Evaluation of the association between the optic nerve sheath diameter and extracorporeal life support time during cardiac surgery in newborns

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Abstract. – OBJECTIVE: Congenital heart disease (CHD), a birth defect, is a major cause of neonatal mortality; however, improvements in surgical procedures and medical treatments have resulted in decreased mortality rates. Nonetheless, postoperative morbidity, particularly cerebral dysfunction, remains an issue in patients receiving extracorporeal life support (ECLS) for cardiac surgeries. Herein, we aimed to assess the association between optic nerve sheath diameter (ONSD) and ECLS time in newborns receiving ECLS for cardiac surgery.

PATIENTS AND METHODS: We enrolled 25 newborn patients who received ECLS for cardiac surgery at our hospital. ONSD was measured at four different time points during the surgery: baseline (T1), 15 min after cross-clamping (T2), after displacement of cross-clamping (T3) and at the end of the surgery (T4). Furthermore, the ECLS time, aortic cross-clamp time, and surgery time were recorded.

RESULTS: The regression analysis revealed a significant association between ONSD and ECLS time, cross-clamp time and surgery time. The correlation analysis showed strong associations between baseline ONSD and ONSD at T2, T3, and T4. Moreover, ONSDs significantly increased at T2 compared with those at baseline during cardiac surgery.

CONCLUSIONS: Our findings suggest an association between ONSD and ECLS time in newborns receiving ECLS for cardiac surgery. Monitoring ONSD may provide valuable information about intracranial pressure changes in these patients.

Key Words: Newborn cardiac surgery, Extracorporeal life support, Intracranial pressure, Optic nerve sheath diameter.

Introduction

Congenital heart disease (CHD), a birth defect, is a major cause of neonatal mortality; however, improvements in surgical procedures and medical treatments have resulted in decreased mortality rates. Thus, more emphasis is being placed on the reduction of neonatal morbidity following cardiac surgery.

According to the Pediatric Extracorporeal Life Support Organization Registry’s global report, children are increasingly receiving extracorporeal life support (ECLS), particularly for cardiac causes. However, up to 70% of patients may have post-ECLS cerebral dysfunction, leading to long-term cognitive and motor impairment, first presenting as brain edema and higher intracranial pressure (ICP). Furthermore, it is difficult to diagnose acute elevations in ICP in pediatric patients since the signs and symptoms are sometimes unclear.

The gold standard for measuring ICP still involves the use of invasive intracranial devices. The ICP monitors have the potential to cause complications, including bleeding in 1.1%-5.8% of cases, malfunction in 6.3%-40% of cases or infection in 0%-15% of cases, with a noticeably higher risk of bacterial colonization after 5 days.

The optic nerve (ON) sheath surrounds ON and covers the optic subarachnoid space, which is attached to the intracranial subarachnoid area. Thus, changes in ICP are directly transferred to the ON sheath. Therefore, the optic nerve sheath diameter (ONSD) is a non-invasive method of measuring ICP.
Long ECLS and aortic cross-clamp (ACC) times have been linked to more frequent computed tomography detection of cerebral oedema. However, there is currently no information on the association between these time points and the ONSD determined by ultrasound.

The primary aim of this study was to identify the association between ONSD and ECLS time in newborns receiving ECLS. We primarily hypothesized that longer ECLS duration during the perioperative period means a higher ONSD value. Our secondary aim was to evaluate the association between ONSD and ACC time, surgery time, and perioperative ONSD variation for the ECLS period.

Patients and Methods

We consecutively enrolled 25 newborn patients who had received ECLS for cardiac surgery at our hospital. The exclusion criteria were as follows: patients who underwent off-pump cardiac surgery; those with a recent history of cerebrovascular accident or intracranial hypertension due to any cause; those with ophthalmological diseases capable of affecting ONSDs and those with a history of increased ICP.

Ethical approval was obtained from the Ethics Committee of Necmettin Erbakan University (2023/4253) on 17 March 2023. This investigation was registered with ClinicalTrials.gov (NCT05930691). This study was carried out according to the Declaration of Helsinki. Informed consent was obtained from the parents of all children included in the study.

