The Effect of Perioperative and Postoperative Theophylline Administration on Inflammation in Patients Undergoing Pediatric Open-Heart Surgery

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ABSTRACT

Introduction: The aim of this study was to evaluate the effects of intraoperative and postoperative theophylline infusion on inflammation in children who underwent open heart surgery with cardiopulmonary bypass (CPB) for congenital heart diseases.

Patients and Methods: This randomized controlled study was carried out with 140 children who underwent open heart surgery with CPB in a tertiary hospital. The patients were randomly enrolled into two groups (theophylline group= 70, control group= 70). Following the induction of anesthesia, theophylline infusion was applied to theophylline recipients from the beginning of the operation to the end of the 24th hour after surgery via a central venous catheter (CVC). The patients in the control group were infused with 0.9% NaCl solution at the same volume and duration via CVC.

Results: Postoperative red blood cell distribution width was significantly higher than preoperative values in the theophylline group (p= 0.003), but no significant difference was found in the control group (p= 0.188). In both groups, postoperative vasoactive-inotropic scores, and lymphocyte and platelet counts were lower than preoperative measurements (p< 0.001 for each in both groups). While preoperative white blood cell counts were similar, postoperative values were found to be lower in the theophylline group (p= 0.022).

Conclusion: In pediatric patients undergoing open heart surgery with CPB, the use of intraoperative and postoperative theophylline may be effective in reducing postoperative inflammation, as demonstrated by lower white blood cell counts; but it does not significantly affect other clinical features.

Key Words: Child; heart surgery; inflammation; theophylline.

Pediatrik Açık Kalp Cerrahisi Yapılan Hastalarda Perioperatif ve Postoperatif Teofilin Uygulamasının İnflamasyon Üzerine Etkisi

ÖZ

Giriş: Bu çalışmanın amacı, konjenital kalp hastalıkları nedeniyle kardiyopulmoner baypas (KPB) ile açık kalp cerrahisi yapılan çocuklarda intraoperatif ve postoperatif teofilin infüzyonunun inflamasyon üzerine etkilerini değerlendirmektir.

Hastalar ve Yöntem: Bu randomize kontrollü çalışma, üçüncü basamak bir hastanede KPB ile açık kalp ameliyatı geçiren 140 çocuk üzerinde gerçekleştirildi. Hastalar rastgele iki gruba alındı (teofilin grubu= 70, kontrol grubu= 70). Anestezi indüksiyonunu takiben teofilin alan kişilere operasyonun başlangıcından ameliyat sonrası 24. saatin sonuna kadar santral venöz kateter (SVK) ile teofilin infüzyonu uygulandı. Kontrol grubundaki hastalara aynı hacim ve sürede %0.9 NaCl solüsyonu SVK ile infüze edildi.

Bulgular: Postoperatif kırmızı kan hücre dağılım genişliği teofilin grubunda preoperatif değerlere göre anlamlı olarak yüksek bulunmuştur (p= 0.003), ancak kontrol grubunda anlamlı fark bulunmamıştır (p= 0.188). Her iki grupta da postoperatif vazoaktif-inotropik skorlar, lenfosit ve trombosit sayıları preoperatif ölçümlerden daha düşük saptanmıştır (her iki grupta p< 0.001). Preoperatif beyaz küre sayıları benzer iken teofilin grubunda postoperatif değerler daha düşük bulunmuştur (p= 0.022).

Sonuç: Kardiyopulmoner baypas ile açık kalp cerrahisi geçiren pediatrik hastalarda intraoperatif ve postoperatif teofilin kullanımı, düşük beyaz kan hücresi sayımlarının gösterdiği gibi postoperatif inflamasyonu azaltmada etkili olabilir; ancak diğer klinik özellikleri önemli ölçüde etkilemez.

Anahtar Kelimeler: Çocuk; inflamasyon; kalp ameliyatı; teofilin.

