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Original Article

Investigating the Use of Therapeutic Hypothermia in Partially Eligible Infants: A Single-centre Experience

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ABSTRACT

Aim: Neonatal encephalopathy remains one of the most significant causes of neonatal morbidity and mortality. The present study compared the risk factors, demographic data, laboratory and imaging findings, and short-term outcomes of two groups of patients.

Materials and Methods: A retrospective analysis was conducted on 45 patients who had undergone therapeutic hypothermia (TH) between January 1st, 2021, and August 31st, 2023. According to blood gas parameters; Group 1 (32 patients) met the criteria (pH ≤7.0 and/or base excess BE ≤-16) for TH, while Group 2 (13 patients) did not (pH >7.0, BE >-16, and with an absence of clinical findings).

Results: A comparison of the demographic data revealed higher incidences of birth trauma (p=0.046) and neonatal risk (p=0.026) in Group 1 than in Group 2, with no other significant differences. Severe amplitude electroencephalogram (aEEG) abnormalities were more common in Group 1 but one patient of Group 2 displayed moderate abnormality during follow-up. A comparison of all imaging findings [aEEG, transfontanelle ultrasonography (USG), abdominal USG, cranial magnetic resonance imaging, echocardiography] revealed no significant differences (p=0.45). At the end of the follow-up period, 35 patients (77.7%) were discharged, while two (4.4%) patients did not survive (both in Group 1). Upon discharge, all patients in Group 2 exhibited normal neurological examination findings.

Conclusion: Re-evaluating the existing criteria for the identification of those infants who may benefit from TH, but who are often deemed ineligible due to incomplete adherence to the treatment criteria, could significantly reduce the mortality and morbidity associated with birth asphyxia.

Keywords: Neonatal encephalopathy, asphyxia, blood gases, therapeutic hypothermia

Introduction

Neonatal encephalopathy (NE) is the third leading cause of death among neonates (1-3). Therapeutic hypothermia (TH) administered to patients diagnosed with moderate (stage 2) and severe (stage 3) encephalopathy according to the modified Sarnat & Sarnat grading scale remains the sole proven therapeutic approach to this condition, requiring initiation within 6 hours following birth. When administered within this recommended timeframe, TH exhibits a greater success rate than in cases where the treatment is started after this critical window (4).

While the initiation criteria of treatment is are determined by the Turkish Society of Neonatology (TSN) guidelines, many centres opt for TH even in cases where the patients do not fully meet these established criteria based on a risk-benefit analysis of such therapy (5). The present study evaluated short-term treatment outcomes through a comparison of two patient groups (Group 1 and Group 2), in order to provide clinicians with insights into the risks and benefits associated with the administration of TH to patients whose eligibility falls within a grey area.

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Materials and Methods

We present here a retrospective analysis of 45 patients diagnosed with stage 2 and stage 3 NE who were treated with TH in the neonatal intensive care unit of our hospital between January 1st, 2021 and August 31st, 2023. Prior to starting, approval for this study was obtained from the Non-Interventional Research Ethics Committee of İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital (decision no.: 2023/6-150, date: June 21st, 2023). The diagnoses of NE and adherence to TH indications were confirmed using the Neonatal Encephalopathy Diagnosis and Treatment Guidelines 2018, as published by the TSN and the clinical severity of NE was assessed using the modified Sarnat & Sarnat grading scale (5,6). The treatment criteria for TH included gestational age equal to or greater than 36 weeks and a postnatal age under 6 hours, with umbilical cord artery or arterial blood gases analysis indicating a pH of 7.0 or lower and/or a BE of -16 mmol/L or lower within the first hour following birth, a 10-minute Apgar score below 5 or the continuous need for resuscitation, or the presence of moderate to severe encephalopathy, as assessed clinically (5).

