

Pre- and postoperative levels of serum brain-derived neurotrophic factor in neonates with congenital heart defects

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ABSTRACT

Background. The objectives of this study were to assess the preoperative and postoperative serum brain-derived neurotrophic factor (BDNF) levels in neonates undergoing surgery for congenital heart defects (CHD). Also to explore the relationship between changes in BDNF levels and the impact of perioperative factors including intraoperative body temperature, aortic cross-clamp time, perfusion time, operation time, inotropic score, vasoactive inotropic score and lactate levels.

Methods. Forty-four patients with CHD and 36 healthy neonates were included in the study. Blood samples for serum BDNF levels were collected three times: preoperatively, and at 24 and 72 hours postoperatively from each patient in the operated group. Additionally, samples were collected once from each individual in the non-operated case group and the control group. Serum BDNF levels were analyzed using the Elabscience ELISA (Enzyme-Linked Immunosorbent Assay) commercial kit. Cranial ultrasonography (USG) was performed on all infants with CHD. Following cardiac surgery, patients underwent second and third cranial USG examinations at 24 and 72 hours postoperatively, respectively.

Results. Forty-four consecutive patients with CHD were divided into two groups as follows: the operated group (n=30) and the non-operated group (n=14). Although there were no differences in the baseline serum BDNF levels between the case and control groups, the preoperative serum BDNF levels were significantly lower in the patients operated compared to the non-operated patients. The serum BDNF levels at the 24th hour postoperatively were higher than the preoperative levels. However, no significant correlation was found between the serum BDNF levels at 24 and 72 hours postoperatively as well as the cranial USG findings at corresponding times.

Conclusions. Serum BDNF levels were initially lower in neonates with CHD who underwent surgery, but increased during the early postoperative period. These results suggest that serum BDNF levels are influenced by CHD and the postoperative period.

Key words: brain derived neurotrophic factor, cardiac surgery, congenital heart defects, neonates.

Congenital heart defects (CHD) are a prominent cause of birth defects in neonates, associated

with significant morbidity and mortality. The ongoing advancements in prenatal fetal echocardiography and ultrasonography, along with postnatal pulse oximetry measurement for early detection of CHD, have been directly linked to an increased frequency in the diagnosis of CHD.

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Received 25th Jan 2024, revised 21st Mar 2024, 19th Apr 2024, accepted 25th Apr 2024.

The determination of perioperative damage to the central nervous system in infants with CHD who undergo cardiac surgery and cardiopulmonary bypass (CPB) remains an area of ongoing research. In these patients, the clinical and biochemical markers that can predict outcomes are not well established. Furthermore, there is growing evidence that perioperative management should be individualized based on the specific characteristics of CHD. This is especially evident in infants with cyanotic CHD, who exhibit differences in organ damage, inflammation, and neurobiomarkers following cardiac surgery or bypass.¹

Ischemia-reperfusion associated tissue damage is a well-known factor following CPB. Despite advancements in CPB equipment and procedures, acute brain injuries related to cardiac surgery still occur. While the pathophysiology of brain damage is not fully understood, recent studies suggest that hypoxia and inflammation play significant roles.²

Cardiopulmonary bypass ensures more stable cerebral blood flow, cardiac output, and organ oxygenation. Although this perioperative management reduces neurological morbidity, brain injury remains a significant postoperative complication. Intraoperative interventions, such as CPB and circulatory arrest techniques, along with adverse events from surgical procedures (such as thromboembolism, strokes, and intracranial hemorrhage), and uncorrectable postoperative hypoxia are principal factors influencing neurodevelopmental outcomes in these patients.^{3,4} The mechanisms underlying the development of brain injury during and after cardiac surgery primarily involve hypoxic-ischemic injury, the reperfusion phase, and a third phase characterized by gliosis, persistent inflammatory receptor activation, and epigenetic modifications.⁵