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INTRODUCTION

Cardiopulmonary bypass (CPB) and cardiac surgery trigger a strong systemic inflammatory response characterized by early and late stages[1]. In these patients, inflammation occurs through both humoral and cellular pathways, including activation of thrombins, complements, cytokines, neutrophils, adhesion molecules, mast cells and multiple inflammatory mediators[2].

The inflammatory response associated with cardiac surgery is largely due to operative trauma including surgery, CPB, and organ reperfusion injury[3]. Although the biocompatibility of CPB circuits have been improved (e.g., heparin coated surfaces etc.), they still cause foreign matter reactions in the circulation, thereby leading to inflammatory activation. The most prominent adverse reaction caused by contact of blood with the air and CPB circuit is the systemic inflammatory response syndrome, which is characterized by hyperpermeability of blood vessels, fever, increase (or decrease) in leukocytes, and abnormal clotting. The pump, artificial lung, cannula, suction and ventilation circuit can also exert shear stress on blood cell components, further exacerbating the inflammatory reaction[4].

The circulatory system of pediatric patients is immature compared to adult patients, and therefore, the effects of systemic inflammatory response caused by hypothermia, circulatory changes, hemodilution, impaired acid-base balance and extracorporeal circulation after cardiac surgery are much greater[4]. Any intervention to reduce or prevent inflammation is of great importance in these patients. Therapeutic strategies used for the prevention of post-CPB inflammation include the modulation of various aspects of inflammatory response, such as coagulation, contact activation, cytokines, neutrophils, intracellular molecular targets and surface proteins[2]. Methylprednisolone has been reported to be effective in reducing inflammation in children who have undergone open heart surgery[5]. Kerbaul et al. reported that high expression of A2A adenosine receptor may be a predictive factor for severe postoperative SIRS after CPB[6]. According to the previously reported research results on theophylline, a non-selective adenosine receptor antagonist, it is well-established that theophylline exerts anti-inflammatory effects through various mechanisms in patients with asthma and chronic obstructive pulmonary disease (COPD)[7-12]. Due to the fact that inflammation is a primary cause of morbidity and mortality in patients undergoing cardiac surgery with CPB, it is important to evaluate the effect of theophylline in reducing inflammation these patients. To date, there have been no studies focusing on this subject in the literature.

The aim of the study was to investigate the effects of intraoperative and postoperative theophylline infusion on inflammation in children who underwent open heart surgery with CPB for congenital heart disease.

PATIENTS and METHODS

This research is a randomized controlled study conducted in Kartal Koşuyolu High Specialization Training and Research Hospital at 2021. The research protocol in line with the Helsinki Declaration was approved by the Clinical Research Ethics Committee of Kartal Koşuyolu High Specialization Training and Research Hospital (Decision no: 2021/1/412, Date: 12.01.2021).

The research group consisted of 140 children aged 1-60 months who were scheduled for open heart surgery using CPB due to having a diagnosis of congenital heart disease. The congenital heart disease diagnoses evaluated in the study were ventricular septal defect (VSD), atrial septal defect (ASD), tetralogy of fallot (TOF), pulmonary stenosis (PS), partial anomalous pulmonary venous drainage (PAPVD), mitral stenosis and tricuspid regurgitation. Patients with an ejection fraction (EF) of at least 65%, placement of cross-clamp on the aorta during surgery and underwent complete correctional surgery were included in the study group, given that they were classified as < 3 by the Risk Adjustment for Congenital Heart Surgery (RACHS-1) categorization system.

The exclusion criteria were: Having an EF less than 65%, having liver/kidney failure, being in the neonatal period (0-21 days), having a history of drug allergy, epilepsy or arrhythmia, having an indication for emergency operation, and needing postoperative extracorporeal membrane oxygenator (ECMO) use.

