Int J Clin Exp Med 2020;13(12):9561-9568
www.ijcem.com /ISSN:1940-5901/IJCEM0115394

Original Article

Analysis of clinical efficacy and safety of hypothermia combined with phenobarbital drugs in the treatment of neonatal hypoxic-ischemic encephalopathy

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Received June 1, 2020; Accepted August 26, 2020; Epub December 15, 2020; Published December 30, 2020

Abstract: Objective: To study the clinical efficacy and safety of hypothermia combined with phenobarbital drugs in the treatment of neonatal hypoxic-ischemic encephalopathy (HIE). Methods: A total of 100 children diagnosed with HIE in our hospital from December 2016 to November 2019 were enrolled and divided into the control group and the observation group according to different treatment methods. The control group (n=49) was treated with phenobarbital, while the observation group (n=51) received the treatment of phenobarbital combined with hypothermia. The clinical efficacy, CK, CK-MB, BUN, SCr, LDH, ALT, AST, MDI, PDI and NBNA scores were observed and compared between the two groups. Results: The time of normal consciousness, muscle tone and original recovery in the observation group were significantly shorter than those of the control group (P<0.05). The effective rate of patients with mild, moderate and severe illness in the control group was 73.34%, 73.34%, and 86.67%, respectively, while that of the observation group was 100%, 90.00% and 93.34% (P<0.05). There was no statistically significant difference in each indicator before treatment in the two groups, including CK, CK-MB, BUN, SCr, LDH, ALT and AST. After treatment, the levels of CK, CK-MB, BUN, SCr, LDH, ALT, and AST in the observation group were significantly lower than those in the control group (P<0.05). PDI evaluation and MDI index of the observation group were significantly higher than those of the control group (P<0.05). NBNA score of the observation group after treatment was significantly higher than that of the control group (P<0.05). Conclusion: The phenobarbital combined with hypothermia in the treatment of HIE can effectively recover the neurological damage and improve the therapeutic effect, which is worthy of clinical application.

Keywords: Phenobarbital, hypothermia, hypoxic-ischemic encephalopathy (HIE)

Introduction

In recent years, hypoxic-ischemic encephalopathy (HIE) has been considered as one of the most common diseases in pediatrics. The mortality will increase if the sick children are not treated in time [1]. The study found that the pathogenesis of HIE is relatively complicated, but the common risk factors include umbilical cord around the neck and abnormal amniotic fluid, which leads to cerebral ischemia and hypoxia in children's brain tissues and causes brain lesions eventually [2]. In the treatment methods of HIE, intravenous therapy is the most widely used, the most convenient and the most effective method.

Phenobarbital is a sedative drug with good anti-neonatal convulsion effect, which can well relieve and treat various brain injuries, and has been widely used in the treatment of HIE. Myocardial injury is a common complication of HIE in the clinical treatment, and treatment with mild hypothermia can effectively protect neurons. The optimal time for hypothermia treatment of HIE is within 6 hours, otherwise, the protective effect of drugs on neurons will be reduced [3].

Some studies have found that the index of CK, CK-MB, BUN, SCr, LDH, ALT, AST in the newborns are related to the myocardium, hepatorenal and gastrointestinal functions in children with HIE [4]. Under normal conditions, the cerebral blood circulation can continue to realize self-regulation, but its ability to self-regulate will suffer a certain degree of disorder when the brain is hypoxic, which will cause spasm in the

smooth muscle of the blood vascular in the brain, and edema will occur in the tissues inside and outside the cells, and then the blood flow in the brain will be significantly reduced [5]. In this study, 100 cases of children with HIE in our hospital were treated with phenobarbital combined with mild hypothermia. The therapeutic effects and safety of the two drugs were analyzed.

