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Evaluation of whole body hypothermia in term neonates with hypoxic ischemic encepholopathy

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Summary

Aim: To investigate the effect of whole body hypothermia on short term neonatal morbidities and long term neurodevelopmental outcome in term neonates with hypoxic ischemic encephalopathy.

Material and Method: Neonates with perinatal asphyxia and hypoxic ischemic encepholopathy (stage 2 and 3) were enrolled. Patients were divided into two groups according to findings observed on amplitude-integrated electroencephalography (aEEG). Patients with abnormal EEG pattern in the first 6 hours after birth were defined as group 1 and others as group 2. Patients in group 1 were treated with whole body hypothermia. Neurodevelopmental outcome was evaluated at 18 months of age in survivors using Bayley Scales of Infant Development II. Mental developmental index and psychomotor development index scores were calculated.

Results: Thirty five patients were enrolled (M/F=17/18) 18 (51%) of whom were treated with hypothermia. Bradycardia was observed in 44.4% of patients in group 1 and 5.9% of patients in group 2 (p=0.04). Incidence of other possible adverse events related to hypothermia were similar between the two groups. Mortality was higher in group 1 (p=0.03). In group 1.70% of the patients and in group 2.86% of the patients were evaluated using Bayley Scales of Infant Development II. Although patients treated with hypothermia had a higher mental developmental index and psychomotor development index scores, the difference was not statistically significant.

Conclusions: Whole body hypothermia can be safely applied in term neonates with HIE. Hypothermia may improve neurodevelopmental outcome. *(Turk Arch Ped 2011; 46: 277-82)*

Key words: Hypothermia, hypoxic ischemic encephalopathy, newborn, perinatal asphyxia

Introduction

Hypoxic ischemic encephalopathy (HIE) is still a common cause of death in newborns and significant neurological disorders can be observed in survivors (1). To decrease the mortality rate and morbidities in infants exposed to hypoxic ischemia neuroprotective treatments in addition to supportive care should be started in the shortest time possible (2). Hypothermia seems to be the strongest and safest option among neuroprotective treatments (3).

In this prospective study, whole body hypothermia was performed in newborns with a diagnosis of HIE selected according to clinical findings and findings of brain function monitorization (BFM) and it was aimed to evaluate the subjects in terms of both post-natal early problems and neurodevelopmental outcomes in the long-term.

Material and Method

The study was conducted in the Neonatal Intensive Care Unit (NICU) of our hospital between June 2008 and January 2011. Approval was given from the local ethics committee for the study (Ethics committee approval number: 8). The families were informed in detail before hypothermia application and written informed consent was obtained.

Study inclusion criteria

• Newborns with a prediagnosis of perinatal asphyxia (PNA) and HIR (stage 2 or 3) with a gestational age ≥ 37 weeks born in our hospital or referred to our hospital during the first 6 hours after delivery

• Subjects who fulfilled at least two of the following criteria were considered to have PNA:

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- Presence of metabolic or mixed acidosis (pH≤7.1 in umbilical artery blood gas analysis or in peripheral arterial blood gas analysis obtained in the first hour),
- An APGAR score of 0-3 after the fifth minute,
- Presence of seizures, hypotonia, coma or neurological findings related to HIA in the early neonatal period,
- Findings related to multiple organ failure in the early neonatal period.

• Staging for hypoxic ischemic encephalopaty was done according to Sarnat Clinical Staging System (5).

Study exclusion criteria

1) Preterm babies with a gestational age of <37 weeks
2) Newborns with severe congenital malformations
3) Newborns in whom BFM could not be started in the first 6 hours after delivery (referred newborns).

Brain function monitorization

BFM was started in the first 6 hours after delivery in the subjects who were included in the study anda EEG records were taken. The device named OLYMPIC BİM 6000 (Natus, Seattle, ABD) and gel electrodes were used in monitorization.

According to this normal, moderately normal and severely abnormal seizure traces were determined (Figure 1-4).

Normal trace: Sleep-awakeness cycle is present, upper limit >10 µV, lower limit >5 µV, limited variance

Moderately abnormal trace: No sleep-awakeness cycle, upper limit >10 µV, lower limit <5 µV, increased variance

Severely abnormal trace: No sleep-awakeness cycle, upper limit <10 µV, substantially decreased variance

Seizure activity: Gradual increase and decrease in the frequency and amplitude, recurring spikes and sharp waves of 5-10 seconds.

aEEG samples of our subjects are shown in Figure 5-8.

