

## ORIGINAL ARTICLE

# Clinical characteristics and short-term outcomes of neonates with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia – a single-center experience from Serbia

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**Summary**

**Aim:** This study aimed to report clinical characteristics and short-term outcomes of neonates with hypoxic-ischemic encephalopathy (HIE) treated with hypothermia. Furthermore, we analyzed the factors associated with short-term outcomes.

**Material and Methods:** We conducted a single-center retrospective study including neonates with HIE treated with hypothermia who survived hospital discharge. The short-term outcomes included normal or abnormal neurological examination findings on discharge.

**Results:** Forty-five neonates with HIE treated with hypothermia were identified. Median Apgar score at 1 minute was 3 (range 0-7), at 5 minutes it was 5 (range 1-10), while the median blood pH in the first post-natal hour was 6.94 (range 6.8-7.2). On admission, there were more neonates with moderate encephalopathy than those with severe encephalopathy according to the modified Sarnat classification (77.8% vs. 22.2%,  $p < 0.001$ ). Twelve (26.7%) neonates presented with complications during hypothermia. The most common complications were coagulopathy presented in 33.3% of cases and arterial hypotension presented in 25% of cases. Twenty-nine (64.44%) neonates had normal neurological examination, whereas 16 (35.56%) presented with abnormal neurological examination findings at discharge (0.006). Twenty-four (53.3%) neonates were discharged from hospital without any therapy. According to univariate analysis, abnormal neurological examination findings on discharge were significantly associated with  $pH < 7$  ( $p = 0.009$ ), 5-minute Apgar score  $\leq 5$  ( $p = 0.010$ ), and the presence of complications during hypothermia ( $p = 0.013$ ). According to multivariate analysis, abnormal neurological examination findings on discharge were significantly associated with  $pH < 7$  ( $p = 0.030$ ) and the presence of complications ( $p = 0.035$ ).

**Conclusion:** Our results during the first five years of experience with hypothermia support the beneficial effect of hypothermia in neonates with HIE.

**Keywords:** neonates, hypoxic-ischemic encephalopathy, therapeutic hypothermia

## INTRODUCTION

Neonatal hypoxic-ischemic encephalopathy (HIE) is one of the leading causes of mortality and neurodevelopmental disability (1-3). Hypothermia has been an important intervention used in the treatment of neonates with HIE in developed and developing countries for many years. Multiple studies have confirmed beneficial effects of hypothermia in term neonates with HIE (4-6). A recently published systematic review evaluated the effects of hypothermia on clinical outcomes and found that hypothermia reduced neurologic disability and cerebral palsy in neonates with HIE. Another important finding of this review was the observation that the setting in which therapeutic hypothermia was implemented affected the outcomes (7). There are no published studies regarding hypothermia treatment in neonatology in Serbia. Therefore, we conducted a study to assess clinical characteristics and short-term outcomes of neonates with HIE managed with hypothermia in a tertiary level hospital in Serbia and to analyze the factors associated with short-term outcomes.

## MATERIAL AND METHODS

The inpatient electronic medical records of neonates with HIE admitted to University Children's Hospital in Belgrade between February 2018 and October 2023 who were treated with therapeutic hypothermia and survived to hospital discharge were reviewed retrospectively. Hypothermia was introduced to the Neonatal Intensive Care Unit (NICU) of the University Children's Hospital in Belgrade therapeutic in February 2018.

Data extracted from the electronic medical records were demographic data, prenatal and perinatal events, the mode of delivery and the following neonatal characteristics: birth weight, restitution at birth, Apgar score, blood gases within the first postnatal hour, severity of encephalopathy on admission according to Sarnat criteria (8), the presence of early seizures, the use of inotropes, electroencephalography (EEG) and brain imaging reports, complications during hypothermia, complications during hospital stay, the duration of mechanical ventilation, NICU and hospital length of stay, and neurological examination findings on discharge. All extracted data were summarized and analyzed. Five neonates who had died were excluded from our study. The study was approved by the Ethics Committee of the University Children's Hospital in Belgrade (number 017 16/108).

