Hindawi
Adsorption Science & Technology
Volume 2022, Article ID 2465490, 8 pages
https://doi.org/10.1155/2022/2465490

Research Article

Clinical Efficacy of Subhypothermia in the Treatment of Neonatal Hypoxic-Ischemic Encephalopathy Combined with Myocardial Damage

XiaoPing Dang,[1] XiaoJian Hu,[2] Xun Jiang,[3] WeiGuo Chen,[4] YuanCui Meng,[1] Qi Pan,[5] and Fen Yang[1]

[1]*Department of Neonata, Second Affiliated Hospital of Xi'an Medical College, Xi'an, 710038 Shaanxi, China*
[2]*Department of Urology, Second Affiliated Hospital of Xi'an Medical College, Xi'an, 710038 Shaanxi, China*
[3]*Department of Neonata, The Second Affiliated Hospital of Air Force Medical University, Xi'an, 710038 Shaanxi, China*
[4]*Department of Cardiovascular Medicine, Second Affiliated Hospital of Xi'an Medical College, Xi'an, 710038 Shaanxi, China*
[5]*Department of Radiology, Second Affiliated Hospital of Xi'an Medical College, Xi'an, 710038 Shaanxi, China*

Correspondence should be addressed to Fen Yang; fenyang2022dang@163.com

Received 31 August 2022; Revised 8 September 2022; Accepted 10 September 2022; Published 27 September 2022

Academic Editor: Rabia Rehman

Objective. To investigate the efficacy of subhypothermia in the treatment of neonatal hypoxic-ischemic encephalopathy (HIE) combined with myocardial damage. *Methods.* 136 children with HIE and myocardial damage admitted to our hospital from October 2019 to October 2021 were included in the study and were divided into study group and control group of 68 cases each according to the random number table method. The control group was given conventional treatment, and the study group was treated with subhypothermia therapy on top of the control group. Comparing the effects of treatment between the two groups. The serum levels of S-100β protein, Tau protein, neuron-specific enolase (NSE), creatine kinase (CK), creatine kinase isoenzyme MB (CK-MB), lactate dehydrogenase (LDH), alpha-hydroxybutyrate dehydrogenase (a-HBDH), myoglobin (Myo), cardiac trophic factor-1 (CT-1), cardiac troponin I (cTnI), superoxide dismutase (SOD), reactive oxygen species (ROS), glutathione peroxidase (GSH-Px), interleukin-1β (IL-1β), interleukin-8 (IL-8), and tumor necrosis factor-a (TNF-a) were measured in both groups before and after treatment, respectively. *Results.* The total effective rate was higher in the study group (88.24%) than in the control group (72.06%) ($P < 0.05$). After treatment, the serum levels of S-100β protein, Tau protein, NSE, CK, CK-MB, LDH, a-HBDH, Myo, CT-1, cTnI, ROS, IL-1β, IL-8, and TNF-a were reduced in both groups, and the study group was lower than the control group ($P < 0.05$). The serum levels of SOD and GSH-Px were higher in both groups after treatment than before treatment and were higher in the study group than in the control group ($P < 0.05$). *Conclusion.* Subhypothermia treatment of children with HIE combined with myocardial injury can further improve the hypoxic-ischemic state; reduce myocardial damage, oxidative stress, and inflammatory response; and has a good overall efficacy.

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE), mainly due to perinatal asphyxia, is an important factor in neonatal mortality, and even if the child survives, it may result in sequelae such as mental retardation, cerebral palsy, cognitive impairment, and motor deficits [1, 2]. The prevalence of HIE is about 1‰ to 8‰ in developed countries and about 26‰ in countries that are relatively underdeveloped, which is very detrimental to the growth and development of affected children [3]. Studies have shown that because the brain tissue of children with HIE is in a state of ischemia and hypoxia, it can induce hypoxemia and metabolic disorders in the body, leading to impaired organ function, especially with very high myocardial oxygen consumption and a corresponding increase in the risk of damage, which has a significant

impact on the prognosis of the children patients [4]. Clinically, it is necessary to timely correct the discomfort of children, control the risk of death, and improve the prognosis. In recent years, subhypothermia therapy has been widely used in the treatment of brain injury. It can reduce brain temperature by 2~6°C through artificial induction, improve brain metabolism, prevent brain edema, reduce energy consumption, and inhibit free radical activity to a certain extent, which can alleviate the degree of brain injury [5]. However, the condition of children with HIE and myocardial damage is more complex, and the value of subhypothermia therapy in the treatment of this condition needs to be further investigated. The aim of this study was to analyze the effect of subhypothermia treatment on children with HIE and myocardial damage and to provide a basis for improving their condition.

2. Materials and Methods

2.1. Study Subjects. 136 children with HIE and myocardial damage admitted to our hospital from October 2019 to October 2021 were included in the study and were divided into 68 cases each in the subcold group and the control group according to the random number table method.

In the study group, there were 20 females and 48 males; gestational age 37-41 weeks, mean39.81 ± 1.02weeks; mode of delivery: 35 cases by caesarean section and 33 cases by normal delivery; birth weight 2853-4046 g, mean3486.43 ± 414.24 g; and HIE classification: moderate 49 cases and severe 19 cases. In the control group, there were 26 females and 42 males; gestational age 37-42 weeks, mean39.56 ± 1.16weeks; mode of delivery: cesarean section in 38 cases and normal delivery in 30 cases; birth weight 2831-4172 g, mean3471.17 ± 402.74g; and HIE classification: moderate in 51 cases and severe in 17 cases. There was no statistical significance in the general data of 2 groups ($P > 0.05$). The study was approved by the ethics committee of our hospital.