Constitution of the groups

The subjects were divided into two groups according to brain function monitorization:

Group 1 (subjects in whom hypothermia was performed): subjects with moderately abnormal and severley abnormal seizure traces and subjects in whom seizure was observed in the first 6 hours, although BFM findings were normal

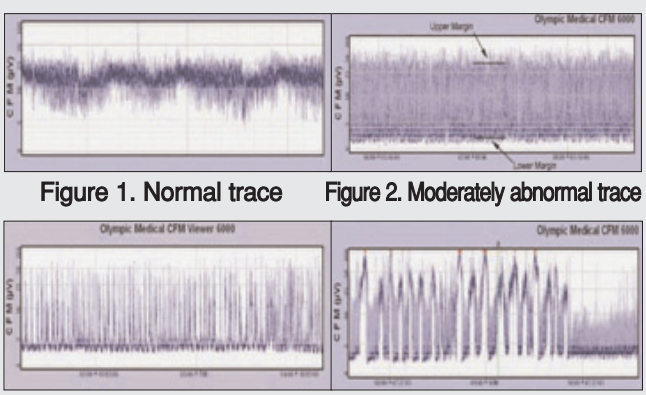

Figure 1. Normal trace Figure 2. Moderately abnormal trace

Figure 3. Severly abnormal trace Figure 4. Seizure trace

Figure 1-4. aEEG trace samples

Group 2 (subjects in whom hypothermia was not performed): Subjects with normal brain function monitorization findings and no seizures in the first 6 hours

Management of hypoxic ischemic encephalopathy

Supportive treatments were performed in all subjects included in the study. $PaCO_2$ was kept in normal limits (40-60 mmHg) with appropriate ventilation techniques. Hypoventilation was avoided by providing adequate perfusion. Fluid-electrolyte treatment was adjusted according to post-natal age, body weight and serum electrolyte levels of the patients. Blood glucose levels were kept within the normal limits (75-100 mg/dL). Nitric oxide or sildenafile treatment was used in patients with resistant pulmonary hypertension found on echocardiogram.

Anticonvulsant treatment was started for all clinical and/or subclinical (found with aEEG) seizures. For anticonvulsant treatment phenobarbital (loading dose: 20 mg/kg IV, in 10-15 minutes, 5 mg/kg additional dose, if necessary, maximum dose 40 mg/kg; maintenance dose: 5 mg/kg/day in two doses every 12 hours, PO) was used as the first choice, phenytoin (loading dose: 20 mg/kg IV, in half an hour, 10 mg/kg additional dose, if necessary, maintenance dose: 5 mg/kg/day in two doses every 12 hours, IV) was used as the second choice and midazolam (loading dose: 0.15 mg/kg, maintenance: 0.01-0.06 mg/kg/hour infusion) was used as the third choice. Rivotril (clonazepam) (0,01-0,03 mg/kg/day, maximum dose: 0.2 mg/kg, PO) was started in subjects in whom seizures could not be controlled despite midazolam infusion.

Hypothermia treatment

Whole body hypothermia was performed for 72 hours in the subjects in Group 1 such as the rectal temperature was kept at 33-34º C. BFM findings were recorded during hypothermia treatment. TECOTHERM (Inspiration, Leicester, UK) was used in the process of hypothermia. Rectal temperature and skin temperature were recorded every one hour during the process. After hypothermia was completed, the body temperature was increased with a rate lower than 0.5 ºC/hour and normal body temperature (36.5ºC) was reached approximately in 6 hours. To

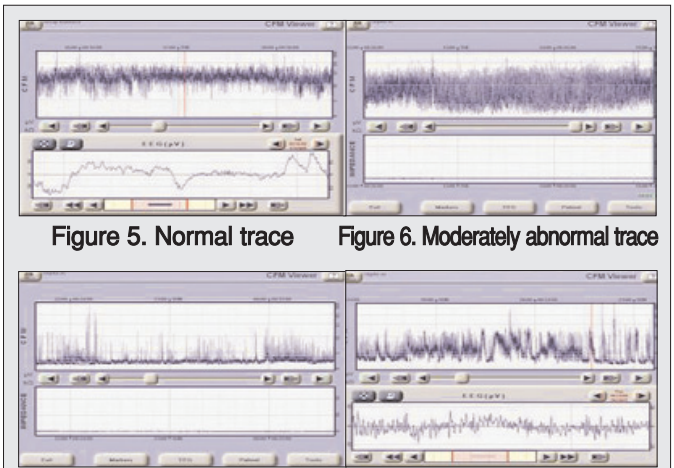

Figure 5. Normal trace Figure 6. Moderately abnormal trace

Figure 7. Severly abnormal trace Figure 8. Seizure trace

Figure 5-8. aEEG trace samples of our subjects

provide analgesia during hypothermia fentanyl (0.5-4 µg/kg/dose, 6-12 times/day IV) was administered to the patients.