Methods of Anesthesia and Cardiopulmonary Bypass (CPB)

All patients underwent standard monitoring procedures, comprising electrocardiography, invasive monitoring of blood pressure, and peripheral oxygen saturation measurements. The same general anesthesia protocol was applied to all patients. The same team of specialists carried out all surgeries: one pediatric cardiovascular anesthesiologist, one pediatric interventional cardiologist, and two pediatric cardiac surgeons.

A colloid solution comprising cleaned same-type red blood cells, plasma, albumin, and 4% succinylated gelatine (Gelofusine) was pre-filled into the STOCKERT-SC roller pump artificial heart-lung machine (Stockert, Munich, Germany). The proper amount of calcium chloride/potassium chloride solution was introduced in the crystalloid solution alongside Ringer’s mannitol and sodium bicarbonate. Extracorporeal membrane oxygenation was set by body weight to achieve systemic hypothermia and hemodilution. Dideco901 membrane oxygenation used a pre-impulse volume of 300-400 mL. Hypothermic low-flow CPB was used during cardiac surgery. Other parameters were also similar: the perfusion flow rate was (100-150 mL)/(kg x min), and the pressure was 45-65 mmHg. The myocardium was protected using the aortic root perfusion method with four cold crystalloid cardioplegia solutions administered at a dose of 10-15 ml/kg. Additional perfusion was provided at intervals of every 35-40 min. The activated clotting time was >480 s with 300 U/kg heparin. The protamine ratio was 1:1.5 after CPB. A 30-minute blood gas analysis was performed.

ONSD Measurement

The diameter of the ON sheath was measured using ultrasound by placing the patient in the supine position with the head at a neutral angle. After coupling gel was applied to the eyelid, three horizontal and vertical measurements were taken for each eye using a 7-10 MHz linear transducer. All measurements were taken 3 mm in front of the point where ON first enters each eye’s sphere. We first determined the average ONSD for each eye and then averaged the results from the two eyes.

The ONSD measurements were analyzed at the baseline (T1), 15 min after cross-clamping (T2), after displacement of cross-clamping (T3) and at the end of the surgery (T4). Peripheral oxygen saturation, blood pressure (systolic, diastolic and mean arterial pressure) and heart rate were recorded at these measurement times. We also recorded ECLS time, ACC time and surgery time.

Statistical Analysis

Based on a similar study, we used the G-power program, the effect size used in the sample size analysis was calculated as 0.740, and the actual power as 0.956 to measure the sample size. The analysis suggested a study sample of at least 22 patients; therefore, the study was planned to stop when the number of patients in both groups reached at least 25 when considering dropout.

SPSS 22.0 (IBM-SPSS Corp., Armonk, NY, USA) was used to analyze the data. In the evaluation of the data obtained from the study, from the descriptive statistical methods, frequency (n),
percent (%), mean ± standard deviation, min (minimum) – max (maximum) and Q25-Q75 (median values and 1st and 3rd quartile values) were used. The Shapiro-Wilk test was used to assess the normality of the data. The Chi-square test was used to compare the qualitative data. The Mann-Whitney U test, one of the non-parametric tests, was used to compare the two groups that did not show a normal distribution in comparing the data according to continuous variables. The Kruskal-Wallis H test was used to compare more than two groups. p < 0.05 was considered statistically significant. Correlation and regression analyses were used to analyze the effects of the data on each other.

Results

We excluded three patients because of intraoperative mortality. Thus, the study included 25 patients [age: newborn to first 28 days]; weight: 4.3-0.59 kg] who underwent surgery for CHD via CPB (Table I). For sex comparison, 15 patients were male, and 10 were female (average weight: 3.14 kg; average height: 48.6 cm). Of these, 22 patients were ASA physical status III, and three were ASA physical status IV. All patients underwent surgery for the transposition of the great arteries, with complete recovery and no mortality after treatment in the intensive care unit. As a demographic and clinical variable, there was a statistically significant difference only in ASA status.

The ONSD measurements are shown in Table II. Regarding changes in ONSD during the study, when comparing time to time, ONSD was greater at T2 in patients than at other time points. In addition, the difference in the ONSD from T1 to T2 was greater (+0.12 mm), and the value at T2 was significantly higher (4.0 vs. 2.8 mm, p = 0.011) in the patients than at other time points.