Materials and methods

Materials

A total of 100 children with HIE admitted to our hospital from December 2016 to November 2019 were selected and divided into the observation group (n=51) and the control group (n=49) according to the digital table method. The observation group included 32 males and 19 females aged from 0.7 h to 9 h, with an average age of 5.7±4.2 h; the control group included 29 males and 20 females aged from 0.4 h to 9 h, with an average age of 5.9±4.7 h. Diagnostic criteria: the included children were diagnosed according to the "*Newborn Hypoxic-Ischemic Encephalopathy (HIE)*" issued by the Neonatal Group of the Pediatric Branch of the Chinese Medical Association in 2005 [6]. Inclusion criteria: patients who suffered from HIE combined with myocardial injury; patients who complied with HIE diagnostic criteria. Exclusion criteria: patients with myocardial injury caused by congenital heart disease; patients who suffered from HIE combined with tumor and blood system diseases. Parents of patients have signed an informed consent. This study has been approved by the Ethics Committee of Tianjin Central Hospital of Obstetrics and Gynecology.

Methods

Control group: Phenobarbital injection was prepared by adding 20 mg/kg of phenobarbital for 5 days.

Observation group: Patients in the observation group were given an extra mild hypothermia head treatment on the basis of treatment in the control group. The child was placed on the infrared radiation platform, and the probe was placed along the nasopharynx and Olympus cooling cap was placed on the head of the child. The skin temperature, rectal temperature and nasopharyngeal temperature were controlled at 33.0-34.5°C, 34.0-35.0°C, and 34.1±0.3°C, respectively, and the mild hypothermia was maintained for 72 hours.

Rating indicators

The basic conditions of the newborn infants, including vital signs, recovery of consciousness, muscle tone, and the primitive reflexes were detected and recorded regularly every day. Therapeutic efficacy evaluation: Marked effect: the newborn child was conscious and sensitive to the surroundings, and their heartbeat and body temperature returned to the normal level; Effective: the newborn child had certain consciousness disorders, the primitive reflexes were not very sensitive, and the heartbeat and body temperature were steady; Ineffective: there was no improvement or even deterioration in consciousness, primitive reflexes and vital signs of the newborn. Total effective rate = (marked effect + effective)/ total number of cases × 100%. The content of enzymes in the body of all newborns after injection of drugs was detected, including CK, CK-Mb, CK-MB, BUN, and SCr, and the cardiac sound and heart rate were also detected. The patients were followed up for 6 months after treatment, and the follow-up rate was 100%. The MDI, PDI and NBNA scores were used to evaluate the development of 100 children's intelligence, motor ability and nervous system, respectively.

Statistical analysis

The statistical software of SPSS18.0 was used for data processing. The measurement data were expressed as mean ± standard deviation (mean ± SD). The t and χ^2 tests were carried out. The counting data were expressed as percentage (%). $P<0.05$ was considered statistically different.

Results

General materials

There was no statistically significant difference in age and gender between the two groups, which were comparable ($P>0.05$) (**Table 1**).

Table 1. Basic clinical materials [n (%)]

Groups	n	Gender		Hour			
		Male	Female	<1	1~3	4~6	7~9
Observation group	51	32 (62.74)	19 (37.25)	3 (5.88)	18 (35.29)	23 (45.09)	7 (13.72)
Control group	49	29 (59.18)	20 (40.81)	2 (4.08)	17 (34.69)	21 (42.85)	9 (18.36)
X^2		0.418			0.693		
P		0.683			0.842		

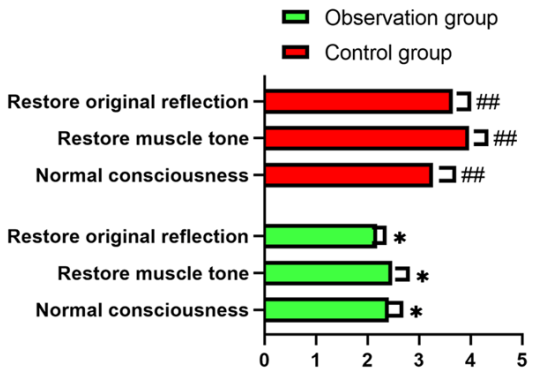

Figure 1. The time for recovering primitive reflexes, normal consciousness and muscle tone after treatment in two groups of children. After treatment, the time for recovering the primitive reflexes, normal consciousness and muscle tone in observation group was significantly shorter than those of the control group (P<0.05), indicating that phenobarbital combined with hypothermia treatment can shorten the recovery time of children's body function.

