Efficacy of Electroencephalographic Monitoring for the Evaluation of Intracranial Injury during Extracorporeal Membrane Oxygenation Support in Neonates and Infants

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**Background:** Neurological complications are a serious concern during extracorporeal membrane oxygenation (ECMO) support in neonates and infants. However, evaluating brain injury during ECMO has limitations. Herein, we report our experience with bedside electroencephalographic monitoring during ECMO support and compared this to post-ECMO brain imaging studies and immediate neurologic outcomes.

**Methods:** We retrospectively reviewed the data for 18 children who underwent ECMO. From these subjects, we reviewed the medical records of 10 subjects who underwent bedside EEG monitoring during ECMO support. We collected data on patient demographics, clinical details of the ECMO course, electroencephalographic monitoring, brain imaging results, and neurologic outcomes.

**Results:** The median age was 4 months (range: 7 days-22 months), the median weight was 5 (3.6-12) kg, and the median length of ECMO therapy was 86 (27-206) hours. Eight patients (80%) were weaned successfully, and seven (70%) survived to discharge. Those with normal to mildly abnormal electroencephalographic findings had non-specific to mildly abnormal brain computed tomography findings and no neurologic impairment. Those patients with a moderately to severely abnormal electroencephalograph had markedly abnormal brain computed tomography findings and remained neurologically impaired.

**Conclusions:** Normal electroencephalographic findings are closely related to normal or mild neurologic impairment. Our results indicate that electroencephalographic monitoring during ECMO support can be a feasible tool for evaluating brain injury although further prospective studies are needed.

**Key Words:** electroencephalography; extracorporeal membrane oxygenation; infant; neonate; neuroimaging.

INTRODUCTION

The first successful extracorporeal membrane oxygenation (ECMO) support was introduced in 1972,[1] and ECMO is currently used as an important mechanical circulatory support in children with severe cardiopulmonary failure.[2,3] Although the long-term neurological outcome after ECMO support in survivors appears to be favorable,[4,5] intracranial injury continues to be a fatal complication. Predicting and evaluating intracranial injury in children during ECMO support has limitations because most patients on ECMO support have unstable vital signs, which limit neuroimaging studies that require moving the patients during ECMO. Neurophysiological monitoring such as electroencephalography (EEG) has been studied in intensive care unit (ICU) settings, but there are limited studies of electroencephalographic monitoring during ECMO support.

Herein, we report a single-center study of bedside neurophysiological EEG monitoring to detect intracranial injury in children during ECMO support and compared this to post-ECMO neuroimaging findings and immediate neurologic impairment.
MATERIALS AND METHODS

We retrospectively reviewed the data for 18 children who underwent ECMO from January 1 to December 31, 2011, at Chonnam National University Hospital (CNUH). We excluded those who were expired before 6 hours of ECMO support and who did not undergo EEG monitoring during ECMO support. From these subjects, we reviewed the medical records of ten subjects who underwent bedside EEG monitoring during ECMO support. We collected data on patient age, weight, sex, and clinical details of the ECMO course, including details on the ECMO cannulation site, type, and duration; type of anticoagulant used; bedside EEG monitoring; post-ECMO brain imaging results; neurological complications following ECMO; and survival in the ten subjects.

EEG monitoring was performed bedside during ECMO using a 16-channel EEG Info Notebook (Compumedics®, Baden-Wuerttemberg, Germany), and the results were evaluated by a pediatric neurologist. Digital EEG was performed using the international 10-20 system. The EEG results were interpreted to assess referential and longitudinal bipolar ("double banana") montages. The children were sedated with morphine (0.01-0.04 mg/kg/hr continuous infusion) or remifentanil (0.4-1 µg/kg/min continuous infusion for infants younger than 2 months and 0.05-1.3 µg/kg/min for older children). When the EEG showed epileptiform abnormalities, including sharp activity or spikes, we administered intravenous antiepileptic drugs such as phenobarbital (15-20 mg/kg in a single dose, followed by 3-8 mg/kg/day in one or two doses as recommended by age) or phenytoin (15-20 mg/kg in a single dose then 5 mg/kg/day in two doses). When we detected slow activity with or without low amplitude, we infused intravenous osmotic agents such as mannitol to treat the suspected brain edema. These interventions were performed immediately after detecting the abnormality, before they were confirmed by a pediatric neurologist, so as not to delay treatment.