Patients were randomly divided into two groups, the theophylline and control group. In the theophylline group, theophylline infusion (0.3 mg/kg/hr for those aged 1-6 months, 0.5 mg/kg/hr for those aged > 6-60 months) was applied to 70 patients after the induction of anesthesia via a central venous catheter (CVC) until the end of the 24th hour after the operation. All patients were followed and monitored within the intensive care unit (ICU) for at least 72 hours after surgery. No adverse effects were observed in any patient during the theophylline infusion process. The patients in the control group (n= 70) were infused with 0.9% NaCl solution at the same volume via CVC, from pre-operation to the end of the 24th hour postoperatively. Any patients that could not be followed or monitored for the planned duration, those with loss of recorded data, and individuals who refused to participate in the study at any time were excluded from the final analyses. A total of 51 patients (26 from the theophylline group and 25 from the control group) were excluded with respect to these conditions, and therefore, the final analyses were performed on 44 patients in the theophylline group and 45 patients in the control group.

After the parents of the patients were given detailed information about the purpose and scope of the study, written informed consent was obtained from those who agreed to participate in the study.

Before the surgery, detailed routine physical examinations of the children undergoing cardiac surgery were performed and their height and body weight were measured with standard measuring instruments. During the evaluation of body weight, the children's clothes and diapers, if any, were removed, and measurements were taken horizontally in young children and while standing in older children. While the height was evaluated, children between 0-2 years old were laid on a flat surface without shoes and measured in a flat position. The height of the older children was measured by placing them in an upright position without shoes on a flat surface. The blood biochemistry analysis results, including inflammation markers, hemogram values and vasoactive inotrope score (VIS) scores of patients in the theophylline and control groups were measured and recorded before and at the 24th hour after the surgery. In addition, sociodemographic data of the children, detailed blood tests, aortic cross-clamp time, total bypass time, RACHS-1 category, intensive care stay, hospital stay and extubation times were recorded.

The risk assessment of the patients in the study group was made with RACHS-1, which is widely used in the evaluation of prognosis and mortality in patients undergoing cardiac surgery. The RACHS-1 classifies patients into 6 categories according to the type of surgical procedure to be performed. The higher the category level, the higher the risk of mortality and morbidity[13].

Vitals, complete blood count [hemoglobin, white blood cell count (WBC), platelet count, neutrophil count, lymphocyte count, red blood cell distribution weight (RDW)], biochemistry analyses [C-reactive protein (CRP), lactate dehydrogenase (LDH)], and liver function tests [aspartate transaminase (AST), alanine transaminase (ALT)] were measured pre-operatively and postoperatively via routine methods in the laboratory.

The inotropic drugs used by the children were recorded together with their doses, and the VIS values of each patient were calculated based on the following formula: VIS= Dopamine dose (μg/kg/min) + Dobutamine dose (μg/kg/min) + 100 x Adrenaline dose (μg/kg/min) + 10 x Milrinone dose (μg/kg/min) + 10000 x Vasopressin dose (unit/kg/min) + 100 x Noradrenaline dose (μg/kg/min)[14].

The primary outcome of the study was the effect of theophylline on inflammation parameters, and the secondary outcomes were drawn by the determination of the effects of theophylline on other clinical features.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check of continuous data, the Shapiro-Wilk test was used. Data are given as mean ± standard deviation (SD) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed between study groups with the independent samples t-test. Non-normally distributed variables were analyzed with the Mann-Whitney U test. In the comparison of pre- and post-operative data (repeated or paired results), normally distributed variables were analyzed with the two-way repeated measures analysis of variance (ANOVA) test; whereas non-normally distributed variables were analyzed with the Wilcoxon Signed Ranks test. Categorical variables were evaluated using Chi-square tests, including Pearson's chi-squared test and Fisher's exact test. $p< 0.05$ values were accepted to be statistically significant.

