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Original Article

The Anti-Inflammatory and Antioxidant Effects of Propofol and Sevoflurane in Children With Cyanotic Congenital Heart Disease

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Objective: The authors aimed to compare the anti-inflammatory and antioxidant effects of propofol and sevoflurane in children with cyanotic congenital heart disease (CCHD) undergoing cardiac surgery with cardiopulmonary bypass.
Design: Prospective, randomized, double-blind study.
Setting: Single center, university hospital.
Participants: Children ages 1-10 years with CCHD undergoing elective cardiac surgery with cardiopulmonary bypass.
Interventions: Children were randomized to receive general anesthesia with either sevoflurane (group S) or propofol (group P). Systemic inflammatory response syndrome (SIRS) occurrence was assessed at the end of the surgery and at the sixth, 12th, and 24th postoperative hours. Blood samples were obtained at 4 times: after anesthesia induction (T0), after release of the aortic cross-clamp (T1), at the end of the surgery (T2), and at the postoperative 24th hour (T3). The serum levels of interleukin 6 and tumor necrosis factor alpha, and the total antioxidant status (TAS) and total oxidant status, were analyzed.
Results: SIRS was more common in group S than in group P at all times ($p = 0.020$, $p = 0.036$, $p = 0.004$, $p = 0.008$). There were no significant differences between the groups in the mean tumor necrosis factor alpha and interleukin 6 levels at any time. The TAS level at T2 was higher in group P than group S ($p = 0.036$). The serum TAS level increased at T2 compared with T0 in group P, but it decreased in group S ($p = 0.041$).
Conclusion: The results showed that propofol provided a greater antioxidant effect and reduced SIRS postoperatively more than sevoflurane in children with CCHD undergoing cardiac surgery.
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Key Words: child; congenital heart disease; sevoflurane; intravenous agents

SYSTEMIC INFLAMMATORY response syndrome (SIRS) has been defined as a nonspecific systemic inflammatory process determined by clinical parameters. Cardiac surgery with cardiopulmonary bypass (CPB) is a primary activator of SIRS because the patient's blood contacts the nonbiocompatible circuit, and there is ischemia-reperfusion injury (IRI) and endothelial cell activation.[1] This response includes the activation of leukocytes and, subsequently, inflammatory mediators, such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α).[1] These mediators lead to fever, vasodilation, an increase in microvascular permeability, the occurrence of interstitial edema, and an increase in total body oxygen

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consumption, which are the components of the systemic inflammatory response. Furthermore, neutrophil activation and IRI during CPB play central roles in the production of reactive oxygen species (ROS). An imbalance between ROS and the antioxidant capacity of the body results in oxidative stress, which leads to lipid, protein, and DNA damage.[2]

The CPB-induced inflammatory response and oxidative stress are associated with postoperative complications, which can delay the recovery of patients and result in multiorgan failure and increased postoperative morbidity and mortality. Pediatric patients undergoing cardiac surgery are more vulnerable to inflammation than adults because of their smaller circulating plasma volume and immature organs.[3] In addition, congenital heart diseases are associated with a decrease in the myocardial antioxidant capacity, and CPB also can consume the plasma antioxidant capacity.[2] Children with cyanotic congenital heart disease (CCHD) are more susceptible to an inflammatory response due to hypoxemia, a deficiency in their defense mechanisms, circulation disorders, and the complex cardiac defect.[2] Furthermore, previous studies have shown that cyanotic patients have significantly higher levels of inflammatory cytokines and lower levels of myocardial antioxidant capacity than acyanotic patients.[2,4,5]

Recent evidence indicates that the cytoprotective effect of sevoflurane in different organs during cardiac surgery is associated with the suppression of inflammatory cytokines.[6] Similarly, propofol decreases the production of inflammatory cytokines and has a protective antioxidant effect on the myocardium by decreasing IRI.[7] In previous studies, propofol and sevoflurane have been compared in pediatric and adult patients undergoing cardiac surgery, but the results were conflicting.[8,9] In addition, there have been no adequate studies investigating the effect of anesthetics on laboratory biomarkers and clinical parameters of SIRS in a frail group of children with CCHD undergoing cardiac surgery with CPB. In this study, the authors aimed to compare the anti-inflammatory and antioxidant effects of propofol and sevoflurane in children with CCHD undergoing cardiac surgery with CPB.

Methods

This prospective, randomized, controlled study was approved by the Çukurova University's Institutional Review Board (approval number: 113/7), and written informed consent was obtained from the parents and participating children of an appropriate age in the trial. The trial was registered before patient enrollment at clinicaltrials.gov (NCT04125550, Date of registration: 07/09/2019). Children aged 1-to-10 years old with an American Society of Anesthesiologists physical status class II or III, undergoing cardiac surgery with CPB for CCHD, were included in the study. Patients with liver or renal dysfunction, hemostatic disorders, inflammatory disease, or preoperative use of anti-inflammatory drugs were excluded.

