ORIGINAL PAPER

doi: 10.5455/medarh.2015.69.362-366
Med Arh. 2015 Dec; 69(6): 362-366
Received: August 25th 2015 | Accepted: November 05th 2015



# Neurodevelopmental Follow Up After Therapeutic Hypothermia for Perinatal Asphyxia

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## ABSTRACT

**Introduction:** Neuroprotective benefit of therapeutic hypothermia in term newborns with hypoxic-ischemic encephalopathy (HIE) was assessed by analyzing survival and neurodevelopmental outcome of neonates subjected to this procedure. **Material and methods:** Newborns with gestational age > 36 weeks and < 6 hours of age with moderate to severe asphyxial encephalopathy underwent cooling protocol at a temperature of 33.5 °C for 72 hours and rewarming period of 6 hours. Outcome measures assessed were death and neurodevelopmental characteristics, which were compared at the different age using ASQ-3. Twenty-five children were assessed at age 3-6, 12-18 and 24-36 months. Median gestational age was 40 weeks, birth weight 3470 g, Apgar score 2/4 and pH on admission to the hospital 7.02. Four (16%) children died. **Results:** At the first assessment developmental categories of communication were normal in 78.9%, problem solving in 63.2%, personal-social in 68.4%, gross motor in 68.4%, and fine motor in 42.1% with a high need of retesting in this area. Second assessment was done in 17 patients: developmental categories of communication normal in 58.8%, problem solving in 70.6%, personal-social in 64.7%, gross motor in 64.7%, and fine motor in 35.3%. Third evaluation was done in 14 patients: developmental categories of communication were normal in 64.3%, problem solving in 71.4%, personal-social in 57.1%, gross motor in 64.3%, and fine motor in 42.9%. **Conclusion:** There was no correlation between baseline parameters and outcome. Results of the study are showing that therapeutic hypothermia in term newborns can provide better survival and less neurologic sequels in HIE patients.

**Key words: perinatal asphyxia, therapeutic hypothermia, neurodevelopmental outcome.**

## 1. INTRODUCTION

Moderate to severe hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia is a major cause of morbidity and mortality in neonates, despite important progress in obstetric and neonatal care during the last decades. Incidence is 0.5 to 1 per 1000 live births in developed countries (1), with numbers much higher in developing countries (2). About 10% to 60% of affected infants die, and at least 25% of survivors have long-term neurodevelopmental sequels (3).

Modalities for treating neonatal encephalopathy after perinatal asphyxia have to be based on the understanding of the mechanisms of neuronal damage and loss following hypoxic-ischemic brain injury. Animal models show that many factors play a role, e.g., etiology, extent of hypoxia or ischemia, maturation stage of the brain, regional cerebral blood flow, and general health prior to the injury (4), but it is not sure that all data from animal studies are applicable to humans. In developing countries different additional factors can play a role, malnutrition of mothers, infections, underdeveloped maternal care. Initial hypoxic-ischemic insult brings immediate cell loss of varying degrees, but delayed impairment in energy metabolism leads to more significant cell loss by apoptotic cell death (5).

Hypothermia is currently the only recognized beneficial therapy (6).

The potential mechanisms of neuroprotection with hypothermia include inhibition of glutamate release, reduction of cerebral metabolism, which in turn preserves high energy phosphates, decrease in intracellular acidosis and lactic acid accumulation, preservation of endogenous antioxidants, reduction of nitric oxide production, prevention of protein kinase inhibition, improvement of protein synthesis, reduction of leukotriene production, prevention of blood-brain barrier disruption and brain edema, and inhibition of apoptosis (7, 8). Children who survive neonatal HIE are at great risk of severe disability, but even those without major disability are at increased risk for long-term intellectual, verbal, and motor deficits (9). In infants with hypoxic-ischemic encephalopathy, moderate hypothermia is associated with a consistent reduction in death and neurological impairment at 18 months (10). More recent Cochrane review by Jacobs et al. (11) has shown that there is evidence from trials that induced hypothermia helps to improve survival and development at 18 to 24 months for term and late preterm newborn babies at risk of brain damage.