Inclusion criteria are as follows: those who meet the relevant diagnostic criteria for HIE [6], are confirmed by CT and MRI, and have a clinical diagnosis of combined myocardial injury; Full-term infants, gestational age ≥37 weeks; pregnant women aged 20-35 years with no previous history of delivery of a child with HIE; and those with informed consent.

Exclusion criteria are as follows: pregnant women with pregnancy complications, such as gestational hypertension and gestational diabetes; children with severe intracranial hemorrhage; children with congenital malformations; and those with central nervous system pathology.

2.2. Methods. The control group was given conventional treatment, including anticonvulsant, cranial pressure lowering, nerve nutrition, oxygenation, and correction of water-electrolyte disturbance. Symptomatic treatment was administered according to the situation. The study group was treated with subhypothermia on top of the control group. Operated by professionals, the child was placed on a low-temperature pad and treated with a subhypothermia apparatus (T1/T2, Zhuhai Black Horse Medical Equipment Co., Ltd.) at an initial temperature of 10°C. The child's anal temperature was checked every 10 min, and the temperature of the apparatus was adjusted according to the change in anal temperature. After 60 min of treatment, the child's anal temperature was basically controlled at about 33.5°C and maintained for 72 h. When treatment is complete, the child needs to be rewarmed naturally, with anal temperature measured at 30-min intervals, and the temperature increase needs to be <0.5°C/h. If the child is not rewarmed naturally after 12 h, then assisted warming (thermal coinjection) is performed.

2.3. Indicator Observation. (i) Evaluation of efficacy includes as follows [7]: for significantly effective, the symptoms of cerebral ischemia and hypoxia of the children were significantly relieved, no abnormality was found in the brain function test, and the vital signs basically returned to normal; for effective, clinical symptoms improved, and brain function and vital signs improved but did not reach the normal standard; for ineffective, symptoms, brain function, and vital signs did not improve. Total effective rate = (significantly effective + effective)/total number of cases × 100%. For (ii) efficacy index test, the efficacy indexes of the two groups were tested before and 1 week after the treatment. 3 ml of peripheral venous blood was collected from the child and centrifuged at 3000 r/min, and the serum was separated and stored at -80°C for testing. The serum levels of S-100β protein, Tau protein, NSE, SOD, ROS, GSH-Px, IL-1β, IL-8, TNF-a, LDH, CT-1, and cTnI were measured by enzyme-linked immunosorbent assay (ELISA), and reagents were purchased from the Shanghai Enzyme Link Biotechnology Co. The serum levels of CK, CK-MB, and Myo were determined by immunosuppression assay, and the reagents were purchased from the Guangzhou Kefang Biotechnology Co. a-HBDH was measured using rate assay, and the reagents were purchased from Desai Diagnostic Systems GmbH, Germany.

2.4. Statistical Analysis. SPSS20.0 statistical software was used to analyze and process the data. The measurement data were described by mean ± standard deviation ($\bar{x} \pm s$), and t-test for independent samples was used for comparison between groups; the count data were expressed as frequencies and percentages, and χ^2 test was used for comparison between groups, and $P < 0.05$ was regarded as statistically significant difference.

3. Results

3.1. MRI Manifestations after Subhypothermia Treatment. Compared with the patient before treatment, T1-weighted images (T1W1) on MRI 2 weeks after subhypothermia treatment showed a significant reduction of speckled high signal in the parasternal posterior horn of the ventricles bilaterally. See Figure 1.

3.2. Comparison of Clinical Outcomes between the Two Groups. The total effective rate of the study group was 88.24%, higher than the control group's 72.06% ($P < 0.05$). See Table 1.

