ISSN: 2754-4923

Journal of Diagnosis & Case Reports

SCIENTIFIC Research and Community

Research Article

Open Access

The Effect and Significance of Mild Hypothermia Adjuvant Therapy on Serum IL-6 and TNF-α in Neonatal Hypoxic-Ischemic Encephalopathy

Mi Nan, Liu Yulu, Wang Dong and Wang Shengli*

Neonatal Intensive Care Unit, The First People's Hospital of Shangqiu, 252 Shengli Middle Road, Hualong District, Puyang City, China

ABSTRACT

Objective: To investigate the effect of systemic mild hypothermia therapy on peripheral blood interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) in neonates with hypoxic-ischemic encephalopathy (HIE) within 6 hours after birth.

Methods: Forty neonates with HIE within 6 hours after birth, who were admitted to the neonatal intensive care unit of Shangqiu First People's Hospital in Henan Province from October 2021 to October 2023, were selected as the research objects. They were divided into the mild hypothermia group and the conventional treatment group according to the treatment method. The children in the conventional treatment group received conventional supportive treatment, while those in the mild hypothermia group were given head mild hypothermia treatment and conventional supportive treatment. Peripheral blood IL-6 and TNF-α were measured in all children at admission and 72 hours after treatment. Neonatal Behavioral Neurological Assessment (NBNA) scale scores were performed at 14 and 28 days after birth.

Results: There was no significant difference in the levels of blood IL-6 and TNF-α in HIE children of the conventional treatment group 72 hours after treatment compared with those at admission ($P > 0.05$). 2. The levels of blood IL-6 and TNF-α in HIE children of the mild hypothermia group 72 hours after treatment were significantly lower than those at admission ($P < 0.05$). 3. 72 hours after treatment, the levels of blood IL-6 and TNF-α in moderate HIE children of the mild hypothermia group were significantly lower than those in moderate HIE children of the conventional treatment group ($P < 0.05$). 4. 72 hours after treatment, the levels of blood IL-6 and TNF-α in severe HIE children of the mild hypothermia group were significantly lower than those in severe HIE children of the conventional treatment group ($P < 0.05$). 5. At 14 and 28 days after birth, the NBNA scores of HIE children in the mild hypothermia group were significantly higher than those in the conventional treatment group ($P < 0.05$). Conclusion Head mild hypothermia treatment for HIE children within 6 hours after birth has an obvious effect. Head mild hypothermia treatment can reduce the levels of serum IL-6 and TNF-α in HIE children, inhibit the indirect neurotoxic effect caused by the increase of IL-6 and TNF-α levels, play a role in brain protection, improve the NBNA score, and obtain a better prognosis.

***Corresponding author**

Wang Shengli, Neonatal Intensive Care Unit, The First People's Hospital of Shangqiu, 252 Shengli Middle Road, Hualong District, Puyang City, 457000, China.

Received: January 10, 2025; **Accepted:** January 20, 2025; **Published:** January 24, 2025

Keywords: Mild Hypothermia, Hypoxic-ischemic Encephalopathy, Regulatory, Tumor Necrosis Factor, Interleukin-6, NBNA Score

Background

Hypoxic-ischemic encephalopathy is neonatal brain damage caused by hypoxia and reduced cerebral blood flow due to various perinatal reasons, resulting in high mortality and long-term neurological dysfunction. Mild hypothermia treatment is the only method proven to have a definite effect on HIE, and generally, the first 6 hours after birth is considered the optimal treatment time window [1,2]. The role of immune inflammation in HIE has received increasing attention. However, there are still few reports on the immunological effects of mild hypothermia treatment on HIE children. This experiment dynamically detected the changes in the levels of serum IL-6 and TNF-α in HIE children after mild hypothermia treatment. The report is as follows.

