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Investigating the Impacts of Preoperative Steroid Treatment on Tumor Necrosis Factor-Alpha and Duration of Extubation Time underwent Ventricular Septal Defect Surgery

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Background: Cardiopulmonary bypass is known to cause inflammatory events. Inflammation occurs due to many known important biological processes. Numerous mechanisms are known to be responsible for the development of inflammatory processes. Currently, there are many defined mediators as a tumor necrosis factor-α (TNF-α) playing an active role in this process.
Aims: This research was to investigate the effects of preoperative steroid use on inflammatory mediator TNF-α and on time to extubation postoperatively in ventricular septal defect patients undergoing cardiopulmonary bypass surgery.
Study Design: Controlled clinical study.
Methods: This study included 30 patients. These patients were assigned into two groups, each containing 15 patients. 5 micrograms/kg methylprednisolone was injected intravenously 2 hours before the surgery to Group I, whereas there was no application to the patients in Group II. TNF-α (pg/mL) level was measured in arterial blood samples obtained at four periods including: the preoperative period (Pre TNF); at the 5th minute of cross-clamping (Per TNF); 2 hours after termination of cardiopulmonary bypass (Post TNF); and at the postoperative 24th hours in cardiovascular surgery intensive care unit (Post 24 h TNF).
Results: The mean cross-clamp time was 66±40 and 55±27 minutes in Group I and Group II respectively. No significant difference was found between the groups in terms of cross-clamp time ($p>0.05$). The mean time to extubation was 6.1±2.3 hours in Group I and 10.6±3.4 hours in Group II. Group I extubation time was significantly shorter than Group II. Group I TNF-α levels at Post TNF and Post24h TNF was lower than Group II. These differences are also statistically significant ($p<0.05$).
Conclusion: There is a strong indication that preoperative steroid treatment reduced the TNF-α level together with shortens duration of postoperative intubation and positively contributes to extubation in ventricular septal defect patients operated in cardiac surgery with cardiopulmonary bypass. (ClinicalTrials.gov Identifier: TCTR20150930001)
Keywords: Airway extubation, cardiopulmonary bypass, congenital heart defect, methylprednisolone, tumor necrosis factor-α

Cardiopulmonary bypass is known to cause inflammatory events (1). Inflammation developed during pediatric heart surgery is associated with interaction of blood with foreign surface during cardiopulmonary bypass, ischemia-reperfusion injury, and temperature changes during heating and cooling periods and durations of these periods, endotoxins, and surgical trauma (2).

Inflammation is a defence mechanism developed by the organism against harmful agents. Inflammation may lead to multiple organ failure in the organism (3-4).Therefore, inflammation is one of the factors that influence morbidity and mortality rates. Inflammation that would occur particularly in the central nervous, respiratory and circulatory systems of

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patients undergoing cardiopulmonary bypass may appear in various clinical pictures. This may either be mild or lead to a more severe clinical condition. Inflammation after pediatric open heart surgery is a parameter affecting also duration of mechanical ventilatory support (5-6).

Cardiac operations with cardiopulmonary bypass cause a systemic inflammatory response that may result organ injury which lead to postoperative morbidity. An inflammatory response after open-heart surgery following to cardiopulmonary bypass, derived by complement activation (C3a, C4a, C5a, and C5b-9), cytokine production and neutrophil sequestration in lungs can cause various complications. Cytokines which are protein in structure called pro-inflammatory mediators play a key role in this systemic inflammation. Cardiopulmonary bypass triggers plasma protein systems through contact, complement and fibrinolytic sytems, intrinsic and extrinsic coagulation, together with blood cells, including platelets, endothelial cells, lymphocytes, neutrophils and monocytes. It has also activation potential of stimulus for the release of proinflammatory cytokines, including TNF-α, IL-1, IL-6, IL-8 and IL-10. These processes are responsible for the common complications of cardiopulmonary bypass, including bleeding thromboembolism, fluid retention, and temporary organ dysfunction (7-9).