The patients included in this study were divided into two groups. Those patients meeting the specified criteria for TH, including a pH of 7.0 or lower and/or a BE of -16 mmol/L or lower in blood gas analyses, were assigned to Group 1, while those treated with TH without entirely meeting the established blood gas criteria (having a pH >7.0 and a BE >-16 mmol/L), yet displaying neurological examination findings consistent with stage 2 or 3 encephalopathy, were assigned to Group 2. The patients in Group 2 had at least three of the pathological neurologic findings (lethargy, obtunded, stupor, decreased activity, no activity, hypotonia, flaccidity, distal flexion posture, decerebrate state, weak sucking, biting, incomplete Moro reflex; constricted, deviated, dilated or nonreactive pupils etc.) which was evaluated as stage 2 or 3 encephalopathy according to the Sarnat & Sarnat classification. Those patients with missing data in their medical records, patients born before 36 weeks gestation, those with a birth weight below 1,800 grams, as well as those with major congenital malformations, chromosomal anomalies, and/or severe intracranial haemorrhage were excluded from this study. In all patients, hypothermia was started during the first 6 hours and was finished within 72 hours. A comparison was made of the prenatal, natal and postnatal risk factors, demographic data, laboratory and imaging findings, as well as the short-term outcomes of those patients who met the treatment criteria and those who did not completely fulfil these criteria.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics (Version 25.0. Armonk, NY: IBM Corp.). Categorical variables were expressed as numbers and percentages. A Kolmogorov-Smirnov test was used to assess the normality of the data distribution, and a simple correlation test was used to evaluate the relationship between two variables. A chi-square test was used to evaluate any differences between categorical variables, and Student's t-test and analysis of variance (ANOVA) were used for comparisons of normally distributed quantitative variables. The Mann-Whitney U test and Kruskal-Wallis test were applied to assess those parameters which did not follow a normal distribution. A p value of less than 0.05 was considered statistically significant in all analyses.

Results

In the study period, 45 patients were diagnosed with NE, of whom 32 (71.1%) were assigned to Group 1 and 13 (28.8%) to Group 2. The one significant difference was the number of natal risk factors being higher in Group 1 (p=0.026). A comparison of the two groups' modified Sarnat & Sarnat grading scale scores revealed the rate of stage 3 encephalopathy to be higher in Group 1, while the rate of stage 2 encephalopathy was higher in Group 2 (p=0.02) (Table I).

In the comparison of groups categorized according to the difference in blood gas parameters, aspartate transaminase, alanine transaminase and Troponin-I values were higher in Group 1 than in Group 2, although the difference was not statistically significant (Table II).

An evaluation of the two groups in terms of their need for respiratory support revealed a significantly higher mean intubation time in Group 1 (5.13±12.5 days) than in Group 2 (0.42±0.6 days) (p=0.045) (Table III). The need for invasive respiratory support upon admission was higher in Group 1 than in Group 2 (p=0.008) (Table IV). When comparing the groups in terms of enteral feeding, no significant difference was observed in the median time for transition to enteral feeding, while the time for transition to total enteral feeding was longer in Group 1 than in Group 2 (p=0.008) (Table V). Of the 45 patients, eight (17.7%) underwent inotropic therapy, with a significantly greater number in Group 1 than in Group 2 (p=0.049).

No birth trauma was noted in 40 of the 45 patients (88.8%), while cephalohematoma was observed in three (6.6%) and clavicular fracture in two (4.4%) patients. The rate of birth trauma was significantly higher in Group 1 than in Group 2 (p=0.046) (Table IV).

Table I. Demographic data and first neurological examination findings

Demographic data	Group 1†	Group 2†	Total†	p value
Maternal age (Mean)	26.5±5.4	29.3±6.2	39.2±1.2	0.32
Gestational week (Mean)	38±1.7	38.9±1.3	27.3±8.6	0.89
The mode of delivery (n)				
NSD C/S	13 19	8 5	21 (46.6%) 24 (53.4%)	0.17
Birth weight (Mean, gr)	3,056±527	3,348±439	3,140±355	0.068
Gender (n)				
Female Male	14 18	8 5	22 (49%) 23 (51%)	0.22
Delivery hospital (n)				
Yes No	13 19	8 5	21 (46.6%) 24 (53.4%)	0.17
Prenatal risk (n)				
No risk	25	9	34 (75.5%)	0.593
Abnormal placental location	3	2	5 (11.1%)	
Maternal hypothyroidism	1	2	3 (6.6%)	
IUGR	1	0	1 (2.2%)	
Enoxaparin sodium use	1	1	1 (2.2%)	
Diabetes mellitus	0	1	1 (2.2%)	
Natal risk (n)				
No risk	11	10	21 (46.6%)	**0.026**
Foetal distress	15	3	18 (40%)	
Placental abruption	6	0	6 (13.3%)	
APGAR 1st min (n) <5	14	3	17 (37.7%)	0.553
APGAR 5th min (n) <5	9	1	10 (22.2%)	0.749
APGAR 10th min (n) <5	7	0	7 (15.5%)	0.09
Sarnat & Sarnat score (n)				
Stage 2 Stage 3	22 10	13 0	35 (77.7%) 10 (22.2%)	**0.02**