Clinical Data

The authors recorded the following demographic and clinical data: age, sex, body weight, diagnosis of congenital anomaly, intensive care unit (ICU) and hospital length of stay (LOS), the time to extubation, the vasoactive−inotropic score (VIS),[10] and mortality. The Risk Adjusted Classification for Congenital Heart Surgery (RACHS1) was used to categorize the surgery.[11] Intraoperative data included the duration of surgery, CPB, and aortic cross-clamp (ACC) times, the lowest body temperature reached during CPB, and the amount of cardioplegia. The authors also recorded the consumption of crystalloid fluid and the volume of blood products given intraoperatively and for 24 hours postoperatively.

Anesthesia, Surgical, and Postoperative Management

All children received 0.5 mg/kg of midazolam orally as a premedication 1 hour before anesthesia. In the operating room, standard American Society of Anesthesiologists monitoring was applied, with a 5-lead electrocardiogram, noninvasive blood pressure, pulse oximetry, end-tidal CO_2, central temperature, bispectral index, near-infrared spectroscopy, and urinary catheter. After anesthesia induction and endotracheal intubation, an arterial line and a central venous catheter were inserted.

The enrolled children were subsequently randomized into 2 groups using a computer-generated random number table as follows:

Group S: Sevoflurane inhalation (2%-8%), 5 μg/kg of fentanyl, and 0.6 mg/kg of rocuronium as a muscle relaxant were used for anesthesia induction. Then, 2% sevoflurane inhalation and 5 μg/kg/h fentanyl infusion were administered for maintenance of anesthesia. At the start of CPB, sevoflurane inhalation was replaced with a constant concentration of 2% sevoflurane using an anesthetic vaporizer (Draeger Vapor Version 19.3 and Version 2000) via the oxygenator fresh gas supply. At the end of CPB, anesthesia was maintained with inhalation of 2% sevoflurane again.

Group P: A dose of 2-to-3 mg/kg of propofol, fentanyl 5 μg/kg, and rocuronium 0.6 mg/kg were used for anesthesia induction. Then, a 10 mg/kg/h propofol infusion and 5 μg/kg/h fentanyl infusion were administered for the maintenance of anesthesia during the intraoperative period.

Children were ventilated to maintain an arterial pCO_2 in the range of 35-to-45 mmHg. A standardized CPB protocol was performed for all children. The CPB prime volume, 1,000-to-1,500 mL calculated by patient's weight, contained Ringer's lactate solution, hetastarch, heparin, and red blood cell concentrate. A nonpulsatile flow (2.4-3.0 L/min/m^2) was used, and a hematocrit of 28%-to-30% was maintained in all patients during CPB. Myocardial protection was provided with an antegrade blood cardioplegia (20 mL/kg with KCl (potassium chloride) 30 mEq/L). Mean arterial pressure was maintained between 30 and 50 mmHg by adjusting the pump flow or by injecting norepinephrine boluses if required.

The blood products were transfused in each patient based on the clinical situation. Packed red blood cells were transfused in the operating room after separation from CPB to maintain the hemoglobin level ≥9 g/dL in cyanotic children or in case of persistent lactic acidosis or low superior vena cava saturation (SvO_2 <70%). Platelet concentrate and fresh frozen plasma were transfused after CPB in the occurrence of abnormal clinical bleeding, based on the platelet count and standard coagulation tests.

All children were admitted to the cardiac ICU postoperatively, and therapeutic regimens of inotropic support, fluid management, and ventilatory support were administered according to the institutional standardized protocol. Patients with adequate spontaneous breathing and who required minimal supplemental oxygen were extubated. The time to extubation was recorded. Children weaned from ventilators and with stable hemodynamics without inotropic support were transferred to the ward.

Biochemical Analysis

Blood samples were obtained at 4 times: after anesthesia induction (T0), after release of the ACC (T1), at the end of the surgery (T2), and at the 24th postoperative hour (T3). The blood samples were centrifuged at 3,000 rotations per minute for 10 minutes at 4°C, and the serum samples were stored at −80°C until analysis. All analyses were performed according to the instructions supplied with the kits. IL-6 and TNF-α levels were determined with enzyme-linked immunosorbent assays (DIAsource IL-6 ELISA kit, lot 171206-1, Belgium; DIAsource TNF-α ELSIA kit, lot 110221-1) as indicators of the systemic inflammatory reaction. These kits are solid-phase enzyme-amplified sensitivity immunoassays performed on microtiter plates.

The total antioxidant status (TAS) and the total oxidant status (TOS) of samples were measured with a colorimetric assay (660 nm for TAS and 530 nm for TOS). The TAS Direct Measurement Kit (Rel Assay Diagnostics, lot ST22125A, Turkey) and the TOS Direct Measurement Kit (Rel Assay Diagnostics, lot ST22140O, Turkey) were adapted to a Beckman Coulter DxC 800 autoanalyzer (United States).

