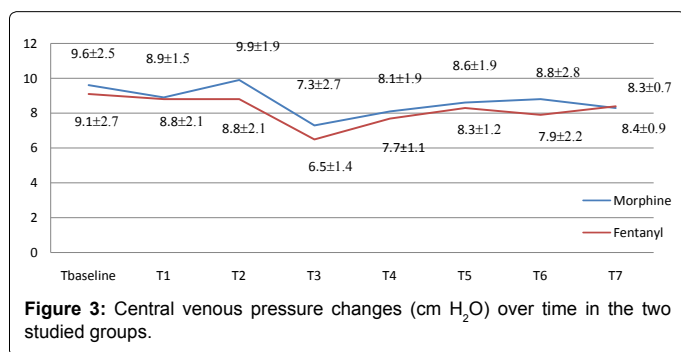


Figure 3: Central venous pressure changes (cm H₂O) over time in the two studied groups.

	Morphine	Fentanyl	Significance
Before start of CPB (baseline)	82.20 ± 6.19	110.86 ± 12.43*	P<0.01
4 hrs post-CPB	182.93 ± 22.99	358.53 ± 53.94*	P<0.001
21 hrs post-CPB	105.35 ± 7.79	219.40 ± 26.68*	P<0.01

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences (p<0.05) by Mann Whitney's test. *P value significantly higher in fentanyl group compared to morphine group (p<0.05)

Table 7: Interleukin-6 concentration changes (pg/ml) in the two studied groups.

In fentanyl group, there was significant decrease from baseline reading at 1 hr, 2 hrs post-bypass and 3 hrs after ICU admission (P<0.001, P<0.01 and P<0.04 respectively), while there were insignificant differences at the other times of the study (Table 5 and Figure 3).

Between groups: there were insignificant differences in CVP as shown in Table 5 and Figure 3.

Intraoperative Arrhythmias

As regarding the incidence of intraoperative arrhythmias there were insignificant statistical differences when comparing between both groups. Three patients (20%) in morphine group and four patients (33%) in fentanyl group were developed ventricular arrhythmias. Electrical defibrillation was used to control the arrhythmias. The number of defibrillations ranged from (1-2) per patient of (20-30) joules.

Temperature Changes (°C)

In morphine group, there was statistically significant increase in body temperature at 4, 6, 8, 10, and 12 hrs post-arrival to ICU compared to its value on arrival to ICU (P<0.001) (Table 6).

In fentanyl group, there was statistically significant increase in body temperature at 2, 4, 6, 8, 10, and 12 hrs post-arrival to ICU compared to its value on arrival to ICU (P<0.001) (Table 6).

Between groups: There was no significant difference in the body temperature between both groups on arrival to ICU and 6 hrs post-arrival to ICU. However, there was statistically significant rise of the temperature in fentanyl group more than morphine group at 2, 4, 8, 10 and 12 hrs post-arrival to ICU (P<0.001, P<0.001, P<0.05, P<0.01 and P<0.05 respectively) (Table 6).

Postoperative Temperature Changes

In both groups hypothermia not detected. The incidence of postoperative hyperthermia (defined as: body temperature >38.0°C) was significantly higher in fentanyl group compared with that in morphine group.

In morphine group only one patient suffered from postoperative hyperthermia at 8 hrs post-arrival to ICU (38°C) where in fentanyl group seven patients were suffered: two patients were suffered 2 hrs post-arrival to ICU (38.0°C, 38.2°C), one patient was suffered 4 hrs post-arrival to ICU (38.0°C), one patient was suffered 6 hrs post-arrival to ICU (38.5°C), one patient was suffered 8 hrs post-arrival to ICU (38.0°C) and two patients were suffered 10 hrs post-arrival to ICU (38.0°C). Postoperative hyperthermia was controlled in both groups by the use of IV paracetamol (15 mg/kg).