Table II. Optic nerve sheath diameter values.

<table>
<thead>
<tr>
<th>Time</th>
<th>Optic nerve sheath diameter (N = 25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0.28 ± 0.04</td>
<td>0.200</td>
</tr>
<tr>
<td>T2</td>
<td>0.40 ± 0.03</td>
<td>*0.011</td>
</tr>
<tr>
<td>T3</td>
<td>0.28 ± 0.04</td>
<td>0.133</td>
</tr>
<tr>
<td>T4</td>
<td>0.28 ± 0.03</td>
<td>0.200</td>
</tr>
</tbody>
</table>

Values listed in cm. Data are presented as the mean (range). T1 = Optic nerve sheath diameter basal; T2 = Optic nerve sheath diameter at 15 min of cross-clamp; T3 = Optic nerve sheath diameter after cross-clamp; T4 = Optic nerve sheath diameter at the end of the surgery. Difference was tested by t-test. *p-value less than 0.05.

We recorded all related time intervals as T3, T4 and T4. However, no significant differences were noted in patients according to the time interval of cardiopulmonary processes (Table III).

We analyzed the primary outcome by performing a regression test at T2 on ONSD. Thus, we provided a significant R square number for ECSL time (R square = 0.768, regression test p = 0.024). We also performed regression tests at T2 and T3. We found that the R square number affected ONSD (numerically, R square = 0.761, regression test p = 0.031 and R square = 0.773, regression test p = 0.023) (Table IV).

According to the correlation of ECSL time points, we got a significant correlation, especially between basal ONSD and 15 min of the cross-clamp time ONSD (Figure 1a). Other strong correlations belonged to basal ONSD and after the cross-clamp time ONSD (Figure 1b). Finally, the other correlation occurred between basal ONSD and end of the operation ONSD (Figure 1c) (Table V). The hemodynamic and respiratory data are shown in Table VI. When comparing patients, the heart rate was lower at ACC time points; however, no difference was noted between the time points regarding heart rate. Significant different-

Table I. Demographic and clinical variables of the study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Days)</td>
<td>11.6 ± 8.9</td>
<td>0.889</td>
</tr>
<tr>
<td>Sex (n)</td>
<td>15 male/10 female</td>
<td>0.424</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.14 ± 0.59</td>
<td>0.200</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>48.6 ±3.41</td>
<td>0.200</td>
</tr>
<tr>
<td>ASA (n)</td>
<td>ASA 3 (22)/ASA 4 (3)</td>
<td>*0.001</td>
</tr>
</tbody>
</table>

Data are presented as the mean (range) or number (%). ASA = American Society of Anaesthesiology. *p < 0.05.

Table III. Time interval of cardiopulmonary processes.

<table>
<thead>
<tr>
<th>Time</th>
<th>All (25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECSL Time</td>
<td>157.5 ± 52.7 min</td>
<td>0.150</td>
</tr>
<tr>
<td>Cross Clamp Time</td>
<td>99.4 ± 41.6 min</td>
<td>0.110</td>
</tr>
<tr>
<td>Surgery Time</td>
<td>267.2 ± 58.2 min</td>
<td>0.110</td>
</tr>
</tbody>
</table>

ECLS: Extracorporeal Life Support. Differences tested using a t-test.
Optic nerve sheath diameter in newborn cardiac surgery

**Discussion**

CPB-induced brain injury and its prevention are the major concerns during surgery. Shortly after CPB, a variety of neuropsychological complications, including seizures, memory and cognitive impairment, cerebral palsy, and long-term language and learning disorders, have been observed. CPB-related ICP damage must be diagnosed and treated quickly. In contrast to other imaging methods, such as computed tomography or magnetic resonance imaging, ONSD measurement is a recent technique of optic ultrasound examination that can be done at the patient’s bedside. The ACC and ECLS times are directly correlated with the length of decreased cerebral perfusion. Herein, we assessed ONSD in newborn patients undergoing cardiac surgery. We found a positive association between the ONSD and ECLS times during newborn cardiac surgery.

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**Table IV.** Time interval effects of regression analyses on optic nerve sheath diameter.