Numerous neuromarkers have been investigated to predict neurodevelopmental outcomes in patients undergoing cardiac surgery for CHD. The most commonly studied neuromarkers include S100 calcium-binding protein B (S100B), neuron-specific enolase

(NSE), and glial fibrillary acidic protein (GFAP).⁶⁻¹² These markers are frequently analyzed due to their roles in indicating neural damage or stress. GFAP has been proposed as a potential marker for assessing perioperative brain damage.⁶

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that influences the survival, growth, and functions of neurons in both the central and peripheral nervous systems. It plays a crucial role in stabilizing synapses and regulating axon and dendrite branching.¹³ Several studies have demonstrated that serum BDNF levels are altered in neonates with conditions such as intracranial hemorrhage (ICH), retinopathy of prematurity (ROP), and hypoxic-ischemic encephalopathy (HIE), as well as in those receiving antenatal and postnatal steroids.¹⁴⁻¹⁷

Our hospital is a tertiary referral academic institution that provides early diagnosis and management of CHD from the fetal period through to 18 years of age. The objectives of this study were to assess the preoperative and postoperative serum BDNF levels in neonates undergoing surgery for CHD and to explore the relationship between changes in BDNF levels as well as the impact of perioperative factors including intraoperative body temperature, aortic cross-clamp time, perfusion time, operation time, inotropic score, vasoactive inotropic score and lactate levels.

Materials and Methods

In this prospective-controlled study, neonates hospitalized due to CHD in the neonatal intensive care unit (NICU) and the pediatric cardiovascular surgery intensive care (CICU) unit of Baškent University Faculty of Medicine between August 2021 and February 2023 were included. The study received approval from the Baškent University Institutional Review Board and Ethics Committee (Project no: KA21/320, dated August 13, 2021). Written informed consent was obtained from the parents of all participating neonates.

Forty-four patients with cyanotic CHD affecting pulmonary blood flow, as well as acyanotic CHD, including obstructive lesions, that would require interventional or surgical treatment were included in this study. All neonates with CHD who met the above criteria were included in this period. CHD patients were divided into two groups as follows: the operated group, consisting of 30 out of the 44 patients who required surgery, and the non-operated group, comprising 14 out of the 44 patients who did not require surgery during the neonatal period. For the control group, 36 healthy neonates who roomed-in with their mothers during hospitalization following delivery, underwent routine blood tests, including bilirubin and thyroid function tests, at the outpatient clinic. They had no history of illness or congenital heart defects and were included in the study.

The exclusion criteria for the study were as follows: premature neonates with a gestational age of less than 36 weeks; neonates diagnosed with HIE, chromosomal abnormalities, congenital metabolic disorders, or ICH before cardiac surgery; and infants born to mothers diagnosed with preeclampsia, gestational diabetes mellitus, or chorioamnionitis. Additionally, neonates born to mothers with major depressive disorder or mental health issues were excluded from the study due to the potential influence of antidepressant treatment on BDNF levels.

The sample size was determined to be a total of 52 neonates, with 26 undergoing surgery for CHD and 26 serving as healthy controls, based on the results of the power analysis. The test power was estimated to be approximately 80% with an alpha (α) level of 0.05.

The decision to operate on the patients was made by the joint council of pediatric cardiology and pediatric cardiovascular surgery. All cardiac surgeries were performed by the same pediatric cardiovascular surgeon. The preoperative and postoperative follow-ups were conducted by a consistent team of neonatal, pediatric cardiovascular surgery, and