## 2. GOAL OF THE STUDY

Goal of the study was to assess follow up of neuroprotective benefit of therapeutic hypothermia in term newborns with hypoxic-ischemic encephalopathy by analyzing survival and neurodevelopmental outcome of neonates subjected to this procedure.

## 3. MATERIALS AND METHODS

Survival and neurodevelopmental outcome of children treated with therapeutic hypothermia for perinatal asphyxia have been followed up in a group of 25 children that were the first ones treated by that procedure at Pediatric Hospital, University Clinical Center Sarajevo.

Criterion for this treatment was that children have completed 36 weeks of gestation. Selection of patients was done by revising TOBY study and so called Bristol Cooling Protocol (12-14) criteria in a way of including results of amplitude-integrated electroencephalography (aEEG) in several patients. Cooling was performed by the Arctic Sun Temperature Management System (Medivance, Louisville, Colorado, USA) as a thermoregulatory device that monitors and controls patient temperature within a range of 32.0C to 38.50C. Cooling and rewarming was done in a preprogrammed way.

Mortality was ascertained up to the each follow up. Children that survived were followed-up regularly for their neurodevelopment at neurology outpatient clinic. Each child enrolled in a study had three visits to clinic, one at age 3-6 months, second at age 12-18 months, and one at age 24-36 months or more. Thorough neurological examination was done by one trained assessor. Further evaluation of their development was done by the parent and assistant, completing questionnaires based on the Ages & Stages Questionnaires(ASQ-3), appropriate for the age of patient, adopted in a way described by Kapci et al. (15), and used as part of the project of introducing early intervention programs in Bosnia and Herzegovina. ASQ shows sensitivity of 92%, 95% specificity, 92% positive predictive value and 95% negative predictive value when used to detect severe developmental delay; and 67% sensitivity, 93% specificity, 92% positive predictive value and 68% negative predictive value when used to detect both severe and mild developmental delay in children with neonatal HIE (16). It has very good correlation with more sophisticated, but time consuming tests, like Bayley scale, which require investigators' thorough education (17). Parents were instructed to fill in the questionnaire during follow up visit. The IBM SPSS 20 software package was used for statistical analyses; descriptive statistics was used for description of the variables, means, medians, ranges and distribution of data. Mann-Whitney U Test was used to show significance of independent variables in relation to dependent (neurodevelopmental outcome). Linear regression was tested.

## 4. RESULTS

Twenty-five patients with therapeutic hypothermia for perinatal asphyxia were followed up during this period. There were 13 male children (52%) and 12 female (48%). Baseline data for enrolled patients are shown at Table 1.

Twenty-two neonates needed resuscitation at 10 min of age (88%). Clinical presentation of epileptic seizures was noticed in 12 children (48%) prior to beginning of cooling process.

Follow-ups were made at the certain age of patients, at the first half of the first year, at the first half of the second year and after age of two years. Drop our rate from study was constant regarding death rate, all of the 4 children (16%) that died were registered at the first follow up at the age 3-6 months. Two of remaining patients (9,5%) did not show at the first follow up, 4 (19%) did not appear at the second follow up, and 7 did not show at the third. Different patients did not appear at follow-ups. Data for the survival and follow up rate are shown at Graphic 1.

Results were analyzed from ASQ-3 questionnaires at visits, and are shown at Table 2 for all developmental categories that were tested.

We tried to correlate neurodevelopmental outcome as good or abnormal defining the first one as the one without abnormalities (children could have result in certain developmental category in retesting zone) and abnormal if there was one or more abnormal developmental outcomes ins soe of the categories. Results are shown at Table 3. Neonatal seizures are often part of hypoxic-ischemic encephalopathy after perinatal asphyxia, 11 patients (44%) in our group had one or more neonatal seizures after admission to neonatal intensive care unit, prior, during, or after therapeutic hypothermia for perinatal asphyxia. Results of follow up of those children regarding development of epilepsy are shown on Graphic 2.