†Data presented as mean ± SD, median (IQR) or count (percentages)
NSD: Normal spontaneous delivery, C/S: Caesarean section, IUGR: Intrauterine growth restriction, SD: Standard deviation, IQR: Interquartile range

All patients receiving TH underwent aEEG monitoring, and of these patients, 38 (84.4%) exhibited normal findings, while one (2.2%) displayed mild abnormality, two (4.4%) moderate abnormality and four (8.8%) severe abnormality. Follow-up aEEG to one patient of Group 2 displayed moderate abnormality (Table V).

Of the 45 patients in this study, 35 (77.7%) were discharged at the end of the follow-up period, while two (4.4%) did not survive. Both of those who did not survive had stage 3 NE based on the modified Sarnat & Sarnat grading scale, and were in Group 1. In an assessment of the patients based on their final neurological examination findings, all of the patients in Group 2 had normal findings upon discharge. Taking into account the two non-survivors,

Table II. Laboratory features of the patients

Laboratory tests	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p value
Blood gas			
pH HCO_3 BE	6.8±0.16 10.3±3.8 -17.5±4.2	7.03±0.3 12.4±2.2 -12.7±2.5	**0.000** **0.028** **0.000**
Urine (mg/dL)	22.5±10.6	26.7±13.3	0.320
Creatinine (mg/dL)	0.83±0.27	0.69±0.3	0.177
AST (U/L)	142±365	81±79	0.379
ALT (U/L)	50±112	27±23	0.293
Troponin (pg/mL)	88±116	51±49	0.140
CRP (mg/L)	3.4±7.2	8.7±21.6	0.400
PT (sec)	18.4±5.4	18.6±5.2	0.893
INR (%)	1.6±0.48	1.5±0.49	0.579
TSH (uIU/mL)	6.5±5	8.9±8.7	0.352
fT4 (ng/dL)	1.67±0.38	1.85±0.36	0.168

AST: Aspartate transaminase, ALT: Alanine transaminase, CRP: C-reactive protein, PT: Prothrombin time, INR: International normalized ratio, TSH: Thyroid-stimulating hormone, fT4: Free T4, SD: Standard deviation

Table III. Duration of intubation, initiation of and reaching full enteral feeding, and length of hospital stay

Data	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	p value
Total intubation days	5.13±12.5	0.42±0.6	**0.045**
First enteral feeding day	3.44±1.9	2.85±1.4	0.365
Days to full enteral feeding	6.59±4.6	4.85±2.4	**0.008**
Duration of hospitalization	16.4±16.4	9±4.5	0.511

SD: Standard deviation

Table IV. Delivery room resuscitation needs and development of birth trauma

Data	Group 1 (n)	Group 2 (n)	p value
Birth trauma			
No trauma Cephalohematoma Clavicular fracture	29 3 0	11 0 2	**0.046**
Respiratory support			
Non-invasive respiratory support Invasive respiratory support	16 16	12 1	**0.008**
Resuscitation			
No need PPV CPR	4 22 6	4 9 0	0.124

PPV: Positive-pressure ventilation, CPR: Cardiopulmonary resuscitation

Table V. Imaging findings

Imaging	Group 1 (n)	Group 2 (n)	p value
aEEG			
Normal Mild abnormality Moderate abnormality Severe abnormality	26 1 1 4	12 0 1 0	0.45
Transfontanelle USG			
Normal Periventricular echogenicity Choroid plexus cyst Unspecified bleeding	24 5 1 2	12 1 0 0	0.57
Abdominal USG			
Normal Unilateral renal agenesis Pelviectasis	25 0 7	9 1 3	0.27
Cranial MRI			
Not available Normal Ischemia Encephalomalacia	16 13 2 1	7 6 0 0	0.72
Echocardiography			
PFO PDA TVR (trace) PDA and TVR (trace) Left ventricular hypertrophy Decreased EF Pulmonary hypertension	14 3 2 2 4 2 5	10 3 0 0 0 0 0	0.15

aEEG: Amplitude electroencephalogram, USG: Ultrasonography, MRI: Magnetic resonance imaging, PFO: Patent foramen ovale, PDA: Patent ductus arteriosus, TVR: Tricuspid valve regurgitation, EF: Ejection fraction