pediatric cardiology specialists in the NICU and pediatric CICU. The recorded data for the neonates included gestational age, gender, birth weight, mode of birth, inborn or outborn status, presence of fetal heart diseases, and APGAR scores. Infants categorized as small, appropriate or large for gestational age (SGA, AGA, and LGA, respectively) were defined as having birth weights below the 10th percentile, between the 10th and 90th percentile, and above the 90th percentile for gestational week, respectively, according to the Fenton preterm growth charts.¹⁸ Additional details documented were the age on the day of surgery, length of stay in both the intensive care unit and hospital, cardiac surgery technique (such as arterial switch, aortic coarctation repair, truncus arteriosus repair, Norwood procedure, or shunt operation), CPB usage, aortic cross-clamp time, perfusion time, intraoperative body temperature, and total operation duration. Preoperative, postoperative 24-hour, and postoperative 72-hour lactate levels were measured from venous blood gas samples. Any lactate level ≥ 2.5 mmol/L was considered elevated, indicating potential tissue hypoxia. The inotropic score (IS) was calculated using the formula: $1 \times \text{dopamine dose } (\mu\text{g/kg/min}) + 1 \times \text{dobutamine dose } (\mu\text{g/kg/min}) + 100 \times \text{adrenaline dose } (\mu\text{g/kg/min})$. The vasoactive inotropic score (VIS) was calculated as: $\text{IS} + 10 \times \text{milrinone dose } (\mu\text{g/kg/min}) + 10000 \times \text{vasopressin dose } (\text{U/kg/min}) + 100 \times \text{norepinephrine dose } (\mu\text{g/kg/min})$. Prostaglandin E1 infusion was administered at doses ranging from 0.01 to 0.1 $\mu\text{g/kg/min}$ as needed.

In terms of additional anomalies and the presence of ICH, cranial ultrasonography (USG) was performed by the same specialist from the department of radiology for all infants with CHD. Following cardiac surgery, patients underwent second and third cranial USG examinations at 24 and 72 hours postoperatively, respectively. Ultrasonographic findings were categorized into stages according to the Volpe intraventricular hemorrhage (IVH) classification¹⁹: Grade 1: germinal matrix hemorrhage with no IVH, or IVH occupying

less than 10% of the ventricular area on the parasagittal view; Grade 2: IVH occupying 10-50% of the ventricular area on the parasagittal view; Grade 3: IVH occupying more than 50% of the ventricular area on the parasagittal view, possibly with periventricular echodensities and periventricular venous hemorrhagic infarction (PVHI); this category may also include cystic periventricular leukomalacia.

Blood sampling and serum BDNF assay

Blood samples for serum BDNF levels were collected three times: preoperatively, and at 24 and 72 hours postoperatively from each patient in the operated group. Additionally, samples were collected once from each individual in the non-operated case group and the control group. Two milliliters of blood were drawn into sterile tubes with yellow caps while other blood samples were being checked. These samples were then centrifuged at 3500 rpm for 10 minutes to separate the serum. The serum samples were transferred into sterile Eppendorf tubes and stored at -80°C until analysis.

BDNF levels in the serum samples were analyzed in the Biochemistry Laboratory of Başkent University using the Elabscience ELISA (Enzyme-Linked Immunosorbent Assay) commercial kit (Catalog No: 201-12-1303, Human BDNF). Concentrations in the samples were automatically calculated from a graph generated by the device, utilizing the standards provided in the kit.

Statistical analysis

Data analysis was conducted using the IBM® SPSS 25.0 statistical software package. Descriptive statistics were presented as frequencies and percentages for categorical variables and as means \pm standard deviations or medians with minimum-maximum (min-max) ranges for continuous variables. The adherence of continuous variables to normal distribution was assessed through both visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests).

For categorical variables, comparisons between independent groups were performed using the χ^2 or Fisher's exact tests. The Cochran's Q test was applied for analyzing three or more dependent categorical groups. In the case of continuous variables, the Mann-Whitney U test was utilized for comparing two independent groups, while the Kruskal-Wallis or Friedman tests were employed for comparing three or more groups. Spearman's rank correlation test was used for correlation analysis between two continuous variables, at least one of which was non-parametrically distributed. A p-value of 0.05 was set as the threshold for statistical significance in all analyses.