BFM was performed also in the subjects in Group 2 for 72 hours. Supportive treatments were used in the subjects in this group. Body temperatures were kept within normal limits and recorded every one hour. Respiratory rates, heart rates and blood pressures were monitored in the subjects in both groups. Urinary and fecal outputs were followed up. Inotropic support was given with dopamine and dobutamine, if necessary. All subjects included in the study were followed up with serum glucose, uric acid, creatinine phosphokinase, lactate dehydrogenase levels, blood gases, serum electrolytes, complete blood count, hepatic and renal function tests and coagulation tests. Blood culture was obtained at hospitalization and repeated, if the clinic state required. Transfontanel ultrasonography (TFUSG) and echocardiography were performed in the first three days and hearing test with otoacoustic emission was performed before discharge in all subjects.

Neurodevelopmental follow up

All subjects were called back for 1st. 3rd. 6th. 12th and 18th month visits to evaluate systemic and neurologic findings. The subjects were assessed with visual (Visual evoked potantial, VEP) and auditory (Brain auditory evoked response, BAER) tests at the 3rd month. Conventional EEG records were obtained at the 3rd month in the subjects who used anticonvulsants and evaluated by a pediatric neurologist. Bayley Scales of Infant Development II was performed by a developmental pediatrician at the 18th month in surviving subjects (6). The scores of Mental Development Index (MDI) and psychomotor development index (PMDI) were calculated. Cranial magnetic resonance imaging could not be performed because of technical inadequacy.

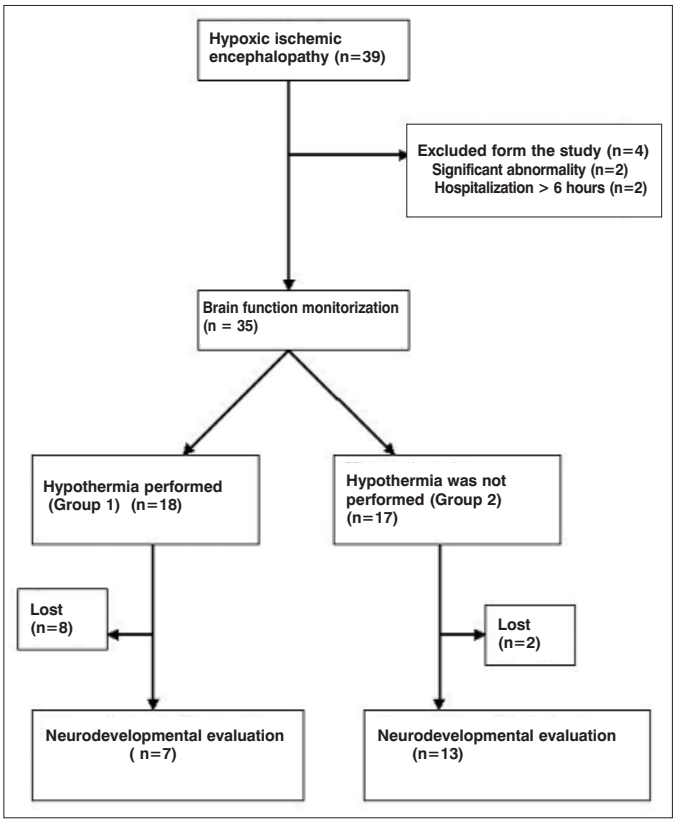

Figure 9. The flowchart of our study

Statistical method

The data of the study were evaluated using SPSS 16.0. The compatibility of continuous variables to the normal distribution was examined using Shapiro-Wilk test. Variables which did not show a normal distribution were evaluated using their logarithms. Mean and standard deviation (SD) values were used for variables which were compatible with the normal distribution and median and interquartile range values were used for variables which were not compatible with the normal distribution. Qualitative variables were shown as numeral and percent values.