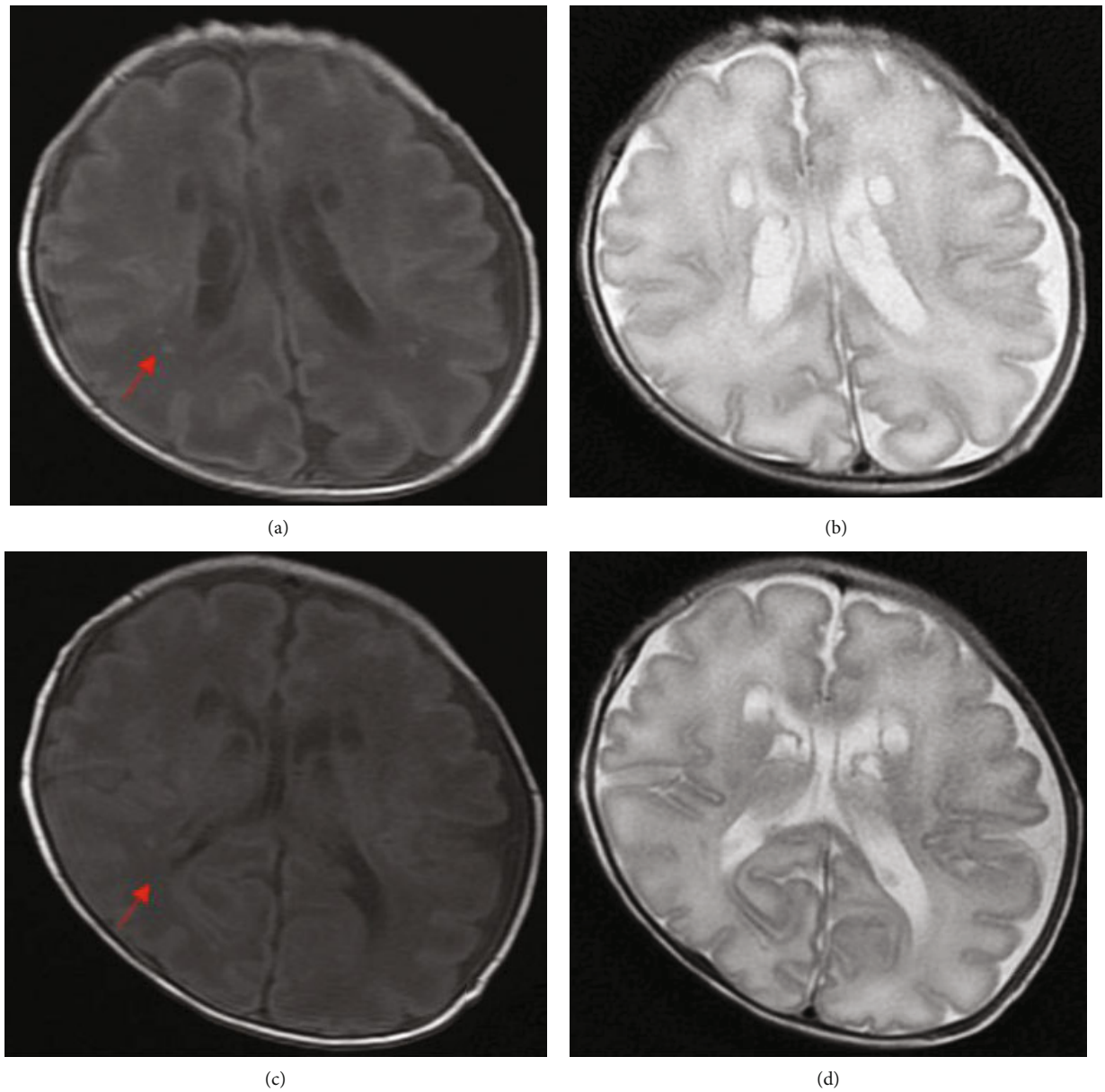

Figure 1: MRI imaging before and after subhypothermia treatment. (a) T1W1 on MRI before treatment; (b) T2W1 on MRI before treatment; (c) T1W1 on MRI 2 weeks after subhypothermia treatment; (d) T2W1 on MRI 2 weeks after subhypothermia treatment. After 2 weeks of subhypothermia treatment, the speckled high signal next to the posterior horn of the bilateral ventricles was significantly reduced; see red arrow.

Table 1: Comparison of clinical outcomes between the two groups [n (%)].

Group	n	Significantly effective	Effective	Invalid	Total effective rate
Study group	68	34 (50.00)	26 (38.24)	8 (11.76)	60 (88.24)
Control group	68	28 (41.18)	21 (30.88)	19 (27.94)	49 (72.06)
χ^2/Z			4.985		5.592
P			0.024		0.018

3.3. Comparison of S-100β Protein, Tau Protein, and NSE Levels between the Two Groups before and after Treatment. There was no difference in the comparison of serum S-100β protein, Tau protein, and NSE between the two groups before treatment ($P > 0.05$). After treatment, all indicators were lower in both groups compared with those before treatment, and the study group was lower than the control group ($P < 0.05$). See Table 2 and Figure 2.

Table 2: Comparison of S-100β protein, Tau protein, and NSE levels before and after treatment between the two groups ($\bar{x} \pm s$).

Group		S-100β protein (ng/mL)	Tau protein (ng/L)	NSE (ng/mL)
Study group ($n = 68$)	Pretreatment	34.56 ± 6.74	8.98 ± 1.24	3.48 ± 0.96
	Posttreatment	17.41 ± 4.07*	5.43 ± 0.68*	1.74 ± 0.42*
t		17.962	20.700	13.693
P		<0.001	<0.001	<0.001
Control group ($n = 68$)	Pretreatment	35.19 ± 5.87	8.84 ± 1.16	3.51 ± 0.85
	Posttreatment	24.74 ± 4.92	6.79 ± 0.92	2.78 ± 0.51
t		11.251	11.418	6.073
P		<0.001	<0.001	<0.001

Note: *$P < 0.05$ compared to control group.