RESULTS

The median age of the children in the study group was 8 (5-41) months, 48 (53.9%) were boys and 41 (46.1%) were girls. The frequency of boys was higher in the control group (p= 0.015). The theophylline and control groups were similar in terms of age (p= 0.511), body weight (p= 0.967), height (p= 0.579), type of surgical method applied (p= 0.179), RACHS-1 category distribution (p= 0.067), CPB duration (p= 0.546), aortic cross-clamp time (p= 0.396), extubation time (p= 0.503), hospitalization time (p= 0.643), duration of stay in the ICU (p= 0.162), and the frequencies of VSD (p= 0.245), TOF (p= 0.066), PS (p= 0.414), PAPVD (p= 0.570), mitral stenosis (p= 0.309) and tricuspid regurgitation (p= 0.309). The frequency of children diagnosed with ASD was significantly higher in the theophylline group (Table 1).

The preoperative and postoperative values for heart rate, lactate, CRP, LDH, hemoglobin, neutrophil, lymphocyte and platelet levels were found to be similar. ALT (p= 0.012), AST (p= 0.007), VIS score (p= 0.035) and RDW (p= 0.014) were significantly lower in the theophylline group compared to controls in the preoperative period; however, postoperative values were similar between the groups. The mean postoperative WBC was found to be significantly lower in the theophylline group, and the preoperative WBC levels were similar between the groups (p= 0.022) (Table 1, Figure 1).

The postoperative values of heart rate, lactate, CRP, AST, LDH, WBC and neutrophil were significantly higher in both the theophylline group and the control group compared to their preoperative values ($p< 0.001$ for each in both groups). The postoperative RDW level was significantly higher in the theophylline group compared to the preoperative level (p= 0.003), but no significant difference was found in the control group (p= 0.188). The postoperative VIS, lymphocyte and platelet levels were significantly lower than preoperative values in both groups ($p< 0.001$ for each in both groups). There was no difference between the preoperative and postoperative levels of ALT and hemoglobin in neither group (Table 2).

Table 1. Summary of the patients' characteristics with regard to groups

	Theophylline (n= 44)	Control (n= 45)	All (n= 89)	p
Gender				
Boy	18 (40.9%)	30 (66.7%)	48 (53.9%)	**0.015**
Girl	26 (59.1%)	15 (33.3%)	41 (46.1%)	
Age (month)	7 (5-28.5)	9 (6-12)	8 (5-41)	0.511
Weight (kg)	7.38 (5.1-12.5)	7.75 (6-10)	7.5 (5.6-39)	0.967
Height (cm)	65 (62-86.5)	67 (62-76)	66 (62-63)	0.579
Diagnosis				
VSD	22 (50%)	17 (37.8%)	39 (43.8%)	0.245
TOF	5 (11.4%)	12 (26.7%)	17 (19.1%)	0.066
ASD	13 (29.5%)	3 (6.7%)	16 (18%)	**0.005**
PS	2 (4.5%)	4 (8.9%)	6 (6.7%)	0.414
PAPVD	1 (2.3%)	2 (4.4%)	3 (3.4%)	0.570
Mitral stenosis	1 (2.3%)	0 (0%)	1 (1.1%)	0.309
Tricuspid regurgitation	1 (2.3%)	0 (0%)	1 (1.1%)	0.309
Surgery				
Complete correction	37 (84.1%)	43 (95.6%)	80 (89.9%)	0.179
VSD closure	6 (13.6%)	2 (4.4%)	8 (9%)	
ASD closure	1 (2.3%)	0 (0%)	1 (1.1%)	
RACHS-1 score				
1	8 (18.2%)	2 (4.4%)	10 (11.2%)	0.067
2	35 (79.5%)	43 (95.6%)	78 (87.6%)	
3	1 (2.3%)	0 (0%)	1 (1.1%)	
CPB time (min)	78 (63-120.5)	90 (70-105)	83 (65-194)	0.546
Aortic cross-clamp time (min)	59 (37-91)	66 (45-90)	62 (43-149)	0.396
Extubation time (h)	6.75 (4-18.5)	8 (4-20)	7 (4-24)	0.503
Length of stay in the ICU (h)	21 (3-40.5)	4 (3-24)	6 (3-142)	0.162
Time of discharge (day)	8 (6.5-10)	8 (7-11)	8 (7-15)	0.643

ASD: Atrial septal defect, CPB: Cardiopulmonary bypass, PAPVD: Partial anomalous pulmonary venous drainage, PS: Pulmonary stenosis, RACHS: Risk adjustment for congenital heart surgery, TOF: Tetralogy of Fallot, VSD: Ventricular septal defect.
Data are given as median (1st quartile-3rd quartile) for continuous variables and frequency (percentage) for categorical variables.