In comparisons between groups, t-test or Mann Whitney U test was used in independent groups for continuous variables and Pearson chi-square or Fisher exact chi-square test was used for qualitative variables. Variance analysis was used in comparisons of repeated measurements performed at different times between groups. Spearman's correlation coefficient was used for evaluation of the relation between variables. A p value of <0.05 was considered to be significant in the study.

Results

During the study, 39 newborns were hospitalized in the NICU with a prediagnosis of asphyxia. 7 subjects had been referred from other centers. Since four of the subjects were excluded from the study because of various reasons, a total of 35 patients (18 female, 17 male) were included in the study (Figure 9).

There was no difference between Group 1 and 2 in terms of demographic and clinical data (Table 1). When the two groups were compared in terms of HIE stage, stage 3 was found in 66.7% of the group who received hypothermia treatment and in 23.5% of the group who did not receive hypothermia (p=0.003).

The median time for starting BFM was 50 minutes (the shortest: 40- the longest : 70 minutes)

in the subjects born in our hospital and 210 minutes (the shortest: 180-the longest : 240 minutes) in the subjects who were referred. However, there was no difference between Group 1 and 2 in terms of the time of starting BFM (p>0.05).

Hypothermia treatment was performed in a total of 18 subjects. The number of subjects who were referred from other centers and who received hypothermia treatment was four (57.1%). The median time to start hypothermia treatment was 120 minutes (the shortest: 73 minutes-the longest: 210 minutes) in the subjects who were born in our hospital and 255 minutes (the shortest: 240 minutes-the longest: 292 minutes) in the subjects who were referred (p=0.04). The mean body temperature in the subjects was 34.1±1.3ºC at the 1-5th hour and 33.2±0.3ºC at the 6-72nd hour in Group 1 and 36.6±0.2ºC at the 1-5th hour and 36.4±0.1ºC at the 6-72nd hour in Group 2. The mean body temperature at hospitalization in the NICU was 36.7±0.7ºC in the subjects who were referred from other centers.

TFUSG was performed in the first three days after delivery in all subjects. There was no difference between the two groups in terms of TFUSG findings (Table 2).

Clinical disorders which were thought to be related to HIA or hypothermia practice were evaluated in all subjects (Table 3). Bradycardia was found in 44.4% of the subjects in Group 1 and in 5.9% of the subjects in Group 2 in the first three days (p=0.04). There was no significant difference between the groups in terms of the frequency of other clinical disorders.

In the first 6 hours, seizure was observed in 6 of the subjects (33.3%) in Group 1. On follow up, subclinical seizure determined by clinical and/or BFM findings occured in all the subjects in Group 2 after the first 6 hours. Anticonvulsant treatment was started for both clinical and subclinical seizures. Phenobarbital was used in all the subjects in Group 1, phenytoin was used in 77.8% and midazolam was used in 38.9%. Phenobarbital was used in all the subjects in Group 2, phenytoin was used in 23.5% and midazolam was used in 5.9%. In addition to these treatments, rivotril treatment was started in one subject in both Group 1 and Group 2. The frequency of anticonvulsant usage was significantly higher in Group 1 compared to Group 2 (p<0.05).

The mean hospitalization time was 10.4±2 days in Group 1 and 12.2±2 days in Group 2 (p>0.05).

44.4% of the subjects in Group 1 (n=8) and 11.8% of the subjects in Group 2 (n=2) were lost (p=0.03). Table 4 shows the mortality rates by HIE stages.

The subjects who survived were called back to evaluate systemic and neurologic findings at the 1st, 3rd, 6th, 12th and 18th months. Visual or auditory defect did not develop in any of the subjects. Epilepsy developed in two patients (11%) in both groups and cerebral palsy developed in two patients in Group 1 and in 4 patients in Group 2. Neurodevelopmental assessment was done in the subjects who survived at the 18th month. Bayley Scales of Infant Development II was performed in 70% of the subjects in Group 1 and in 86% of the subjects in Group 2 (Figure 12). The median MDI score was calculated to be 100 (the lowest: 48-the hgihest: 125) and the median PMDI score was calculated to be 106 (the lowest: 54-the highest:111) in Group 1. The

Table 1. Demographic and clinical properties of the subjects included in the study

