Value of electroencephalographic monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia

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ABSTRACT

Background: The values of electroencephalography (EEG) in neonatal hypoxic-ischemic encephalopathy (HIE) during therapeutic hypothermia (TH) are still uncertain. Aims: The aim of this study is to detect EEG background, the prevalence of seizures during cooling, and to determine different EEG patterns that can predict brain injury in magnetic resonance imaging (MRI).

Patients and Methods: Thirty-nine newborns with HIE were subjected to TH. Continuous monitoring by video-EEG was carried out throughout cooling and during rewarming. MRI was done for all newborns after rewarming. The predictive value of EEG background for MRI brain injury was evaluated at 6-h intervals during cooling and rewarming. Results: At all-time intervals, normal EEG was associated with no or mild MRI brain injury. At the beginning of cooling, normal background was more predictive of a favorable MRI outcome than at later time points. After 24 h of monitoring, diffuse burst suppression and depressed patterns had the greatest prognostic value. In most patients, a discontinuous pattern was not associated with poor prognosis. Thirty-one percent developed electrical seizures, and 8% developed status epilepticus. Seizures were subclinical in 42%. There is a significant association between duration of seizure patterns detected on the EEG and severity of brain injury on MRI. Conclusions: Continuous EEG monitoring in newborns with HIE under cooling has a prognostic value about early MRI brain injury and identifies electrographic seizures, approximately 50% of which are subclinical. Treatment of clinical and subclinical seizure results in a reduction of the total duration of seizure pattern supports the hypothesis that subclinical seizures should be treated.

Key words: Electroencephalographic monitoring, hypoxic-ischemic encephalopathy, therapeutic hypothermia

Introduction

Perinatal asphyxia is a significant cause of brain damage in the human newborns and can result in long-term neurodevelopmental disability.1 Neonatal seizures are important risk factors for impaired neurodevelopment in neonatal hypoxic-ischemic encephalopathy (HIE). Most studies of neonatal seizures depend on clinically diagnosed seizures. However, increased use of continuous electroencephalographic (EEG) monitoring has clarified the fact that seizures in newborns are often subclinical.

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and that neonatologists have difficulties in distinguishing seizures from nonepileptic spells. There had been conflicts as to the importance of seizures that are electrographic without clinical manifestations as compared with those that manifest obvious clinical signs. Previous studies found a clear relationship between seizure load and injury on magnetic resonance imaging (MRI). However, little is known regarding frequency of seizure, its distribution, its time of onset and seizure expression, and their relationship to MRI brain injury during therapeutic hypothermia (TH). Our aim was to determine the value of video-EEG monitoring in newborns with HIE treated by hypothermia through determination of EEG background, prevalence of seizures during TH, determination of EEG patterns that can predict MRI brain injury and value of detection, and treatment of subclinical seizures.

### Patients and Methods

This work was conducted on 39 full-term newborns with HIE admitted to the Neonatal Intensive Care Unit (NICU) of Al Hada and Taif Military Hospitals, Saudi Arabia. Their gestational ages ranged from 37 to 40 weeks with a mean of 38 ± 1.8. Their weights ranged from 3.1 to 3.8 kg with a mean of 3.32 ± 0.56; 46% were males and 54% were females. All cases were subjected to TH with whole-body cooling according to standard protocols.

Inclusion criteria for TH included:
1. Gestational age at birth ≥36 weeks.
2. Any of the following:
   a. pH < 7.0 of cord or first blood gas
   b. Base deficit > 12 of cord or first blood gas
   c. 10-min Agar score < 5.

Exclusion criteria included premature babies known or suspected cases of metabolic disorders and congenital anomalies. TH was initiated as early as possible after birth with whole-body cooling (target temperature 33.5°C) for 72 h followed by rewarming over 6 h. Antiepileptic drugs were used to control seizures according to guidelines. Sedation was done for all patients using continuous infusion of morphine in a dose of (10–25 µg/kg/h) all over cooling to prevent any abnormal movement.

Newborns with seizure were subdivided into two groups: Group 1 included newborns with a treatment of both types of (clinical and subclinical) seizures (12 cases). Group 2 included newborns with the treatment of clinical seizures only (7 cases).

