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Effect of fructose diphosphate combined with large−dose vitamin C therapy on the myocardial oxidative stress injury after neonatal asphyxia

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ABSTRACT

Objective: To study the effect of fructose diphosphate combined with large-dose vitamin C therapy on the myocardial oxidative stress injury after neonatal asphyxia. **Methods:** 40 patients with neonatal asphyxia who were treated in our hospital between June 2013 and April 2016 were collected and divided into the control group (n=20) who received large-dose vitamin C therapy and the observation group (n=20) who received fructose diphosphate combined with large-dose vitamin C therapy according to the double-blind randomized control method, and the treatment lasted for 10 d. Immediately after admission and after 10 d of treatment, RIA method was used to detect the serum levels of oxidative stress indexes, color Doppler diasonograph was used to determine left cardiac function parameters, and the myocardial enzyme spectrum detector was used to determine myocardial enzyme spectrum index levels. **Results:** Immediately after admission, the differences in the systemic oxidative stress degree, the left cardiac function damage degree and the myocardial enzyme spectrum index levels were not statistically significant between two groups of patients (P>0.05). After 10 d of treatment, serum malondialdehyde (MDA), advanced oxidation protein products (AOPP), creatine kinase isoenzyme (CK-MB), N-terminal pro-brain natriuretic peptide (Nt-proBNP), heart-type fatty acid-binding protein (H-FABP) and troponin I (cTnI) contents of observation group were lower than those of control group (P<0.05) while superoxide dismutase (SOD) content was higher than that of control group (P<0.05), and the left cardiac function parameter ejection time (ET) level was higher than that of control group (P<0.05) while left ventricular isovolumetric contraction time (ICT) and left ventricular isovolumetric relaxation time (IRT) levels were lower than those of control group (P<0.05). **Conclusion:** Fructose diphosphate combined with large-dose vitamin C can reduce the systemic oxidative stress of neonatal asphyxia and reduce the resulting myocardial injury.

1. Introduction

Neonatal asphyxia is the fetal hypoxia caused by a variety of perinatal factors, it causes that the fetus cannot establish regular breathing within 1 min after birth or is even completely without spontaneous breathing, and it is currently one of the main causes of early neonatal death[1,2]. After neonatal asphyxia is confirmed, positive measures should to be taken to save the children's lives, but the effect of current conventional treatment is not ideal, and it is the clinical research focus to find effective reasonable adjuvant treatment measures. The inhibition of cellular normal aerobic metabolism after ischemia hypoxia is the main harm of neonatal asphyxia and also one of the root causes of the important viscera tissue damage, vitamin C can resist redox and repair tissue, fructose diphosphate can adjust certain enzyme activity in glycometabolism, the combination of the two is expected to improve the patient's degree of hypoxia, but current clinical research is mostly limited to the analysis of overall treatment effectiveness and fails to deeply study the specific mechanism and target organ damage. In this

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research, fructose diphosphate and large-dose vitamin C were used together for the treatment of neonatal asphyxia, and the effect of fructose diphosphate combined with large-dose vitamin C therapy on the myocardial oxidative stress injury after neonatal asphyxia was specifically analyzed.

2. Information and methods

2.1. Case information

40 patients with neonatal asphyxia who were treated in our hospital between June 2013 and April 2016 were selected, all of them conformed to the diagnostic criteria for neonatal asphyxia by Chinese Medical Association Perinatology Branch, and families of children signed the informed consent. According to the double-blind randomized controlled method, the included children were divided into observation group and control group (n=20). On the basis of conventional treatment, the control group received high-dose vitamin C therapy, and observation group received fructose diphosphate combined with large-dose vitamin C therapy. Control group included 11 male cases and 9 female cases, the gestational age at birth was 36–41 weeks, and the birth weight was 2.28–3.31kg and (2.79±0.42) kg in average; observation group included 12 male cases and 8 female cases, the gestational age at birth was 37–41 weeks, and the birth weight was 2.31–3.25 kg and (2.75±0.47) kg in average. Two groups of children were not statistically significant in gender, gestational age and birth weight distribution (P>0.05). The study was discussed and approved by the hospital ethics committee.