The time for recovering normal consciousness, primitive reflexes and muscle tone of the two groups

After treatment, the time for recovering normal consciousness, muscle tone and primitive reflexes of the observation group were 2.97±0.56, 3.05±0.57 and 2.58±0.39, which were significantly shorter than 4.12±0.85, 4.65±0.68 and 4.24±0.59 of the control group (t=2.14, 3.17, 3.59, P<0.05) (**Figure 1**).

The therapeutic effect of the two groups

The total effective rates of patients with mild, moderate and severe illness were 73.34%, 73.34% and 86.67%, respectively, in the control group, and 100.0%, 90.00% and 93.34%, respectively, in the observation group (P<0.05), indicating that the treatment method can effectively relieve the disease (**Table 2**; **Figure 2**).

The changes of myocardial injury markers of the two groups

There was no statistically significant difference in the changes of CK, CK-MB, BUN, SCr, LDH, ALT and AST indices between the control group and the observation group before treatment (P>0.05). After treatment, the changes of the indices in the observation group were significantly lower than those in the control group (P<0.05) (**Table 3**; **Figure 3**).

The MDI, PDI and NBNA scores of the two groups

After treatment, the MDI and PDI indicators of the observation group were significantly higher than those of the control group, and the NBNA score of the observation group was significantly higher than that of the control group (P<0.05), indicating that phenobarbital combined with dobutamine treatment has significant effects on HIE, which can reduce the indicator scores and relieve the symptoms of hypoxia (**Table 4**; **Figure 4**).

Discussion

The main cause of HIE is the disorder of blood circulation and gas exchange between the mother and the fetus, which leads to the decrease of blood oxygen concentration and ultimately triggers suffocation [7, 8]. The incidence of HIE caused by intrauterine asphyxia accounts for 50%, by asphyxiation during delivery accounts for 40%, and by congenital diseases accounts for 10% [9, 10]. If not treated in time, it is easy to cause harm to the children. It is an urgent, rapid-developing critical disease, which is easy to damage the neuronal tissue of children [11, 12]. Although the etiological agent and treatment methods of HIE are different, the basis and purpose of the treatment are the same. The first is to ensure

Table 2. Comparison of therapeutic effects of two groups of children with different degrees of illness (%)

Events		n	Marked effect	Effective	Ineffective	Total effective	χ^2	*P*
Mild	Control group	49	22 (44.89)	19 (38.77)	8 (16.32)	41 (83.67)	3.01	<0.05
	Observation group	51	26 (50.98)	25 (49.01)	0 (0.00)	51 (100.0)		
Moderate	Control group	49	28 (57.14)	13 (26.53)	8 (16.32)	41 (83.67)	4.25	<0.05
	Observation group	51	27 (52.94)	20 (39.21)	4 (7.84)	47 (92.15)		
Severe	Control group	49	22 (44.89)	25 (51.02)	2 (4.08)	47 (95.91)	2.94	<0.05
	Observation group	51	25 (49.01)	25 (49.01)	1 (1.96)	50 (98.03)		