Inflammatory Markers

Interleukin-6 (IL-6)

In morphine group, compared to the baseline reading, there was significant increase in the mean value of the serum level of IL-6 at 4 hrs post-CPB (P<0.001), but there was insignificant increase at 21 hrs post-CPB. However, the level of IL-6 at 21 hrs post-CPB was significantly lower than that at 4 hrs post-CPB (P<0.001), Table 7 and Figure 4.

In fentanyl group, compared to the baseline reading, there was significant increase in the mean value of the serum level of IL-6 at 4 hrs post-CPB (P<0.001) and at 21 hrs post-CPB (P<0.03). However, the level of IL-6 at 21 hrs post-CPB was significantly lower than its value at 4 hrs post-CPB (P<0.01), Table 7 and Figure 4.

Between groups comparison: the mean value of IL-6 was significantly lower in morphine group than in fentanyl group before the start of CPB (baseline) (P<0.01), 4 hrs post-CPB (P<0.001) and 21 hrs post-CPB (P<0.01), Table 6 and Figure 4.

Interleukin-10 (IL-10)

In morphine group, the mean value of serum level of IL-10 was

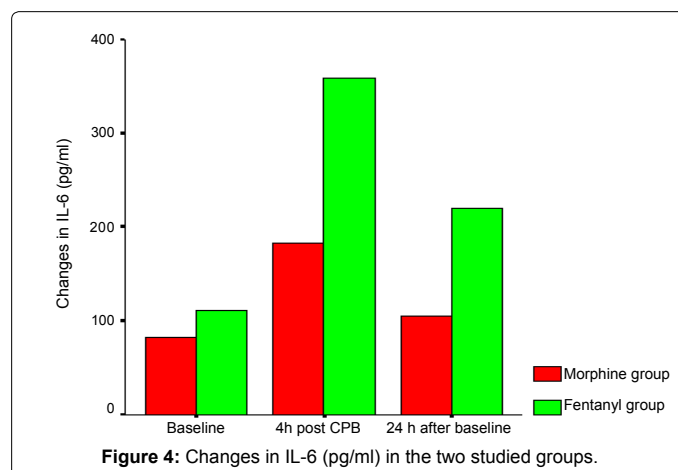


Figure 4: Changes in IL-6 (pg/ml) in the two studied groups.

	Morphine	Fentanyl	Significance
Before start of CPB (baseline)	10.02 ± 1.88	15.25 ± 2.86*	N.S
4 hrs post-CPB	243.96 ± 32.13	680.60 ± 75.50*	P<0.001
21 hrs post-CPB	17.30 ± 2.28	53.75 ± 3.86*	P<0.001

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences by Mann Whitney. *P value significantly higher in fentanyl group compared to morphine group (p<0.05). N.S=Non Significant

Table 8: Interleukin-10 concentration changes (pg/ml) in the two studied groups.

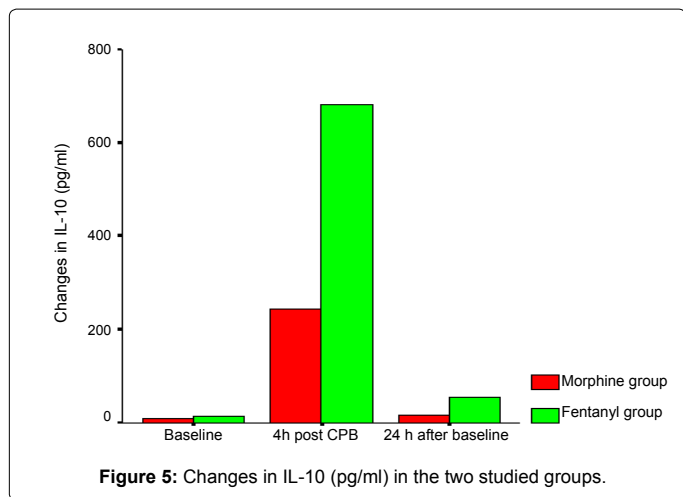


Figure 5: Changes in IL-10 (pg/ml) in the two studied groups.