Table VI. Final neurological examination findings at discharge

Final neurological examination findings	Group 1 (n)	Group 2 (n)	p value
Normal neurological examination	18	13	0.24
Exitus or poor neurological examination	6	0	
Discharged with poor neurological examination	4	0	
Unavailable data due to being referred to other facilities	8	0	

and adding the patients with poor neurological examination results, there were a total of six patients in Group 1 who displayed neurological examination findings indicating sequel changes (death, hypoactivity, poor oral feeding and spasticity) (Table VI).

Discussion

Our sample was 51% male, while in a study conducted by Odd et al.'s (7) in 2017, 69% of the 130 NE patients were male, with this ratio not being consistent with our study. The C/S rate was reported as 25.8% in the study of Peebles et al. (8) and 62% in the study by Azak et al. (9). The present study features a high rate of Caesarean births at 53.4%, which can be attributed to the increased preference for C/S over NSD in recent years, and the trend of advising patients with antenatal complications to opt for C/S.

Our study reported a rate of prenatal risk factors for NE of 24.5%, and a rate of natal risk factors of 53.3%, which is consistent with the study conducted by Nelson et al. (10) in 2012 (56%). In a prospective study, a higher rate of maternal hypothyroidism was observed, which is considered a potential risk factor for NE, although its specific pathogenesis remains unidentified (10). The rate of maternal hypothyroidism in the present study was 6.6%.

In another study, infants with a 10-minute Apgar score below 3 exhibited higher rates of mortality and permanent sequelae (11). In the present study, no patient in Group 2 had a 10-minute Apgar score below 5, and in this group, patients were started on TH based on their neurological status rather than their Apgar scores. No significant differences were found in the 5-minute Apgar scores of the two groups. This finding suggests that while the Apgar score can be considered when assessing patients for eligibility for TH, those with unexpectedly higher Apgar scores and those not meeting the blood gas criteria may be overlooked. While the Apgar scoring system follows clear rating steps,

its subjective nature can lead to potential overrating, even in the most experienced centres, due to the assessment's dependence on individual interpretations.

A comparison of the need for respiratory support in the present study in the groups revealed that the Group 1 patients with poorer blood gas parameters had a significantly greater need (p=0.008) for invasive respiratory support, and their intubation times were also longer (p=0.045). In the study by Volpe (12), no neurological deficits were reported during the follow-up of patients with hospital stays of less than one week. In our study, the hospital stays of all patients identified with neurological deficits were longer than two weeks, with a median duration of 36.1 days.

In a study published by Gumus et al. (13) in 2020 comparing the C-reactive protein (CRP) levels of healthy infants with those of infants diagnosed with NE, the authors reported elevated CRP levels in those with NE. The present study did not identify any significant differences in the laboratory features (including CRP) of Group 1 and Group 2.

In our study, 31 cases underwent resuscitation, with PPV being the most frequently administered form (68.8%). In a study conducted by Azak et al. (9) in 2021, 33 patients (66%) underwent resuscitation, PPV being the most frequently administered form (60%) (9). Also in the present study, six patients who underwent CPR were assigned to Group 1. As expected, the patients in Group 1, who exhibited poorer blood gas parameters, required resuscitation more frequently.

In a study conducted by ter Horst et al. (14), approximately 40% of patients with NE exhibited normal aEEG findings, in contrast to the present study, in which 84.6% of patients had normal aEEG findings. In our study, four patients, all of whom were in Group 1, displayed burst suppression under aEEG monitoring. During follow-up, one patient in Group 2 displayed moderate abnormality under aEEG monitoring. Although this patient had moderate abnormality under aEEG monitoring, the final neurological examination findings of this patient were normal at discharge, which underlines the potential neuroprotective effects of TH administered to Group 2 patients who may typically be considered ineligible for TH in many centres. It is plausible that the therapy prevented the onset of neurological deficits, resulting in a higher number of patients showing normal aEEG recordings.