Results

This prospective-controlled study involved 44 neonates with CHD and a control group of 36 healthy neonates. All but 5 neonates (11.4%) in the CHD group and 1 neonate (2.8%) in the control group were delivered at our hospital. Demographic and clinical characteristics are summarized in Table I.

The comparison of diagnostic and clinical data for operated and non-operated patients is presented in Table II. Out of the 30 neonates who underwent cardiac surgery, corrective surgery was performed on 24 (80%) patients, while palliative surgery was conducted on 6 (20%) patients (shunt operation in 4 patients and Norwood surgery in 2 patients). CPB was utilized in 27 (90%) patients. The median (min-max) aortic cross-clamp time was 87.5 (27-150) minutes, the perfusion time was 140 (106-228) minutes, the operation time was 210 (150-315) minutes, and the intraoperative body temperature was maintained at 25 (22-31) °C.

There was no significant difference in the serum BDNF levels between AGA, SGA and LGA groups ($p > 0.05$). The baseline median (min-max) serum BDNF levels were 2.1 (0.8-8.6) ng/mL in the case group and 2.1 (0.6-6.6) ng/mL in the control group, showing no significant difference ($p = 0.92$). However, the preoperative

Table I. Demographic and clinical characteristics of the study and control groups.

	CHD (n= 44)	Control (n= 36)	P
Gestational week, median (min-max)	38.4 (36.0-39.5)	38.3 (36.0-40.3)	0.92
Birth weight, g, median (min-max)*	3175 (1800-4100)	3200 (2200-3800)	
AGA, n (%)	35 (81.4)	27 (75.0)	0.77
SGA, n (%)	4 (9.3)	7 (19.4)	
LGA, n (%)	4 (9.3)	2 (5.6)	0.38
Gender, n (%)			0.87
Male	24 (54.5)	19 (52.8)	
Female	20 (45.5)	17 (47.2)	
Mode of delivery, n (%)			0.01
Vaginal delivery	0 (0.0)	5 (13.9)	
Cesarean section	44 (100.0)	31 (86.1)	
APGAR scores, median (min-max)			
1st min	8 (6-9)	9 (7-9)	<0.001
5th min	9 (7-10)	10 (8-10)	<0.001
Postnatal age (day), median (min-max)	7.2 (1.4-25.6)	2.9 (1.5-7.2)	<0.001

*One patient's birth weight data could not be accessed (missing data) AGA: appropriate for gestational age, CHD: congenital heart defects, LGA: large for gestational age, SGA: small for gestational age.

Table II. Comparison of diagnostic and clinical data of operated and non-operated patients.

	CHD, n (%)		P
	Operated (n=30)	Non-operated (n=14)	
Diagnostic classification			
Transposition of the great arteries [‡]	19 (63.3)	0 (0.0)	
Pulmonary atresia	3 (10.0)	2 (14.3)	
Coarctation of aorta	1 (3.3)	4 (28.6)	
Hypoplastic left heart syndrome	2 (6.7)	2 (14.3)	
Hypoplastic right heart syndrome	1 (3.3)	3 (21.4)	0.002
Tetralogy of Fallot	1 (3.3)	1 (7.1)	
Taussig-Bing anomaly	2 (6.7)	0 (0.0)	
Truncus arteriosus	1 (3.3)	0 (0.0)	
DORV	0 (0.0)	2 (14.3)	
Cardiac catheterization	9 (30.0)	3 (21.4)	0.72
Prostaglandin E1 infusion	22 (73.3)	2 (14.3)	<0.001
Antenatal diagnosis	27 (90.0)	12 (85.7)	0.64
Length of stay in NICU and pediatric CICU			
median (min-max) (day)	14 (5-36)	5 (2-49)	0.008
Total hospitalization period			
median (min-max) (day)	18 (10-48)	5 (2-49)	0.002

[‡] Difference between groups in post-hoc analysis is statistically significant

CHD: congenital heart defects, CICU: cardiovascular surgery intensive care unit, DORV: double outlet right ventricle, NICU: neonatal intensive care unit.

median (min-max) serum BDNF levels were significantly lower in the operated group at 1.9 (0.8-7.8) ng/mL compared to 2.7 (1.4-8.6) ng/mL in the non-operated group ($p = 0.04$). In the operated group ($n=30$), the use of prostaglandin E1 was associated with higher preoperative serum BDNF levels (2.1 ng/mL and 1.2 ng/mL, $p=0.01$). However, no correlation was found between the use of prostaglandin E1 and baseline serum BDNF levels in the case group ($n=44$) ($p=0.58$).

