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Application of Simple Head Cooling Combined with Gangliosides in Neonatal Hypoxic-ischemic Encephalopathy

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ABSTRACT

Objective To investigate the effect of simple head cooling combined with ganglioside therapy on neonatal hypoxic-ischemic encephalopathy (HIE) and its clinical efficacy. **Methods** A total of 100 children with HIE admitted in the neonatal ward of our hospital from August 2018 to October 2020 were selected as the research objects, and were divided into control group and observation group according to the random number table method, with 50 cases in each group. The control group was treated with gangliosides, and the observation group was treated with simple head cooling combined with gangliosides. Observe and compare the clinical performance improvement time, the level of relevant hematological examination indexes before and after treatment, and the neonatal behavioral neurological assessment (NBNA), clinical efficacy, and adverse reactions. **Results** The improvement time of convulsions, disturbance of consciousness, pupil changes, hypotonia, and gastrointestinal dysfunction in the observation group was significantly lower than that in the control group (all $P < 0.001$). After treatment, the NSE, IL-6, CK, CK-MB of the two groups of children were significantly lower than before treatment, and the serum calcium and NBNA scores were significantly higher than before treatment, and the decrease or increase in the observation group was significantly higher than that of the control Group (all $P < 0.001$). The total effective rate of treatment of children in the observation group (82.00%) was higher than that of the control group (62.00%) ($P < 0.05$). There were no obvious adverse reactions in both groups. **Conclusion** The simple head cooling combined with gangliosides in the treatment of HIE can improve the clinical symptoms, blood test index levels, and NBNA scores. The clinical effect is clear and superior to the single use of gangliosides.

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1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is one of the common results in neonatal brain damage caused by hypoxic-ischemia because of perinatal asphyxia. HIE seriously threatens the health and life of newborns, About 25%-30% of surviving sick newborns are at risk of neurological sequelae, including epilepsy, intellectual disability, cerebral palsy, etc^[1]. The pathophysiological changes of HIE are not yet fully understood, leading to lack of breakthrough treatment methods. At present, comprehensive support and symptomatic treatment are still the main components of standard treatment programs. Mild hypothermia therapy has a clear neuroprotective effect, which can reduce the mortality of HIE and the rate of long-term severe disability. It has been regarded as the standard treatment for moderate and severe HIE^[2]. In consideration of the safety, complexity and cost of standard hypothermia therapy, we use simple head cooling to achieve the purpose of treatment in clinic. At the same time, drug therapy is also an important part of HIE treatment. Gangliosides can maintain membrane integrity and regulate brain development. They can prevent cell apoptosis and reduce brain damage. They are widely used as auxiliary drugs for HIE in my country. Under treatment^[3]. There are not many clinical reports about simple head cooling combined with ganglioside in the treatment of HIE. This study aims to explore the clinical effect of this treatment regimen in the treatment of HIE and its influence on related observation indicators.

2. Information and Methods

2.1 General Information

100 children with HIE admitted in the neonatal ward of our hospital from August 2018 to October 2020 are selected as the research objects, and the random number table method is used to divide them into the control group and the observation group with 50 cases each. The comparison of general data (gender, delivery method, clinical scale, gestational age, birth weight, Apgar score at 5 minutes after birth) between the two groups showed no significant difference ($P>0.05$) and was comparable. Inclusion criteria: (1) Meet the diagnostic criteria for neonatal hypoxic-ischemic encephalopathy established by the Neonatal Group of the Pediatric Branch of the Chinese Medical Association^[4], and determine the clinical scale based on this diagnostic criteria; (2) both Full-term infant and birth weight $\geq 2500\text{g}$; (3) Receive treatment within 6 hours of onset of illness; (4) With the informed consent of the child's family member and sign a letter of commitment.

Exclusion criteria: (1) Patients with pregnancy complications during pregnancy; (2) Patients with spontaneous bleeding tendency; (3) Patients with complicated and refractory congenital malformations, acute brain-related diseases, congenital infections and other related diseases (4) Those who are contraindicated with this treatment drug; (5) Those who give up treatment. This clinical study followed the Declaration of Helsinki and passed the review of the Medical Ethics Committee of our hospital.