	Morphine	Fentanyl	Significance
Before start of CPB (baseline)	222.64 ± 33.66	304.93 ± 60.41	N.S
4 hrs post-CPB	32.87 ± 4.58	90.24 ± 14.86*	P<0.001
21 hrs post-CPB	145.02 ± 20.08	492.45 ± 71.88*	P<0.001

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences by Mann Whitney. *P value significantly higher in fentanyl group compared to morphine group (p<0.05). N.S=Non Significant

Table 9: CD 11b concentration changes (pg/ml) in the two studied groups.

significantly increased at 4 hrs post-CPB (P<0.001), but insignificantly increased at 21 hrs post-CPB when compared to its base measurement value. However, the level of IL-10 at 21 hrs post-CPB was significantly lower than that at 4 hrs post-CPB (P<0.001), Table 8 and Figure 5.

In fentanyl group, patients have the same pattern of changes in IL-10 as those in morphine group. The mean value of serum level of IL-10 was significantly increased at 4 hrs post-CPB (P<0.001), but insignificantly increased at 21 hrs post-CPB when compared to its base measurement value. However, the level of IL-10 at 21 hrs post-CPB was significantly lower than that at 4 hrs post-CPB (P<0.001), Table 8 and Figure 5.

Between groups comparison: there was insignificant difference in the mean value of interleukin-10 before the start of CPB (baseline), while it was significantly lower in morphine group than in fentanyl group 4 hrs post-CPB (P<0.001) and 21 hrs post-CPB (P<0.001) (Table 8 and Figure 5).

CD11b

In morphine group compared to its baseline reading, there was significant decrease in the mean value of serum level of CD11b at 4 hrs post-CPB (P<0.001) and at 21 hrs post-CPB (P<0.02). However, its level at 4 hrs post-CPB was significantly lower than that at 21 hrs post-CPB (P<0.001) Table 9 and Figure 6.

In fentanyl group compared to the baseline reading, there was

significant decrease in the mean value of serum level of CD11b at 4 hrs post-CPB (P<0.001), while its level insignificantly increased at 21 hrs post-CPB. The level of CD11b was significantly lower at 4 hrs post-CPB than that at 21 hrs post-CPB (P<0.001) Table 9 and Figure 6.

Between groups comparison, there was insignificant difference when comparing the mean value of CD11b before the start of CPB (baseline), while it was significantly lower in morphine group than in fentanyl group 4 hrs post-CPB (P<0.001) and 21 hrs post-CPB (P<0.001), Table 9 and Figure 6.

CD11c

In morphine group there was significant decrease in the mean value of the serum level of CD11c at 4 hrs post-CPB (P<0.001) and at 21 hrs post-CPB (P<0.001) compared to its baseline reading. The value of CD11c at 4 hrs post-CPB was significantly lower than that at 21 hrs post-CPB (Table 10 and Figure 7).

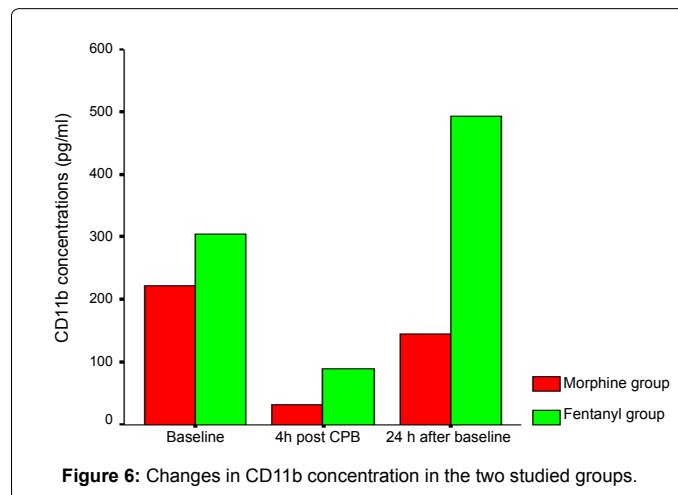


Figure 6: Changes in CD11b concentration in the two studied groups.