Head US was performed daily during ECMO support in patients with an open anterior fontanelle, usually those younger than 6 months of age. After successful weaning from ECMO, when their vital signs were stable, the patients underwent brain computed tomography (CT) and/or brain magnetic resonance imaging (MRI), and were evaluated by a pediatric neurologist. Brain MRI was performed only in patients with abnormal findings in Brain CT with or without delayed milestone.

Neurologic outcomes were assessed at follow up by standard neurological examinations. Gross motor, fine motor, social-personal, language, and cognitive-adaptive milestones were assessed in all patients. Muscle power and tone, balance, coordination, deep tendon reflexes, and cranial nerve examinations were also assessed, if available.

This study protocol was approved by the Institutional Review Board approval for a retrospective data review (CNUH-2012-191). As this study was a retrospective study using medical records, informed consent was exempted by the Review Board.

RESULTS

We retrospectively reviewed ten subjects who received bedside EEG monitoring during ECMO support. The patient population and outcomes are summarized in Table 1. The median age was 4 months (range: 7 days-22 months), the median weight was 5 (range: 3.6-12) kg, and the male-to-female ratio was 1:1.5. The underlying reason for ECMO was cardiogenic shock in seven patients, failure to wean from cardiopulmonary bypass in two patients, and acute respiratory failure in one subject. The cannulation approach for ECMO was transthoracic in nine patients and transcervical in one subject. Of the nine subjects who underwent ECMO via a transthoracic approach, eight had venoarterial ECMO with the venous cannula in the right atrium and arterial cannula in the ascending aorta, and one had venovenous ECMO with cannulas located in the right atrium and main pulmonary artery. In the subject with a transcervical approach, the cannulas were located in the right carotid artery and right internal jugular vein. The median duration of ECMO support was 86 (27-206) hours (Table 1).

Anticoagulants were used in all subjects during ECMO. The first six subjects who underwent ECMO were given intermittent bolus intravenous infusions of heparin, whereas the four subjects who underwent it most recently received a continuous intravenous infusion of nafamostat mesilate. The activated clotting time was maintained at 150-200 seconds and activated partial thromboplastin time was maintained at 60-80 seconds. Of the nine subjects (90%) who were successfully weaned from ECMO, eight (80%) underwent neuroimaging and seven (70%) were discharged without additional support.

All subjects underwent bedside EEG monitoring during ECMO support. The EEG was interpreted as normal in four patients and abnormal in six patients. Among those with an abnormal electroencephalograph, the results were interpreted as mildly abnormal in two patients; one of these patients had a moderate- to high-amplitude background without epileptiform discharge, while the other had transient frontal sharp activity. The EEG were interpreted as moderately abnormal in three patients;
Table 1. Summary of the demographics and clinical details of the ECMO course

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (mon)</th>
<th>Sex</th>
<th>BW (kg)</th>
<th>Diagnosis</th>
<th>ECMO duration (h)</th>
<th>Approach</th>
<th>Mode of ECMO</th>
<th>Weaning</th>
<th>Survived to discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>F</td>
<td>9</td>
<td>Post-CPR</td>
<td>45</td>
<td>Transthoracic</td>
<td>Venoarterial</td>
<td>Successful</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>M</td>
<td>5.9</td>
<td>TOF</td>
<td>33</td>
<td>Transthoracic</td>
<td>Venoarterial</td>
<td>Successful</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>F</td>
<td>3.7</td>
<td>PA VSD</td>
<td>27</td>
<td>Transthoracic</td>
<td>Venoarterial</td>
<td>Failed</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>F</td>
<td>4.1</td>
<td>TGA</td>
<td>83</td>
<td>Transthoracic</td>
<td>Venoarterial</td>
<td>Successful</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>M</td>
<td>7.2</td>
<td>TOF</td>
<td>121</td>
<td>Transthoracic</td>
<td>Venoarterial</td>
<td>Successful</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>M</td>
<td>7.8</td>
<td>Myocarditis</td>
<td>206</td>
<td>Transthoracic</td>
<td>Venoarterial</td>
<td>Failed</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>F</td>
<td>3.6</td>
<td>RF</td>
<td>137</td>
<td>Transthoracic</td>
<td>Venovenous</td>
<td>Successful</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>M</td>
<td>12</td>
<td>Myocarditis</td>
<td>103</td>
<td>Transcervical</td>
<td>Venoarterial</td>
<td>Successful</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
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<td>F</td>
<td>3.8</td>
<td>TAPVR</td>
<td>89</td>
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<td>Venoarterial</td>
<td>Successful</td>
<td>Yes</td>
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<tr>
<td>10</td>
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<td>F</td>
<td>3.8</td>
<td>IAA</td>
<td>63</td>
<td>Transthoracic</td>
<td>Venoarterial</td>
<td>Successful</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Table 2. Electroencephalographic monitoring, neuroimaging studies, and neurologic outcomes

