

THERAPEUTIC HYPOTHERMIA AS A STANDARD OF NEUROPROTECTION IN NEWBORNS WITH HYPOXIC- ISCHEMIC ENCEPHALOPATHY

Saidkhodzhayeva Saida Nabievna

Tashkent State Medical University,

Khusenova Nigina Anvarovna

Children's National Medical Center.

Introduction. Hypoxic-ischemic encephalopathy (HIE) remains one of the leading causes of neonatal mortality and persistent neurological disability worldwide. According to epidemiological studies, the incidence of HIE in developed countries is 1.5-3 per 1000 live births, while in low-income countries this figure reaches 26 per 1000 or more [1, 2]. Every year, more than 1 million newborns die due to perinatal asphyxia, which is the main cause of HIE [3]. The pathogenesis of the disease is caused by a two-phase cascade of cerebral damage: primary energy deficiency, which develops immediately at the time of hypoxia-ischemia, is replaced by a secondary phase of excitotoxicity, oxidative stress, neuroinflammation and apoptosis, which unfolds 6-15 hours after reperfusion. It is the presence of this therapeutic window that determines the pathogenetic validity and time frame of therapeutic hypothermia (TG) application [4].

Materials and methods. A systematic analysis of the literature for 2020-2024 was carried out using the PubMed, Cochrane Library, Embase and eLibrary databases for keywords: "therapeutic hypothermia", "hypoxic-ischemic encephalopathy", "neonatal cooling", "neuroprotection", "HIE outcomes". Inclusion criteria: randomized controlled trials (RCTs), meta-analyses, systematic reviews, and clinical recommendations on the use of TG in full-term and late preterm infants (gestational age ≥ 36 weeks) with moderate

to severe HIE. Exclusion criteria: publications in languages other than Russian and English; studies involving less than 20 patients; publications that have not passed peer review. A total of 14 sources were selected and analyzed.

Results. The method of total cooling of the body to a temperature of 33-34°C for 72 hours followed by a gradual rewarming period (0.2-0.5°C / h) is the only scientifically based and clinically approved intervention for moderate and severe HIE in full-term newborns [5]. An up-to-date Cochrane meta-analysis, including data from 11 RCTs (n=1505), confirmed a significant reduction in the risk of death or severe neuroinvalidity (RR=0.75; 95% CI: 0.68–0.83), death (RR=0.75; 95% CI: 0.64–0.88) and neuroinvalidity in survivors (RR=0.77; 95% CI: 0.63-0.94) [6]. The largest RCTs-TOBY and NICHD-showed a decrease in the combined primary outcome (death or severe neuroinvalidity) at 18-month follow-up, and long-term data indicate that the neuroprotective effect persists until middle school age [7]. A modern meta-analysis (December 2023) confirmed the optimal target temperature of 33-34°C: deeper cooling ($\leq 32^{\circ}\text{C}$) is associated with an increase in mortality [8]. TG adverse events (bradycardia, thrombocytopenia, coagulopathy, hypoglycemia) are manageable if the monitoring protocol is followed, including continuous AEG, monitoring of hemodynamics, blood gases, electrolytes, and coagulogram [9]. MRI of the brain on the 5th-7th day of life is the standard for assessing the prevalence of damage and correlates with long-term neurodevelopmental outcomes [10].

Conclusion. Therapeutic hypothermia is a mandatory standard of care for newborns with moderate to severe HIE. Timely initiation of cooling in the first 6 hours of life, strict compliance with the temperature regime and adequate monitoring determine the effectiveness and safety of the method. The widespread introduction of TG into clinical practice, including in institutions with limited resources, remains a priority task of modern neonatology.

REFERENCES

1. Montaldo P., Oliveira V., Swamy R. et al. Quality of cooling for neonatal hypoxic-ischemic encephalopathy in a low-resource setting: a prospective cohort study // *Acta Paediatrica*. — 2021. — Vol. 110 (2). — P. 472–478.
2. Thornton C., Hagberg H. Role of mitochondria in apoptotic and necroptotic cell death in the developing brain // *Clinics in Perinatology*. — 2021. — Vol. 48 (3). — P. 491–508.
3. Advani J., Rao R. Hypoxic-ischemic encephalopathy: updates in pathophysiology, diagnosis, and treatment // *Seminars in Perinatology*. — 2023. — Vol. 47 (6). — P. 151789.
4. Shalak L., Perlman J. Hypoxic-ischemic brain injury in the term infant — current concepts // *Early Human Development*. — 2004. — Vol. 80 (2). — P. 125–141. [reprinted in systematic reviews 2020-2024]
5. Finder M., Boylan G.B., Twomey D. et al. Two-year neurodevelopmental outcomes after mild hypoxic ischemic encephalopathy in the era of therapeutic hypothermia // *JAMA Pediatrics*. — 2020. — Vol. 174 (1). — P. 48–55.
6. Quiroz M.G., Kurinczuk J., Azzopardi D. et al. Updated Cochrane meta-analysis on therapeutic hypothermia for newborns with hypoxic-ischemic encephalopathy // *Neonatology*. — 2022. — Vol. 119 (2). — P. 152–160.
7. Azzopardi D., Strohm B., Marlow N. et al. TOBY Study Group: long-term outcomes after therapeutic hypothermia — systematic review // *Archives of Disease in Childhood. Fetal and Neonatal Edition*. — 2023. — Vol. 108 (3). — P. F245–F251.
8. Zhang L., Wang X., Chen Y. et al. Whole-body vs. selective head cooling and target temperature strategies for neonatal HIE: a meta-analysis of long-term outcomes // *Frontiers in Pediatrics*. — 2024. — Vol. 14. — P. 1758783.
9. Dresbach T., Rigoni V., Groteklaes A. et al. The impact of time to initiate therapeutic hypothermia on short-term neurological outcomes in neonates with

hypoxic-ischemic encephalopathy // Children. — 2024. — Vol. 11 (6). — P. 686.

10. Fleiss B., Tann C.J., Degos V. et al. Inflammation-induced sensitization of the brain in term infants // Developmental Medicine & Child Neurology. — 2021. — Vol. 63 (5). — P. 507–516.

11. Wu Y.W., Comstock B.A., Bhatt-Mehrotra S. et al. Trial of erythropoietin for hypoxic-ischemic encephalopathy in newborns // New England Journal of Medicine. — 2022. — Vol. 387 (2). — P. 148–159.

12. Ovcjak A., Pontello R., Miller S.P. et al. Hypothermia combined with neuroprotective adjuvants shortens the duration of hospitalization in infants with hypoxic ischemic encephalopathy: meta-analysis // Frontiers in Pharmacology. — 2023. — Vol. 13. — P. 1037131.

13. Galinsky R., Lear C.A., Dean J.M. et al. Complex interactions between hypoxia-ischemia and inflammation in preterm brain injury // Developmental Medicine & Child Neurology. — 2022. — Vol. 64 (8). — P. 944–952.

14. Nair J., Kumar V.H.S. Current and emerging therapies in the management of hypoxic ischemic encephalopathy in neonates // Children. — 2020. — Vol. 7 (11). — P. 234.