Materials and Methods

The study included moderate and severe asphyxia neonates admitted to the neonatal intensive care unit of Shangqiu First People's Hospital from October 2021 to October 2023. Inclusion criteria: All children met the diagnostic criteria of HIE and were diagnosed as neonatal hypoxic-ischemic encephalopathy [3]. They were all admitted to the hospital within 6 hours after birth, with a birth weight of 2.5 - 4.0 kg and a gestational age of 37 weeks ≤ gestational age < 42 weeks; the Apgar score at 1 minute after birth was ≤ 3, and the Apgar score at 5 minutes after birth was ≤ 5. Exclusion criteria: Children had severe congenital diseases (congenital malformations, congenital metabolic disorders); other craniocerebral injuries (severe intracranial hemorrhage, skull fracture); pulmonary hemorrhage and bleeding tendency; severe anemia (hemoglobin less than 120g/L). A total of 40 HIE children were included in this study. According to different treatment methods, they were divided into the mild hypothermia group and the control group, with 20 cases in each group. There were 12 cases

of moderate HIE and 8 cases of severe HIE in the control group, and 10 cases of moderate HIE and 10 cases of severe HIE in the mild hypothermia group. There was no significant difference in gestational weeks ($t = 1.204$), birth weight ($t = 0.841$), and clinical classification ($\chi^2 = 0.089$) between the two groups ($P > 0.05$). This study was approved by the hospital medical ethics committee, and the guardians of the children signed the informed consent form.

Treatment Methods

(1) Normothermia treatment group: Maintain normal blood pressure and arterial blood gas, maintain acid-base balance, limit fluid intake, control seizures, reduce intracranial pressure, and provide nutritional support. Respiratory support treatment was given when necessary. (2) Mild hypothermia treatment group: In addition to conventional treatment, selective head mild hypothermia was performed within 6 hours after birth. The cooling cap was wrapped around the child's head with appropriate tightness. The skin temperature probe of the cooling instrument was fixed in the middle of the forehead. The cooling instrument was turned on, and the water temperature was controlled at 6 - 13 °C. The surface skin temperature was (33.5 ± 0.05) °C, and the rectal temperature was (34.0 ± 0.05) °C. The treatment lasted for 72 hours. The skin and rectal temperatures were detected by a multifunctional bedside monitor. After the end of hypothermia treatment, far-infrared radiation was used for rewarming at a rate of 0.5 °C/h. The skin and rectal temperatures were restored to ≥ 36 °C within 6 hours.

Sample Collection and Detection

Peripheral venous blood (3 ml) was collected from the children in both groups before treatment within 6 hours after birth and 72 hours after treatment. 1.5 ml of the blood was injected into a test tube containing 30 μl of 10% EDTA-Na_2 and centrifuged at 1000 r/min (centrifugal radius 10 cm) for 15 minutes to collect plasma. The other 1.5 ml was injected into another test tube and centrifuged at 1000 r/min (centrifugal radius 10 cm) for 15 minutes to collect serum. The samples were stored in a -20 °C refrigerator for centralized detection. Hemolyzed samples were discarded. The concentrations of IL-6 and TNF-α were determined by the double-antibody sandwich ELISA method according to the kit instructions [4]. The kits were all produced by RD Company in the United States.

Neonatal Neurological Function Evaluation

All children in the group were evaluated by the NBNA score. At 14 and 28 days after birth, based on the 20-item neonatal behavioral neurological examination method, the evaluation was carried out from five aspects: behavioral ability, passive muscle tone, active muscle tone, primitive reflexes, and general assessment. The full score was 40 points. A score of ≥ 35 points indicated that the child's behavioral neurological function was normal, and a score of < 35 points indicated that the neonatal behavioral neurological function was abnormal.

Statistical Analysis

SPSS 25.0 was used for statistical analysis of the data results. Measurement data conforming to the normal distribution were expressed as mean ± standard deviation (`x ± s`). Independent sample t-tests were used for comparison between groups. Count data were expressed as percentages (%). Chi-square tests were used for comparison between groups. $P < 0.05$ was considered to indicate a significant difference.