The preoperative and postoperative data of the operated patients is presented in Table III. The post-hoc analysis revealed that the statistical difference was attributable to the increase between the preoperative serum BDNF levels and the levels at the 24th postoperative hour. Both IS and VIS scores peaked at the postoperative 24th hour, indicating the highest level of inotropic support during this time. No statistically significant correlation was found between the preoperative, postoperative 24th-hour, and 72nd hour serum BDNF levels and IS, VIS, or lactate levels in the operated patients. Additionally, there was no significant correlation between the serum BDNF levels at the postoperative 24th and 72nd hours and the intraoperative body temperature, aortic cross-clamp time, perfusion time, or operation time ($p>0.05$).

There was no difference median serum BDNF levels at the postoperative 24th and 72nd hours between in patients who underwent CPB ($n=27$) compared to those who did not ($n=3$) ($p=0.052$ and $p=0.14$, respectively). No significant correlation was found between lactate levels ≥ 2.5 mmol/L at the postoperative 24th hour and serum BDNF levels ($p=0.77$). However, at the

postoperative 72nd hour, serum BDNF levels were significantly lower in patients with lactate levels ≥ 2.5 mmol/L (2.3 ng/mL vs 1.1 ng/mL, $p=0.005$).

The cranial USG results for the 44 patients were normal before surgery. After cardiac surgery, IVH was detected in 7 patients (23.3%) at the postoperative 24th hour and in 8 patients (26.7%) at the 72nd hour ($p=0.002$). The cranial USG findings, classified according to the Volpe grading system, identified periventricular hemorrhagic infarction in one patient, grade 3 IVH in one patient, grade 2 IVH in one patient, and grade 1 IVH in five patients. There was no significant correlation between the serum BDNF levels at the postoperative 24th and 72nd hours and the cranial USG findings at these corresponding times ($p=0.17$ and $p=0.56$, respectively), nor with the surgical technique used ($p=0.34$ and $p=0.60$, respectively).

Discussion

In this study, we investigated serum BDNF levels in neonates with CHD during both the preoperative and postoperative periods, as well as in healthy neonates. The serum BDNF levels measured at the 24th hour postoperatively were higher than the preoperative levels. Additionally, the preoperative serum BDNF levels in the operated neonates were lower compared to those in the non-operated group. We hypothesize that the decrease in serum BDNF levels observed in patients requiring surgery in the early neonatal period may be attributed to alterations in cerebral blood flow and oxygen delivery. The subsequent increase in BDNF levels during the postoperative reperfusion period lends support to this hypothesis. To the

Table III. The preoperative and postoperative data of the operated patients.

	Preoperative	Postoperative 24- hour	Postoperative 72-hour	p
Serum BDNF (ng/mL)	1.9 (0.8-7.8)	2.3 (0.9-15.6)	2.3 (1.0-9.3)	0.04
Inotropic score	0 (0-7)	20.5 (5-50)	5 (0-22)	<0.001
Vasoactive inotrope score	0 (0-7.5)	27.5 (10-57.5)	7.5 (0-27)	<0.001
Lactate (mmol/L)	2.8 (1.4-9.8)	2 (1-14.8)	1.4 (0.7-7)	<0.001

BDNF: brain-derived neurotrophic factor.

best of our knowledge, this is the first study in the literature to evaluate serum BDNF levels in neonates undergoing surgery for CHD during the neonatal period.