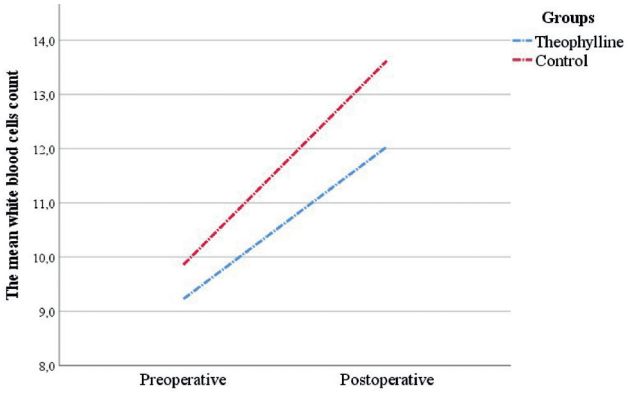

Figure 1. The mean white blood cells count with regard to groups.

DISCUSSION

Inflammation that occurs after pediatric cardiac surgery is independently associated with postoperative morbidity and this inflammatory process may further impair lung, myocardium, kidney, liver, intestine and brain functions[15,16]. In the present study, we evaluated the effect of peri- and post-operative theophylline infusion on inflammation associated with heart surgery.

Theophylline, a non-selective adenosine receptor antagonist, is a drug derived from methylxanthine (a purine derivative) that has various effects on various parts of the body. The known mechanisms of action of theophylline include elevation of intracellular cAMP concentration, activation of protein kinase A, inhibition of TNF-alpha and leukotriene synthesis, and non-selective inhibition of phosphodiesterase (type III and type IV phosphodiesterase inhibitor), prevention of the translocation of the proinflammatory transcription factor to the nucleus by inhibiting nuclear factor-kappaB, reduction of the expression of inflammatory genes, stimulation of the secretion of interleukin-10 (which has anti-inflammatory effects), activation of histone deacetylase 2 by inhibiting phosphoinositide 3-kinase-