Results

(1) Before treatment, there was no significant difference in the levels of IL-6 and TNF-α in the blood of moderate and severe HIE children between the mild hypothermia group and the control group ($P > 0.05$). (2)There was no significant difference in the levels of IL-6 and TNF-α in the blood of severe HIE children between the mild hypothermia group and the control group 72 hours after treatment ($P > 0.05$). (3)There was no significant difference in the levels of IL-6 and TNF-α in the blood of moderate and severe HIE children in the control group and severe HIE children in the mild hypothermia group 72 hours after treatment compared with those before treatment ($P > 0.05$). (4)72 hours after treatment, the level of IL-6 in the blood of moderate HIE children in the mild hypothermia group was significantly lower than that in the control group ($P < 0.05$), and the level of TNF-α was significantly lower than that in the control group ($P < 0.05$). (5)The level of IL-6 in the blood of moderate HIE children in the mild hypothermia group was significantly lower than that before treatment ($P < 0.05$), and the level of TNF-α was significantly lower than that before treatment ($P < 0.05$). On the 14th and 28th days after birth, the NBNA scores of moderate HIE children in the mild hypothermia group were significantly higher than those in the control group ($P < 0.05$), but there was no significant difference in the NBNA scores of severe HIE children between the mild hypothermia group and the control group ($P > 0.05$).

Discussion

Mild hypothermia treatment has a significant neuroprotective effect on HIE [4]. Mild hypothermia can significantly reduce the mortality and the incidence of long-term neurological diseases in full-term HIE children [5]. Many countries have listed mild hypothermia treatment as a routine treatment method for neonatal HIE.IL-6 is a multifunctional cytokine that has both neuroprotective effects and can cooperate with other inflammatory cytokines to exert cytotoxic effects [6,7]. This study showed that there was no significant difference in the level of IL-6 in the blood of severe HIE children between the mild hypothermia group and the control group 72 hours after treatment ($P > 0.05$). There was no significant difference in the level of IL-6 in the blood of moderate and severe HIE children in the control group and severe HIE children in the mild hypothermia group 72 hours after treatment compared with those before treatment ($P > 0.05$). 72 hours after treatment, the level of IL-6 in the blood of moderate HIE children in the mild hypothermia group was significantly lower than that in the control group ($P < 0.05$). The concentration of serum IL-6 in HIE children treated with mild hypothermia was significantly lower 72 hours after treatment than before treatment, indicating that a higher concentration of IL-6 is related to acute brain injury, and mild hypothermia therapy has an obvious inhibitory effect on the early massive secretion of IL-6. Some scholars believe that the immune response and inflammation play an important role in neonatal HIE. Hypoxia-ischemia causes an inflammatory cascade reaction in blood vessels. At the same time, stressed or dead neurons cause the activation of brain resident immune cells and the infiltration of peripheral immune cells into the brain. These immune cells release neurotoxic substances (such as reactive oxygen species and inflammatory cytokines) through which finally lead to secondary neuronal death [8]. Mild hypothermia treatment can not only reduce the metabolic rate of brain cells but also inhibit the massive secretion of IL-6, block the secondary neurological function damage mediated by IL-6, reduce brain edema, improve cerebral perfusion, improve the hypoxic-ischemic state of brain tissue, and promote the recovery of the structure and function of nerve cells, thereby improving the clinical prognosis [9,10].

TNF-α is the earliest and most important inflammatory mediator in the inflammatory reaction process [11]. In the central nervous system, it is synthesized by nerve astrocytes, microglia, and

vascular endothelial cells. After a child has brain damage, glial cells will be damaged. TNF-α can invade brain tissue through the damaged blood-brain barrier and release TNF-α in the brain, thereby increasing the penetrability of epithelial cells, up-regulating the adhesion ability of lymphocytes and neutrophils, and also inducing the production of acute-phase reactant proteins, further leading to tissue damage. Therefore, TNF-α can be used as an effective indicator to evaluate HIE brain injury [12-15]. This study showed that 72 hours after treatment, the level of IL-6 in the blood of moderate HIE children in the mild hypothermia group was significantly lower than that in the control group ($P < 0.05$), and the level of TNF-α was significantly lower than that in the control group ($P < 0.05$). Therefore, the decrease in the level of serum TNF-α in HIE children after mild hypothermia treatment indicates that mild hypothermia can improve the prognosis of HIE children.