### Hypothermia method

Whole-body hypothermia therapy was initiated in all neonates admitted in the first 6 postnatal hours if they met the physiological and neurological criteria (5). The

physiological criteria included a pH < 7.0, or base deficit  $\geq 16$  mmol/l in a sample of blood during the first hour after birth. If pH was 7.01-7.15, the base deficit 10-15.9 mmol/l, or blood gas was not available, additional criteria were required. These were acute perinatal events and either a 10-min Apgar score < 5 or assisted ventilation at birth for at least 10 min. The neurological criteria were the presence of seizures or confirmation of moderate or severe encephalopathy based on the modified Sarnat classification (8).

All neonates received whole-body cooling using the cooling system (Criticool-MTRE, Israel)

Core temperature was monitored via a rectal probe attached to the monitor. The target temperature was 33.5°C. Surface temperature was measured via a skin probe. Rewarming started after 72 h, and the temperature was increased gradually at a rate of 0.5 °C/h.

### Clinical data

During hypothermia therapy, all vital signs, blood gases, EEG reports, serum electrolytes, and laboratory analyses were monitored and collected. All complications that occurred during hypothermia therapy were recorded. These included thrombocytopenia (<100,000 per  $\mu$ l), coagulopathy requiring treatment, persistent metabolic acidosis (persistent after 24 postnatal hours), arterial hypotension requiring treatment, intracranial hemorrhage, and pulmonary hypertension requiring treatment. Furthermore, complications that occurred during hospital stay, the duration of mechanical ventilation, NICU, and hospital length of stay were collected. All these data were summarized and analyzed.

### Short-term outcomes

Short-term outcomes were defined as normal or abnormal neurological examination findings on discharge, assessed by attending neonatologist and pediatric neurologist.

### Statistical analysis

The results were presented as whole numbers (N) and percentages (%), while continuous values were presented as mean values (MV) with standard deviation (SD) and medians with ranges. Student's t-test and Mann-Whitney U test were applied to compare continuous variables depending on the normality of distribution, and Chi-square test or Fishers exact test were used for categorical variables. The degree of association of different neonatal data with short-term outcome were expressed using odds ratio and 95% confidence interval. Neonatal data with  $p < 0.05$  using univariate analysis were included in the multivariate logistic regression model. A value of  $p < 0.05$  was considered as statistically significant.

## RESULTS

The current study included 45 neonates with HIE treated with therapeutic hypothermia who survived hospital discharge. The maternal characteristics of these neonates are presented in **Table 1**. The type of delivery was vaginal in 48.89% of cases and cesarean section in 51.11% of cases ( $p=0.833$ ).

**Table 1.** Maternal characteristics (n = 45)

Complications during pregnancy - n (%)	
Diabetes	4 (8.89%)
Hypertension	6 (13.33%)
Chorioamnionitis	3 (6.67%)
Hemorrhage	1 (2.22%)
Pre-labor rupture of membranes	1 (2.22%)
None	23 (51.11%)
Data were not available	7 (15.6%)
Complications during labor or delivery - n (%)	
Meconium-stained amniotic fluid	8 (17.78%)
Abnormal fetal heart rate	5 (11.11%)
Placental abruption	3 (6.67%)
Uterine rupture	1 (2.22 <sup>^</sup> )
Cord prolapse	1 (2.22 <sup>^</sup> )
Placenta previa	1 (2.22 <sup>^</sup> )
None	21 (46.67%)
Data were not available	5 (11.11%)
Mode of delivery - n (%)	
Cesarean section	23 (51.11%)
Vaginal	22 (48.89%)