In the TAS test, antioxidants in the sample reduce dark blue-green colored ABTS (2,2-azinodi-[3-ethylbenzthiazoline sulphonate]) radical to colorless ABTS form. The change of absorbance at 660 nm is related to the TAS of the sample. The assay is calibrated with a stable antioxidant standard solution, which is named as Trolox Equivalent (vitamin E analog).

In the TOS test, oxidants present in the sample oxidize the ferrous ion–chelator complex to ferric ion. The ferric ion makes a colored complex with chromogen in an acidic medium. The color intensity measured spectrophotometrically is related to the total number of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide.

The oxidative stress index (OSI) is an indicator for oxidative stress and was calculated with the following formula:

$$OSI = [(TOS,\ \mu mol\, H_2O_2\, equivalent/L)/(TAS,\ \mu mol/lt)] \times 100$$

Systemic Inflammatory Response Syndrome

The occurrence of SIRS was assessed based on the pediatric sepsis consensus criteria.[12] The children were diagnosed with SIRS when at least 2 of the following clinical parameters were observed, one of which must be an abnormal leukocyte count or body temperature: (1) core body temperature >38.5°C or <36°C; (2) tachycardia or for children <1 year of age bradycardia; (3) a mean respiratory rate above normal for age or mechanical ventilation not related to neuromuscular disease or general anesthesia; and (4) leukocyte count elevated or depressed for age. An increased heart rate above the cut-off value due to cardiac pacemaker and an abnormal respiratory rate caused by mechanical ventilation were disregarded. The occurrence of SIRS was assessed at the end of the surgery (S1) and at the sixth (S2), 12th (S3), and 24th (S4) postoperative hours.

Primary and Secondary Outcomes

The primary outcomes were perioperative plasma IL-6, TNF-α, TAS, and TOS levels. The secondary outcomes were postoperative extubation time, ICU and hospital LOS, and postoperative adverse events (eg, reintubation, requirement of extracorporeal membrane oxygenation, and renal failure).

Sample Size

Based on the Geng et al.'s[13] study, the sample size needed to show a significant difference in IL-6 and TNF-α levels measured at T0, T1, T2, and T3 between the P and S groups (effect sizes for the interaction term were 1.6569 and 1.4988 for IL-6 and TNF-α, respectively) was calculated as at least 4 patients per group, with a two-sided design at a significance level of 5% and a power of 90%. However, because of the lack of reference studies examining TAS, TOS, OSI, etc, in cyanotic children, the authors planned to conduct a study with 20 patients per group, because the variability might be high.

Statistical Analysis

Categorical variables are expressed as numbers and percentages, whereas continuous variables are summarized as mean and standard deviation and as median and minimum-maximum where appropriate. The chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the

Shapiro-Wilk test. For comparison of continuous variables between the 2 groups, Student's t-test was used for parametric data and the Mann-Whitney U-test was used for nonparametric data. For comparison of continuous variables between the 2 groups, Student's t-test was used for parametric data and the Mann-Whitney U-test was used for nonparametric data. For multiple testing, Bonferroni correction was applied to control Type I error. To evaluate the change in the measurements over time, the Generalized Estimating Equations method was applied. All analyses were performed using IBM SPSS Statistics Version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) statistical software package. For all tests, $p < 0.05$ was considered to be statistically significant.

Results

Forty children were enrolled for this study. Six children were excluded because of missing blood samples. Hence, 34 patients were analyzed: 16 in group P and 18 in group S. The patient distribution and assignment are outlined in the CONSORT flow diagram (Fig 1). There was no difference between the groups with regard to baseline demographic data, intraoperative variables, and the RACHS1 categorization of cardiac diseases (Table 1). The duration of surgery, CPB and ACC times, and the lowest body temperature reached during CPB were comparable in both groups (Table 1). In addition, consumption of crystalloid and blood products was not significantly different between the 2 groups ($p > 0.05$).