In general, cranial MRI scans are normal in approximately 15-30% of cases. In the present study, among the 22 patients with available MRI scan records, the findings were normal in 19 patients (86%). In a study published by Coşkun et al. (15) in 2021, among the 63 patients with MRI scan records, 33 (52.4%) infants had totally normal MRI findings. Twenty-one of 33 (63.6%) infants had mild, while 12 (36.4%) infants had severe NE. On the other hand, 30 (47.6%) infants had at least one pathology in their MRIs (15). Our study might have shown an overrepresentation of normal MRI findings due to circumstances in which patients with severe NE may not have survived long enough to undergo cranial MRI scans. Furthermore, patients with severe and unstable clinical conditions, and with neurological deficits, might remain intubated for extended periods.

Patients diagnosed initially with mild NE may later progress to moderate-to-severe NE during the follow-up period, and such a progression could potentially result in missed opportunities for TH within the critical 6-hour window. One study documented neurological sequelae in 16% of those patients diagnosed with mild NE, while another study indicated that perinatal asphyxia could induce brain damage, particularly in the basal ganglia and thalamus, affecting 11-40% of those patients diagnosed with mild NE (16-19). Animal-based studies have demonstrated the effectiveness of TH in reducing neuronal loss, particularly in cases with mild selective hippocampal damage (20). In a meta-analysis of 11 randomized and controlled studies, TH resulted in a decrease in mortality and neurological sequelae in those infants with moderate-to-severe NE (21). In hospitals similar to our centre, where the primary focus is on labour, it is common to encounter intermediate cases which do not strictly adhere to the recommendations outlined in standard guidelines or individuals with mild NE. A meta-analysis published by Conway et al. (22) in 2018 examined patients with mild NE who had undergone TH and those who had not, and reported a rate of patients experiencing either mortality, cerebral palsy or low neurodevelopmental test scores at 29% in the TH group, compared to 37% in the non-TH group (22). In a meta-analysis, the rate of poor prognosis was 19.6% among those patients diagnosed with mild NE who underwent TH, compared to 19.7% in those with mild NE who did not receive TH (23). A survey conducted in the United Kingdom in 2018 revealed that 75% of the respondent centres used TH to treat patients with mild NE (24,25). The findings of the present study revealed no differences in the neurological examination findings upon discharge of Groups 1 and 2, and only one patient in Group 2 exhibited abnormal aEEG findings during follow-up. While no direct comparison was possible due to the lack of a group with Group 2 characteristics who did not undergo TH, the authors advocate for an extension of the indications for TH in order to improve neonatal prognosis, considering the

absence of severe complications during TH and the similar discharge assessments observed in both groups.

Study Limitations

This study had several limitations. First of all, it was a retrospective study with a small sample size which decreased the power of our analysis. The cranial MRI device was not located in our clinic, as it was in the main building and at a certain distance. Due to difficulties in transportation, the cranial MRI scan rates of those infants with NE were not enough, leading to the small sample for our study. Secondly, our study was conducted at a single centre, which may not be representative of other hospitals or regions. Last but not the least, short-term outcomes were primarily assessed, which may not fully capture the long-term effects of TH or the full range of potential neurological sequelae. Long-term follow-up would provide more comprehensive insights into the effectiveness of TH. Addressing these limitations in future studies could help validate our findings and provide more robust evidence for the use of TH in partially eligible infants.

Conclusion

The present study investigated the rationale behind the administration of TH to patients who do not entirely meet the established criteria, revealing a need for further studies to reassess and potentially revise the existing indications for TH. The authors emphasize the importance of increasing the availability of the required equipment for TH, as well as the number of centres capable of administering this therapy, which could aid physicians in decision-making when encountering clinically uncertain cases. Most importantly, expanding the eligibility criteria for potentially affected infants with obscure acute period who do not completely meet the criteria, but who may benefit from TH, and allowing their access to such therapy will only be possible through a revision of the existing criteria to include a broader spectrum of cases.

Ethics

Ethics Committee Approval: Prior to starting, approval for this study was obtained from the Non-Interventional Research Ethics Committee of İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital (decision no.: 2023/6-150, date: June 21st, 2023).

Informed Consent: Retrospective analysis.

Authorship Contributions

Surgical and Medical Practices: B.C., S.G., Concept: B.C., Design: B.C., S.G., Data Collection and/or Processing: B.C., Analysis and/or Interpretation: B.C., S.G., Literature Search: B.C., S.G., Writing: B.C.

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