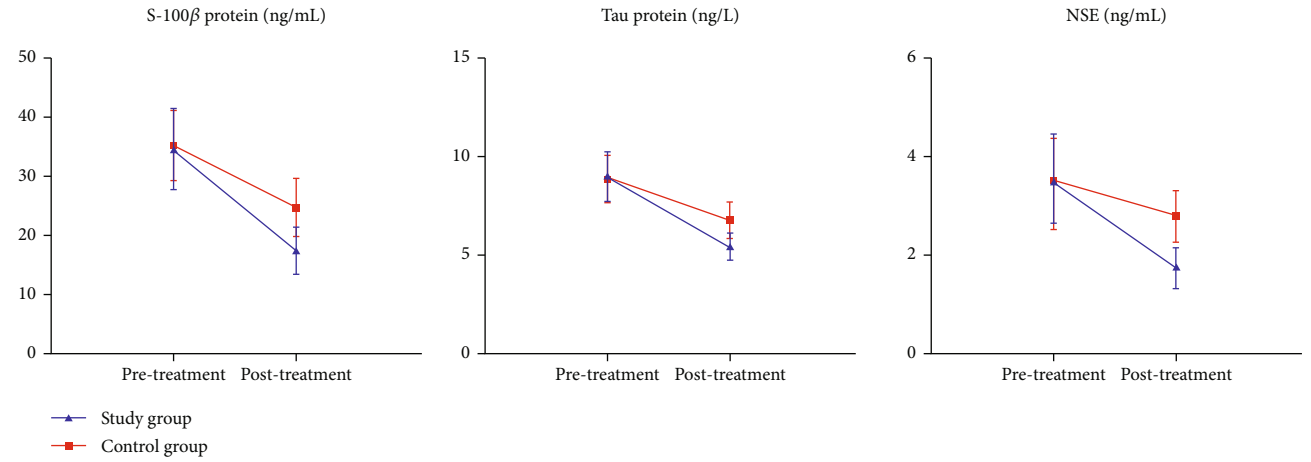

Figure 2: Comparison of serum S-100β protein, Tau protein, and NSE levels before and after treatment between the two groups.

3.4. Comparison of Myocardial Function Indexes between the Two Groups before and after Treatment. Before treatment, there was no difference in the comparison of myocardial function indexes between the two groups ($P > 0.05$). After treatment, all indexes in both groups were lower than before treatment, and the study group was lower than the control group ($P < 0.05$). See Table 3 and Figures 3 and 4.

3.5. Comparison of Oxidative Stress and Inflammatory Factors between the Two Groups before and after Treatment. There was no difference in the comparison of oxidative stress and inflammatory factors between the two groups before treatment ($P > 0.05$). After treatment, SOD and GSH-Px increased in both groups compared with those before treatment and were higher in the study group than in the control group. ROS, IL-1β, IL-8, and TNF-a decreased in both groups compared with those before treatment and were lower in the study group than in the control group ($P < 0.05$). See Table 4 and Figures 5 and 6.

4. Discussion

HIE is an important factor in neonatal brain cell damage and can lead to neurological deficits in children. Its clinical manifestations include coma, hypotonia, drowsiness, loss or weakening of the sucking reflex, and convulsions. If the lesion is in the thalamus or brainstem, it can induce pupillary changes, central respiratory failure, intractable convulsions, and in severe cases, sequelae such as mental retardation and cerebral palsy [8, 9]. Myocardial damage is also common in children with HIE. The main symptoms in children are low heart sounds, arrhythmias, pallor and skin pattern, etc. The pathogenesis is complex and may be related to the abnormal myocardial regulatory compensatory mechanisms due to prolonged hypoxia and ischemia in children [10]. In addition, in neonates, the catecholamine ratio is very low, and the myocardium is not mature enough to withstand the hypoxic alterations that can easily result in impaired myocardial function [11]. Once myocardial damage occurs in children with HIE, it can lead to abnormalities in the metabolism of nerve cell energy, promoting the production of oxygen radicals, causing changes in neurological function, leading to increased nerve cell damage and cell death, and increasing the risk of death [12]. Currently, it has been proposed that in addition to conventional treatments such as lowering cranial pressure and oxygen inhalation, artificially induced cooling is required for children with HIE to reduce brain cell metabolism and alleviate the

Table 3: Comparison of myocardial function indexes between the two groups before and after treatment ($\bar{x} \pm s$).

Group		CK (U/L)	CK-MB (μ/L)	LDH (U/L)	a-HBDH (U/L)	Myo (ng/mL)	CT-1 (pg/mL)	cTnI (ng/L)
Study group ($n = 68$)	Pretreatment	4.63 ± 0.88	89.95 ± 6.49	322.60 ± 26.74	386.52 ± 24.85	307.65 ± 38.49	195.35 ± 29.37	69.02 ± 7.98
	Posttreatment	1.74 ± 0.15*	31.86 ± 7.15*	141.52 ± 34.95*	92.74 ± 16.04*	90.47 ± 17.64*	69.25 ± 12.44*	24.65 ± 4.52*
t		26.696	49.608	33.932	81.907	42.299	32.601	39.865
P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Control group ($n = 68$)	Pretreatment	4.51 ± 0.79	87.69 ± 5.14	326.85 ± 24.71	379.64 ± 27.04	300.74 ± 40.52	191.67 ± 31.74	67.24 ± 8.35
	Posttreatment	2.27 ± 0.63	48.74 ± 7.98	184.39 ± 29.46	147.68 ± 22.65	176.95 ± 27.89	94.35 ± 19.37	38.90 ± 4.07
t		18.281	33.838	30.552	54.228	20.752	21.583	25.158
P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: *$P < 0.05$ compared to control group.