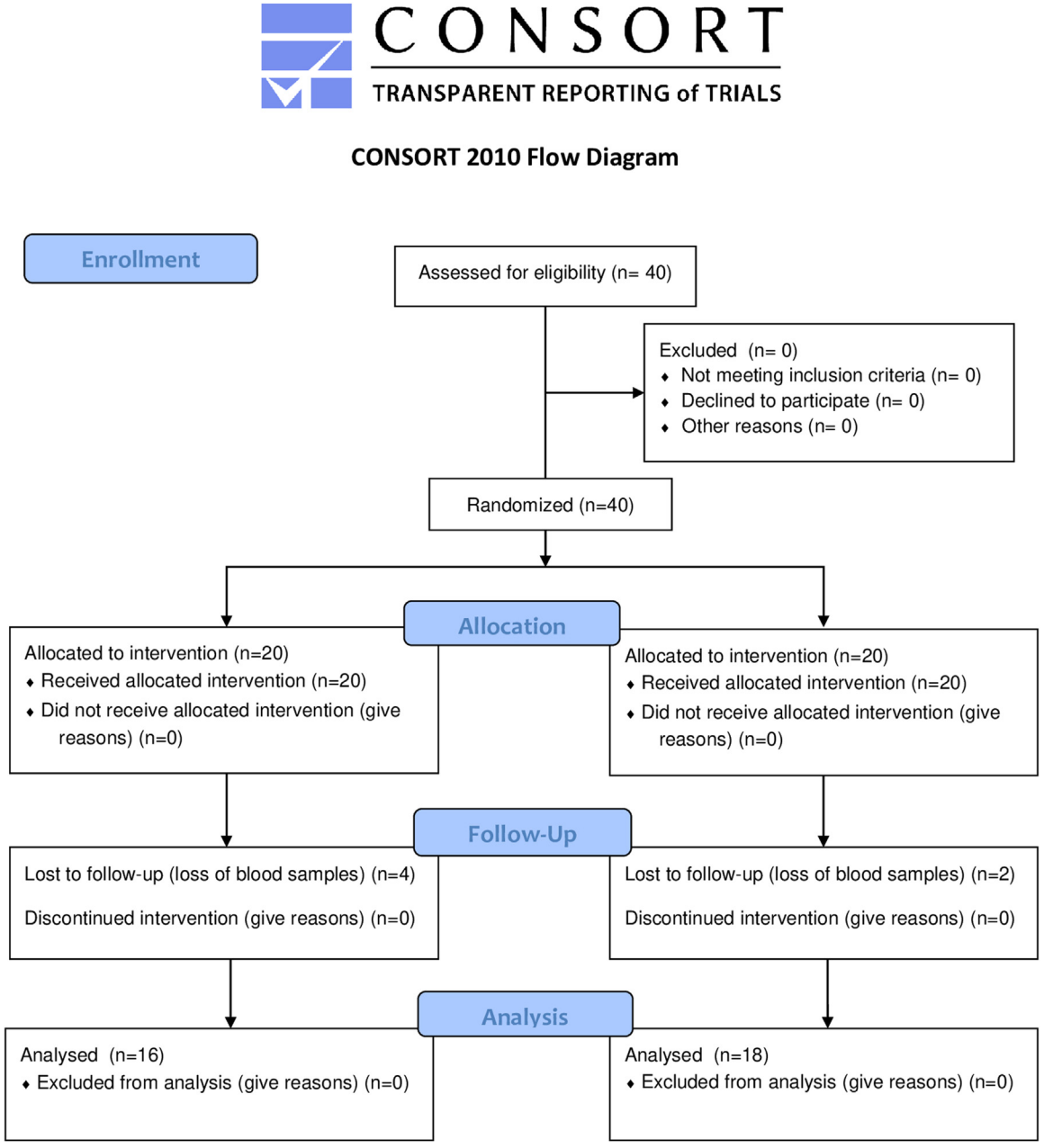

Fig 1. Consort flow diagram.

Table 1
Patient Demographic and Perioperative Data

	Group P (n = 16)	Group S (n = 18)	p
Age (mo)	44.7 ± 37.0	38.4 ± 38.9	0.330
Weight (kg)	13.7 ± 7.7	12.6 ± 5.8	0.798
Sex (F/M)	7/9	7/11	0.083
Diagnoses (n)			
TOF	4	4	
TOF+MAPCA	2	5	
TOF+PA	0	2	
TOF+PA+MAPCA	1	0	
TGA (Fontan procedure)	4	0	
DILV	0	1	
DORV	2	1	
TA	2	3	
TA+PA	1	1	
Ebstein anomaly	0	1	
RACHS1			
2	6 (37.5%)	9 (50.0%)	0.379
3	8 (50.0%)	9 (50.0%)	
4	2 (12.5%)	0 (0.0%)	
Surgery time (min)	222.8 ± 53.4	229.7 ± 55.3	0.746
CPB time (min)	93.1 ± 40.5	102.2 ± 34.0	0.528
ACC time (min)	66.6 ± 32.6	59.7 ± 22.1	0.825
Preoperative SaO_2 (%)	77.13 ± 6.96	78.28 ± 6.89	0.631
Postoperative SaO_2 (%)	92.71 ± 7.81	93.27 ± 6.66	0.821
Cardioplegia (mL/kg)	28.8 ± 12.7	21.8 ± 9.7	0.126
Preoperative Hb (mg/dL)	18.2 ± 3.8	16.1 ± 2.9	0.077
Postoperative Hb (mg/dL)	11.9 ± 2.4	12.5 ± 1.9	0.407
Preoperative Htc (%)	55.2 ± 10.9	49.2 ± 8.6	0.082
Postoperative Htc (%)	36.1 ± 7.2	38.6 ± 5.7	0.281
Preoperative lactate	1.26 ± 0.58	1.20 ± 0.48	0.772
Postoperative lactate	2.39 ± 1.58	2.08 ± 0.80	0.772
Lowest nasopharyngeal temperature during CPB (°C)	30.5 ± 2.3	29.2 ± 2.7	0.163
Extubation time (h)	29.44 ± 43.05	39.44 ± 84.16	0.986
LOS ICU (d)	6.44 ± 5.86	8.00 ± 6.49	0.330
LOS hospital (d)	11.31 ± 8.74	13.44 ± 11.08	0.422