Characteristics of neonates are presented in **Table 2**. Among them 28 (62.2%) were males and 17 (37.8%) were females ( $p=0.020$ ). Median Apgar score at 1 minute was 3 (range 0-7) and Apgar scored at 5 min. was 5 (range 1-10). Almost 90% of neonates were intubated and over 90% of them had already been intubated in the delivery room. More than half of the neonates (64.4%,  $p=0.006$ ) did not require resuscitation at birth, whereas more than half of those who did (62.5%,  $p<0.001$ ) required only chest compressions. The median blood pH in the first postnatal hour was 6.94 (range 6.8-7.2), and the median base deficit was 19.82 (range 32-12) mmol/l. We found it statistically significant ( $<0.001$ ) that more neonates on admission had moderate than severe encephalopathy according to the modified Sarnat classification (77.8% vs. 22.2%). Twenty-one of 45 (46.7%) neonates had early clinical seizures. When we analyzed EEG data during cooling, we found that in 40 (88.9%) neonates, EEG recordings were abnormal and that in 22 (55%) of these neonates EEG recordings revealed non-specific encephalopathy as a predominant pattern. Furthermore, we found that 10 (25%) neonates had seizures present on EEG.

Twelve (26.7%) neonates presented with complications during hypothermia therapy. Eleven neonates had one complication, whereas one neonate developed coagulopathy with thrombocytopenia and intracranial (intraparenchymal) hemorrhage and in this case, cooling was discontinued due to complications. The most common

complications were coagulopathy presented in 4 (33.3%) cases and arterial hypotension presented in 3 (25%) cases, followed by persistent metabolic acidosis in 2 (16.7%), thrombocytopenia in 2 (16.7%), intracranial hemorrhage in 2 (16.7%), and pulmonary hypertension in 1 (8.3%) case.

**Table 2.** Neonatal characteristics (n = 45)

Male - n (%)	28 (62.2%)
GA (weeks) - mean $\pm$ SD	38.71 $\pm$ 1.93
Birth weight (g) - mean $\pm$ SD	3233.82 $\pm$ 477.53
Apgar score at 1 min - median (range)	3 (range 0-7)
Apgar score at 5 min - median (range)	5 (range 1-10)
Intubations - n (%)	40 (88.89%)
Intubation in delivery room - n (%)	37 (82.22%)
Resuscitation at birth - n (%)	16 (35.56%)
Chest compressions only - n (%)	10 (22.22%)
First blood pH - median (range)	6.94 (range 6.8-7.2)
First base deficit (mmol/l) - median (range)	19.82 (range 32-12)
Fist lactate level (mmol/l) - median (range)	13.29 (range 6-24)
Moderate encephalopathy - n (%)	35 (77.78%)
Severe encephalopathy - n (%)	10 (22.22%)
Early clinical seizures - n (%)	21 (46.67%)
Inotropic support - n (%)	7 (15.56%)
Abnormal EEG during hypothermia - n (%)	40 (88.89%)
Seizures on EEG - n (%)	10 (22.22%)

Moreover, we analyzed the complications that occurred during hospital stay and found that 16 (35.6%) neonates developed some complications. Four (25%) neonates developed culture-proven early-onset sepsis, 3 (18.7%) developed hyperglycemia, 2 (12.5%) of each developed hyperbilirubinemia and hypoglycemia, and 2 (12.5%) of each presented with respiratory distress and symptomatic patent ductus arteriosus. One (6.2%) neonate developed necrotizing enterocolitis.

The mean duration of mechanical ventilation was 4.14 $\pm$ 2.98 days. Most neonates (88.9%) required respiratory support > 48 hours.

Unfortunately, brain magnetic resonance imaging (MRI) was performed on only 6 (13.3%) neonates before discharge, and 4 (66.7%) of these had signs suggestive of HIE, while a CT scan was performed on 2 (4.4%) neonates before discharge. In neonates with serious complications in whom hypothermia was discontinued, both MRI and CT scans of the brain were performed during hospital stay.