### Video-electroencephalographic monitoring

Full 10–20 system of electrodes for neonatal EEGs was done. A NicoletOne EEG monitor was used to record continuous video-EEG recordings for 72 h. It started early after birth. Vital data were reported simultaneously with the EEG record. EEG background at the onset of the recording was classified into one of five patterns: (1) transient discontinuity for less than one-half of the recording is considered normal for gestational age. (2) Excessively discontinuous, with an existence of discontinuity for more than one-half of the recording. (3) Depressed and undifferentiated, there is an absence of faster frequencies with persistence of a low background activity. There is also often a suppression of amplitude (5–15 µV), and the tracing may be more discontinuous that would be expected for gestational age. (4) Burst suppression (BS) pattern is characterized by periods of excessively suppressed background (≤5 µV) interrupted by bursts of abnormal activity. This pattern is not reactive to stimulation and very monomorphic [Figure 1]. (5) Extremely low voltage, with amplitude < 5 µV or with no perceptible cerebral activity. A repetitive rhythmic activity of > 10 s duration identifies an electrographic seizure, with a sharp beginning, middle, and end with clear evolution. These features are important in differentiating of ictal rhythmic discharges from artifacts [Figure 2]. When electrographic seizure activity was continued for at least half an hour or recurs for at least one‑half of 1–3 h recording time, status epilepticus (SE) was identified.

### Brain magnetic resonance imaging

Neonates were imaged with conventional T1-weighted, T2-weighted, and diffusion-weighted imaging sequences. After rewarming, infants were imaged at a median age of 5 days. Basal ganglia/thalamus score < 2 and watershed score < 3 identify normal to mild MRI injury. Basal ganglia/thalamus score ≥ 2 or watershed pattern ≥ 3 identifies moderate to severe MRI injury.

### Statistical analysis

Data were analyzed with SPSS, and variables were analyzed with t-test and Chi-square. P value was considered significant below 0.05. Specificity and sensitivity were used to assess the prognostic value of EEG background patterns at different
intervals. Linear regression analysis was used to test the relationship between the duration of seizure patterns and MRI scores.

**Results**

The results of our study are shown in the tables and figures.

All clinical characteristics were not significantly associated with brain injury in MRI [Table 1].

**Beginning of cooling**

At the beginning of cooling, no one of newborns whom background was normal had moderate to severe injury. In 12 newborns whom background pattern was excessively discontinuous, 9 (75%) had normal or mild injury and 3 (25%) had moderate to severe injury. BS or extremely low-voltage pattern was found in 16 newborns, 10 (62.5%) had moderate to severe injury and 6 (37.5%) newborns had a normal MRI or only a mild injury. EEG improved in all six newborns with BS or extremely low-voltage pattern by 12–18 h of recording and background normalized by the middle of cooling [Table 2].

**Middle of cooling**

During this interval, one newborn whom EEG improved from a discontinuous pattern to a normal one at the beginning of cooling had moderate to severe injury. In 11 infants with a discontinuous EEG pattern, the background had moderate to severe injury in (2/11, 18%). All newborns (7/7, 100%) with BS or extremely low-voltage patterns had moderate to severe injury [Table 2].

**End of cooling**

Among the 11 infants whom background was normal, 2 (18%) of them showed moderate to severe MRI injury. Furthermore, among the 15 infants with an excessively discontinuous pattern, 2 (13%) of them showed moderate to severe MRI injury. Compared to all five infants (100%) whom background had BS or extremely low voltage [Table 2].

**After cooling**

The same two newborns whom background was normal (13%) at this time point showed moderate to severe injury. After rewarming, all six infants with BS or extremely low-voltage patterns had moderate to severe injury [Table 2].

**Electrographic seizures**

Twelve newborns (31%) showed electrographic seizures, 3 of them had SE. Seizure onset was in the first few hours of recording in most of cases. Seizures recurred during the middle of cooling in two infants and during rewarming in another two. Among the 12 infants with electrographic seizures, 5 infants (42%) did not show a clinical correlate (subclinical seizure). Among the five infants with subclinical seizure, three of them showed subclinical SE. All three infants with SE showed BS or extremely low-voltage patterns with the start of cooling.

Patients with moderate to severe MRI injury had isolated or recurrent seizures more frequently than those with no or mild injury (47% vs. 21%, P = 0.05), and the SE was seen only in infants with moderate to severe injury (P = 0.01) [Table 3].

A normal EEG background at the start of cooling was more predictive of a favorable MRI outcome than at later time points with a specificity of 100% and 80%, respectively. BS pattern or extremely low-voltage background is of a prognostic value for moderate to severe injury that increased from the start of cooling (75% specificity) to the middle of cooling and later (100% specificity) [Table 4].