2.2 Method

After admission, the two groups were actively treated with routine treatments, namely three maintenance treatments (maintain good ventilation and ventilation function; maintain sufficient blood perfusion of the whole body and various organs; maintain high normal blood glucose), three symptomatic treatments (control convulsions, Convulsions; reduce intracranial pressure; eliminate brainstem symptoms). The control group was treated with monosialotetrahexose ganglioside sodium (produced by Harbin Medical University Pharmaceutical Co., Ltd., approval number: Zhunzi H20060422, specification: 20mg) on the basis of conventional treatment. The injection was dissolved and diluted with 20ml 5% glucose, injected intravenously with a dosage of 20 mg each time, once a day, for continuous treatment for 14 days; the observation group was given a simple head cooling treatment based on the treatment of the control group, starting within 6 hours of onset, using ice force Apply the cooling patch to the skin of the child's forehead. At the same time, use a gel ice pack to evenly wrap around the child's head. Replace every hour during the operation to ensure that the temperature of the ice pack and cooling patch is at 7-10°C, and monitor the child's anus. Keep the rectal temperature at 33-34°C, and monitor the vital signs of the child. Continuous treatment for 72 hours, and slowly and naturally rewarming after the treatment.

2.3 Observation Indicators

(1) Collect and compare the general data of the two groups of children; (2) Record and compare the improvement time of related clinical manifestations (convulsions, consciousness disturbance, pupil changes, hypotonia, gastrointestinal dysfunction) of the two groups of children; (3) Compare the blood test index levels of the two groups of children before and after treatment. Before and after treatment, 5ml of radial venous blood was drawn from the two groups of children. All blood samples were placed in blood collection tubes. After centrifugation at 3500r/min, the serum was separated and stored in a freezer at -15°C

Table 1. Comparison of general information of the two groups of children

Groups	Cases	Gender (male/female)	Delivery method (eutocia/caesarean section)	Clinical grade (moderate/severe)	Gestational age ($\bar{x}\pm s$, weeks)	Admission age ($\bar{x}\pm s$, hours)	Birth weight ($\bar{x}\pm s$, kg)	Apgar score at 5 minutes after birth ($\bar{x}\pm s$, points)
control group	50	27/23	24/26	26/24	39.56 \pm 1.25	3.61 \pm 1.22	3.28 \pm 0.25	3.86 \pm 0.83
observation group	50	28/22	27/23	25/25	39.76 \pm 1.04	3.52 \pm 1.37	3.36 \pm 0.18	3.84 \pm 1.13
χ^2/t	-	0.040*	0.360*	0.040*	-0.870	0.353	-1.656	0.101
P	-	0.841	0.548	0.841	0.386	0.725	0.101	0.920

Note: * is the value of χ^2 .

for inspection. Enzyme-linked immunosorbent assay (ELISA) detects serum neuron-specific enolase (NSE) and serum interleukin-6 (IL-6) levels. The kits are all made by Kamisu (Provided by Shanghai) Biotechnology Co., Ltd. The operation method is strictly in accordance with the instruction manual. Use a biochemical analyzer to detect serum calcium, creatine kinase (CK) and MB isoenzyme of creatine kinase (CK-MB) levels; (4) Compare the nerve function score of the two groups of children before and after treatment. Before and after treatment, a systematically trained specialist used the 20-item neonatal behavioral neurological assessment (NBNA) developed by Professor Bao Xiulan^[5] to conduct behavioral neurological assessment and scores on the two groups of children. , Including 5 parts of behavioral ability, passive muscle tone, active muscle tone, original reflex and general evaluation. There are 20 assessment items, using a 0-2 point scoring system, with a full score of 40 points, and a total score of ≥ 35 points as neurological Normal function, a total score of less than 35 points is regarded as abnormal neurological function. The lower the score, the more serious the brain injury and the worse the behavioral neurological evaluation. (5) Compare the clinical efficacy of the two groups of children after treatment. An attending and above specialist physician will evaluate the treatment effect of the children. After treatment, related clinical symptoms such as consciousness disturbance, respiratory failure, abnormal muscle tone, seizures, pupil changes, etc. returned to normal, the amplitude integrated EEG was normal, and the blood test indicators returned to normal, it is remarkable. After treatment, the above-mentioned clinical symptoms and related examinations have been significantly improved and have basically returned to normal after treatment, it is effective. After treatment, the above-mentioned clinical symptoms and related examinations are not significantly improved, or even worse than before, it is invalid. Total effective rate = (remarkable number + effective number)/total \times 100%. (6) Record the adverse reactions during the treatment of the two groups of children.