The mean NICU length of stay was 6.84 $\pm$ 2.82 days while the mean hospital length of stay was 17.69 $\pm$ 8.99 days. Out of 45 neonates with HIE treated with hypothermia, 29 (64.44%) had normal neurological examination findings, whereas 16 (35.56%) neonates presented with abnormal neurological examination findings on discharge and the difference was significant ( $p=0.006$ ). Moreover, 24 (53.3%) neonates were discharged from hospital without therapy, whereas 21 (46.7%) neonates were discharged with anticonvulsant therapy.

**Table 3.** Associations between abnormal neurological examination findings on discharge and selected neonatal parameters.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Sex				
female	1		-	-
male	2.438 (0.633-9.380)	0.195		
Gestational age				
< 37 GN	1		-	-
≥ 37 GN	1.458 (0.249-8.539)	0.676		
Birth weight				
< 2500g	1		-	-
≥ 2500g	1.458 (0.249-8.539)	0.667		
Blood pH				
pH ≥ 7	1			
pH < 7	7.091 (1.643-30.607)	0.009	6.656 (1.200-36.917)	0.030
Base deficit				
≤ 16 mmol/l	1		-	-
> 16 mmol/l	3.684 (0.695-19.528)	0.125		
Apgar score at 5 min				
>5	1			
≤ 5	5.775 (1.521-21.932)	0.010	4.642 (0.995-21.655)	0.051
Early seizures				
no	1		-	-
yes	1.231 (0.362-4.182)	0.739		
Sarnat classification				
severe encephalopathy	1		-	-
moderate encephalopathy	0.458 (0.110-1.916)	0.285		
Use of inotropes				
no	1		-	-
yes	0.256 (0.028-2.341)	0.227		
Seizures present on EEG				
no	1		-	-
yes	2.182 (0.522-9.120)	0.285		
Complications during hypothermia				
no	1			
yes	6.250 (1.480-26.387)	0.013	5.897 (1.134-30.662)	0.035

Furthermore, using univariate analysis (**Table 3**), we found that abnormal neurological examination findings on discharge were significantly associated with pH < 7 in first postnatal hour (p=0.009), 5-min Apgar score ≤ 5 (p=0.010) and the presence of complications during hypothermia (p=0.013). According to multivariate analysis, abnormal neurological examination findings on discharge were significantly associated only with pH < 7 (p=0.030) and the presence of complications during hypothermia (p=0.035). For Apgar score ≤ 5 as a risk factor, the significance was borderline (p=0.051).

## DISCUSSION

In this study, we reported clinical characteristics and short-term outcomes of neonates with HIE treated with therapeutic hypothermia. Furthermore, among different neonatal data, we assessed which of them could be associated with abnormal neurological examination findings on discharge.

We found 45 neonates with HIE treated with therapeutic hypothermia who survived hospital discharge during the period of 5 years. Although our institution is a tertiary level hospital, hypothermia was only introduced to our center in February 2018. The fact that in our center, neonates with HIE received hypothermia only if they were admitted to the NICU in the first six postnatal hours, could influence the number of neonates in our study. Possibly, some neonates with HIE who met the criteria for hypothermia were not treated if they were admitted after the sixth hour, especially given the fact that many neonates were born in hospitals located far from our hospital and that there were many problems with transporting these children. Limited transport services with trained medical staff for neonatal care and insufficient equipment are the most frequent reasons for delayed transfer to the NICU.

We used the six-hour limit according to the recommendations (3, 5, 9-11) and data that hypothermia should be initiated within the first six hours for effective neuroprotection (12), although there are different data in the literature. It was suggested that cooling should be started



in the first three hours, to achieve an optimal neuroprotective effect (13). On the other hand, in some studies, hypothermia therapy was started after the sixth hour of life, within the first eight hours (14).