<table>
<thead>
<tr>
<th>Time</th>
<th>All (25) mean ± SD</th>
<th>Regression test p-values</th>
<th>Regression analyses R square</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECSL Time</td>
<td>157.5 ± 52.7 min</td>
<td>0.024</td>
<td>α 0.768</td>
</tr>
<tr>
<td>Cross Clamp Time</td>
<td>99.4 ± 41.6 min</td>
<td>0.031</td>
<td>α 0.761</td>
</tr>
<tr>
<td>Surgery Time</td>
<td>267.2 ± 58.2 min</td>
<td>0.023</td>
<td>α 0.773</td>
</tr>
</tbody>
</table>

ECLS: Extracorporeal Life Support. α R square value of < 0.3 is weak, a Value between 0.3 and 0.5 is moderate, and a Value > 0.7 means a strong effect on the dependent variable. *p-value less than 0.05

**Figure 1.** Scattergram of T1 vs. (A) T2, (B) T3 and (C). T4 time points for about ECSL times. Optic nerve sheath diameter at T1 = baseline; T2 = 15 min after cross-clamping; T3 = after displacement of cross-clamping and T4 = at the end of the surgery.

**Table V.** ONSD variations using the partial correlation between the time points compared with ECSL time.

<table>
<thead>
<tr>
<th>Time</th>
<th>All (25) mean ± SD</th>
<th>Correlation test p-values</th>
<th>Pearson correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-T1</td>
<td>0.28 ± 0.04 cm</td>
<td>*0.001</td>
<td>β 0.772</td>
</tr>
<tr>
<td>T1-T2</td>
<td>0.40 ± 0.03 cm</td>
<td>*0.001</td>
<td>β 0.710</td>
</tr>
<tr>
<td>T1-T3</td>
<td>0.28 ± 0.04 cm</td>
<td>*0.001</td>
<td>β 0.901</td>
</tr>
<tr>
<td>T1-T4</td>
<td>0.28 ± 0.03 cm</td>
<td>*0.001</td>
<td></td>
</tr>
</tbody>
</table>

β A correlation coefficient of −1 or +1 indicates a perfect linear association, and the association between two variables is generally considered strong when their r value is larger than 0.7. T1 = baseline; T2 = 15 min after cross-clamping; T3 = after displacement of cross-clamping and T4 = at the end of the surgery. *p < 0.05.
By 24 hours after surgery, the ONSD values had recovered to baseline levels, according to research by Rivas-Rangel et al\(^1\). The median change from baseline to 24 hours was 0.31 mm (interquartile range, 0.055 to 0.78 mm). The findings of our study revealed a positive association between ONSD and ECLS time in newborns undergoing cardiac surgery. The observed association suggests that, as ONSD increases, the ECLS time also increases. The ability to predict the ECLS time based on ONSD measurements can have important implications for clinical decision-making, resource allocation, and patient management strategies. Rivas-Rangel et al\(^1\) measured ONSD at 6 and 24 h post-operatively; however, we assessed ONSD at preoperative, intraoperative and postoperative time points. This broader assessment of ONSD allows for a more detailed analysis of the temporal association between ONSD measurements and ECLS time. Furthermore, it may help identify the critical time points during which changes in ONSD are the most significant or predictive of adverse outcomes.

Lan et al\(^3\) utilized a non-invasive cerebral edema dynamic monitor for the measurement of cerebral electrical impedance coefficients. Their findings revealed that 20 minutes after aortic cross-clamping, the cerebral electrical impedance coefficients on both the left and right sides were significantly elevated in the ECLS-B subgroup compared to the ECLS-A subgroup ($p < 0.05$). These results suggest that prolonged ECLS and ACC durations are associated with increased severity of cerebral edema. Our findings are in line with these results, demonstrating a positive association between ONSD measurements and ECLS and ACC times. However, in addition to these variables, we analyzed surgery time as an intraoperative variable and identified a positive association between ONSD measurements and surgery time. This novel finding suggests that the duration of the surgical procedure contributes to changes in ONSD measurements, indicating the potential development of cerebral edema. Moreover, prolonged surgery times may impose additional stress on cerebral circulation, leading to alterations in ONSD measurements. These findings emphasize the significance of considering the cumulative effect of various intraoperative factors on cerebral physiology. In addition, our study particularly focused on newborn patients, which differs from Lan et al’s study\(^3\).