There are many studies suggesting that steroidal drugs have anti-inflammatory effects by suppressing proinflammatory mediators (10-12). In the present study, preoperative steroid treatment reduce the level of TNF-α and the duration of postoperative mechanical ventilation who undervent ventricular septal defect surgery. Thus, the major hypothesis of this study was to investigate i) the preoperative steroid treatment who undervent ventricular septal defect surgery reduce the level of TNF-α and, ii) shortens extubation time for postoperative mechanical ventilation.

MATERIALS AND METHODS

Clinical data

These two groups included 30 patients undergoing surgery with cardiopulmonary bypass due to ventricular septal defect. These patients were assigned into two groups, first patient directly included in group one, second patient included in group two. Then chosen odd numbered patients were participated in group I and even numbered patients were participated in group II. Both group containing 15 patients. A signed informed consent form from patient's parents for each case was obtained. This work had been approved by the University Ethical Board. Exclusion criteria were recognized chromosomal anomalies, genetic syndromes, prior intracardiac surgery, complex heart disease or excessive pulmonary hypertension. All patients had a preoperative cardiac catheterization. Additionally, selection of the patients was based on the ratio of volume of pulmonary flow (Qp) and systemic flow (Qs) for pulmonary tension:

$Qp/Qs = (Sat_{AO} - Sat_{MV}) / (Sat_{LA} - Sat_{PA})$

Where Sat_{AO} is the aortic blood oxygen saturation, Sat_{MV} is the mixed venous blood oxygen saturation, Sat_{LA} is the left atrial blood oxygen saturation, and Sat_{PA} is the pulmonary artery blood oxygen saturation.

Thus, patients approximately with 2 Qp/Qs ratio were considered. Group I (n: 15) received methylprednisolone at a dosage of 5 micrograms/kg intravenously 2 hours (h) before surgery. On the other hand, Group II has not received methylprednisolone or placebo (n: 15) as this research was not designed as a clinical study. TNF-α (pg/mL) level was measured in arterial blood samples obtained at the preoperative period (Pre TNF), at the 5th min of cross-clamping (Per TNF), 2 hours after termination of cardiopulmonary bypass (Post TNF) and at the postoperative 24th hours in cardiovascular surgery intensive care unit (Post 24th TNF). Distribution of ventricular septal defect patient types in both groups was given in Table 1.

The extubation criterias are; weaning is completed; the patient is sufficiently awake with intact airway reflex, functional respiratory muscle and normal muscle strength, stable cardiovascular status, normal body temperature, manageable secretions. The negative inspiratory force is more than -20 cm H_2O, the vital capacity is greater than or equal to 10 mL/kg and stable blood gas measurements include PaO_2>60 mmHg or SO_2>95%, $PaCO_2$<50 mmHg, pH 7.35 - 7.45 (13). The standard application of this study was to extubate whole suitable patients. The final decision to implement extubation in the intensive care unit was made by the surgeon and physician in the final stage of the procedure. When the patient was breathing spontaneously with acceptable respiratory variables, then the patient was extubated, and oxygen was applied via a nasal cannula.

Anesthesia

All patients were examined preoperatively by the anaesthesiologist. The same anaesthetic technique was used in all patients. Fentanyl (3 micrograms/kg/h), vecuronium bromide

TABLE 1. Distribution of ventricular septal defect patient types in two groups

Ventricular septal defect types	Group I	Group II
Outlet	9	10
Inlet	3	3
Subpulmonary	3	-
Double committed	-	2

(intubating dose 0.10 milligram/kg, a continuous infusion of 1 micrograms/kg/min) and inhalation agent (sevoflurane) were applied to the patients. However, vecuronium bromide was not applied to none of these two groups in last 45 minutes of the operation. Inhalation agent sevoflurane (%0.5-2) was used while the patient was on cardiopulmonary bypass. Inotropic drugs (dopamine hydrochloride, dobutamine hydrochloride, milrinone lactate) were given if necessary. Children undergoing surgical repair of ventricular septal defect were received low-dose fentanyl (0.5 micrograms/kg/h), during postoperative 12 hours.