Abbreviations: ACC, aortic cross-clamp; CPB, cardiopulmonary bypass; DILV, double-inlet left ventricle; DORV, double- outlet right ventricle; Hb, hemoglobin; Htc, hematocrit; ICU, intensive care unit; LOS, length of stay; MAPCA, major aortopulmonary collateral arteries; PA, pulmonary atresia; RACHS1, The Risk Adjusted Classification for Congenital Heart Surgery; TA, tricuspid atresia; TGA, transposition of great arteries; TOF, Tetralogy of Fallot; VIS, vasoactive inotropic score.

The clinical occurrence of SIRS was more common in group S than in group P at all control times (p = 0.020 for the end of the surgery [S1], p = 0.036 for the sixth postoperative hour [S2], p = 0.004 for the 12th postoperative hour [S3], and p = 0.008 for the 24th postoperative hour [S4]; Table 2).

There were no significant differences in the mean TNF-α and IL-6 levels at any time between the groups (Table 3; Fig 2). In group S, while serum IL-6 concentrations increased at T1, T2, and T3 compared with T0, TNF-α concentrations decreased at other times compared with T0. In group P, TNF-α and IL-6 levels increased at T1, T2, and T3 compared with T0 (Table 3). In addition, there was no significant difference between the groups within time at T0, T1, T2, and T3 in serum TNF-α and IL-6 concentrations (Table 3).

Table 2
Postoperative Systemic Inflammatory Response Syndrome (SIRS) and Leukocyte Count

	Group P (n = 16)	Group S (n = 18)	p
Diagnose of SIRS at S1	3/16	12/18	**0.020***
Diagnose of SIRS at S2	2/16	10/18	**0.036***
Diagnose of SIRS at S3	2/16	13/18	**0.004***
Diagnose of SIRS of S4	1/16	10/18	**0.008***
Count of leukocyte at S1	11.6 ± 6.4	16.7 ± 6.3	0.068*
Count of leukocyte at S2	12.8 ± 6.1	16.4 ± 4.0	**0.040***
Count of leukocyte at S3	13.2 ± 5.2	16.4 ± 4.6	0.100*
Count of leukocyte at S4	12.7 ± 5.3	15.6 ± 4.1	**0.036***

Abbreviations: S1, end of the surgery; S2, postoperative sixth hour; S3, postoperative 12th hour; S4, postoperative 24th hour.
* Bonferroni corrected p value.

Serum TAS levels at T2 were higher in group P than group S (p = 0.036; Fig 2). In addition, while serum TAS level increased at T2 compared with T0 in group P, it decreased in group S. There was significant difference between the groups within time at T0, T1, T2, and T3 in serum TAS levels (p = 0.041; Table 4).

Serum TOS levels and the OSI at T0, T1, T2, and T3 were comparable between the groups (Fig 2). There was no significant difference between the groups within time at T0, T1, T2, and T3 in TOS serum levels (p > 0.05).

There was no death in the study groups. Postoperative adverse events, VIS values, time to extubation, and ICU and hospital LOS were similar between the groups (p > 0.05). Two children in group P and 3 children in group S were reintubated after extubation because of hypoxia. One child in each group required extracorporeal membrane oxygenation postoperatively.

Discussion

The results have shown that propofol was superior to sevoflurane in reducing SIRS and oxidative stress in children with CCHD undergoing cardiac surgery with CPB. However, sevoflurane and propofol were comparable in terms of serum IL-6 and TNF-α concentrations and clinical outcomes.

From a clinical point of view, SIRS is defined as a nonspecific generalized inflammatory state, and is frequently observed in pediatric patients after cardiac surgery.[3] Data from previous studies have suggested that an elevated leukocyte count in the first 24 postoperative hours, fever, and heart rate can be used to diagnose a systemic inflammatory response after cardiac surgery with CPB.[14] Leukocytosis is considered the first step of inflammation induced by CPB. It is followed by the production of free radicals, which triggers IRI.[2] Several studies have indicated that sevoflurane mainly inhibits the activation of leukocytes and decreases the leukocyte count and inflammatory mediators in patients undergoing cardiac surgery with CPB.[15] Propofol has been shown to alleviate the CPB-induced inflammation by inhibiting neutrophil function, reducing production of proinflammatory cytokines, and modifying the expression of nitric oxide.[7]