Surgical trauma, ischemia and reperfusion injury are all potential trigger factors of inflammation following CPB.² The endothelial damage caused by oxygen free radicals during myocardial hypoxia, ischemia and reperfusion may influence the response to BDNF secretion. Inflammation and oxidative stress have been demonstrated to increase BDNF levels after adult CPB.²⁰ Our results could not be compared as there are not enough studies in the literature investigating the effect of congenital heart defects and surgery on BDNF levels in newborns.

Brain damage often does not manifest clinical signs in neonates following CHD surgery, making evaluation during this period challenging. Therefore, there is a need for postoperative neuromarkers that can provide insights into both acute and long-term developmental outcomes. The most frequently investigated neuromarkers are S100B protein, NSE and GFAP. To date, only two studies have been published on serum BDNF levels in children with CHD.^{7,21} In the study of Sanchez-de-Toledo et al., inclusion criteria were age between 1 day and 17 years. Forty-eight children were included, of whom 15 (31.5 %) were under 2 months of age.⁷ In this study, serum BDNF levels were measured at three different time points in patients undergoing pediatric cardiac surgery: preoperatively, immediately after CPB, and 16 hours postoperatively. While they noted a decrease in serum BDNF levels immediately after CPB and an increase at the 16th postoperative hour, there were no significant differences in levels at the three measured time points. The key distinctions between their study and ours include the age range of the patients and the specific timing for postoperative sample collection. In the study by Chiperi et al, the cyanotic and acyanotic CHD included in this study were different from ours. Inclusion criteria were age from the neonatal

period until 5 years. Additionally, there was no control group in this study.²¹ In contrast, our study assessed serum BDNF levels following cardiac surgery during the early neonatal period. In their study, the results showed lower postoperative BDNF values in both cyanotic and non-cyanotic groups.

In an animal study aimed at determining the effects of hypoxic-ischemic injury, BDNF levels measured in the brain and serum at the outset and 4 hours after the hypoxic event were found to be elevated compared to those in healthy controls.²² However, it has been demonstrated that intermittent hypoxia can impair hippocampal neuronal excitability and decrease BDNF release in mice.²³ Furthermore, it was observed that administering BDNF to newborn rats after a hypoxic-ischemic injury could reduce brain tissue loss.²⁴

BDNF levels are elevated in the cerebrospinal fluid of asphyxiated newborns.¹⁷ Liu et al. found no significant differences in serum BDNF levels at the 24th hour, 72nd hour, and 7th day post-event in newborns with HIE. However, in the moderate-severe HIE group, serum BDNF levels were higher at the 24th hour and 7th day compared to the mild HIE group. Additionally, when comparing the control group with the HIE group, the HIE group exhibited significantly higher serum BDNF levels.²⁵ This underscores the importance of BDNF in neuroprotection, as decreased levels could render neonates more vulnerable to brain injury.

The half-life of BDNF in the brain and serum remains unknown. In numerous human studies, biomarkers were collected at intervals ranging from 16 hours to 7 days following cardiac surgery or hypoxic ischemic encephalopathy in neonates.^{7,8,25} In our study, blood samples for serum BDNF levels were taken at three different times: preoperatively, and at 24 and 72 hours postoperatively.

In the study by Amoureux et al., involving adult patients undergoing CPB, blood samples for serum BDNF were collected before

CPB initiation, 15 minutes before the aortic clamp was released (ischemia sample), and 15 minutes after the aortic cross-clamp was opened (reperfusion sample). They observed that serum BDNF levels during the reperfusion period after CPB were significantly higher than the basal levels, indicating that inflammation and oxidative stress could elevate BDNF levels.²⁰ The key differences between this study and ours are the patient demographics (adults versus neonates) and the specific timings for serum BDNF measurement, which in their case were 15 minutes before and after the aortic cross-clamp was opened.