There were no differences between groups regarding clinical characteristics. The duration (median ± standard deviation) of seizure patterns was 42 ± 83 min in Group 1, compared with 86 ± 134 min in Group 2 [Figure 3]. No significant

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**Table 1: Clinical characteristics of newborns in relation to brain injury**

| Character                        | Normal/mild MRI injury | Moderate/severe MRI injury | P  |
|---------------------------------|------------------------|----------------------------|----|
| Gestational age, mean±SD        | 38±1.2                 | 38±1.6                     | 0.7|
| Sex ratio, male: female         | 1:1                    | 1:1.4                      | 0.5|
| Birth weight, mean±SD           | 3.3±0.4                | 3.1±0.3                    | 0.8|
| Cord or blood gas pH, mean±SD   | 6.98±0.22              | 6.82±0.13                  | 0.06|
| 10-min Apgar score median (range)| 5 (1-8)               | 4 (0-7)                    | 0.08|

SD: Standard deviation, MRI: Magnetic resonance imaging
Previous studies for prediction of seizures were based on clinically diagnosed seizures, confirmed by intermittent EEG recordings. Subclinical seizures constitute about two-thirds of neonatal seizures and require video-EEG monitoring to be diagnosed. Continuous video-EEG monitoring is considered the most accurate test for neonatal seizure detection. The potential of neuroprotective therapies, such as hypothermia, has raised the importance of accurate prediction of outcome in the first hours of life. Our study showed that none of the clinical characteristics were associated with brain injury in MRI. These data were concordant with that reported by Murray et al., 2009, who reported neither the condition at birth nor the degree of metabolic acidosis reliably predicts the occurrence of seizures. Throughout all treatment periods, a normal EEG was associated with no or mild MRI brain injury. At the start of cooling, a normal EEG background had better predictive value (100% specificity) than at later time points (80% specificity). Over the first 24 h of monitoring, only one newborn with moderate to severe MRI injury showed improvement in the EEG background from excessively discontinuous to normal. Our data are in agreement with Monod et al., 1972, Holmes et al., 1982, Holmes and Lombroso, 1993, and Nash et al., 2011, who reported that normal EEG background at the start of cooling had better predictive value than at later time points with a specificity of 100% and 93%, respectively. However, BS pattern or extremely low-voltage background is of a prognostic value for moderate to severe injury that increased from the start of cooling (75% specificity) to middle of cooling and later (100% specificity), reflecting six newborns with these patterns at the start of recording who were protected from further injury by middle of cooling. Similar results were reported by Nash et al., 2011 and Biagioni et al., 1999. Poor neurological outcomes are associated with severely abnormal EEG background activity. Abnormal EEG background activity continuous for 24 h or more or getting worse denotes poor prognosis. Good prognostic features include improvement of EEG background activity in the form of increase in voltage, decrease in discontinuity, or appearance of sleep-wake cycles within 12–24 h after

### Table 2: Electroencephalographic background during cooling in relation to magnetic resonance imaging brain injury

| EEG background | Phase of hypothermia | Start | Middle | End | After |
|---------------|---------------------|-------|--------|-----|-------|
|               | None/mild | Moderate/severe | None/mild | Moderate/severe | None/mild | Moderate/severe | None/mild | Moderate/severe |
| Normal        | 7 (100)    | 0       | 13 (82) | 3 (18) | 9 (82) | 2 (18) | 13 (87) | 2 (13) |
| Excessively discontinuous | 9 (75) | 3 (25) | 9 (82) | 2 (18) | 13 (87) | 2 (18) | 9 (75) | 3 (25) |
| Depressed and undifferentiated | 2 (50) | 2 (50) | 2 (40) | 3 (60) | 2 (25) | 6 (75) | 2 (33) | 4 (67) |
| Burst suppression | 3 (38) | 5 (62) | 0       | 4 (100) | 0       | 3 (100) | 0       | 4 (100) |
| Extremely low voltage | 3 (38) | 5 (62) | 0       | 3 (100) | 0       | 2 (100) | 0       | 2 (100) |

Values are n (%). EEG: Electroencephalography

### Table 3: Background of electroencephalographic, seizures, status epilepticus, and outcome of magnetic resonance imaging brain outcome

| EEG background pattern, median (range) | Normal/mild MRI injury (n=24) | Moderate/severe MRI injury (n=16) | P |
|---------------------------------------|--------------------------------|----------------------------------|---|
| Start of cooling                       | 3 (1-5)                        | 3 (1-5)                          | 0.009 |
| Middle of cooling                     | 2.5 (1-3)                      | 2 (1-5)                          | 0.001 |
| End of cooling                        | 2 (1-3)                        | 1 (1-5)                          | 0.007 |
| After cooling                         | 2 (1-3)                        | 2 (1-5)                          | 0.006 |
| Seizures, n (%)                       | 5 (21)                         | 7 (47)                           | 0.05 |
| Status epilepticus, n (%)             | 0                               | 3 (20)                           | 0.01 |

Scoring of EEG background: Normal=1; excessively discontinuous=2; depressed and undifferentiated=3; burst suppression=4; extremely low voltage=5. MRI: Magnetic resonance imaging, EEG: Electroencephalography

### Figure 3: Duration of seizure patterns for the clinical and subclinical seizure treatment Group 1 and the clinical seizure treatment Group 2. The horizontal lines indicate the median. The vertical lines indicate the limit lines: Ranges