Table 3
Perioperative Evaluation of Inflammation Biomarkers

	Group P	Group S	p
TNF-α T0	383.97 ± 264.59	324.85 ± 288.29	0.999*
TNF-α T1	397.00 ± 312.95	284.79 ± 190.39	0.999*
TNF-α T2	384.63 ± 215.28	315.44 ± 175.95	0.999*
TNF-α T3	393.75 ± 275.85	325.24 ± 208.57	0.999*
TNF-α over time			0.311†
IL6 T0	147.89 ± 65.24	142.74 ± 64.15	0.999*
IL6 T1	153.31 ± 65.37	145.07 ± 46.46	0.999*
IL6 T2	171.23 ± 70.76	161.10 ± 51.21	0.999*
IL6 T3	158.42 ± 58.18	152.82 ± 60.95	0.999*
IL6 over time			0.686†

Abbreviations: IL-6, interleukin-6; TNF-α, tumor necrosis alpha; T0, induction of anesthesia; T1, postoperative sixth hour; T2, postoperative 12th hour; T3, postoperative 24th hour.

* Bonferroni corrected p value.

† Generalized Estimating Equations analysis result.

Yang et al.[16] compared the effects of sevoflurane and propofol on inflammatory mediators in adult patients undergoing cardiac surgery, and concluded that sevoflurane reduced the inflammatory mediators more than propofol. Bettex et al.[9] found no difference in postoperative inflammatory mediator levels between the sevoflurane and propofol groups in their study on cyanotic and acyanotic children undergoing cardiac surgery. In the present study, while the incidences of SIRS and leukocytosis were higher in group S than group P, the levels of IL-6 and TNF-α were comparable between the groups. To the best of the authors' knowledge, this was the first study to compare the anti-inflammatory effects of sevoflurane and propofol in cyanotic children. In this patient group, the presence of inflammation and elevated levels of cytokines before the cardiac surgery may have changed the anti-inflammatory effects of anesthetic drugs. Therefore, there is a need for extensive studies on this subject.

Inflammation, hemolysis, and IRI during CPB produce ROS.[3] In CCHD, the myocardium is more susceptible to oxidative injury due to the pressure overload, hypoxia, reduced ATP stores, and antioxidant enzymes.[2] In addition, cyanotic patients reoxygenated with CPB produce abundant ROS, which need to be scavenged.[17] The antioxidant effects of sevoflurane and propofol have been demonstrated in previous studies.[8,16] Ballester et al.[18] reported that sevoflurane reduced oxidative stress more than propofol in adult patients during off-pump coronary artery surgery. Dumaresq et al.[8] found no