2.2. Treatment methods

Both groups received routine therapy for neonatal asphyxia, specifically as follows: heat preservation, oxygen uptake, acid-base balance maintenance, electrolyte disorder correction, seizures and brain edema prevention, and adenosine triphosphate energy support. On the basis of conventional treatment, the control group received the high-dose vitamin C therapy, which was specifically as follows: intravenous drip of vitamin C for injection (China National Medicines Guorui Pharmaceutical Co., Ltd., approved by H20046669), 250 mg/(kg • d) in 20 mL of 10% glucose liquid, 1 time/d, and 10 d as a course of treatment.

On the basis of conventional treatment, the observation group received fructose diphosphate combined with large-dose vitamin C therapy, specifically as follows: intravenous drip of fructose diphosphate (Hebei Changtian Pharmaceutical Co., Ltd., approved by H10980072), 250 mg/(kg • d), 1 time/d and 10 d as a course of treatment.

2.3. Oxidative stress indexes

Immediately after admission and after 10 d of treatment, 0.5–1.0 mL of peripheral venous blood was extracted from two groups of children at the same point in time, anti-coagulated, let stand at room temperature for 6 h and centrifuged at low speed to get supernatant, and RIA method was used to detect the contents of oxidative stress indexes, including the malondialdehyde (MDA), superoxide dismutase (SOD) and advanced oxidation protein products (AOPP).

2.4. Myocardial injury indexes

Immediately after admission and after 10 d of treatment, the tissue Doppler imaging (TDI) mode in the color Doppler diasonograph (Shanghai Hanfei Medical Instrument Co., LTD., model E8) was used to determine the left cardiac function parameters of two groups of children, including ejection time (ET), left ventricular isovolumetric contraction time (ICT) and left ventricular isovolumetric relaxation time (IRT). At the same point in time, peripheral blood serum was obtained from two groups of children in the same way, and myocardial enzyme spectrum detector (China Healthcare International Trade Co., LTD., model cobas h232) was used to determine the contents of creatine kinase isoenzyme (CK-MB), N-terminal pro-brain natriuretic peptide (Nt-proBNP), heart-type fatty acid-binding protein (H-FABP), troponin I (cTnI) and other myocardial enzyme spectrum indexes.

2.5. Statistical analysis

The data obtained in the study were recorded and calculated by professional personnel, measurement data was in terms of mean ± standard deviation, comparison within group before and after treatment was by paired t test, separate comparison between groups before and after treatment was by grouping t test, and P<0.05 was the standard of statistical significance in differences in the study.

3. Results

3.1. Oxidative stress indexes

Before treatment, the differences in serum oxidative stress indexes MDA, SOD and AOPP contents were not statistically significant between two groups of patients (P>0.05); after 10 d of treatment, serum MDA and AOPP contents of both groups were lower than those before treatment while SOD contents were higher than those before treatment, and differences within group were statistically significant (P<0.05). After 10 d of treatment, serum MDA and AOPP

contents of observation group were lower than those of control group while SOD content was higher than that of control group, and differences between groups were statistically significant ($P<0.05$), shown in Table 1.

3.2. Left cardiac function parameters

Before treatment, the differences in left cardiac function parameters ET, ICT and IRT levels were not statistically significant between two groups of patients ($P>0.05$); after 10 d of treatment, left cardiac function parameter ET levels of both groups were higher than those before treatment while ICT and IRT levels were lower than those before treatment, and differences within group were statistically significant ($P<0.05$). After 10 d of treatment, left cardiac function parameter ET level of observation group was higher than that of control group while ICT and IRT levels were lower than those of control group, and differences between groups were statistically significant ($P<0.05$), shown in Table 2.