2.4 Statistical Processing

Use spss26.0 statistical software for statistical analysis and processing of all data. The measurement data conforming to the normal distribution are expressed by the mean \pm standard deviation ($\bar{x}\pm s$), the comparison within the group adopts the paired design t test, and the comparison between the groups adopts the t test of the mean of two independent samples; the count data is expressed by [n(%)] Indicates that the χ^2 test is used. $P < 0.05$ means the difference is statistically significant.

3. Results

3.1 Comparison of the General Data of the Two Groups of Children

There was no statistical difference in the general data of the two groups of children (gender, delivery method, clinical grade, gestational age, birth weight, admission age, Apgar score at 5 minutes after birth) Significance ($P > 0.05$). See Table 1.

3.2 Comparison of the Improvement Time of the Related Clinical Manifestations of the Two Groups of Children

The improvement time of the related clinical manifestations including convulsions, disturbance of consciousness, pupil changes, hypotonia, and gastrointestinal dysfunction in the observation group was lower than that of the control group. Academic significance ($P < 0.001$). See Table 2.

3.3 Comparison of Blood Test Index Levels before and after Treatment between the Two Groups of Children

Before treatment, there was no statistically significant difference between the two groups of children in the NSE, IL-6, serum calcium, CK, and CK-MB index levels ($P > 0.05$), comparable. After treatment, the levels of NSE, IL-6, CK, and CK-MB of the two groups of children were

Table 2. Comparison of improvement time of related clinical manifestations between the two groups of children ($\bar{x}\pm s, d$)

Groups	Cases	Convulsions	Disturbance of consciousness	Pupil changes	Hypotonia	Gastrointestinal dysfunction
Control group	50	6.54±2.12	5.46±1.72	3.46±1.66	8.82±1.88	4.66±1.36
Observation group	50	3.70±1.15	3.60±1.44	2.32±0.98	6.34±1.77	3.22±1.18
<i>t</i>	-	8.328	5.865	4.191	6.792	5.638
<i>P</i>	-	0.000	0.000	0.000	0.000	0.000

Table 3. Comparison of blood test index levels before and after treatment in the two groups of children ($\bar{x}\pm s$)

Groups	Cases	NSE(ug/L)		IL-6(ng/L)		Serum calcium(mmol/L)		CK(U/L)		CK-MB(U/L)	
		before treatment	after treatment	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Control group	50	49.17±6.22	29.75±4.39*	81.36±8.48	46.38±9.05*	1.68±0.22	1.83±0.21*	309.51±36.19	198.33±19.64*	52.83±8.22	33.09±6.49*
Observation group	50	48.78±5.83	19.58±3.75*	80.77±7.94	29.53±8.33*	1.70±0.23	2.04±0.19*	311.59±36.25	165.55±17.79*	53.27±8.49	25.23±4.07*
<i>t</i>	-	0.323	12.453	0.353	9.687	-0.227	-5.113	-0.287	8.744	-0.269	7.266
<i>P</i>	-	0.747	0.000	0.725	0.000	0.821	0.000	0.775	0.000	0.789	0.000

Note: Compared with before treatment, * $P < 0.001$.