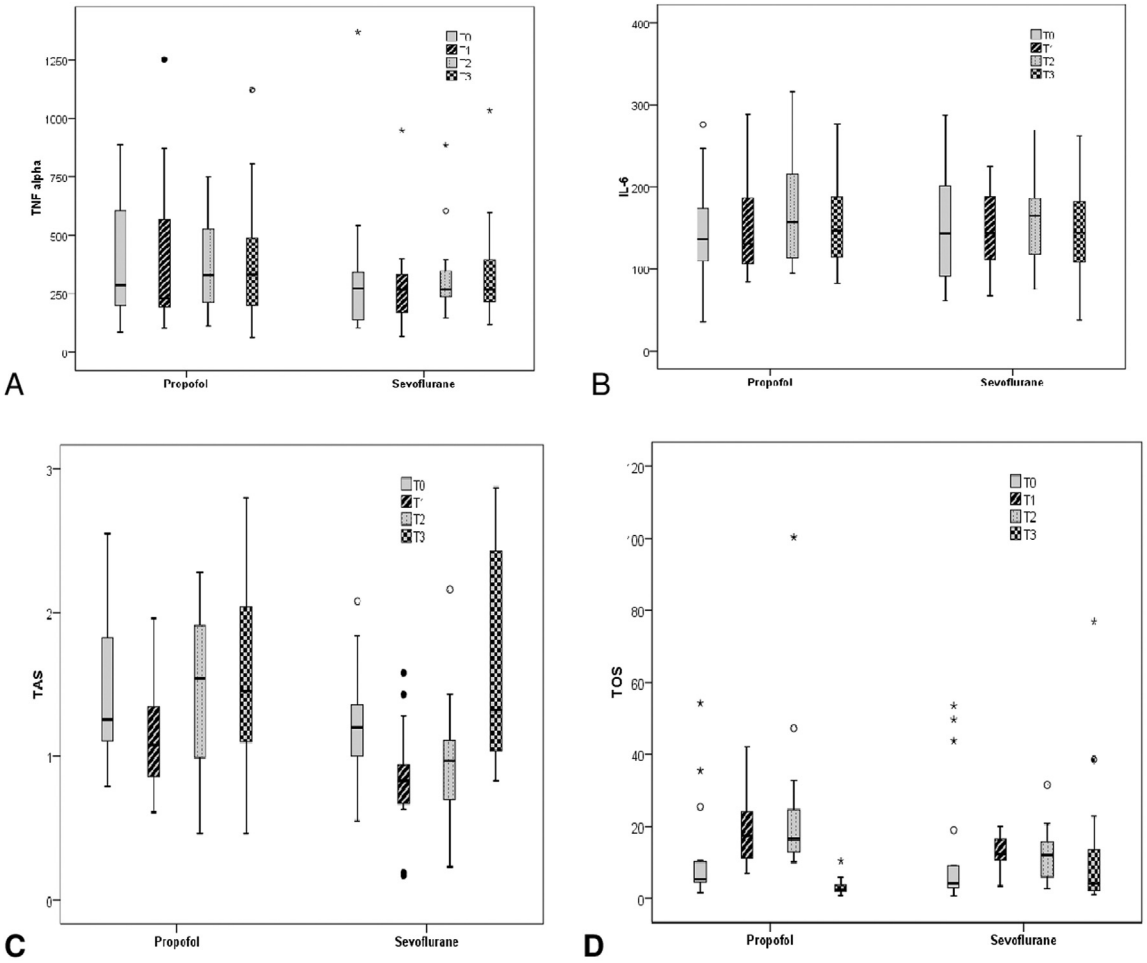

Fig 2. Levels of tumor necrosis alpha (TNF-α), interleukin-6 (IL-6), total antioxidant status (TAS), and total oxidant status (TOS) at 4 time points: after anesthetic induction (T0), after release of the ACC (T1), at the end of the surgery (T2), and at the postoperative 24th hour (T3).

Table 4
Perioperative Evaluation of Oxidation Biomarkers

	Group P	Group S	p
TAS T0	1.44 ± 0.48	1.22 ± 0.36	0.999*
TAS T1	1.12 ± 0.37	0.85 ± 0.35	0.148*
TAS T2	1.46 ± 0.52	0.97 ± 0.43	**0.036***
TAS T3	1.51 ± 0.65	1.62 ± 0.72	0.999*
TAS over time			**0.041**†
TOS T0	11.53 ± 14.55	12.50 ± 17.36	0.999*
TOS T1	19.26 ± 10.17	12.80 ± 4.66	0.300*
TOS T2	24.22 ± 22.51	22.19 ± 20.24	0.999*
TOS T3	3.12 ± 2.31	12.33 ± 18.90	0.352*
TOS over time			0.452†
OSI (T0)	0.77 ± 0.83	0.88 ± 1.04	0.999*
OSI (T1)	1.80 ± 0.97	1.71 ± 0.79	0.999*
OSI (T2)	1.69 ± 1.11	1.39 ± 0.72	0.999*
OSI (T3)	0.22 ± 0.15	0.62 ± 0.70	0.221*
OSI over time			0.877†

Abbreviations: OSI, oxidative stress index; TAS, total antioxidant status; TOS, total oxidant status; T0, induction of anesthesia; T1, postoperative sixth hour; T2, postoperative 12th hour; T3, postoperative 24th hour.

* Bonferroni corrected p value.

† Generalized Estimating Equations analysis result.

significant difference between the antioxidant effects of sevoflurane and propofol in acyanotic children undergoing cardiac surgery with CPB. Unlike these results, the authors' study has shown that propofol provides a greater antioxidant effect than sevoflurane in children with CCHD.

In vitro experiments and animal and human studies have shown that sevoflurane with an ischemic preconditioning-like effect reduces ROS, attenuates IRI, and improves cardiac function.[18,19] However, chronically hypoxic infant rabbit hearts could not be conditioned.[20] Furthermore, sevoflurane reduced mortality in patients with no previous history of angina, but did not in patients with a history of angina.[21] In a meta-analysis, serum IL-6 and IL-8 levels were higher in adult patients who received postoperative treatment with sevoflurane than those who received pretreatment with sevoflurane during cardiac surgery with CPB.[22] These studies, in correlation with the results of the present study, suggest that further conditioning may not be possible in chronic hypoxic patients.

Propofol has a chemical structure similar to phenol-based antioxidants, such as the endogenous antioxidant vitamin E. Its antioxidant effect includes acting as a free radical scavenger, increasing the tissue antioxidant capacity and inhibition of plasma membrane calcium channels, and is not related to ischemic preconditioning.[23] Therefore, it seems likely that propofol would have a stronger antioxidant effect than sevoflurane in children with CCHD.

Allen et al.[17] used a leukocyte-depleting filter in cyanotic infants during CPB. They observed that when the number of leukocytes decreased, ROS generation was reduced and the antioxidant reserve capacity was preserved, compared with the unfiltered cyanotic children. The authors' data supported these results. In the present study, the incidence of SIRS and the number of leukocytes were higher, and the TAS was lower in group S compared with group P. However, there was no significant difference between the groups in terms of clinical outcomes such as extubation time, VIS, and ICU and hospital LOS.

Limitations

This study had several limitations. First, although the patients were randomly assigned to the study groups by a computer-generated random number list, the anesthesiologists could not be blinded to the anesthetic technique used in each group. However, the researchers who collected the postoperative data, the ICU team, and the laboratory staff were blinded to the randomization. Second, the authors did not measure concentrations of sevoflurane and did not use target-controlled infusion for propofol because of technical restrictions. Third, the sample size was relatively small to analyze clinical outcomes.