3.3. Serum myocardial enzyme spectrum indexes

Before treatment, the differences in serum myocardial enzyme spectrum indexes CK-MB, Nt-proBNP, H-FABP and cTnI contents were not statistically significant between two groups of patients ($P>0.05$); after 10 d of treatment, serum CK-MB, Nt-proBNP, H-FABP and cTnI contents of both groups were lower than those before treatment, and the differences within group were statistically significant ($P<0.05$). After 10 d of treatment, serum CK-MB, Nt-proBNP, H-FABP and cTnI contents of observation group were lower than those of control group, and differences between groups were statistically significant ($P<0.05$), shown in Table 3.

4. Discussion

After the occurrence of neonatal asphyxia, children's normal cellular aerobic metabolism is restrained and the energy production is with obstacle, the body accelerates compensatory anaerobic metabolism capacity, and meanwhile, the lactic acid is massively produced and leads to acidosis and several important viscera damage[3,4]. Vitamin C is considered as the reliable drug to optimize neonatal asphyxia, it can exert anti-redox effect after large-dose application, but its overall effect is limited, and other auxiliary drugs are needed to expand the curative effect. Fructose diphosphate belongs to the human cell metabolite that can adjust the activity of multiple enzyme systems in the process of glucose metabolism, and effectively improve cell hypoxia condition, so it is considered as the reliable drug to treat hypoxic diseases[5,6]. In the research, fructose diphosphate in combination with large-dose vitamin C was used for the treatment of neonatal asphyxia so as to looking for efficient and reasonable new ways to treat the disease.

Oxidative stress theory is considered as the important reason for

Table 1

Comparison of serum oxidative stress index contents before and after treatment (n=20, $\bar{x}\pm s$).

Groups	Time point	MDA (μmol/L)	SOD (μg/mL)	AOPP (μmol/L)
Observation group	Before treatment	11.38±1.95	28.21±4.54	8.23±0.94
	After treatment	3.71±0.45^{ab}	56.28±8.51^{ab}	2.16±0.32^{ab}
Control group	Before treatment	11.46±1.85	29.62±4.18	8.26±0.91
	After treatment	7.09±0.84^{a}	42.34±5.52^{a}	5.74±0.68^{a}

Compared with same group before treatment, $^{a}P<0.05$; compared with control group after treatment, $^{b}P<0.05$.

Table 2

Comparison of left cardiac function parameter levels before and after treatment (n=20, ms,$\bar{x}\pm s$).

Groups	Time point	ET	ICT	IRT
Observation group	Before treatment	165.38±20.17	45.38±5.19	51.27±5.88
	After treatment	174.72±20.85^{ab}	38.21±4.53^{ab}	42.58±5.09^{ab}
Control group	Before treatment	164.79±19.65	45.41±5.07	51.32±5.94
	After treatment	168.95±20.61^{a}	41.74±4.59^{a}	47.66±5.32^{a}

Compared with same group before treatment, $^{a}P<0.05$; compared with control group after treatment, $^{b}P<0.05$.

Table 3

Comparison of serum myocardial enzyme spectrum index contents before and after treatment (n=20, $\bar{x}\pm s$).

Groups	Time point	CK-MB (U/L)	Nt-proBNP (pmol/mL)	H-FABP (ng/mL)	cTnI (ng/mL)
Observation group	Before treatment	12.38±2.15	732.84±89.63	24.38±3.52	1.21±0.23
	After treatment	3.09±0.42^{ab}	290.12±34.65^{ab}	3.61±0.45 ^{ab}	0.23±0.04 ^{ab}
Control group	Before treatment	12.29±2.09	728.66±84.37	24.21±3.09	1.19±0.21
	After treatment	7.18±0.85^{a}	434.27±56.82^{a}	6.82±0.83^{a}	0.78±0.09^{a}

Compared with same group before treatment, $^{a}P<0.05$; compared with control group after treatment, $^{b}P<0.05$.