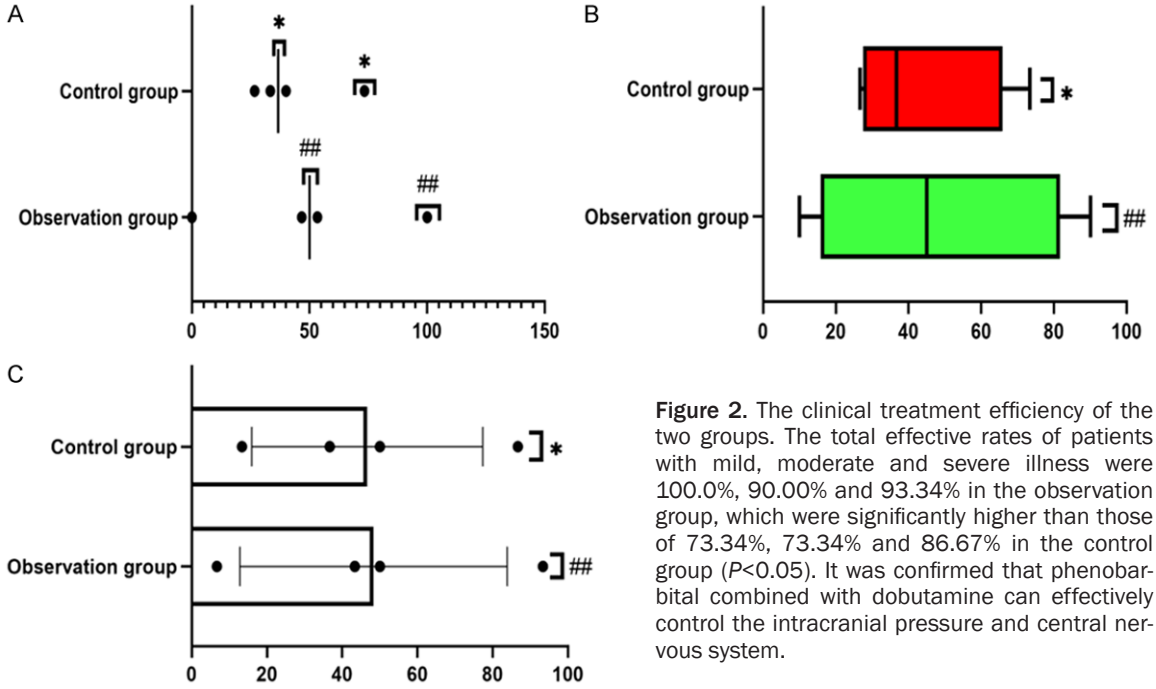

Figure 2. The clinical treatment efficiency of the two groups. The total effective rates of patients with mild, moderate and severe illness were 100.0%, 90.00% and 93.34% in the observation group, which were significantly higher than those of 73.34%, 73.34% and 86.67% in the control group ($P<0.05$). It was confirmed that phenobarbital combined with dobutamine can effectively control the intracranial pressure and central nervous system.

the normal supply of cerebral blood flow and maintain the normal energy metabolism of the brain. When the deprivation of oxygen causes asphyxia and results in the occurrence of various symptoms of the brain, it is necessary to minimize the nervous lesion of the brain and improve and repair the diseased neurological system, so as to stimulate the repair mechanism of the newborn to the greatest extent and promote rapid regeneration of the injured nerves [13, 14]. In this study, hypothermia combined with phenobarbital, a widely used method, was used in the treatment of HIE. It has significant efficacy in inhibiting cerebral edema and reducing metabolic efficiency of the brain, and has good sedative effects in children with convulsions and vasospasm. HIE myocardial injury can effectively reflect the degree of correlation with the content of myocardial enzymes in clinical practice [15, 16].

Studies have shown that the hypothermia combined with phenobarbital in the treatment of HIE children can greatly shorten the time required for recovering three main symptoms and significantly improve the treatment efficiency. Phenobarbital is widely used in the treatment of unexplained convulsions in neonates, which can inhibit cerebral edema and reduce metabolic efficiency of brain. In addition, it has good sedative effects on treating children with convulsions and on anti-vasospasm [17, 18]. Studies have shown that the indices of CK, CK-MB, BUN, SCr, LDH, ALT, and AST in newborns are significantly reduced after the application of hypothermia combined with phenobarbital, which provides evidence that this treatment method can significantly improve the cerebral blood circulation and contribute to the recovery of cardiac muscle, hepatorenal function, and gastrointestinal function.