	Morphine	Fentanyl	Significance
Before start of CPB (baseline)	47.83 ± 3.63	48.77 ± 4.08	N.S
4 hrs post-CPB	24.02 ± 2.84	35.62 ± 3.58	P<0.01
21 hrs post-CPB	29.35 ± 2.59	47.99 ± 2.79	P<0.001

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences by Mann Whitney. *P value significantly higher in fentanyl group compared to morphine group (p<0.05). N.S=Non Significant

Table 10: CD 11c concentration changes (pg/ml) in the two studied groups (mean ± SD).

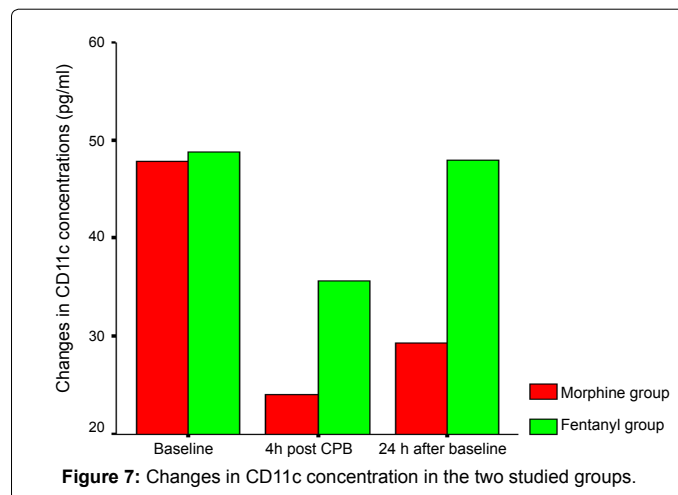
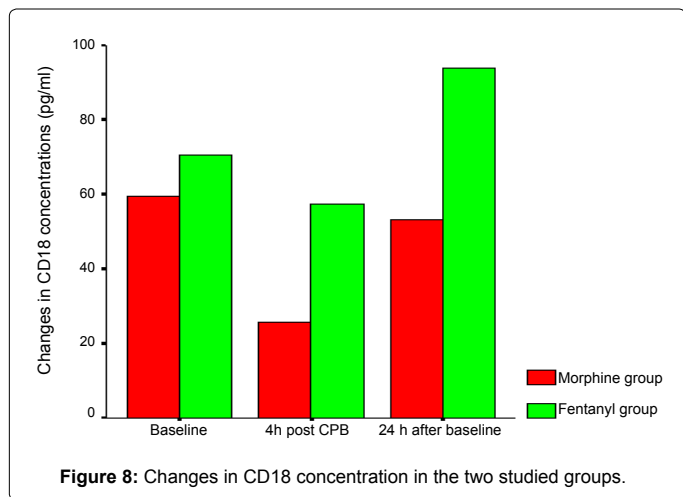


Figure 7: Changes in CD11c concentration in the two studied groups.

	Morphine	Fentanyl	Significance
Before start of CPB (baseline)	59.49 ± 7.13	70.36 ± 9.81	N.S
4 hrs post-CPB	25.63 ± 2.03	57.44 ± 6.11*	P<0.01
21 hrs post-CPB	53.09 ± 6.27	93.61 ± 11.88*	P<0.01

Data presented as median (interquartile range). P value by Kruskal-Wallis. Intergroup differences by Mann Whitney. *P value significantly higher in fentanyl group compared to morphine group (p<0.05). N.S=Non Significant

Table 11: CD18 concentration changes (pg/ml) in the two studied groups (mean ± SD).



In fentanyl group there was significant decrease in the mean value of the serum level of CD11c at 4 hrs post-CPB (P<0.01), but insignificant decrease at 21 hrs post-CPB compared to its baseline reading. The serum level of CD11c was significantly lower at 4 hrs post-CPB than that at 21 hrs post-CPB (P<0.01), Table 10 and Figure 7.

Between groups comparison, while there was insignificant difference when comparing the mean value of CD11c before the start of CPB (baseline), it was significantly lower in morphine group than in fentanyl group 4 hrs post-CPB (P<0.01) and 21 hrs post-CPB (P<0.001) (Table 10 and Figure 7).