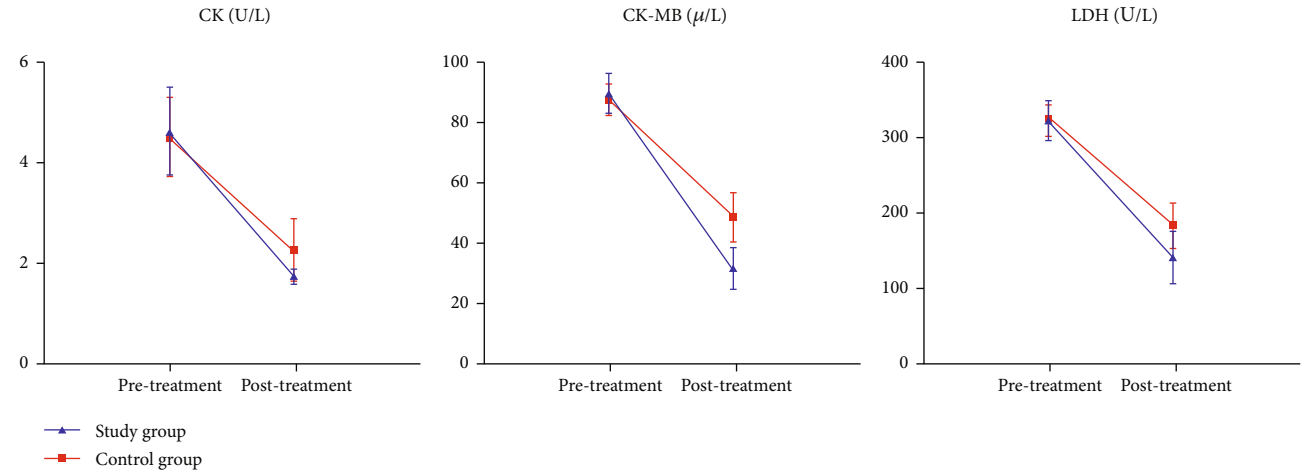

Figure 3: Comparison of serum CK, CK-MB, and LDH levels before and after treatment between the two groups.

condition [13]. Subhypothermia can inhibit toxic amino acids, apoptosis, and oxygen free radical activities of brain cells and reduce energy consumption of organs by artificially induced cooling, which has certain application value in brain injury treatment [14].

S-100β protein has a wide range of biological activities and is expressed in brain tissue. When brain tissue is damaged, it can stimulate an abnormal increase in S-100β protein, which participates in the circulation through the blood-brain barrier and enters the bloodstream, leading to an increase in serum S-100β [15]. Tau proteins are microtubule-associated proteins that are stimulated to be released in large amounts after brain injury, resulting in increased expression [16]. NSE is expressed in neurons, and brain injury can cause nerve cell necrosis, resulting in the release of large amounts of NSE into the cerebrospinal fluid and into the blood through the blood-brain barrier, resulting in increased serum NSE [17]. In this study, it was found that subhypothermia therapy on the basis of conventional treatment significantly increased the total effective rate (up to 88.24%), and the serum S-100β protein, Tau protein, and NSE levels were further downregulated in children with HIE and myocardial damage. Liao et al. [18] found that subhypothermia treatment improved clinical efficiency, which is consistent with the present findings. The main effect of subhypothermia therapy is to reduce the temperature of basal ganglia and deep intracranial vulnerable structures to 32~34°C through artificial induction, which can block the apoptosis pathway and inhibit the apoptosis of brain cells by regulating the expression of apoptotic genes [19]. In addition, subhypothermia also reduce the rate of glucose as well as oxygen metabolism in brain cells, alleviate energy depletion, reduce the accumulation of related metabolites (e.g., nitric oxide and lactic acid) in the brain and alleviate the degree of brain tissue damage [20]. The above-mentioned reasons may be important mechanisms for subhypothermia therapy to alleviate brain tissue damage and improve related indicators.

In children with HIE and myocardial damage, myocardial cells are in an abnormal metabolic state, which can disrupt the cell membrane structure, cause abnormal cell permeability, and promote the release of large amounts of