Table 3. Comparison of the changes of each indicator of the two groups before and after treatment (mean ± SD)

Groups		CK	CK-MB	BUN	SCr	LDH	ALT	AST
Control group (n=49)	Prior treatment	813.59±115.32	51.17±10.91	101.51±15.24	10.92±2.17	390.50±55.22	53.61±23.12	81.52±36.51
	Post treatment	202.68±99.66$^{\#}$	39.28±11.22$^{\#}$	82.17±9.26$^{\#}$	7.82±1.99$^{\#}$	192.64±39.11$^{\#}$	31.64±19.5$^{\#}$	39.80±20.63$^{\#}$
Observation group (n=51)	Prior treatment	809.61±125.24	53.51±11.54	101.20±16.18	11.53±8.25	390.21±59.65	56.57±22.9	85.52±37.20
	Post treatment	135.20±85.17$^{*,\Delta}$	20.83±5.36$^{*,\Delta}$	54.82±12.31$^{*,\#}$	3.40±1.52$^{*,\Delta}$	103.46±25.18$^{*,\Delta}$	18.96±15.9$^{*,\Delta}$	21.41±17.65$^{*,\Delta}$

Note: Before and after treatment, the comparison between the two groups, $^{*}P<0.05$; the comparison of each indicator of the two groups before and after treatment, $^{\#}P<0.05$, $^{\Delta}P<0.01$.

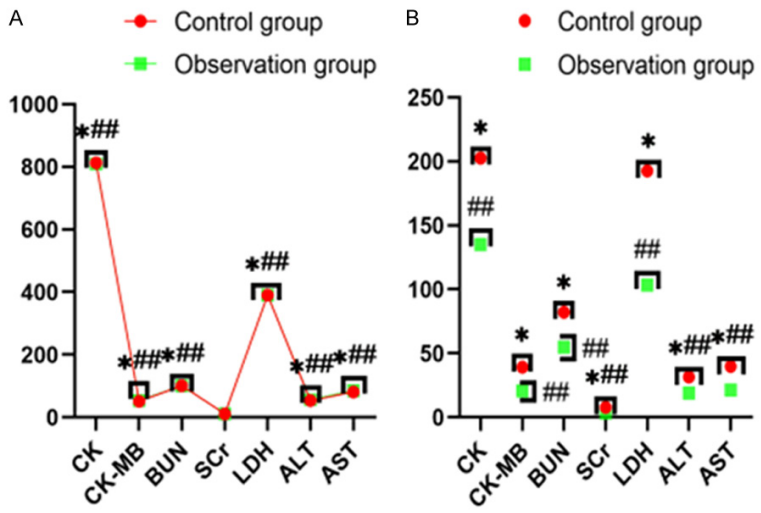

Figure 3. Changes of myocardial injury marker before and after treatment in the two groups. There was no statistically significant difference in CK, CK-MB, BUN, LDH, ALT, SCr and AST between the observation group and the control group before treatment ($P>0.05$). After treatment, the above-mentioned indicators in the observation group were significantly lower than those in the control group, indicating that the treatment schedule in the observation group could relieve hypoxemia and hypercapnia in children.

Table 4. Comparison of the results of MDI, PDI and NBNA of the two groups after 6 months (mean ± SD)

	MDI	PDI	NBNA
Observation group (n=51)	65.6±8.5	71.2±8.7	51.2±9.8
Control group (n=49)	86.2±9.1	88.8±9.3	40.9±9.6
t	3.54	2.97	4.13
P	<0.05	<0.05	<0.01