CD18

In morphine group compared to the baseline reading, there was significant decrease in the mean value of the serum level of CD18 at 4 hrs post-CPB (P<0.001), but it insignificantly decreased at 21 hrs post-CPB. The value of CD18 at 4 hrs post-CPB was significantly lower than that at 21 hrs post-CPB (P<0.001) (Table 11 and Figure 8).

In fentanyl group compared to the baseline reading, while there was insignificant decrease in the mean value of the serum level of CD18 at 4 hrs post-CPB, its value insignificantly increased at 21 hrs post-CPB. The value of CD18 at 4 hrs post-CPB was significantly lower than that at 21 hrs post-CPB (P<0.01) (Table 11 and Figure 8).

Between groups comparison, while there was insignificant difference when comparing the mean value of CD18 before the start of CPB (baseline), it was significantly lower in morphine group than in fentanyl group 4 hrs post-CPB (P<0.01) and 21 hrs post-CPB (P<0.01) (Table 11 and Figure 8).

Duration of tracheal intubation and length of icu and ward stay, There were insignificant differences between the two studied groups as regarding the duration of tracheal intubation (hrs), length of ICU stay (days) and length of postoperative ward stay (days) (P>0.5)

Discussion

Cardiopulmonary bypass is well known to be associated with a systemic inflammatory response that presents itself as a long standing issue and an intractable problem [8]. CPB during cardiac surgery provokes a vigorous inflammatory response via a variety of mechanisms, mainly including contact of blood to the foreign surfaces of the CPB circuit, surgical trauma and endotoxaemia [1]. The results of our study revealed that there was no significant difference between the studied groups as regard patient characteristics and operative data. Furthermore, we found a statistical significant decrease in HR and MAP in morphine group compared to fentanyl group. However, there were no statistical significant differences between both groups in CVP and the incidence of intra operative arrhythmias.

Stoelting and Gibbs, [12,13] studied the effect of morphine in patients who either had aortic valve or coronary vein graft operations. They agree with our result which found that a dose of 1mg/kg of morphine used alone or with nitrous oxide significantly lowered the arterial pressure. However Camu et al. [14] found that morphine caused a significant reduction in MAP in patients after major vascular surgery. Alavi et al. [15] compared IV sufentanil and morphine for post-cardiac surgery pain relief using patient-controlled analgesia (PCA) device. They found that, systolic blood pressure was reduced more in morphine group than sufentanil group. Noorizan Abd Aziz et al., found that, both groups showed a transient increase in MAP during the first hour postoperatively, especially in the dexmedetomidine group, followed by decrease in MAP [16]. Frank et al., also suggested that the use of morphine intra-operatively may reduce the incidence of postoperative fever by attenuating the inflammatory response to surgery and CPB [17].

In addition Murphy et al. [5] demonstrated that lower incidence of postoperative hyperthermia in the morphine group which had been clarified by morphine's modulation of inflammatory responses to surgery in cardiac patients received either morphine (40 mg) or fentanyl (1000 µg) as part of a standardized opioid-isoflurane anesthetic technique underwent elective coronary artery bypass graft and the patients. In the current study, similar results were obtained in spite of the lower doses of both drugs which were used.

In the present study, the level of IL-6 was increased in both groups at 4 hrs and 24 hrs post-CPB, but this increase was significantly attenuated in morphine group. Welters et al., found that pretreatment of mice or human mononuclear cell cultures with morphine before lipopolysaccharide-induced cell stimulation resulted in significant inhibition of the production of IL-6 compared to control groups [6]. In addition to its role in the regulation of acute-phase protein production and the growth and differentiation of B- and T-cells, IL-6 also acts as a pyrogen and a myocardial depressant. An association between increased IL-6 concentrations and peak postoperative temperatures has been reported [5].