In this study, hypothermia was applied more often in males than in females. These results are consistent with some of the previously published studies where in the group of newborns treated with hypothermia, the male gender was more common (14-16). Furthermore, the median Apgar score at 1 min, at 5 min, and median blood pH of the neonates was similar to other studies (14, 16-18). In our study group, nearly 90% of neonates were intubated, and over 90% of them were already intubated in the delivery room. A large number of intubated and ventilated neonates on admission to the NICU could be a true reflection of the neonates' degree of illness in this study. However, it is statistically significant that more neonates on admission had moderate (77.8%) than severe encephalopathy (22.2%). This could explain the good outcome in more than half of neonates (64.44%) in our study bearing in mind that hypothermia is shown to be more beneficial in neonates with moderate encephalopathy compared to those with severe encephalopathy (4,19,20). Other authors studying hypothermia treatment reported more neonates with moderate than severe encephalopathy as well (14-17, 21). In the current study, 25% of neonates had seizures present on EEG, consistent with the rate reported in a large study from the USA involving over 900 children (22).

Approximately one-quarter of neonates (26.7%) presented with complications during hypothermia therapy in this study. The most common complication was coagulopathy requiring treatment presented in 33.3% of cases, which is in accordance with the published data [18-43%] (5,6,17). On the other hand, some authors reported higher frequencies of complications [48-50%] (14,18). In some of the previously published studies, none of the neonates with coagulopathy had significant bleeding (14). In our study, one neonate developed coagulopathy with thrombocytopenia and that was probably the reason for the occurrence of intracranial hemorrhage. This was the only case in our study when cooling was discontinued due to complications. The second most frequent complication was arterial hypotension requiring treatment with inotropes. It was confirmed in 25% of cases. In previously published studies these data were variable, reported in 17-40% of cases (14,18).

In addition, we found that hospital length of stay was 17.6 days, which is longer compared to other studies (13-14 days) (17, 22). Severe illness in the newborns on admission and a large number of intubated and ventilated neonates could have affected the length of hospital stay in the current study.

In the current study, 64.44% of neonates had a normal neurological examination, whereas 35.56% presented with abnormal neurological examination findings on

discharge, which was a similar finding to a study in India. Catherine et al. studying 78 neonates with HIE treated with hypothermia, reported more normal survivors on discharge than those with neurological abnormality (23). Moreover, 53.3% of neonates in our study, were discharged from hospital without any therapy.

Another important finding in this research is that abnormal neurological examination findings on discharge were significantly associated with pH < 7, 5-min Apgar score  $\leq$  5, and the presence of complications during hypothermia. Furthermore, in multivariate analysis perinatal and postnatal data significantly associated with abnormal neurological examination findings with pH < 7 and the presence of complications. Recently, Suppiej et al. found that a severe outcome, defined as death or severe neurological sequelae at 12 months of age, was significantly associated with Apgar score, Sarnat score, and cesarean section (24). However, in our study the significance of the Apgar score as a risk factor for abnormal neurological examination was borderline and we did not find a significant association with the Sarnat score. Wayock et al. studying early predictors of neurologic injury in neonates with HIE treated with hypothermia found that initial blood pH predicted a significantly increased risk of severe brain injury such as abnormal brain MRI at 7-10 days or death. These authors did not find that a 5-minute Apgar score <5 was associated with severe brain injury (25). Moreover, Ambalavanan et al. identified metabolic acidosis as a risk factor for brain injury related to HIE and indicated its importance in predicting neonatal outcomes. (26). To our knowledge, this is the only study that showed the presence of complications during hypothermia treatment was significantly associated with abnormal neurological examination findings on discharge.

Our study has several limitations. We collected data retrospectively. A small number of newborns were included and therefore only survivors were studied because the number of neonates who died was too small for statistical analysis. It is partly because this is a single-center experience and hypothermia was introduced quite late to our center. The fact that we did not assess the long-term outcomes, and neurodevelopmental impairments at one and/or two years of age is the most significant limitation of this study. However, it was shown that discharge exams may have predictive value for death and disability, more precisely an abnormal neurological exam at discharge was associated with a greater risk of death or disability (27). Another limitation is a lack of brain imaging data. Magnetic resonance imaging was performed on only 6 (13.3%) neonates before discharge from hospital due to the lack of trained pediatric radiologists and unavailable equipment.