Cardiopulmonary bypass technique

Standard non-pulsatile cardiopulmonary bypass was utilized, and the circuit primed with Plasmalyte A (Baxter Healthcare Corporation; Deerfield, IL, USA), and 1 unit of fresh-frozen plasma. Banked, packed red blood cells (PRBC) were added to achieve a hematocrit of approximately 28–30% during cardiopulmonary bypass. Moderate (27°C to 30°C) hypothermia was employed, and myocardial preservation was obtained with cold blood cardioplegia at 20 min. intervals. The pH-stat regimen was used during cooling, and alpha-stat for rewarming. Protamine was given at 0.6:1 protamine to heparin ratio. Blood product transfusions following cardiopulmonary bypass were administered as necessary to achieve satisfactory haemostasis and a target haematocrit of >30%. Standard transatrial or transventricular closure of the ventricular septal defect was employed in all patients. The ascending aorta is used for arterial cannulation. Bicaval cannulation is used for venous cannulation. In order to accomplish venting the heart, we introduce a vent catheter to the left atrium through the right superior pulmonary vein.

Postoperative care

Standardized postoperative care was provided. Postoperative monitoring included continuous registration of heart rate and rhythm, arterial blood pressure, central venous pressure, diuresis, and blood gases. Dopamine in the dose of 3-5 micrograms/kg/minute was given to the whole patients. However, high dose of dopamine (15 micrograms/kg/minute) during the first 24 hours of postoperative period was given to 2 and 1 patients with inlet ventricular septal defect in Group I and II respectively. Nitrogliserin with appropriate dose was given to the whole patients for peripheral vasodilatation. Furosemide infusion was given to the whole patients for 12 hours with the dose of 0.01 milligram/kg/hour. There were no postoperative infections observed. There were only two patients had urination difficulty temporarily however this was recovered short after. In this prospective study, physicians were not informed about steroid treatment to reduce variation in the extubation.

TABLE 2. Demographic characteristics of the patients

Variables	Grup I n: 15 Mean±SD	Grup II n: 15 Mean±SD	p
Age at operation, years	2.3±1.5	2.2±1.3	0.608 a
Sex (female/male)	7/8	6/9	0.565 b
Body weight, kg	14.1±8.3	13.8±5.6	0.601 a
Qp/Qs	2.25±0.65	2.30±0.76	0.700 a
CPB time, minute	90.2±42.2	75.3±33.7	0.465 c
Aortic cross-clampduration, minute	66.3±40.9	55.41±27.8	0.567 c
Duration of intubation, hours	6.1±2.4	10.6±3.4	0.001 c
Mean arterial blood pressure, mm Hg			
Pre TNF	61.8±18.3	73.8±17.1	0.805 a
Per TNF	36.8±14.4	43.6±16.2	0.451 a
Post TNF	87.6±13.6	85.9±18.2	0.860 a
Post 24h TNF	84.9±11.5	86.4±17.9	0.900 a
Heart rate, beats/min			
Pre TNF	98.7±16.4	96.4±11.7	0.650 a
Per TNF	-	-	
Post TNF	125.1±10.8	121.4±12.9	0.708 a
Post 24h TNF	107.5±19.9	110.5±16.8	0.654 a
Diuresis, mL/kg/h			
Pre TNF	2.4±1.9	2.1±2.1	0.576 c
Per TNF	4.4±2.2	3.1±1.8	0.431 c
Post TNF	3.6 ±3.5	3.8±4.0	0.545 c
Post 24h TNF	3.4±2.8	4.5±2.3	0.398 c
Duration in ICU	3±1	4±1	0.451 c
Duration in Hospital	6±2	7±2	0.384 c

SD: standart deviation; Qp/Qs: pulmonary/systemic flow ratio; TNF: tumor necrosis factor; CPB: cardiopulmonary bypass; ICU: intensive care unit a: T-test; b: Chi square test; c: Mann Whitney U test

TABLE 3. Mean tumor necrosis factor-alpha (TNF-α) levels of Group I and Group II at Periods