Conclusion

The results of this study have shown that propofol provides a greater antioxidant effect and reduces SIRS postoperatively more than sevoflurane in children with CCHD undergoing cardiac surgery with CPB. However, the authors could not demonstrate any difference in clinical outcomes between the study groups. Hence, the authors believe that large and specific studies are needed to demonstrate the clinical effects of anesthetic agents in children with CCHD.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2022.09.094.

References

1 Schmid E, Krajewski S, Bachmann D, et al. The volatile anesthetic sevoflurane inhibits activation of neutrophil granulocytes during simulated extracorporeal circulation. Int J Immunopharmacol 2012;14:202–8.
2 Fudulu D, Angelini G. Oxidative stress after surgery on the immature heart. Oxid Med Cell Longev 2016;2016:1971452.
3 Durandy Y. Minimizing systemic inflammation during cardiopulmonary bypass in the pediatric population. Artif Organs 2014;38:11–8.
4 Sharma R, Bolger AP, Li W, et al. Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease. Am J Cardiol 2003;92:188–93.
5 Nassef YE, Hamed MA, Aly HF. Inflammatory cytokines, apoptotic, tissue injury and remodeling biomarkers in children with congenital heart disease. Indian J Clin Biochem 2014;29:145–9.
6 El-Azab SR, Rosseel PMJ, DeLange JJ, et al. Effect of sevoflurane on the ex vivo secretion of TNF-α during and after coronary artery bypass surgery. Eur J Anaesth 2003;20:380–4.
7 Samir A, Gandreti N, Madhere M, et al. Anti-inflammatory effects of propofol during cardiopulmonary bypass: A pilot study. Ann Card Anaesth 2015;18:495–501.
8 Dumaresq DMH, de Vasconcelos RC, Guimarães SB, et al. Metabolic and oxidative effects of sevoflurane and propofol in children undergoing surgery for congenital heart disease. Acta Cir Bras 2011;26(Suppl 1):66–71.

9 Bettex DA, Wanner PM, Bosshart M, et al. Role of sevoflurane in organ protection during cardiac surgery in children: A randomized controlled trial. Interact Cardiovasc Thorac Surg 2015;20:157–65.
10 Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med 2010;11:234–8.
11 Jenkins KJ, Gauvreau K, Newburger JW, et al. Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 2002;123:110–8.
12 Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.
13 Geng YJ, Wu QH, Zhang RQ. Effect of propofol, sevoflurane, and isoflurane on postoperative cognitive dysfunction following laparoscopic cholecystectomy in elderly patients: A randomized controlled trial. J Clin Anesth 2017;38:165–71.
14 Squiccimarro E, Labriola C, Malvindi PG, et al. Prevalence and clinical impact of systemic inflammatory reaction after cardiac surgery. J Cardiothorac Vasc Anesth 2019;33:1682–90.
15 Cho EJ, Yoon JH, Hong SJ, et al. The effects of sevoflurane on systemic and pulmonary inflammatory responses after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2009;23:639–45.
16 Yang XL, Wang D, Zhang GY, et al. Comparison of the myocardial protective effect of sevoflurane versus propofol in patients undergoing heart valve replacement surgery with cardiopulmonary bypass. BMC Anesthesiol 2017;17:37.
17 Allen BS, Rahman S, Ilbawi MN, et al. Detrimental effects of cardiopulmonary bypass in cyanotic infants: Preventing the reoxygenation injury. Ann Thorac Surg 1997;64:1381–7;discussion 1387-8.
18 Ballester M, Llorens J, Garcia-de-la-Asuncion G, et al. Myocardial oxidative stress protection by sevoflurane vs. propofol: A randomised controlled study in patients undergoing off-pump coronary artery bypass graft surgery. Eur J Anaesthesiol 2011;28:874–81.
19 Hanouz J-L, Zhu L, Lemoine S, et al. Reactive oxygen species mediate sevoflurane- and desflurane-induced preconditioning in isolated human right atria in vitro. Anesth Analg 2007;105:1534–9.
20 Baker JE, Holman P, Gross GJ. Preconditioning in immature rabbit hearts role of KATP channels. Circulation 1999;99:1249–54.
21 Jakobsen CJ, Berg H, Hindsholm KB, et al. The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. J Cardiothorac Vasc Anesth 2007;21:664–71.
22 Yu QB, Li HM, Li LL, et al. Sevoflurane downregulates interleukin-6 and interleukin-8 levels in patients after cardiopulmonary bypass surgery: A meta-analysis. Genet Mol Res 2015;14:19016–27.
23 Suleiman MS, Zacharowski K, Angelini GD. Inflammatory response and cardioprotection during open-heart surgery: The importance of anaesthetics. Br J Pharmacol 2008;153:21–33.