In our study, we observed no correlation between the use of prostaglandin E1 and the basal serum BDNF levels in the case group. However, within the operated group, the use of prostaglandin E1 was associated with higher preoperative serum BDNF levels. We speculate that the increase in serum BDNF levels could be attributed to changes in perfusion following the administration of prostaglandin E1 in these patients.

Elevated lactate levels in the early postoperative hours were found to be associated with increased mortality and morbidity.²⁶ In neonates and children who underwent cardiac surgery, it was discovered that those with newly developed neurological deficits (such as stroke, seizures, ICH, or brain atrophy) had higher lactate levels in the first 24 hours postoperatively.¹¹ In our study, no significant correlation was found between lactate levels ≥ 2.5 mmol/L at the postoperative 24th hour and serum BDNF levels. When evaluating levels at the 72nd postoperative hour, it was noted that serum BDNF levels were significantly lower in patients with lactate levels ≥ 2.5 mmol/L. An increase in lactate levels indicating tissue hypoxia and a decrease in BDNF values were found to be noteworthy.

Vergine et al. indicated that GFAP levels could predict long-term neurodevelopmental outcomes. They found positive correlations between GFAP levels and the duration of surgery

and CPB, while noting a negative correlation with intraoperative body temperature. It has been suggested that temperature fluctuations during CPB represent a critical period for neurological damage development.¹⁰ However, in our study, no significant correlation was observed between serum BDNF levels and intraoperative body temperature.

There is abundant evidence indicating preoperative neuroimaging abnormalities in neonates with CHD.^{27,28} Mild unilateral ventriculomegaly, marked by increased cerebrospinal fluid (CSF) spaces due to reduced brain volume, stands out as the most prevalent structural brain abnormality. The expansion of these spaces is attributed to delayed brain growth.²⁸ In our study, neither ventriculomegaly nor ICH was detected in any patient during the preoperative cranial USG examination. Additionally, we did not find any significant correlation between serum BDNF levels at the 24th and 72nd postoperative hours and the cranial USG findings during the same time intervals.

When comparing term infants with and without CHD, research has demonstrated that 32% of infants with critical CHD exhibit white matter damage on preoperative MRI imaging.²⁷ This type of damage is believed to be associated with alterations in fetal brain blood flow and oxygen delivery.²⁹ However, we speculate that ischemic lesions and white matter damage may not have been detectable in our study due to the utilization of cranial USG as the imaging modality for both preoperative and postoperative assessments of the brain.

This study has several limitations. Firstly, serum BDNF levels during and immediately after the intraoperative period were not assessed, which hindered the determination of the effect of ischemia and reperfusion before and after aortic cross-clamping. Nevertheless, the rise in baseline serum BDNF levels at the postoperative 24th hour indicates a sustained effect of reperfusion. Secondly, while our study compared early cranial ultrasound findings

with serum BDNF levels, further investigations incorporating long-term neurological outcomes alongside serum BDNF levels could be considered for future studies.

In conclusion, serum BDNF levels were initially lower in neonates with CHD who underwent surgery, but increased during the early postoperative period. These results suggest that serum BDNF levels are influenced by CHD and the postoperative period. Given the significance of hypoxia and ischemia in the neurodevelopmental prognosis following cardiac surgery in neonates, utilizing serum BDNF values as a biomarker for early outcomes and prognosis warrants further investigation. Future studies should involve larger patient cohorts and compare serum BDNF levels with other biomarkers to enhance their clinical utility and reliability.

Ethical approval

The study was approved by Başkent University Institutional Review Board and Ethics Committee (Project no: KA21/320, August 13th, 2021). Written informed consent was obtained from the parents of patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: FK, TO, EI, EAN; data collection: FK, TO, CT, EI, OM, AM²; analysis and interpretation of results: KF, TO, OM, AM⁶, CT, AID; draft manuscript preparation: FK, TO, AID, EAN. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The study was supported by Başkent University Research Fund (No: 56054).

Conflict of interest

The authors declare that there is no conflict of interest.

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