	Group I Median (Min-Max)	Group II Median (Min-Max)	p*
Pre TNF	0.6 (0.1-2.8)	0.75 (0-5)	0.318
Per TNF	1.4 (0.2-21)	6.2 (0-18)	0.770
Post TNF	0.6 (0.1-15)	6.95 (0.54-38)	0.003
Post 24h TNF	0.4 (0-6.6)	4.3 (0.1-25)	0.018
			Power=72.3%
p^{+}	0.009	0.003	

* Mann Whitney test; + Repeated Measurement Analysis

Laboratory tests

For the analyses of serum TNF-α, 2 mL of arterial blood samples (for each analysis) were transferred to the laboratory in biochemistry tubes and analysed by micro-enzyme-linked immunosorbent assay (ELISA) method.

Statistical analysis

Statistical analyses of data were performed by the Statistical Package for the Social Sciences version 19.0 (SPSS, Inc.; Chicago, IL, USA). Categorical variables were summarized as number and percentages, whereas continuous variables (such as time to extubation and total cross-clamp time) were summarized as mean standard deviation, median, and minimum-maximum, where appropriate.

The normality of distribution for continuous variables was confirmed with the One Sample Kolmogorov test. Multivariate repeated measures analysis was used to compare the changes in continuous variables over time (Pre TNF, Per TNF, Post TNF and Post 24h TNF). In addition to analysing the changes in repeated measurements within the group, this method also analyses the difference between repeated measurements. The study observed power was obtained as 72.3% Chi-square test was used for comparison of gender by groups. The Mann-Whitney U test was used for comparison of non-normally distributed data by groups. Thus, this test was not used to analyse the changes in time, it was only used to understand the differences of measurement values for two groups at any time period.

RESULTS

Demographic characteristics of the patients were given in Table 2. There were no significant statistically difference comparing the groups about variables such as age, sex, body weight, Qp/Qs, cardiopulmonary bypass time, aortic cross-clamp time, mean arterial blood pressure, heart rate, diuresis in Table 2. There was no significant difference between Groups I and II in terms of TNF-α levels at Pre TNF ($p=0.318$) and Per TNF ($p=0.800$) (Table 3). A significant difference was determined between Group I and II in terms of TNF-α levels at Post TNF ($p=0.003$). There was also a significant difference between Groups I and II in terms of TNF-α levels at Post24h TNF ($p=0.18$). As a result of repeated measures analysis, TNF-α level was increased initially then there was a decrease for both groups. These results were statistically significant. The significance level was set at $p<0.05$ for all tests.

The mean time to extubation for Group I and Group II is presented in Table 2. The mean time to extubation was 6.13±2.35 hours in Group I and 10.60±3.40 hours in Group II. A significant difference was found between the groups in terms of mean time to extubation ($p=0.001$).

There was no difference between both groups statistically about length of stay at the hospital ($p=0.384$), although significant difference was found between two groups in terms of mean time to extubation ($p=0.001$).

There was a change in TNF α measurements for group I and II over time in the range of 0.009 and 0.003 respectively. TNF α measurements at per operative has the highest amongst others for group I, whereas per op and post op TNF alfa in group II significantly higher than others.

DISCUSSION

Cytokines consist of group of polypeptides derived by various cell types. There is an increasing attention on the functions of cytokines as a metabolic mediator. The cytokine response of patients operated cardiac surgery during cardiopulmonary bypass is well understood and managed by the proinflammatory cytokines IL-6, TNF-α and IL-8 and the anti-inflammatory cytokine IL-l0. The main source of these cytokines at cardiac ischemia during cardiopulmonary bypass is the myocardium. The occurrence of proinflammatory cytokines as a result of cardiopulmonary bypass increases the risk of harmful effects of cardiopulmonary bypass for myocardium. These mechanisms have strong relationship with ischemia-reperfusion of the myocardium and also other organs (14).