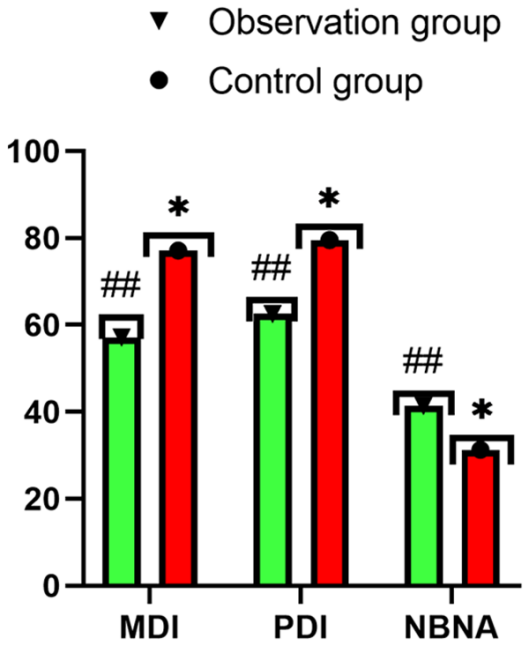

Figure 4. MDI, PDI and NBNA scores of the two groups after 6 months of treatment. The score of NBNA in the observation group was significantly higher than that in the control group ($P<0.05$), and the scores of MDI and PDI in the observation group were lower than those in the control group ($P<0.05$).

The cerebral blood circulation can continue to maintain self-regulation under normal conditions, but its self-regulation ability will appear a certain degree of disorder when the brain is hypoxic, and it will cause spasm in the vascular smooth muscle of the brain and edema in the inner and outer cells of the tissue, resulting in a significant decrease of blood flow [19, 20]. Hypoxia in the brain can damage myocardial cells to a certain extent, resulting in the release of a large number of myocardial enzymes in the myocardial cells. Moreover, the process of energy oxidative phosphorylation in the myocardium will also be severely hindered, leading to the reduction of ATP synthesis in the body and the impaired myocardial systolic function in children. The above factors will lead to a serious decrease in cardiac output and a significant increase in blood transport resistance, leading to decreased blood perfusion in all organs, including the heart, brain, liver, and kidneys [21, 22]. Mild hypothermia refers to the use of physical methods to control the body temperature of newborns with HIE at a low level, which is helpful to reduce the consumption of adenosine triphosphate in brain cells, slow down the metabolism of brain cells, effectively control anaerobic glycolysis, delay or even inhibit secondary energy failure, reduce the production of cytotoxins and inflammatory mediators such as nitric oxide and oxygen free radicals, control degeneration and necrosis of brain cells, and thus protect the brain. However, the effect of mild hypothermia therapy alone is not ideal. Scholars at home

and abroad all advocate the combination of cerebral neuroprotective agents and mild hypothermia therapy to achieve the ideal effect. This study found that although some neonates with severe HIE can effectively control the risk of death after treatment, the risk of poor prognosis such as epilepsy, hyperactivity, dyskinesia, and mental retardation is still high, which needs to be paid more attention. Therefore, attention should be paid to the improvement of cerebral electrical activity during the clinical treatment of neonatal HIE, so as to lay the foundation for the control of the risk of poor prognosis.

Through the score of MDI, PDI and NBNA, this study found that the treatment of hypothermia combined with phenobarbital can effectively improve the children's mental and nervous system recovery. Other studies have shown that hypothermia combined with phenobarbital treatment can effectively improve the regenerative capacity of neurons in children and reduce the number of nerve cells detachment and death, and it will effectively stimulate the mental development of children and further reduce intellectual disabilities and neurological sequelae [23, 24].

However, due to the small sample size included in this study, some clinical data have not been analyzed. In the future, the sample size will be increased to improve the treatment plan for neonatal HIE.

In summary, the treatment of hypothermia combined with phenobarbital can effectively shorten the recovery time of all symptoms, improve the treatment efficiency, and reduce the incidence of visceral damage, mental retardation, and neurological sequelae. Therefore, this method is worthy of clinical application.

Disclosure of conflict of interest

None.

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