Conclusion

In conclusion, mild hypothermia can reduce the levels of serum IL-6 and TNF-α in moderate and severe HIE children, reduce brain edema, improve cerebral perfusion, improve the hypoxicischemic state of brain tissue, and promote the recovery of the structure and function of nerve cells. It is worthy of clinical application. However, the sample size of this study is small, and further expansion of the clinical sample size is needed to confirm the conclusions of this study.

Finance

Supported by Joint construction Project of Henan Medical Science and Technology Research Plan, number: LHGJ20221056.

References

1. Leifsdottir K, Mehmet H, Eksborg S, Eric Herlenius (2018) Fas-ligand and interleukin-6 in the cerebrospinal fluid are early predictors of hypoxic-ischemic encephalopathy and long-term outcomes after birth asphyxia in term infants. J Neuroinflammation 15: 223.
2. Jia W, Lei XP, Dong WB, Qingping Li (2018) Benefits of starting hypothermia treatment within 6 h vs.6-12 h in newborns with moderate neonatal hypoxic-ischemic encephalopathy. BMC Pediatr18: 50.
3. Hachet O, Guenancia C, Stamboul K, Benoit Daubail, Carole Richard, et a1. (2014) Frequency and predic- tors of stroke after acute myocardial infarction l specific aspects of in-hospital and postdischarge events E Stroke 45: 3514-3520.
4. Dixon B, Reis C, Ho W, Jiping Tang, John H Zhang (2015) Neuroprotective strategies after neonatal hypoxic ischemic encephalopathy. Int J Mol Sci 16: 22368-22401.
5. Shetty AN, Lucke AM, Liu PY, Magdalena Sanz Cortes, Joseph L Hagan, et al. (2019) Cerebral oxygen metabolism during and after therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy: a feasibility study using magnetic resonance imaging. Pediatr Radiol 49: 224-233.
6. Azzopardi D, Robertson NJ, Cowan FM, Rutherford MA, Rampling M, et al. (2000) Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics 106: 684-694.
7. Szakmar E, Jermendy A, Eldib M (2019) Correction: Respiratory management during therapeutic hypothermia for hypoxicischemic encephalopathy. Journal of Perinatology 9: 891-895.
8. Marina A, Kiran T, Kathleen S, David Carola, Kolawole Solarin, et al. (2019) Apgar scores at 10 m-i nutes and outcomes in term and late preterm neonates with hypoxic-ischemic encephalopathy in the cooling era. American Journal of Perinatology 36: 545-554.
9. Ulrike H, Martina P, Erich S, Laura Egloff, Sarah Ittig, et al. (2019) Plasma and serum brainderived neurotrophic factor(BDNF)levels and their association with neurocognition in a-t risk mental state, first episode psychosis and chronic schizophrenia patients. World Journal of Biological Psychiatry 20: 545-554.
10. Kurinczuk JI, White-Koning M, Badawi (2010) N.Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev 8: 329-338.
11. Filippi L, Fiorini P, Catarzi S, Elettra Berti, Letizia Padrini, et al. (2018) Safety and efficacy of topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia (NeoNAT: a feasibility study. J Matern Fetal Neonatal Med 31: 973-980.
12. Gunn AJ, THORESEN M (2019) Neonatal encephalopathy and hypoxicischemic encephalopathy. Handb Clin Neurol 162: 217-237.
13. Gulczynska E, Gadzinowski J (2012) Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy. Ginekol Pol 83: 214-218.
14. Saw CL, Rakshasbhuvankar A, Rao S, M Bulsara, Sanjay Patole (2019) Current practice of therapeutic hypothermia for mild hypoxic ischemic encephalopathy. J Child Neurol 34: 402-409.
15. Sarnat HB (1976) Neonatal encephalopathy following fetal distress. Arch Neurol 33: 696.