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Intra-ECMO brain CT/MRI</th>
<th>Neurological complications</th>
<th>Follow-up (mon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-ECMO head US</td>
<td>Intra-ECMO EEG</td>
<td>Post-ECMO brain CT/MRI</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NS</td>
<td>Severely abnormal</td>
<td>Hypoxic ischemic injury</td>
</tr>
<tr>
<td>2</td>
<td>NS</td>
<td>Mildly abnormal</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>NS</td>
<td>Normal</td>
<td>Subdural hygroma</td>
</tr>
<tr>
<td>4</td>
<td>Hemorrhage</td>
<td>Moderately abnormal</td>
<td>Hemorrhage with venous infarction</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>Moderately abnormal</td>
<td>Asymmetric lateral ventricle</td>
</tr>
<tr>
<td>7</td>
<td>NS</td>
<td>Mildly abnormal</td>
<td>Acute multiple infarctions</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>Moderately abnormal</td>
<td>Minimal hemorrhaging</td>
</tr>
<tr>
<td>9</td>
<td>NS</td>
<td>Normal</td>
<td>NS</td>
</tr>
</tbody>
</table>

ECMO: extracorporeal membrane oxygenation; EEG: electroencephalography; NS: non-specific.

One patient had low-amplitude irregular slow activity with paroxysmal repetitive sharp activity, one had diffuse high-amplitude irregular delta-range background activity without an apparent vivid epileptiform discharge, and the last patient had marked asymmetric background activity with low-amplitude slow activity. The EEG was interpreted as severely abnormal in one patient with diffuse, low-amplitude, irregular slow activity. Interventions were completed according to our protocol. Among those patients with a moderately to severely abnormal EEG, antiepileptic drugs were used in two patients and an osmotic agent was used in all patients.

For neuroimaging, head US and brain CT/MRI were performed. Head US was performed daily during ECMO support in eight subjects; non-specific findings were found in five subjects, one subject had an intracranial hemorrhage, one had subdural fluid collection, and one had an asymmetric lateral ventricle. Brain CT/MRI was also performed immediately after successful weaning from ECMO in seven subjects and the other two patients could not be weaned off of ECMO support. Non-specific findings were observed in two patients and abnormal findings were found in six patients. Among those patients with abnormal findings, mildly abnormal findings were observed in three patients, including a small subdural hygroma, asymmetric lateral ventricle, and minimal hemorrhage. Moderately to severely abnormal findings were found in the other three patients, including hypoxic ischemic injury, multiple hemorrhages with venous infarction, and multiple arterial infarctions (Table 2).

All of those patients with a moderately to severely abnormal EEG, except for one who could not be weaned off of ECMO support, showed markedly abnormal brain CT findings and all of them remained neurologically impaired after weaning from ECMO. Those with normal to mildly abnormal electroencephalographic findings showed non-specific to mildly abnormal brain CT findings and no immediate neurologic impairment was presented.

Normal motor function and milestones were found in five patients (50%), moderately impaired motor function in one patient (10%), and severe motor and neurologic impairment in two pa-
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Fig. 1. Subject 1. (A) EEG showed diffuse low-amplitude irregular slow activity. (B) Brain CT revealed a global hypoxic ischemic brain injury and subacute subdural hemorrhage. (C) Brain MRI revealed the same findings. EEG: electroencephalography.

Fig. 2. Subject 5. (A) EEG showed low-amplitude irregular slow activity. (B) Paroxysmal repetitive sharp activity and (C) high-amplitude rhythmic slow or fast activity. (D) Brain CT revealed a hemorrhage and venous infarction. (E) Brain MRI showed venous infarctions. EEG: electroencephalography.

tients (20%). Three patients (30%) had cerebral palsy. We have summarized these cases below. The median follow-up period was 20 (range: 4–25) months.

1. Case 1

A 6-month-old girl was placed on venoarterial ECMO. Head US during ECMO did not reveal abnormal findings. The EEG findings were described as a severely abnormal background with diffuse, low-amplitude, irregular slow activity (Fig. 1A). This patient received intravenous osmotic agents during ECMO support. Post-ECMO brain CT revealed a global hypoxic ischemic brain injury involving the cerebral and cerebellar hemispheres bilaterally, a subacute subdural hemorrhage along the cerebellum and left occipital lobe, and mild communicating hydrocephalus (Fig. 1B). Brain MRI taken 11 days post-ECMO revealed the same findings (Fig. 1C). This child survived and was discharged after successful weaning from ECMO; however, she remained severely impaired. At 25 months, she had spasticity and rigidity in her muscle tone and was microcephalic with a head circumference below the 3rd percentile. She also had hearing loss.