Table 2. Summary of the measurements with regard to groups

	Theophylline (n= 44)	Control (n= 45)	p[a]
Heart rate (pulse/min)			
Preop	128 (113-130)	128 (124-131)	0.662
Postop	140 (130-146.5)	141 (132-152)	0.339
p[b]	< 0.001	< 0.001	
Lactate			
Preop	1.2 (0.95-1.5)	1.2 (1-1.5)	0.924
Postop	2.65 (2-3.4)	2.95 (1.8-3.85)	0.602
p[b]	< 0.001	< 0.001	
CRP			
Preop	3.1 (3.1-3.11)	3.1 (3.1-3.11)	0.474
Postop	30.3 (25-43.7)	30 (25-41)	0.908
p[b]	< 0.001	< 0.001	
ALT			
Preop	15.25 (14-20)	19 (16-21.6)	**0.012**
Postop	18 (15-22)	18.3 (17-22)	0.408
p[b]	0.060	0.721	
AST			
Preop	32.5 (28.5-44)	42 (35-51)	**0.007**
Postop	159 (111.5-221.5)	165 (139-218)	0.574
p[b]	< 0.001	< 0.001	
LDH			
Preop	307.5 (280-353)	328 (283-364)	0.094
Postop	663 (541.5-780)	658 (572-750)	0.967
p[b]	< 0.001	< 0.001	
VIS			
Initial	10 (5.5-13)	13 (10-13)	**0.035**
24th hour	7.5 (4-10)	10 (5-10)	0.345
p[b]	< 0.001	< 0.001	
WBC			
Preop	9.23 ± 1.78	9.86 ± 1.85	0.104
Postop	12.03 ± 2.93	13.62 ± 3.47	**0.022**
p[b]	< 0.001	< 0.001	
Hemoglobin			
Preop	12.05 (11.3-12.8)	12 (11-13)	0.831
Postop	12 (11.1-13)	11.6 (11-13)	0.492
p[b]	0.902	0.139	
Neutrophil			
Preop	2.7 (1.82-3.7)	2.2 (1.7-3.2)	0.209
Postop	8.6 (7-12.6)	8.9 (7.3-10.3)	0.931
p[b]	< 0.001	< 0.001	
Lymphocyte			
Preop	4.85 (3.2-6.35)	5.5 (3.7-7.1)	0.185
Postop	1.6 (0.95-2.2)	1.5 (1.1-2.2)	0.702
p[b]	< 0.001	< 0.001	
RDW			
Preop	13.6 (13.15-14.55)	14.7 (13.4-15.8)	0.014
Postop	14.3 (13.9-15.2)	14.9 (14-15.9)	0.197
p[b]	0.003	0.188	
Thrombocyte			
Preop	337 (288 - 433)	345 (299 - 407)	0.990
Postop	149.5 (106 - 201)	169 (108 - 203)	0.799
p[b]	< 0.001	< 0.001	

[a] Between groups, [b] Within group.
VIS: Vasoactive inotrope score.
Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and frequency (percentage) for categorical variables.

delta, and stimulation of the apoptosis of inflammatory cells (T cells, neutrophils)[9]. It has been reported that theophylline inhibits the proliferation of CD4 + and CD8 + lymphocytes and the chemotactic response of T lymphocytes, and reduces the neutrophil ratio in bronchoalveolar lavage in patients with asthma and COPD[17]. In the study of Finnerty et al., it was reported that theophylline exerts anti-inflammatory effects related to both bronchial cell number and IL-4 expression in asthma patients[7]. Mascali et al. reported that the production of IL-10 is increased by theophylline, and thus, inflammation can be alleviated[18]. In another study, 4 weeks of theophylline treatment was reported to alleviate neutrophil-associated inflammation in the airways of patients with mild to moderate COPD[8]. In our literature review, we could not identify any studies evaluating the effect of theophylline on inflammation after cardiac surgery, and thus, direct comparisons to our research cannot be performed. In previous studies, the effects of aminophylline, another adenosine receptor antagonist, on prevention of acute kidney injury associated with cardiac surgery was evaluated, but no evaluation was made on its effect on inflammation[19-21]. In the current study, postoperative WBC in the theophylline group was found to be significantly lower than in the control group. A less-researched source of cardiac surgery-related inflammatory response is inflammation due to the presence of preoperative cardiovascular or other diseases[3]. In this context, the differences we found in preoperative VIS, ALT and AST levels between the groups may have influenced our conclusion on the effect of theophylline on inflammation. Although no significant difference was found in terms of other important inflammation parameters, such as CRP, the difference found for WBC shows that theophylline may be effective in reducing inflammation in children undergoing cardiac surgery with CPB.

Since the circulatory system is not as developed as adult patients in the childhood, the hemodynamics of each patient can vary greatly depending on the disease, age and anatomical features, and these differences may also extend to the post-operative period[4]. As a result of decreased blood flow during cardiac surgery with CPB, physiological balance disorders can occur, including temperature fluctuations, low hematocrit levels, non-pulsatile perfusion and susceptibility to end organ dysfunction[22]. Factors such as the child's body weight, corrected gestational age, maturation level of the hemostatic system, morphological diagnosis, systemic and pulmonary vascular resistance balance, the degree of hemodilution and hemostatic changes caused by surgery and CPB, and the duration and complexity of the surgical procedure are determinants of bleeding risk and transfusion requirement during cardiac surgery[23]. In the present study, pre-operative and post-operative values of hemoglobin were similar between the theophylline and control groups. The preventive measures taken during the operation, as well as transfusion administrations, may have been effective in keeping the hemogram values of the patients stable.