## 5. DISCUSSION

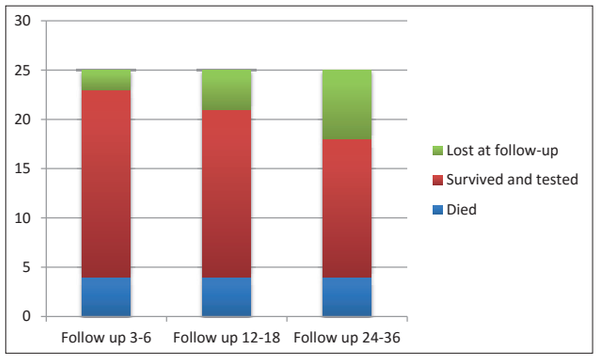
Interventions to improve poor prognosis of neonates with moderate to severe perinatal asphyxia are at extensive and intensive investigation in previous decades. Hypoxic-ischemic encephalopathy as a result of birth asphyxia presents is responsible for significant morbidity

| | | Average | Std. Dev. | Median | Range |
|---|---|---|---|---|---|
| Gestational age - weeks | | 39,6 | 1,39 | 40 | 37 - 42 |
| Birth weight - g | | 3375 | 509 | 3470 | 2220 - 4950 |
| Head circumference - cm | | 35,12 | 1,107 | 35 | 33 - 37 |
| Apgar score at 1/5 minutes | 1 | 2,26 | 1,772 | 2/4 | 0/2 – 6/6 |
| | 5 | 4,37 | 1,363 | | |
| Age at starting cooling - hours | | 4,32 | 2,33 | 4 | 2 - 8 |
| pH at admission to hospital | | 6,99 | 0,186 | 7,02 | 6.49 – 7.25 |

Table 1. Baseline data at birth for patients enrolled in study

and mortality rates, leading to a significant burden on society. Only new treatment that shows results is therapeutic hypothermia (6, 11).

Method is in widespread use in developed countries

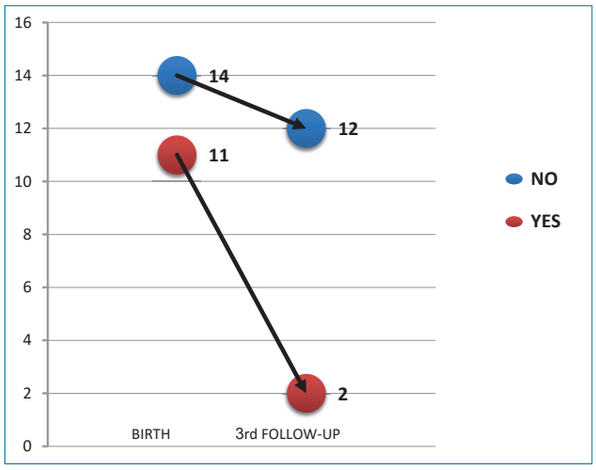



Graphic 1. Survival rate of followed patients.

in previous 5 years. Randomized trials are still quite rare, and data from them are sometimes contradictory. Recent Cochrane database systematic review (11) states that there is evidence from trials to show that induced hypothermia helps to improve survival and development at 18 to 24 months for term and late preterm newborn babies at risk of brain damage, but also finds some adverse effects of hypothermia, as sinus bradycardia and a significant increase in thrombocytopenia.

| | Asymp. Sig. (2-tailed) | Exact Sig. (1-tailed Sig.) (Not corrected for ties) |
|---|---|---|
| Seizures Prior to Hypothermia (Yes/No) | ,718 | .784 |
| Seizures During Hypothermia (Yes/No) | ,410 | .528 |
| Initial Brain Ultrasound (Normal/Abnormal) | ,233 | .356 |
| Plantar Grasp Reflex at Discharge From Hospital (Normal/Abnormal) | .314 | .421 |
| Palmar Grasp Reflex at Discharge From Hospital (Normal/Abnormal) | .310 | .398 |
| Muscle Tone at Discharge From Hospital (Normal/Abnormal) | .354 | .429 |
| Moro Reflex at Discharge From Hospital (Normal/Abnormal) | .314 | .402 |

Table 3. Correlation of different neurological examination findings recorded in hospital on neurodevelopmental outcome, level of statistical significance.




Graphic 2. Neonatal seizures at birth and epileptic seizures and epilepsy at follow-up.