### Discussion

Early prediction of long-term outcome in newborns with HIE is very crucial. Some complicating factors are encountered during TH in the form of sedation and clinical changes that occur during cooling. Brain MRI provides structural details only and its sensitivity for HIE in the first few days of life is of a limited value. Video-EEG monitoring is considered the gold standard test for assessment of brain functions and for detection of subclinical seizure in neonatal HIE. Previous studies for prediction of seizures were based on clinically diagnosed seizures, confirmed by intermittent EEG recordings. Subclinical seizures constitute about two-thirds of neonatal seizures and require video-EEG monitoring to be diagnosed. Continuous video-EEG monitoring is considered the most accurate test for neonatal seizure detection.
Specificity %
Previous studies 100
54
75
In
Phase of hypothermia
73
67
In our study, by the 2nd day of life coinciding with birth.[21] In our study, by the 2nd day of life coinciding with the time of middle of cooling, a BS or extremely low-voltage EEG becomes of high predictive value for detection of moderate to severe MRI injury. Thoresen et al., 2010, studied the effect of cooling on amplitude-integrated EEG in infants with asphyxia. He found that a severely abnormal EEG background pattern in the cooled infants was not specific for abnormal developmental outcome until the 2nd day of life.[14] Serial EEGs are preferred to single recordings so that persistence of abnormalities can be determined. Single recordings may have little significance; however, if the pattern persists for several weeks, it may be of more prognostic value. As an example, an EEG obtained soon after birth can show significant abnormalities due to stress of birth; these abnormalities may disappear completely within a few days and thus have little clinical significance.[12] Severity of neonatal EEG abnormalities correlates with the severity of neurological insult to the neonate. This makes EEG in this age group a valuable tool in predicting outcome of at-risk neonates. Markedly abnormal and normal EEGs have the greatest reliability in predicting poor and good outcomes, respectively.[11,20] Between these two extremes, there are many background patterns with different prognostic values that are difficult to use with different studies giving varying results. In such conditions, other neuroimaging studies and evoked potentials in conjunction with clinical evaluation and EEG monitoring can determine the

Sensitivity %

Specificity %

Start

Middle

End

After

1 versus 2, 3, 4, 5
100
29
80
54
87
37.5
87
54
1, 2 versus 3, 4, 5
80
62.5
67
92
73
92
67
92
1, 2, 3 versus 4, 5
67
75
47
100
33
100
40
100
1, 2, 3, 4 versus 5
33
87.5
20
13
100
13
100
13
Normal=1; excessively discontinuous=2; depressed and undifferentiated=3; burst suppression=4; extremely low voltage=5. *Sensitivity: Percent detected as positive by EEG giving moderate to severe injury. **Specificity: Percent detected as negative by EEG giving no moderate to severe injury. EEG: Electroencephalography

Figure 4: Relationship between duration of seizure patterns and magnetic resonance imaging scores (linear regression) in Group 1
SE had severely abnormal MRI while not all newborns with isolated or recurrent seizures were associated with moderate to severe brain injury. These findings are in concordance of other authors who reported that newborns with SE had a significantly worse outcome in comparison to newborns with recurrent seizures. Furthermore, we were able to show that immediate treatment of clinical and subclinical seizure patterns detected in EEG results in a reduction of total duration of seizure patterns, and there is a significant association between duration of seizure patterns detected in the EEG and severity of brain injury as seen on MRI. The finding that treatment of clinical and subclinical seizures results in a reduction of total seizure duration supports the hypothesis that subclinical seizures should be treated. In most NICUs doing EEG monitoring, treatment of subclinical seizures is recommended. Whether this policy has a positive impact on prognosis has not yet proven, but there is some evidence for the best outcome for treating infants. There are some limitations to our study; we used MRI as a short-term outcome measure and long-term outcome is not known in our patients. Although cooling does not affect the prognostic value of MRI in newborns with HIE, long-term developmental follow-up of our patients to confirm our results is recommend. Finally, we did not include a control group in our study as the protocol in our unit to subject any case fulfilling the criteria of TH to early cooling. This was based on safety and benefits of TH as well as the lack of other effective therapies. Further studies are recommended to clarify that EEG patterns are attributed to either brain injury or therapeutic intervention (hypothermia and medications).

Conclusions

We can conclude that EEG monitoring in newborns with HIE is very crucial in seizure management and prognosis. EEG remains a gold standard test even during cooling. A trend was found for a reduction in the duration of seizure patterns when clinical and subclinical seizures were treated. This trend and the significant association of seizure duration and severity of brain injury found on MRI scans suggest that recognition and treatment of neonatal seizures (clinical and subclinical) in infants with HIE can reduce brain injury.

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Conflicts of interest

There are no conflicts of interest.

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