It is well established that RDW (together with ferritin) is primarily used for its distinct ability in diagnosis of iron deficiency anemia[24]. On the other hand, in the study of Jo et al., RDW was reported to be associated with 28-day mortality in patients with severe sepsis and septic shock[25]. In another previous study, it was reported that RDW increase in patients with gram-negative bacteremia was an independent predictor of mortality[26]. In a research evaluating children who underwent cardiac surgery, it was reported that there was an independent relationship between elevated RDW and mortality[27]. In the current study, RDW level in the theophylline group was found to be significantly higher in the postoperative measurement than the preoperative measurement, while no significant change was observed in the control group. The reason for the difference in the alteration of RDW between the two groups may be that the pre-operative RDW value was found to be higher in the control group. However, considering the above-mentioned studies and our results, we believe it would be valuable to further assess the possible role of RDW in this population.

Based on data showing that inflammation is reduced with the use of theophylline in patients with asthma and COPD, it was predicted that theophylline may have effects that reduce length of stay in the hospital or the ICU when administered to pediatric recipients of cardiac surgery with CBP[7,17]. In the study by Shahbazi et al., it was reported that the use of aminophylline resulted in shorter ICU stay and earlier extubation[28]. In the current study, the theophylline and control groups were found to be similar in terms of hospital stay and ICU stay. The fact that there was no difference between groups in terms of inflammatory parameters other than WBC may be one of the reasons for this result.

This study has some limitations. Despite randomization, the differences in the diagnosis of congenital heart diseases and gender distribution between the two groups may have affected the results of the study by causing heterogeneity between the groups. Also, the current study has been conducted at a single center with a small number of patients, which may have reduced the analysis power of the study, particularly with respect to clinical outcome parameters. Another limitation was the inability to obtain results regarding important inflammatory markers such as procalcitonin, erythrocyte sedimentation rate and brain natriuretic peptide. In relation, the lack of longer-term evaluation of the parameters measured in the study may be noted as a limitation. Despite demonstrating a reduction in WBC level with theophylline application, we neither assessed different doses of theophylline nor other treatment options used to prevent intraoperative or postoperative inflammation. However, considering the lack of data on this topic, this study is valuable in that it is the first study evaluating the effects of theophylline on inflammation in pediatric cardiac surgery performed with CPB.

CONCLUSION

The postoperative WBC value, which is one of the important markers of inflammation in children who undergo cardiac surgery with CPB, was lower in recipients of theophylline compared to those in the control group. Although no significant difference was found between the groups in terms of other inflammation parameters and clinical features, it can be said that theophylline reduced postoperative inflammation by reducing WBC. In addition, the absence of any adverse effects related to theophylline indicates that theophylline infusion can be used safely in children undergoing cardiac surgery. However, the close monitoring should be applied during post-operative period in terms of possible adverse events. In order to achieve better results with theophylline as a targeted potential therapeutic approach to reduce inflammation in children undergoing cardiac surgery with CPB, it will be critical to determine optimal dosage and duration of administration in future studies. More comprehensive research is needed on the effects of theophylline in children undergoing cardiac surgery with CPB.

Ethics Committee Approval: The research protocol in line with the Helsinki Declaration was approved by the Clinical Research Ethics Committee of Kartal Koşuyolu High Specialization Training and Research Hospital (Decision no: 2021/1/412, Date: 12.01.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - YY, SA; Analysis/Interpretation - YY, AY; Data Collection - FI, YY; Writing - YY, FG; Critical Revision - AY, FG; Final Approval - YY, SA, AY, FI, FG; Statistical Analysis - FG, AY; Overall Responsibility - YY.

Conflict of Interest: The authors have no conflicts of interest to declare

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