In last couple of years neonatology centers in developing countries have started "cooling programs", and first cooling attempts at Pediatric Hospital in Sarajevo were done in 2010-2011. Results from these countries vary, and sometimes are different to those from developed countries. Possible reasons are nutrition, scope of prenatal and perinatal infections, lack of maternal care services, late admission to hospital and lengthy decision-makings for cesarean section. In this article we

| FIRST FOLLOW-UP 3-6 MONTHS | Communication | Gross Motor | Fine Motor | Problem Solving | Personal - Social |
|---|---|---|---|---|---|
| Normal | 15 (78,9%) | 13 (68,4%) | 8 (42,1%) | 12 (63,2%) | 13 (68,4%) |
| Abnormal | 2 (10,5%) | 4 (21,1%) | 7 (36,8%) | 3 (15,8%) | 3 (15,8%) |
| Retesting zone | 2 (10,5%) | 2 (10,5%) | 4 (21,1%) | 4 (21,1%) | 3 (15,8%) |
| Total | 19 | 19 | 19 | 19 | 19 |
| SECOND FOLLOW-UP 12-18 MONTHS | Communication | Gross Motor | Fine Motor | Problem Solving | Personal - Social |
| Normal | 10 (58,8%) | 11 (64,7%) | 7 (41,2%) | 12 (70,6%) | 11 (64,7%) |
| Abnormal | 5 (29,4%) | 5 (29,4%) | 6 (35,3%) | 4 (23,5%) | 3 (17,6%) |
| Retesting zone | 2 (11,8%) | 1 (5,9%) | 4 (23,5%) | 1 (5,9%) | 3 (17,6%) |
| Total | 17 | 17 | 17 | 17 | 17 |
| THIRD FOLLOW-UP 24-36 MONTHS | Communication | Gross Motor | Fine Motor | Problem Solving | Personal - Social |
| Normal | 9 (64,3%) | 9 (64,3%) | 5 (35,7%) | 10 (71,4%) | 8 (57,1%) |
| Abnormal | 4 (28,6%) | 5 (35,7%) | 6 (42,9%) | 3 (21,4%) | 3 (21,4%) |
| Retesting zone | 1 (7,1%) | 0 (0%) | 3 (21,4%) | 1 (7,1%) | 3 (21,4%) |
| Total | 14 | 14 | 14 | 14 | 14 |

Table 2. Neurodevelopmental outcome according to results from ASQ-3

tried to compare neurodevelopmental outcome results from Bosnia and Herzegovina with the results from other highly developed countries.

We were able to follow up a sample of 25 children that underwent therapeutic hypothermia for perinatal asphyxia for neurodevelopmental outcome. During three visits to neuropediatric outpatient clinic data were collected and analyzed. Mortality rate for the followed period, 4 out of 25 patients (16%), was comparable or lower than in most other studies (18, 19, 20, 21). All the children in our study died in period of the first couple of months after the birth, and were recorded at the first follow up visit. This number was too small for proper statistical analyses, and to correlate it with baseline characteristics of these patients.

Developmental outcome was observed at different ages of patients, with different dropout of patients at each visit. Cross-sectional analysis has been done during this period, as pilot results of the study. Overall results are encouraging in all tested domains: communication, problem solving, personal – social performances, gross and fine motor development. Results of ASQ-3 had good correlation with structured neurodevelopmental examinations performed by child neurologists and psychologists. Nonetheless, usability of ASQ-3 has to be further proven regarding issues of sensitivity, specificity, positive predictive value, negative predictive value, interobserver agreement reliability (15). Our reviewers praised the simplicity of the questionnaire, and time needed to complete evaluation. This makes it very affordable for child health care systems with limited resource. These results should be compared with more sophisticated tools, such as Bayley Scale of Infant Development (Bayley N. Bayley Scales of Infant and Toddler Development, 3rd ed. Pearson Education, San Antonio, TX, 2006) to have complete understanding of their reliability.

Follow up in this study was in period up to 24-36 months. There are no studies assessing how long follow-up period is needed for definite prediction of neurodevelopmental outcome in these children. Longer follow-ups are certainly better, and we hope that studies following these children for 7-15 years will start emerging. Perez et al. (9) in their recent study of long-term neurodevelopmental outcome for children after hypoxic-ischemic encephalopathy without major disability found at mean age of 11.2 years lower full-scale and performance IQ scores compared with norms and the proportion of children with an IQ <85 higher than expected (P = .04). Motor performance on the Zurich Neuromotor Assessment was affected in the pure motor, adaptive fine motor, and gross motor domains, as well as in the movement quality domain (all P < .001).