neonatal asphyxia to cause multiple organ damage, and the tissue cells produce a large number of oxygen free radicals and metabolites in hypoxia state, which weaken the body's own antioxidant ability while lead to cellular structure damage in multiple organs and the normal cell function impairment[7,8]. MDA is one of the most typical oxygen metabolites, and its content can quantitatively reflect the oxygen free radical content and the lipid peroxidation level in the tissue; AOPP belongs to macromolecular oxidative stress markers, it is the product of protein in the oxidative stress state, and a number of studies have confirmed that it is a sensitive index to reflect the degree of protein oxidation[9,10]. SOD is a major enzyme to scavenge free radicals, and SOD content can understand the body's ability to scavenge free radicals[11]. In the study, serum oxidative stress index contents were compared between two groups of children after different treatment, and it was found that serum MDA and AOPP contents of both groups after treatment were lower than those before treatment ($P<0.05$) while SOD contents were higher than those before treatment ($P<0.05$); serum MDA and AOPP contents of observation group after treatment were lower than those of control group ($P<0.05$) while SOD content was higher than that of control group ($P<0.05$), showing that both therapies can reduce the systemic oxidative stress, and fructose diphosphate in combination with large-dose vitamin C can more effectively reduce the oxidative metabolite release and increase the body's antioxidant ability.

Myocardial cells sensitivity to hypoxia is higher than other organ cells, so myocardial cells may be injured early after asphyxia, and the specific injury severity is directly related to the duration of asphyxia and the properness of treatment[12]. After injury, myocardial contraction capacity reduces and the blood pumped reduces, systemic blood perfusion decreases and the degree of hypoxia increases, so the neonatal asphyxia severity is directly correlated with the degree of myocardial injury, and detection of children's cardiac function can macroscopically reflect the disease severity, clinical treatment effect and so on. TDI parameters can quantitatively reflect left cardiac systolic function, ET is shortened after myocardial injury, and the total blood pumped decreases; ICT and IRT levels are negatively correlated with the myocardial contraction ability, and the myocardial contraction ability reduces when ICT and IRT are extended[13,14]. After different therapies were used to treat neonatal asphyxia, TDI parameters were detected to evaluate their curative effect and it was found that ET levels of both groups after treatment were higher than those before treatment ($P<0.05$) while ICT and IRT levels were lower than those before treatment ($P<0.05$), and ET level of observation group was higher than that of control group ($P<0.05$) while ICT and IRT levels were lower than those of control group ($P<0.05$), it shows that both therapies can optimize the left cardiac contraction ability, but the fructose diphosphate in combination with large-dose vitamin C can more effectively enhance the myocardial contraction ability, and this is related to its anti-oxidative stress ability.

Myocardial injury is characterized by the content change of a variety of molecules in cells, and macro cardiac contraction ability abnormality can appear when the content changes of indexes reach a certain extent[15]. CK-MB, Nt-proBNP, H-FABP and cTnI are the serum factors closely related to the early myocardial function change, their contents are little in peripheral blood under physical condition, but in the case of ischemia hypoxia, they can be released from myocardial cells into peripheral blood and be detected[16,17]. After different treatment, peripheral blood myocardial enzyme spectrum index contents of two groups of children were detected, and it was found that after treatment, serum CK-MB, Nt-proBNP, H-FABP and cTnI contents of both groups were lower than those before treatment ($P<0.05$), and serum CK-MB, Nt-proBNP, H-FABP and cTnI contents of observation group were lower than those of control group ($P<0.05$), it indicates that both therapies can reduce the myocardial cell injury, but adding fructose diphosphate can more effectively protect myocardial cells, and this is the direct cause of the optimized left cardiac function of observation group in the study, and also the inevitable result after the fructose diphosphate reduces the oxidative stress in the body.

In the study, comparison and analysis of clinical data come to the following conclusion: fructose diphosphate combined with large-dose vitamin C can reduce the systemic oxidative stress response in neonatal asphyxia, effectively reduce myocardial injury and enhance the capacity of left cardiac contraction, and it is expected to become the new auxiliary therapy to treat the disease and optimize the neonatal outcome. And the exact role for fructose diphosphate and vitamin C to reduce the oxidative stress damage of myocardial cells remains to be confirmed by further molecular biology experiments.

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