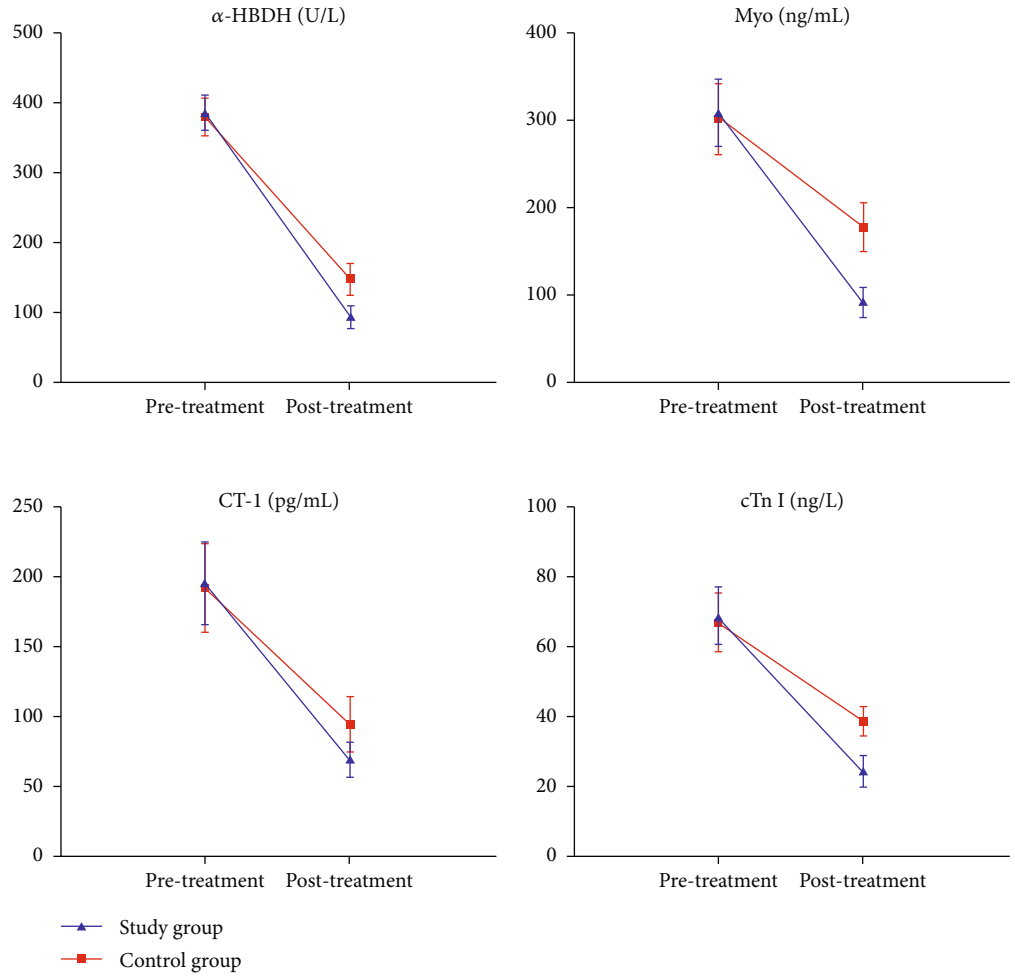

Figure 4: Comparison of serum *a*-HBDH, Myo, CT-1, and cTnI levels before and after treatment between the two groups.

Table 4: Comparison of oxidative stress and inflammatory factors between the two groups before and after treatment ($\bar{x} \pm s$).

Group		SOD (μ/mL)	ROS (U/mL)	GSH-Px (mg/L)	IL-1β (ng/L)	IL-8 (pg/mL)	TNF-*a* (ng/L)
Study group ($n = 68$)	Pretreatment	107.85 ± 21.42	729.85 ± 49.64	5.27 ± 0.98	51.42 ± 7.14	90.41 ± 16.34	32.95 ± 3.78
	Posttreatment	194.65 ± 16.95*	249.65 ± 31.41*	14.95 ± 1.42*	25.71 ± 4.78*	28.52 ± 10.41*	17.19 ± 5.14*
t		26.204	67.410	46.265	24.674	26.342	20.369
P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Control group ($n = 68$)	Pretreatment	109.96 ± 19.34	731.69 ± 52.70	5.34 ± 0.86	50.37 ± 6.95	92.34 ± 19.37	33.64 ± 4.92
	Posttreatment	151.41 ± 20.06	427.91 ± 38.95	8.37 ± 1.04	34.96 ± 6.12	41.24 ± 12.64	25.78 ± 3.91
t		12.267	38.226	18.515	13.722	18.218	10.314
P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: * $P < 0.05$ compared to control group.

isoenzymes and cardiac enzymes, leading to changes in myocardial enzyme profiles [21]. At this stage, the clinical assessment of myocardial damage is mainly done by measuring CK, CK-MB, cTnI, and other related indicators. In this study, we found that children with HIE and myocardial damage had increased myocardial function indicators that were further reduced by subhypothermia therapy, indicating that subhypothermia therapy was more effective in reducing myocardial damage. Subhypothermia therapy may improve the associated myocardial damage indicators by correcting tissue hypoxia and ischemia, inhibiting cytotoxicity, and promoting the restoration of myocardial regulatory compensatory mechanisms in children patients. Children with HIE and myocardial injury are associated with impaired oxygen

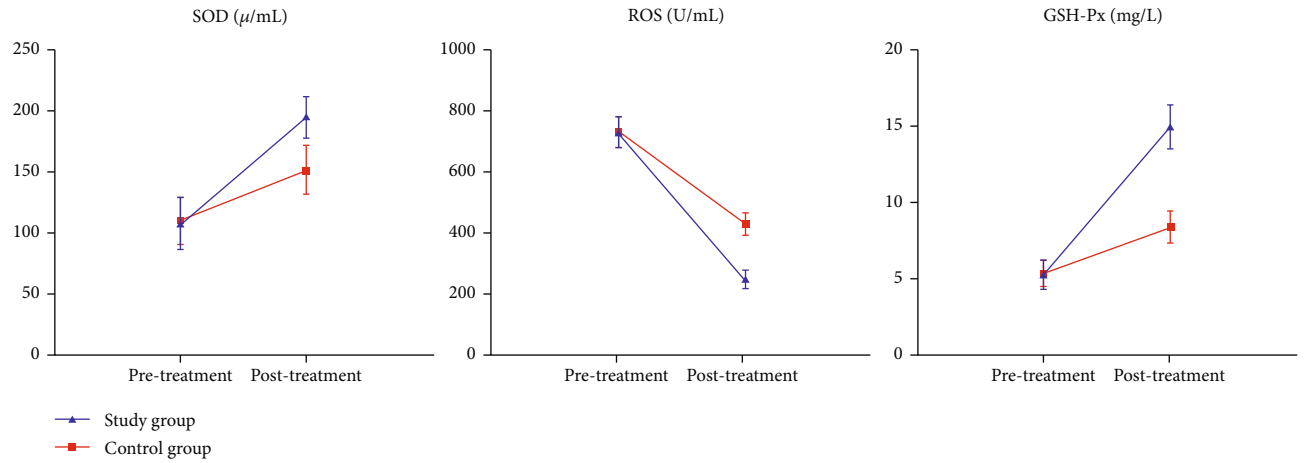

Figure 5: Comparison of serum SOD, ROS, and GSH-Px levels before and after treatment between the two groups.