Azzopardi et al. (2012) find in their study that there were no significant differences in the clinical characteristics, aEEG prior to cooling, and the age in hours after birth when cooling was started between the infants with or without 2-year outcome data available (20). Our results are compared to TOBY report (11) that finds 27% of patients with severe neurodevelopmental disability in cooled group, and survival without neurologic abnormality in 44%. On the part of gross and fine motor development we had little less good results as they have found a normal GMFCS score in 71%, which is somehow higher than our results where about one third of children were having clearly abnormal gross motor development (half of them with hemiparesis) and further 10% were in retesting zone. Even bigger percent of our group had abnormal fine motor development, but with lot of children in retesting zone. We consider that 8 (38,1% of survived children) of the patients that we followed had completely normal development, in all categories, but all of them did not show up at the last follow-up, so the percent at Table 2 does not show it. However, those results are quite comparable to the studies mentioned above. All those follow-ups were quite short and we need longer periods, as meta-analysis from 2010 states: „Continued follow-up of the children enrolled in the studies included in our meta-analysis is essential to determine whether these benefits are maintained in later childhood“ (10).

As a part of standard procedure on admission to hospital we have recorded numerous parameters, prior to starting cooling, during cooling and after it we. We tested correlation of those with neurodevelopmental outcome, but statistical methods used were restricted by a small number of patients in our group. We were not able to show that any of the studied parameters had statistically significant influence on neurodevelopmental outcome. Larger groups of patients in multicenter studies are needed. Not too many studies have addressed this problem until now. Wyatt et al. (18) at sample of 218 children have found a correlation of developmental outcome with treatment, lower encephalopathy grade, lower birth weight, greater amplitude-integrated electroencephalographic amplitude, absence of seizures, and higher Apgar score, with better outcomes for children with these parameters (Wyatt). Bennet et al. (22) investigated potential biomarkers of hypoxic-ischemic encephalopathy and called for better understanding of their role. Possible reason for not having correlation in our study was also sample size. Better standardized tests should be created for early assessment of neurodevelopmental predictors (23), so we can be able to do early intervention in these children.

At the beginning of follow-up period our hospital did not have aEEG equipment, and we had it for only short period. It is now standard equipment in mots of the hospitals treating children with therapeutic hypothermia, with its role in patient selection for procedure, as well as a tool that can be helpful in prediction of outcome (24). Study examining predictive role of aEEG on survival and disability (25) found that the aEEG background pattern at <9 hours did not significantly enhance the predictive value of HIE stage at <6 hours in predicting death and disability at 18 months. Time needed to normalize aEEG was a better predictor than the time to establish normal sleep-wake cycling in prediction of outcome (26). Recovery of the background pattern within 24 hours was associated with a lower rate of disability (defined as death, cerebral palsy, or developmental quotient <85) at 2 years (27).

Out of 44% of our patients that had neonatal seizures, prior, during therapeutic hypothermia, or immediately after it, only 2 developed epilepsy (8%). Some other studies (28, 29) have shown a decreased seizure burden in neonates with moderate HIE who underwent cooling. It is also one of the possible explanations for better neurodevelopmental outcome seen in children who had moderate HIE, and were treated by therapeutic hypothermia.

## 6. CONCLUSIONS

Our study is adding some more data about neurodevelopmental outcome of children treated with therapeutic hypothermia for neonatal asphyxia, and is one of the rare ones coming from developing countries. The results are highly promising. Children treated with therapeutic hypothermia after perinatal asphyxia for prevention of hypoxic-ischemic brain damage showed remarkable good outcome. No clear correlation between baseline findings upon admission and on discharge from hospital and neurodevelopmental outcome have been established. Relatively small number of patients and limits of study design make our conclusions less reliable, but we think that this can be a start of continuous assessing of results of therapeutic hypothermia in preventing mortality and disability in countries with limited resources, and greater potential risk of having children with hypoxic-ischemic encephalopathy due to perinatal asphyxia.

CONFLICT OF INTEREST: NONE DECLARED.

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