Variables	Group 1 (n=18)	Group 2 (n=17)	p value
Gestational age, weeks (mean±SD)	39.5±1.4	38.8±1.1	0.10
Birth weight (grams)	3348±341	3194±593	0.35
Gender (male), (n%)	9 (50.0%)	8 (47.1%)	1.00
Maternal age(years), (maen±SD)	27.7±5,4	30.5±5.5	0.14
Mode of delivery, (cesarean), n (%)	13(72.2%)	12 (70.6%)	1.00
Meconium-stained amniotic fluid, n(%)	4 (22.2)	8 (47.1)	0.12
pH, (mean±SD)	6.9±0.40	6.9±0.30	0.66
HCO_3, (mean±SD)	13.5±6,1	16.0±6.8	0.26
Base excess, (mean±SD)	18.0±4.5	18.0-3.5	0.93

Table 2. Evaluation of transfontanel ultrasonographic findings by groups

Finding	Group 1 (n=18)	Group 2 (n=17)	p value
Stage ≤2 intracranial bleeding, n (%)	4 (22)	4 (22)	1.00
Stage ≥3 intracranial bleeding, n (%)	0 (0%)	1 (0.05%)	0.5
Ischemic changes, n (%)	2 (11%)	0 (0%)	0.5
Edema, n (%)	1 (0.05%)	2 (11%)	0.6

Table 3. Clinical disorders observed in the patients

Clinical disorder (%)	Group 1 (n=18)	Group 2 (n=17)	p value
Seizure, n(%)	18 (100)	17 (100)	>0.05
Respiratory distress, n (%)	17 (94)	16 (94)	>0.05
Sinus bradycardia, n (%)	8(44)	1 (6)	p=0.03
Hypotension, n (%)	5 (28)	4 (25)	>0.05
Resistant pulmonary hypertension, n (%)	3 (16)	2 (11)	>0.05
Sepsis, n (%)	3 (16)	2 (11)	>0.05
Dysphagia, n (%)	1 (5)	0 (0)	>0.05
Need for dialysis, n (%)	2 (11)	2 (11)	>0.05
Coagulation disorder, n (%)	6 (33)	5 (29)	>0.05
Abnormal hepatic function tests, n (%)	18 (100)	17 (100)	>0.05
Abnormal renal function, n (%)	5 (27)	4 (23)	>0.05
Hypoglycemia, n (%)	6 (33)	5 (29)	>0.05
Thrombocytopenia <100 000, n (%)	5 (27)	6 (35)	>0.05
Hyponatremia, n (%)	4 (22)	4 (23)	>0.05
Hypocalcemia, n (%)	3 (16)	3 (18)	>0.05
Hypokalemia, n (%)	0 (0)	1 (5)	>0.05

Table 4. The mortality rates by HIE stages in the groups

Stage	Group 1		Group 2	
	Survivors	Lost	Survivors	Lost
Stage 2	4	2	13	-
Stage 3	6	6	2	2

median MDI score was calculated to be 97 (the lowest:48-the highest 110) and the median PMDI score was calculated to be 106 (the lowest : 28- the highest:118) in Group 2. There was no statistically significant difference between the groups in terms of MDI and PMDI scores.

Discussion

It is proposed that hypothermia treatment is the strongest and safest treatment option in hypoxic ischemic brain damage (7,8). The neuroprotective effect of hypothermia treatment depends on the severity of HIE, the method of hypothermia, the time of starting treatment and the intensity and time of hypothermia (7). This study evaluated newborns followed up with a diagnosis of HIE in whom hypothermia was performed to investigate the short and long-term outcomes of hypothermia treatment.

Hypothermia treatment can be performed as whole body hypothermia or selective head hypothermia. The superiority of these two treatments to each other is controversial (9). Hypothermia was performed as whole body hypothermia in the subjects of this study.

Application of hypothermia treatment is a difficult treatment method which requires an equipped and experienced team and may lead to various life-threatening advers effects. Therefore, the patients in whom this treatment will be performed should be selected carefully. In infants with hypoxic ischemic encephalopathy, BFM may also be used in determining background activity, in specifying the presence and grade of damage, in defining seizures, in evaluation of the efficiency of treatment and in predicting the neurodevelopmental prognosis as well as in selection of the subjects who will be given hypothermia treatment. It is known that the prognosis is poorer in patients with abnormal BFM findings in the first 6 hours (10-12). In all subjects with a diagnosis of HIE included in our study, BFM was started in a short time after delivery and BFM findings were assessed in the decision for hypothermia treatment.