In the same way other reported that IL-6 concentrations increased in all patients of both morphine and fentanyl groups after CPB. This augmentation was significantly attenuated in the morphine group at 3 and 24 hrs post-CPB [5]. However Winterhalter et al. compared a remifentanyl infusion to intermittent fentanyl boluses as regards the inflammatory activation. They established that IL-6 was significantly higher at some perioperative time points in the fentanyl group compared to the remifentanyl group [18]. However, CPB times and aortic cross-clamp times were longer in the fentanyl group, which may to some extent account for the differences [18].

We found that, the level of IL-10 was significantly increased at 4 hrs post-CPB. This increase was significantly attenuated at 24 hrs post-CPB but still above the baseline. However, there were insignificant differences between its values at 24 hrs post-CPB compared with baseline. The increase in morphine group was significantly attenuated than in fentanyl group at 4 hrs and 24 hrs post-CPB.

Galley et al., established that higher IL-10 concentrations after CPB may be associated with poorer outcome after cardiac surgery [19]. LIU Jian-hua et al., investigated the effect of fentanyl on cytokines in valve replacement surgery during CPB using 3 different doses which were 30, 60, 100 µg/kg in thirty adult patients who were randomly divided into 3 groups (A, B, C respectively) [20]. They found that levels of IL-6 and IL-10 after the CPB in the 3 groups were significantly higher than before the operation.

They concluded that larger dose fentanyl seemed to be effective in reducing CPB-induced inflammatory response, but at the same time the duration of ICU stay and time of endotracheal extubation was longer. Davorka Messmer et al. found that chronic morphine treatment during the development of the human dendritic cells from monocytes augmented lipopolysaccharide resulted in reduction of IL-10 secretion [21]. As regard adhesion molecules expression (CD 11b, CD 11c and CD 18), there were a significant reduction in their value at 4 hrs post-CPB from baseline, then their levels were significantly increased at 24 hrs post-CPB. Their levels were significantly lower in morphine group than fentanyl group at 4 hrs and 24 hrs post-CPB.

Welters et al. found that morphine may suppress the expression of adhesion molecules on the inflammatory cells and reduce binding of the cells to the endothelium [6]. Incubation of human polymorphonuclear neutrophils with morphine for 10-150 min resulted in a significant decrease in the expression of surface receptors. This was in agreement with our results that showed the same effect of morphine on adhesion molecule expression. Murphy et al., found reductions in expression of adhesion molecules in both morphine and fentanyl groups 15 min and 3 hrs post-CPB [5]. However, a significant reduction in CD11b and CD18 expression was noted in morphine group.

In our study there were insignificant differences between the two groups regarding the duration of tracheal intubation, length of ICU stay and length of postoperative ward stay. In addition Murphy et al., studied 90 patients were randomized to receive either morphine (40 mg) or fentanyl (600 µg) as part of a standardized opioid-isoflurane anesthetic technique underwent cardiac surgery with CPB. They established that the use of morphine provided early recovery and reduced the postoperative febrile reactions compared with fentanyl in elective cardiac surgery patients, which was comparable to our results [22].

We concluded that, the use of morphine when compared to fentanyl as a part of a balanced anesthetic technique in valve replacement surgery after CPB, can allow better hemodynamic stability, attenuates the release of inflammatory cytokine (IL-6) and anti-inflammatory cytokine (IL-10), produce a greater reduction in adhesion molecule expression, and reduce the incidence of postoperative hyperthermia without affecting the duration of tracheal intubation, the length of ICU stay and the length of postoperative ward stay.

Study of Limitation

There are numerous limitations of this assessment. Initially, this study was limited by measurement of inflammatory biomarkers only in a small number of patients included in the study. Also, the effect of

drugs used in management of rheumatic heart diseases on the studied biomarkers is also a limitation. It remains to be determined if high-risk patients such as those with prolonged bypass may benefit more from propofol than thiopental sodium, were not measured in this study. Finally, this study was only a clinical observational trial in a single centre. Effective myocardial tissue concentration of morphine and fentanyl were not perceived in this clinical trial. Multi-centre clinical trials involving larger sample size are needed to determine the clinical effect of morphine and fentanyl in open cardiac surgery. In addition CPB might play a potential role regarding release of certain apoptotic biomarkers.

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