## CONCLUSION

The current study has shown that more than half of the neonates with HIE treated with hypothermia had normal neurological examination findings at discharge and were discharged from hospital without any therapy. We found that not only low initial blood pH but also different complications during hypothermia therapy were significantly associated with abnormal neurological examination on discharge. Further larger studies are required to assess mortality and long-term neurodevelopmental outcomes among survivors.

## Conflict of interest

None to declare.

## Author Contributions

Biljana Medjo, Marija Karlicic, Miljana Z Jovandacic, Marina Atanaskovic-Markovic, Misela Raus, Dimitrije M. Nikolic and Dejan P. Nikolic gave critical contribution in writing the paper and formulating basic idea of this work, acquisition and interpretation of data, drafting the work, as well as defining conclusions.

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## KLINIČKE KARAKTERISTIKE I KRATKOROČNI ISHODI NOVOROĐENČADI SA HIPOKSIČNO-ISHEMIJSKOM ENCEFALOPATIJOM LEČENIH PRIMENOM TERAPIJSKE HIPOTERMIJE – ISKUSTVO JEDNOG CENTRA U SRBIJI

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### Sažetak

**Cilj rada:** Cilj ovog istraživanja bio je da se opišu kliničke karakteristike i kratkoročni ishodi novorođenčadi sa hipoksično-ishemijskom encefalopatijom (HIE) koja su lečena hipotermijom. Porede toga, analizirali smo faktore udružene sa kratkoročnim ishodima.

**Metode:** Ova retrospektivna studija obuhvatila je preživelu novorođenčad sa HIE, koja su lečena hipotermijom u jednom centru. Kratkoročni ishodi obuhvatili su normalan ili patološki neurološki nalaz na otpustu iz bolnice.

**Rezultati:** Identifikovano je 45 novorođenčadi sa HIE lečenih hipotermijom. Mediana Apgar skora u 1. minutu iznosila je 3 (opseg 0-7), u 5. minutu 5 (opseg 1-10), dok je medijana pH krvi u prvom satu života bila 6,94 (opseg 6,8-7,2). Na prijemu je bilo više novorođenčadi sa srednjom nego sa teškom encefalopatijom prema Sarnatovoj klasifikaciji (77,8% vs. 22,2%,  $p < 0.001$ ). Dvanaestoro (26,7%) novorođenčadi imalo je komplikacije tokom hi-

potermije. Najčešće komplikacije bile su koagulopatija u 33,3% slučajeva i arterijska hipotenzija u 25% slučajeva. Bilo je 29 novorođenčadi (64,44%) sa normalnim nalazom, dok je njih 16 (35,56%) imalo patološki nalaz pri neurološkom pregledu na otpustu (0,006). Dvadeset četiri (53,3%) novorođenčeta su otpuštena iz bolnice bez terapije. Univarijantnom analizom utvrđeno je da je patološki nalaz pri neurološkom pregledu na otpustu značajno povezan sa  $pH < 7$  ( $p=0,009$ ), petominutnim Apgar skorom  $\leq 5$  ( $p=0,010$ ) i prisustvom komplikacija tokom hipotermije ( $p=0,013$ ). Multivarijantnom analizom, utvrđeno je da je patološki nalaz pri neurološkom pregledu na otpustu značajno povezan sa  $pH < 7$  ( $p=0,030$ ) i prisustvom komplikacija ( $p=0,035$ ).

**Zaključak:** Naši rezultati i prvo, petogodišnje iskustvo sa terapijskom hipotermijom ukazuju na povoljan efekat ove terapije kod novorođenčadi sa HIE.

**Ključne reči:** Novorođenčad, Hipoksično-ishemična encefalopatija, Terapijska hipotermija

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