In hypoxic ischemia, brain damage occurs in two periods as acute damage (primary energy deficiency) and delayed (secondary) brain damage (13). Hypothermia treatment is most efficient in the period before secondary energy deficiency develops (14). Therefore, hypothermia treatment is recommended to be started in the first two hours after delivery or in the first 6 hours at the latest (15). In our study, it was found that hypothermia was started in the first 3.5 hours at the latest in infants born in our hospital who were considered as HIE. However, it was noted that hypothermia was started later in infants who were referred from external centers. It is satisfactory that hypothermia treatment could be started at a time when it is most effective in infants born in our hospital.

For an efficient hypothermia treatment the application time should be 48-72 hours (1,16). In our study, hypothermia treatment was continued for 72 hours and afterwards the body temperature was gradually increased and normal body temperature was achieved.

Although hypothermia treatment is an efficient treatment, various advers effects may be observed during application. In a metaanalysis where the safety of hypothermia treatment was evaluated, the most common complications which occured during hypothermia treatment were reported to include sinus bradycardia and thrombocytopenia (7). In our study, the frequency of sinus bradycardia was higher in the subjects with HIE who received hypothermia treatment compared to the subjects with HIE who did not receive hypothermia treatment which was compatible with the literature. However, no significant arrhythmia was observed in any patient. Nevertheless, there was no difference between the two groups in terms of the frequency of thrombocytopenia and other advers effects. The results of our study are compatible with the results of other studies which reported that hypothermia treatment was a safe treatment option.

It has been reported that hypothermia treatment affects neurodevelopmental outcomes positively and decreases the mortality rate in term infants with HIE. Gluckman et al. (17) started hypothermia treatment in the first 6 hours with only head hypothermia method with a target rectal temperature of 34.5±0.5ºC in term babies with moderate-severe HIE and abnormal aEEG findings and continued for 72 hours in a multi-center study they performed. Although there was no difference between the two groups in terms of mortality rate and neurodevelopmental findings, the mortality rate was found to be lower and neurodevelopmental disorder was found with a lower rate in the group displaying moderate aEEG change in the assessment of subgroups. In another randomized controlled study performed by Shankaran et al. (18), whole body hypothermia starting in the first 6 hours was performed for 72 hours in 239 newborns with moderate-severe HIE who experienced severe acidosis and perinatal complications and who were resuscitated and it was observed that the mortality was lower and the rate of neurodevelopmental delay was lower at the 20th month in the group who received treatment. 325 newborns with HIE were included in a randomized controlled multi-center study performed by Azzopardi et al. (19) and whole body hypothermia started in the first 6 hours was continued for 72 hours. It was observed that the mortality rate was lower, neurodevelopmental disorder was observed with a lower rate on the 18th month, the rate of sequela-free survival was higher and the rate of development of cerebral palsy was lower in the group who received hypothermia treatment. Although there are studies which reported that hypothermia treatment decreased the mortality rate, the mortality rate was found to be higher in the subjects who received hypothermia treatment in our study. The reason for this may be the fact that our study was not a randomized controlled study and the frequency of stage 3 HIE was higher in the subjects who received hypothermia treatment.

In many studies which evaluated the efficiency of hypothermia treatment, hypothermia treatment was found to affect neurodevelopmental outcomes positively (20). The subjects included in our study were assessed by Bayley Scales of Infant Development II at the 18th month in terms of neurodevelopment. MDI and PMDI scores were found to be higher in patients who received hypothermia treatment compared to the patients who did not receive hypothermia treatment, though not statistically significantly. While there was no difference

between the two groups in terms of the frequency of development of epilepsy, the frequency of cerebral palsy was found to be lower in the patients who received hypothermia treatment. In our study, no difference was found between the two groups in terms of MDI and PMDI scores. This may be related to two reasons. Firstly, the number of subjects in our study was lower compared to other studies related to this subject. Secondly, the rate of stage 3 HIE was higher in the subjects who received hypothermia treatment.

Conclusively, hypothermia is considered as a neuroprotective treatment option in patients with HIE. Our study is significant in that it is the first study conducted on this subject. Although hypothermia application was reported to affect the neurodevelopmental outcomes positively in large series where the efficiency of hypothermia treatment was investigated, our study could not reach this conclusion, since the number of subjects who could be evaluated was low. Multi-center randomized-controlled studies investigating other neuroprotective treatments in addition to hypothermia treatment will guide the specification of HIE treatment protocol.

Conflict of interest: None declared.

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