2. Case 5

A 5-month-old boy was placed on venoarterial ECMO for cardiogenic shock after cardiac surgery due to tetralogy of Fallot. Head US during ECMO support revealed some fluid in the frontal area with intracranial hemorrhaging. Bedside EEG monitoring during ECMO showed moderately abnormal findings with low-amplitude irregular slow activity, especially in both posterior head lesions (Fig. 2A), and paroxysmal repetitive sharp activity in the right centrotemporal area (Fig. 2B). Additionally,
Fig. 3. Subject 8. (A) EEG showed marked asymmetric background activity with low-amplitude slow activity in the right hemisphere. (B) Brain CT revealed multifocal acute infarctions in the right hemisphere. (C) Brain MRI revealed chronic infarctions involving the right hemisphere. EEG: electroencephalography.

high-amplitude rhythmic slow or fast activity was recorded in the same area (Fig. 2C). This patient was in a non-convulsive state and did not show any abnormal activity. He received both antiepileptic drugs and osmotic agents as soon as these abnormalities on bedside EEG were found. Post-ECMO brain imaging studies revealed an enlarged vein of Galen and dural sinuses, a hypoattenuated lesion in the cortex, and a subcortical lesion in the left frontal and left parietal lobes with hemorrhaging, indicating a venous infarction. Additionally, gyral hyperattenuation and diffuse subdural fluid were observed in both cerebral hemispheres (Fig. 2D, 2E). This child survived and was discharged home after successful weaning from ECMO; however, he remained neurologically impaired on the left side of his body. At 20 months, the neurologic complications were greatly resolved with remaining mild discomfort on the left side of the patient’s body.

3. Case 8

A 22-month-old boy was placed on venoarterial ECMO support by a transcervical approach for cardiogenic shock with acute myocarditis. Bedside EEG monitoring showed marked asymmetric background activity with low-amplitude slow activity in the right hemisphere (Fig. 3A). This patient received both antiepileptic drugs and an osmotic agent due to a severely abnormal EEG and an apparent significant convulsive seizure on the left side of his body. Post-ECMO brain CT showed multifocal acute infarctions in the right cerebral hemisphere with gyral swelling, but no evidence of acute intracranial hemorrhaging (Fig. 3B). Brain MRI 36 days post-ECMO revealed chronic infarctions involving the right cerebral hemisphere and right basal ganglia along with diffuse brain atrophy and communicating hydrocephalus (Fig. 3C). This child survived and was discharged home after successful weaning from ECMO; however, he remained neurologically impaired on the left side of his body. At 20 months, the neurologic complications were greatly resolved with remaining mild discomfort on the left side of the patient’s body.

DISCUSSION

In this study, we reported a single-center experience of bedside electroencephalographic monitoring to detect intracranial injury in neonates and infants during ECMO support and compared this to post-ECMO brain imaging studies and immediate neurologic impairment. Normal or mildly abnormal electroencephalographic findings resulted in normal or mildly abnormal brain imaging results with no short-term neurologic impairment. However, in those patients with moderately to severely abnormal electroencephalographic findings, there was cerebrovascular infarction, hypoxic ischemic encephalopathy, and intracranial hemorrhaging in brain imaging studies after weaning from ECMO; in these patients, severe neurologic impairment was observed.

Neurological complications are among the most serious concerns to physicians during ECMO since it may impact quality of life and survival. Joffe et al.[6] reviewed previously reported survival and neurological outcomes to determine a cumulative survival rate of 45% in children with cardiac ECMO and neurologic impairment rate of 51%.

Among children in the Extracorporeal Life Support Organization Registry, an intracranial hemorrhage was reported in 7.4% of patients, cerebral infarction in 5.7%, and clinically diagnosed seizures in 8.4%.[7] This retrospective study represents an effort at predicting neurologic outcome during ECMO support; we had three patients (30%) with severe neurologic impairment after successful weaning from ECMO.