Contact of blood with artificial surfaces of the extracorporeal circuit, ischemia-reperfusion injury, and release of endotoxin cause an inflammatory response in cardiopulmonary bypass. This inflammation process activates various systems such as, free radicals by polymorphonuclear neutrophils, leucocytes, and endothelial cells with secretion of cytokines, arachidonic acid metabolites and proteases. This inflammatory response plays an important role in major organ dysfunction (15).

Corticosteroids application to the children undergoing congenital heart surgery to reduce the inflammatory response after cardiopulmonary bypass is still a controversial process within the literature (16). Cardiopulmonary bypass is known to result in the release of inflammatory mediators, such as cytokines, by causing complement and leukocyte activation (17,18). These mediators contribute to pulmonary and cardiac dysfunctions developed after cardiac surgery (19). The present study demonstrated that TNF-α levels were increased after two hours of the termination of the cardiopulmonary bypass with patients who did not receive steroid preoperatively and showed a peak at Post TNF-α Moreover, increases in the plasma levels were observed to continue at the postoperative 24th h. TNF-α is a primary mediator of septic shock and is released from activated monocytes and macrophages. TNF-α is known to cause fever, tachycardia, hypotension and increase in microvascular permeability. Additionally, TNF-α has impacts on the multiple organ failure and myocardial dysfunction and its release is enhanced during cardiopulmonary bypass procedure due to ischemia-reperfusion, endotoxin release, and complement activa-

tion (20). In the present study, TNF-α level was observed to be lower at patients who received steroid preoperatively as compared to other Group, and the duration of mechanical ventilatory support was shorter in received steroid Group. Systemic inflammatory response is triggered by cardiac and pulmonary reperfusion rather than cardiopulmonary bypass itself. Indeed, leukocytes are known to accumulate in coronary and vascular beds during cardiac procedures performed under cardiac arrest (21,22). Additionally, adhesion and activation of leukocytes are facilitated due to stationary blood flow. Removal of aortic cross-clamp leads activated leukocytes to permeate to the organs through the systemic circulation and thus systemic inflammatory response occurs. Cardiac surgery is associated with endotoxemia and a marked inflammatory response. Therefore, endotoxin must be regarded as a pathophysiologic mediator. The endotoxin levels were higher after induction of anaesthesia, immediately after the start of cardiopulmonary bypass and after release of the cross-clamp (23). However in our study in group 2 at the second and third period also shows significant change of inflammatory mediators. Additionally in third period (post TNF-α) statically significant p (0.003).

Systemic inflammation and mechanical ventilatory support are known to potentiate the effects of each other (24). Short extubation avoids; i) the effects of positive pressure ventilation on the cardiopulmonary surgery, ii) ventilator-acquired pneumonias, iii) patient or parental stress in children, relative to long extubation (25).The present study, a significant difference was determined between both groups I and II in terms of time to extubation, which indicated that time to extubation postoperatively was significantly shortened with the preoperative steroid use. Based on this result, we believe that preoperative steroid use may shorten duration of entubation time.

In the current study, we concluded that preoperative steroid use might prevent potential changes in TNF-α level and minimize respiratory problems likely to develop in the postoperative period.

In conclusion, there is a strong indication that preoperative steroid use shortens duration of postoperative intubation and positively contributes to extubation in ventricular septal defect patients undergoing cardiac surgery with cardiopulmonary bypass. Additionally, this process is more closely associated with suppressing at the postoperative period TNF-α level which are inflammatory mediators.

Limitations

Complex heart disease or excessive pulmonary hypertension cases are excluded in this study. It is clear that various studies which include complex cases are needed to evaluate the effects of Steroid. The steroid response could better evaluate with other inflammatory markers in larger groups.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University School of Medicine.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - H.H.P., Z.D.; Design - Ş.D., M.K.A.; Supervision - Ş.D., M.K.A.; Resource - M.K.A., A.A., B.Ç.; Materials - A.A., B.Ç.; Data Collection and/or Processing - M.K.A., A.A., B.Ç.; Analysis and/or Interpretation - A.A., B.Ç.; Literature Search - H.H.P., Z.D.; Writing - İ.B., F.T., H.H.P.; Critical Reviews - H.H.P., Z.D., Ş.D.

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