Table 4. Comparison of NBNA scores of the two groups of children before and after treatment ($\bar{x}\pm s$, points)

Groups	Cases	before treatment	after treatment	<i>t</i>	<i>P</i>
Control group	50	26.31±2.84	33.22±2.97	-79.866	0.000
Observation group	50	25.91±2.88	37.39±3.60	-80.067	0.000
<i>t</i>	-	0.717	-6.333		
<i>P</i>	-	0.475	0.000		

lower than before treatment, and the difference was statistically significant ($P < 0.001$); after treatment, the levels of serum calcium index of the two groups of children were both Higher than before treatment, the differences were statistically significant ($P < 0.001$). After treatment, the levels of NSE, IL-6, CK, and CK-MB in the observation group were significantly lower than those in the control group, and the differences were statistically significant ($P < 0.001$); after treatment, the observation group Serum calcium index levels were significantly higher than those in the control group, and the difference was statistically significant ($P < 0.001$). See Table 3.

3.4 Comparison of NBNA Scores between the Two Groups of Children before and after Treatment

Before treatment, there was no significant difference

in NBNA scores between the two groups of children ($P > 0.05$), and they were comparable. After treatment, the NBNA scores of the two groups of children were higher than those before treatment, and the difference was statistically significant ($P < 0.001$). After treatment, the NBNA scores of children in the observation group were higher than those in the control group, and the difference was statistically significant ($P < 0.001$). See Table 4.

3.5 Comparison of Clinical Efficacy between the Two Groups of Children after Treatment

The total effective rate of treatment in the observation group (82.00%) was higher than that of the control group (62.00%), and the difference was statistically significant ($P < 0.05$). See Table 5.

Table 5. Comparison of the clinical efficacy of the two groups of children

Groups	Cases	Remarkable (n)	Effective (n)	Invalid (n)	Total effective [n(%)]
Control group	50	12	20	19	31(62.00)
Observation group	50	18	23	9	41(82.00)
χ^2	-				4.960
P	-				0.026

3.6 Adverse Reactions during the Treatment of the Two Groups of Children

No obvious adverse reactions occurred in the two groups of children.

4. Discussion

Neonatal encephalopathy after postpartum related events is one of the main causes of neonatal diseases in the world. Under the condition that there is a causal relationship between neonatal encephalopathy and hypoxic-ischemic brain damage, it is called neonatal hypoxic-ischemic encephalopathy (HIE). Refers to the complex pathophysiological and cellular molecular changes caused by severe hypoxic-ischemic brain damage in the neonatal period. HIE is not a single event, but a continuous process^[6]. Existing studies have shown^[7] that the pathophysiological reaction process of HIE is mediated by an excitatory oxidation cascade, and the first energy failure that occurs is characterized by the reduction of ATP production and the increase in lactic acid or acidosis. the second energy failure seems to be related to oxidative stress, inflammatory response, excitotoxicity and eventual cell death. The continuous cascade of reactions will further prevent neuronal regeneration or aggravate brain damage, thereby forming a tertiary brain injury . The above cascade can also be summarized into five main events, namely oxidative stress, mitochondrial dysfunction, intracellular calcium ion overload, excitotoxicity and inflammation. After modern basic medicine gradually understood the progress of the brain injury mediated by this cascade reaction at the cellular molecular level and better clarified its basic mechanism, it began to actively study different potential neuroprotective therapies and adjuvant therapies, through intervention in the cascade reaction or an important step to protect the brain tissue. These promising neuroprotective agents have been tested in animal models and preliminary clinical studies of HIE, targeting different stages of injury: early excitotoxicity, oxidative stress and apoptosis, late inflammation, and neuronal and Regeneration of oligodendrocytes, a variety of drug treatments designed,

such as mitochondrial membrane stabilizers, neurotrophic factors, etc.^[8]. Experimental studies have shown^[9] that hypothermia treatment can inhibit key steps in the cascade, including reducing the destructive effects of secondary energy failure on the brain, slowing down oxidative stress, antagonizing the release of excitatory neurotransmitters, and reducing cells Apoptosis and so on. With the emergence of mild hypothermia treatment and its widespread clinical application, the prognosis of moderate HIE has been significantly improved, and early hypothermia treatment within 3 hours after birth has gradually attracted the attention of clinicians^[10].