Systemic anticoagulation is essential to prevent thrombosis during ECMO support, and the use of heparin, nafamostat mesylate (a synthetic protease inhibitor), argatroban (direct thrombin inhibitor), and lepirudin (direct thrombin inhibitor) has been
reported.[8-10] In this study, we used heparin for the first six patients, and one of these patients remained severely impaired. We used nafamostat mesylate to reduce bleeding complications during ECMO support in the most recent four patients, and two of these patients remained moderately to severely neurologically impaired. However, additional studies are needed to determine the correlation between the type of anticoagulant and neurologic outcome.

EEG monitoring provides valuable information about the patient’s functional neurological status, enabling early intervention. EEG monitoring is widely used in the ICU, particularly in comatose patients or patients with convulsive or non-convulsive status epilepticus, acute structural brain lesions, and traumatic brain lesions.[11-15] EEG monitors are portable and can be used relatively inexpensively at the bedside of patients with unstable vital signs. All of the patients in this study underwent bedside EEG monitoring during ECMO support and received appropriate interventions according to the changes in EEG. Antiepileptic drugs were used by physicians or nurses when the EEG showed frequent sharp waves or spikes, and osmotic agents were used when the EEG showed slow waves with or without a low amplitude. Marked brain edema is known to produce slow waves by pressure, and the amount of slowing observed by EEG is known to parallel the perfusion-weighted MRI lesion volume and amount of brain edema.[16,17] EEG is thought to be a useful tool for monitoring brain perfusion, especially in cases of ischemic brain injury, because it changes as cerebral blood flow changes.[18] The children on ECMO support are exposed to decreased brain perfusion, as well as increased brain edema, and in this study we surmised that an osmotic agent would help before any aggressive interventions were done.

Many studies have assessed the effective and early detection of neurologic complications. Head US is useful for evaluating infants on ECMO support, especially those younger than 6 months, while the fontanelles are still open. Head US is feasible for screening before and during ECMO support as it is portable and does not produce radiation. Bulas et al.[19] reported that head US identified 94% of major intracranial hemorrhages, allowing their acute management. However, head US has some limitations: it can only be performed in young infants and gives a limited view for identifying non-hemorrhagic lesions such as generalized edema or diffuse hypoxic ischemic injuries.[20] Furthermore, Doppler tracing is not always successful due to the reduced pulsatility in patients on venoarterial ECMO. In this present study, we performed head US in those under 6 months of age during ECMO support. Head US revealed fluid collections and hemorrhaging but failed to detect ischemic lesions.

Brain CT and MRI provide better images and additional information in 72–93% of ECMO patients.[19,20] CT or MRI is recommended for identifying non-hemorrhagic and small hemorrhagic lesions.[19,21] Nevertheless, CT and MRI are not portable and are difficult to perform in patients on ECMO support with unstable vital signs. In this study, we performed brain CT in eight patients who survived and were successfully weaned from ECMO. Brain MRI was performed in those patients with abnormalities to see the details. Initial brain MRI would have given better information than brain CT, but we thought that brain CT would be safer to perform because it takes less time to gather the images and most patients immediately weaned from ECMO have unstable vital signs.

We could not statistically analyze our results due to the small number of patients and have simply described the results of the study. In this study, we reported a relatively high incidence of successful ECMO weaning. This could be due to the fact that we had two patients with cardiopulmonary bypass weaning failure that needed short-term support after open heart surgery. It is also known that in neonates, infants, and young children, transcervical cannulation is preferred to a transsthoracic approach. In this study, nine of ten patients had a trans-sternal approach, and the remaining patient with acute myocarditis underwent a transcervical approach. Seven patients underwent open heart surgery and were more prone to a sternotomy. Two other patients with myocarditis and respiratory failure also underwent a trans-sternal approach. The patient with myocarditis had compromising heart function and unstable failure, and we decided to give full support by a trans-sternal approach. In the patient with respiratory failure, a trans-sternal approach was performed since double lumen catheters for venovenous support are not yet available in our country.

In conclusion, we used EEG monitoring during ECMO support to predict neurologic complications earlier and reduce secondary damage to the brain. Our early experience with bedside EEG monitoring during ECMO support suggests that normal electroencephalographic findings during ECMO support did not always result in normal brain imaging findings after ECMO weaning. However, normal EEG findings are closely related to a normal neurologic outcome. Moderately to severely abnormal EEG findings during ECMO support not only result in moderately to severely abnormal brain imaging findings after weaning from ECMO, but are also closely related to moderate to severe neurologic impairment. We believe that EEG monitoring is a useful tool for predicting acute cerebral injury during ECMO.
support and can help physicians to inform their parents about the short term neurologic outcome. Additional prospectively designed studies are required to support the use of EEG monitoring in neonates and infants receiving ECMO support.

REFERENCES