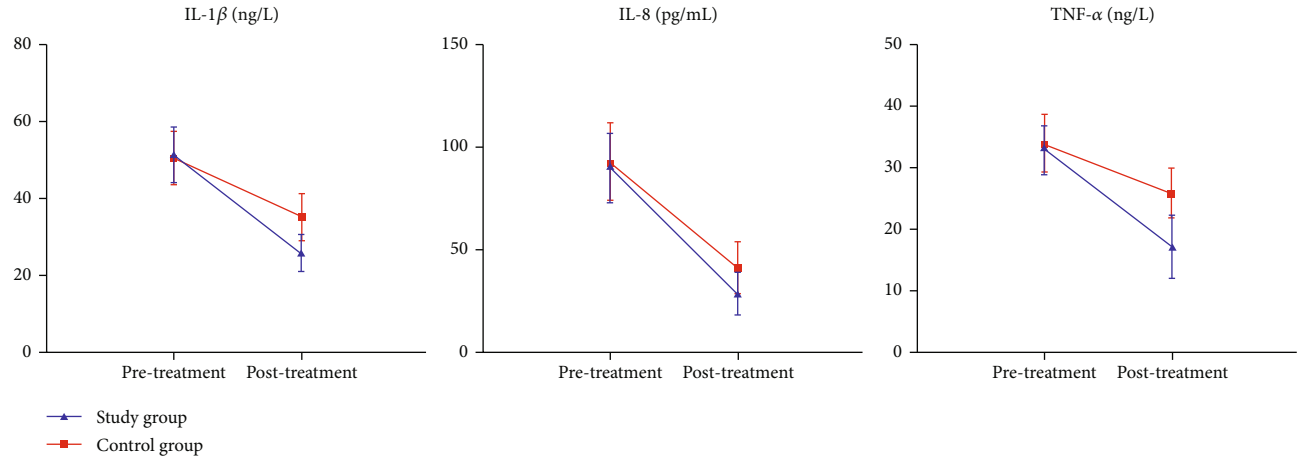

Figure 6: Comparison of serum IL-1β, IL-8, and TNF-a levels before and after treatment between the two groups.

metabolism, in which case there is a significant increase in ROS synthesis, which promotes the onset of oxidative stress and leads to a significant depletion of SOD and GSH-Px [22]. In addition, inflammatory factors can promote damage to the microvascular system, activate the coagulation system, and increase the risk of thrombosis, thereby inducing damage to cardiomyocytes [23]. In this study, we found that subhypothermia therapy further upregulated SOD and GSH-Px levels and downregulated ROS, IL-1β, IL-8, and TNF-a levels, indicating that this method can more effectively alleviate oxidative stress and inflammatory responses. Subhypothermia therapy has an inhibitory effect on free radical generation, which can alleviate the lipid peroxidation response and reduce the effect of neuronal depletion on oxidative stress and inflammation. Foreign studies have confirmed that subhypothermia therapy can reduce brain damage in children with HIE [24], but fewer indicators were included in this study. The present study, however, further analyzed the effect of subhypothermia therapy on myocardial damage, oxidative stress, and inflammation in children, which further confirmed the effectiveness of the method.

In conclusion, subhypothermia therapy has a high therapeutic value in children with HIE and myocardial injury. It can not only alleviate brain injury more effectively, but also improve myocardial injury, oxidative stress, and inflammatory response, which is worth promoting in clinical practice. In addition, there are limitations in this study, as long-term follow-up was not possible due to the time constraints of the study, and the effect of subhypothermia on the long-term outcome of the children has not yet been observed, and the long-term prognosis should be observed through follow-up in the future.

Data Availability

The data used in this study are available from the author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

XiaoPing Dang and XiaoJian Hu contributed equally to this work as co-first authors.

Acknowledgments

This work was supported by the Shaanxi Province Health and Health Research Project(2022E029) and the Second Affiliated Hospital of Xi'an Medical College Hospital-Level Scientific Research Fund (22KY0112).

References

[1] M. Nabetani, H. Shintaku, and T. Hamazaki, "Future perspectives of cell therapy for neonatal hypoxic-ischemic encephalopathy," *Pediatric Research*, vol. 83, no. 1-2, pp. 356–363, 2018.

[2] J. Malmqvist and O. Olsen, "Reply to: planned home birth and the association with neonatal hypoxic ischemic encephalopathy," *Journal of Perinatal Medicine*, vol. 46, no. 2, pp. 229-230, 2018.

[3] H. Cong, W. N. Ju, H. Jin, X. Sun, and G. Zhao, "Molecular chaperones and hypoxic-ischemic encephalopathy," *Neural Regeneration Research*, vol. 12, no. 1, pp. 153–160, 2017.