Mild hypothermia treatment is part of the standard treatment plan in developed areas, but it is still an expensive and unacceptable treatment in a resource-limited environment and requires a professional team to implement it. Taking into account the limitations of professional hypothermia treatment, low-cost, easy-to-access and use cooling methods and treatment plans are required in clinical work to ensure its applicability^[11]. Studies have shown that^[12] gel ice packs can be safely and effectively successfully induced hypothermia. Therefore, we adopted the above-mentioned low-cost and reusable simple head cooling method, which is more acceptable to family members of patients. During treatment no obvious adverse reactions occurred. Sheng et al.^[13] evaluated 10 Chinese RCT trials with 987 newborns and concluded that monosialoganglioside adjuvant treatment of HIE can provide additional benefits in improving short-term clinical effects and reducing long-term neurodevelopmental disorders. Exogenous monosialogangliosides can stably bind to nerve cell membranes, leading to changes in membrane function. Its mechanism of action is to promote nerve cell survival, axon growth and synaptic growth, which makes monosialogangliosides in my country is widely used in the clinical adjuvant treatment of HIE and has shown reliable results. At present, the application effect of these two common clinical treatments for HIE is still unclear. We conducted research on this basis.

The serum level of NSE is very low at physiological level, only exists in nerve cells, and is released outside the

cell when neuron damage occurs, and enters the peripheral blood through the blood-brain barrier. NSE can be used as an early sensitive indicator of nerve cell damage. The severity of HIE is positively correlated and decreases as the disease improves^[14]. IL-6 is a multifunctional immune mediator that regulates cellular immunity and inflammatory response. A few minutes after hypoxia and ischemia, the levels of IL-6 and other inflammatory cytokines increase rapidly, by inducing neuronal apoptosis and increasing toxic factors. Nitric oxide levels promote hypoxic-ischemic brain damage^[15]. Hypocalcemia is a common disease of HIE. In the reperfusion stage after hypoxic-ischemic injury, rapid calcium influx into cells is ATP-dependent $\text{Na}^+ - \text{K}^+$ pump failure and cell necrosis secondary to membrane depolarization. Or the main cause of apoptosis, the influx of calcium ions into the cells of multiple damaged organs will reduce the serum calcium concentration^[16]. When a newborn is asphyxiated, hypoxia and hemodynamic pathological changes can cause hypoxic-ischemic myocardial damage and abnormal levels of myocardial enzyme spectrum^[17]. In terms of the above hematological examination indicators, this study shows that after the single use of ganglioside treatment, the levels of related indicators are improved compared to before treatment, which indicates that gangliosides can promote nerve cell regeneration and reduce nerve cell destruction. Nutritional effect may inhibit the inflammatory response after injury, calcium influx into cells and hypoxic-ischemic myocardial damage; and after simple head cooling combined with ganglioside treatment, the improvement effect of related index levels is better than that of using ganglioside alone. Better, it indirectly suggests that the combination therapy can repair nerve damage to a greater extent, inhibit cell apoptosis and oxidative stress, and better inhibit the production of active mediators to participate in pathophysiological reactions, thereby reducing IL-6 secretion and reducing calcium ion internal Intracellular overload caused by flow and promote the recovery of myocardial enzyme spectrum level. In terms of NBNA score, in this study, the NBNA score after combined treatment was higher than that of ganglioside alone, which shows that combined treatment may have a more positive effect on nervous system rehabilitation and long-term nervous system development. This is also true in terms of clinical symptom improvement time and therapeutic efficacy. The total clinical effective rate and related clinical symptom improvement time after combined treatment are better than single treatment. This reflects that simple head cooling can exert the effect of hypothermia treatment. This combined treatment It may have a synergistic effect to effectively prevent the further progression of the disease, thereby improving

the overall efficacy. The disadvantage is that the study is retrospective, conducted in one center, and the data is limited. Future studies may need to increase the sample size and conduct multi-center cooperation.

5. Conclusion

The current research on the treatment of HIE has shifted from single hypothermia treatment to seeking to improve the prognosis of children by adding adjuvant drug therapy to the treatment of mild hypothermia^[18]. This study introduces a Basically similar treatment options for limited conditions. In summary, simple head cooling combined with gangliosides for HIE can significantly improve clinical symptoms, blood test index levels, and NBNA scores. The clinical efficacy is clear and superior to single ganglioside therapy.

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