Increased ICP is associated with an ONSD of >4 mm in children aged <10 years and >5 mm in those aged >10 years\(^15\). The specificity and sensitivity of the ONSD measurement are 38%-100% and 36%-100%, respectively, although they vary greatly between several studies\(^16,17\). Haque et al\(^18\) reported that the limit for ONSD in pediatric patients was >4 mm in newborns, >4.71 mm in patients aged 1-10 years and >5.43 mm in patients over the age of 10 (sensitivity 100%, with specificity 60%-66.7%). Beare et al\(^19\) compared optic ultrasound ONSD measurements in children with acute neurological diseases, with and without clinical signs of increased ICP. The
mean ONSD was 5.4 (4.3-6.2) mm in 14 children with clinical signs of increased ICP. Seven children without clinical signs of increased ICP had an ONSD of 3.6 (2.8-4.4) mm. Using 4.2 mm as the upper limit of normal for ONSD, ONSD had 100% sensitivity and 86% specificity for increased ICP. Later, other researchers proposed higher ONSD cut-offs that might be associated with increased ICP. In 72 pediatric patients undergoing neurosurgical procedures, Kerscher et al\textsuperscript{20} compared ultrasound ONSD values to invasive ICP measurements and recommended 5.28 and 5.57 mm (odds ratio of 22.5 and 7.2 and the area under the curve of 0.782 and 0.733, respectively) as the best ONSD cut-off values for detecting an ICP of 15- and 20-mm Hg.

Yapicioglu et al\textsuperscript{21} measured ONSD in 554 newborn babies and reported that the mean ONSD of the newborn was 4.0 (3.3-4.6) mm and suggested that measurements above 4.0 mm (bilaterally) correspond with elevations in ICP of >20 mmHg. Our study found that at eight of the 100 measurement points, the ONSD was higher than the previously reported normal values of ONSD of >4.0 mm at the age of <1 year. Nevertheless, it should be noted that the measured values in our study did not surpass the thresholds reported by Kerscher et al\textsuperscript{13,20} for increased ICP. Thus, although higher than the previously established normal range, the observed ONSD values in our study did not reach levels directly associated with increased ICP. Additionally, we observed that ONSD was greater in patients at T2. Furthermore, the difference in the ONSD from T1 to T2 was greater (+0.12 mm). The ONSD value at T2 was also significantly higher than that at T1 (4.0 vs. 2.8 mm, respectively; \(p = 0.011\)).

**Limitations**

Although our study provides valuable insights into the association between ONSD and ECLS time in newborn patients undergoing cardiac surgery, it is important to acknowledge certain limitations. First, our study had a relatively small sample size, which may limit the generalizability of our findings to a larger population. A larger sample size would provide more robust results and increase the statistical power of our analysis. Second, this was a single-center study, which may introduce potential bias and limit the external validity of our findings. Multicenter studies including diverse populations would be beneficial to validate our results and enhance the generalizability of the findings.

**Conclusions**

In summary, we assessed the ON sheath in newborn patients undergoing cardiac surgery and found positive associations between ONSD measurements and ECLS, ACC, and surgery times. These results suggest that longer ECLS, ACC, and surgery times lead to increased ONSD measurements, potentially indicating the presence of ICP.

**Conflict of Interest**

The authors have no relevant financial or non-financial interests to disclose.

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**Authors’ Contribution**

All authors contributed to the study’s conception and design. Material preparation, data collection and analysis were performed by Aydın Mermer. The first draft of the manuscript was written by Aydın Mermer. Eyyüp Aydoğan, Abdullah Celep, Murat Şimşek, Hüseyin Dursin, Yasin Tire, Rabia Korkmaz and Betül Kozanhan reviewed and edited previous versions of the manuscript. All authors read and approved the final manuscript.

**Ethics Approval**

The study protocol was approved by the Ethics Committee of Necmettin Erbakan University (Approval Number: 2023/4253). The study adhered to Helsinki Declaration and its latest amendments.

**Informed Consent**

Informed consent was obtained from all individual participants included in the study.

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Data Availability Statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References