[4] P. Greco, G. Nencini, I. Piva et al., "Pathophysiology of hypoxic–ischemic encephalopathy: a review of the past and a view on the future," *Acta Neurologica Belgica*, vol. 120, no. 2, pp. 277–288, 2020.

[5] U. Kariholu, P. Montaldo, T. Markati et al., "Therapeutic hypothermia for mild neonatal encephalopathy: a systematic review and meta-analysis," *Archives of Disease in Childhood-Fetal and Neonatal Edition*, vol. 105, no. 2, pp. 225–228, 2020.

[6] S. M. Lobmaier, A. Muller, and E. Huhn, "Hypoxic-ischemic encephalopathy," *American Journal of Perinatology*, vol. 17, no. 3, pp. 113–120, 2000.

[7] M. Perlman and P. S. Shah, "Hypoxic-ischemic encephalopathy: challenges in outcome and prediction," *The Journal of pediatrics,*, vol. 158, no. 2, pp. e51–e54, 2011.

[8] S. Adhikari and R. K. Seshagiri, "Neurodevelopmental outcome of term infants with perinatal asphyxia with hypoxic ischemic encephalopathy stage II," *Brain and Development*, vol. 39, no. 2, pp. 107–111, 2017.

[9] R. Okeda, "Strictly, hypoxic-ischemic encephalopathy?," *Neuropathology*, vol. 38, no. 1, pp. 108-109, 2018.

[10] G. Liu, Z. G. Li, and J. S. Gao, "Hypothermia in neonatal hypoxic-ischemic encephalopathy (HIE)," *European Review for Medical and Pharmacological Sciences*, vol. 21, 4 Suppl, pp. 50–53, 2017.

[11] S. L. Bonifacio and S. Hutson, "The term newborn: evaluation for hypoxic-ischemic encephalopathy," *Clinics in Perinatology*, vol. 48, no. 3, pp. 681–695, 2021.

[12] M. V. Johnston, "Hypoxic-ischemic encephalopathy," *Current Treatment Options in Neurology*, vol. 2, no. 2, pp. 109–115, 2000.

[13] C. Marie-Coralie, P. Archana, A. Fang et al., "Predictive value of early EEG for seizures in neonates with hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia," *Pediatric Research*, vol. 84, no. 3, pp. 399–402, 2018.

[14] B. B. Abate, M. Bimerew, B. Gebremichael et al., "Effects of therapeutic hypothermia on death among asphyxiated neonates with hypoxic-ischemic encephalopathy: a systematic review and meta-analysis of randomized control trials," *PLoS One*, vol. 16, no. 2, article e0247229, 2021.

[15] V. Chaparro-Huerta, M. E. Flores-Soto, M. E. M. Sigala et al., "Proinflammatory cytokines, enolase and S-100 as early biochemical indicators of hypoxic-ischemic encephalopathy following perinatal asphyxia in newborns," *Pediatrics and Neonatology*, vol. 58, no. 1, pp. 70–76, 2017.

[16] I. Duda, U. Krzych, H. Jdrzejowska-Szypuka, and J. Lewin-Kowalik, "Serum levels of the S100B protein and neuron-specific enolase are associated with mortality in critically ill patients," *Acta Biochimica Polonica*, vol. 64, no. 4, pp. 647–652, 2017.

[17] M. Shimy, N. M. El-Raggal, R. A. El-Farrash et al., "Cerebral blood flow and serum neuron-specific enolase in early-onset neonatal sepsis," *Pediatric Research*, vol. 84, no. 2, pp. 261–266, 2018.

[18] W. Liao, X. U. Huiying, J. Ding, and H. Huang, "Mild hypothermia therapy for moderate or severe hypoxicischemic encephalopathy in neonates," *Iranian Journal of Public Health*, vol. 47, no. 1, pp. 64–69, 2018.

[19] I. Goswami, M. Guillot, and W. Y. Tam Emily, "Predictors of long-term neurodevelopmental outcome of hypoxic-ischemic encephalopathy treated with therapeutic hypothermia," *Seminars in Neurology*, vol. 40, no. 3, pp. 322–334, 2020.

[20] E. M. Chin, S. Jayakumar, E. Ramos et al., "Preschool language outcomes following perinatal hypoxic-ischemic encephalopathy in the age of therapeutic hypothermia," *Developmental Neuroscience*, vol. 40, no. 5-6, pp. 1–11, 2019.

[21] C. Endisch, E. Westhall, M. Kenda et al., "Hypoxic-ischemic encephalopathy evaluated by brain autopsy and neuroprognostication after cardiac arrest," *JAMA Neurology*, vol. 77, no. 11, pp. 1430–1439, 2020.

[22] H. Friberg and T. Cronberg, "Hypoxic-ischemic encephalopathy," *Seminars in Neurology*, vol. 37, no. 1, pp. 003-004, 2017.

[23] T. Al-Shargabi, R. B. Govindan, R. Dave et al., "Inflammatory cytokine response and reduced heart rate variability in newborns with hypoxic-ischemic encephalopathy," *Journal of Perinatology*, vol. 37, no. 6, pp. 668–672, 2017.

[24] I. R. Goswami, H. Whyte, P. Wintermark et al., "Characteristics and short-term outcomes of neonates with mild hypoxic-ischemic encephalopathy treated with hypothermia," *Journal of Perinatology*, vol. 40, no. 2, pp. 275–283, 2020.