Journal of Hainan Medical University

http://www.hnykdxxb.com

Assessment of adjuvant ademetionine therapy for the bilirubin metabolism and target organ function of neonatal jaundice

Fang Xu✉, Xin−Dong Wei

Department of Pediatrics, Hubei Jianghan Oilfield General Hospital, Qianjiang City, Hubei Province, 433121

ARTICLE INFO

Article history:
Received 2 Nov 2017
Received in revised form 9 Nov 2017
Accepted 12 Nov 2017
Available online 28 Nov 2017

Keywords:
Neonatal jaundice
Ademetionine
Bilirubin
Target organ injury

ABSTRACT

Objective: To study the effect of adjuvant ademetionine (SAMe) therapy on the bilirubin metabolism and target organ function of neonatal jaundice. **Methods:** A total of 68 children who were diagnosed with neonatal jaundice in Hubei Jianghan Oilfield General Hospital between March 2015 and April 2017 were selected as the research subjects and randomly divided into the SAMe group who received ademetionine combined with blue ray irradiation and the control group who received blue ray irradiation. The serum contents of bilirubin metabolism indexes and target organ injury markers before treatment as well as 3 d and 7 d after treatment. **Results:** 3 d and 7 d after treatment, serum TBIL, ALT, AST, GGT, TBA, CK-MB, cTnT, MYO, HBDH, NSE, S100B and GFAP levels of both groups were lower than those before treatment, and serum TBIL, ALT, AST, GGT, TBA, CK-MB, cTnT, MYO, HBDH, NSE, S100B and GFAP levels of SAMe group were lower than those of control group. **Conclusion:** Adjuvant ademetionine therapy can improve the bilirubin metabolism of neonatal jaundice and reduce the central nerve, myocardial and liver injury.

1. Introduction

Neonatal jaundice is a common disease in the neonatal period, which specifically refers to the jaundice that occurs within 28 d after birth, is mainly characterized by abnormal bilirubin metabolism, and is manifested as the yellowing of skin mucosa and sclera. The bilirubin has anti-oxygen free radical effect in the body, but the anomaly of bilirubin metabolism in neonatal jaundice duration can lead to the increased formation of unconjugated bilirubin, and then damage multiple organs in the body[1,2]. The central nervous system, myocardium and liver are the commonly involved target organs in neonatal jaundice, and without timely treatment and processing, it can result in the occurrence of serious complications and leave behind neurological function injury. Blue ray irradiation is the primary method for current clinical treatment of neonatal jaundice, but the curative effect is not significant after some children are exposed to blue ray[3]. Ademetionine is a compound developed in recent years, and its active component is S-adenosine-L-methionine, which can participate in the regulation of various biochemical reaction processes in the body and promote the metabolism of bilirubin. In the following studies, we specifically analyzed the effects of assisted ademetionine therapy on the bilirubin metabolism and target organ function of neonatal jaundice.

✉Corresponding author: Fang Xu, Department of Pediatrics, Hubei Jianghan Oilfield General Hospital, Qianjiang City, Hubei Province, 433121.

Fund Project: Projects of Qianjiang Science and Technology Bureau No: 150826.

2. Case information and research methods

2.1 General case information

A total of 68 children who were diagnosed with neonatal jaundice in Hubei Jianghan Oilfield General Hospital between March 2015 and April 2017 were selected as the research subjects, all children are in accordance with the diagnosis of neonatal jaundice and with TBIL＞257 μmol/L, and the children combined with congenital malformation and congenital diseases were ruled out. Random number table was used to divide the 68 children into two groups, each with 34 cases. SAMe group included 21 male cases and 13 female cases, the body mass was (2 313.4±336.4) g, 9 cases were premature and 25 cases were full-term, and the gestational age was 35-39 weeks; control group included 20 male cases and 14 female cases, the body mass was (2 383.4±319.3) g, 10 cases were premature and 24 cases were full-term, and the gestational age was 35-40 weeks. There was no significant difference in general information between the two groups (P>0.05).

2.2 Therapy

Both groups of children were given blue ray irradiation, the child were placed in blue ray treatment box, the eyes, perineum and anus were covered with black cloth, the other parts were bare and exposed to blue ray, and the treatment lasted for 12 h each group, and conducted once a day for 7 d in a row. On the basis of the blue ray irradiation, SAMe group received adjuvant ademetionine therapy: 80 mg/kg/d Ademetionine 1,4-Butanedisulfonate Enteric Coated Tablets, taken orally, for 7 consecutive days. The exchange transfusion was performed if hemolysis occurred in the two groups of children during treatment; intravenous drip of albumin was provided if the unconjugated bilirubin exceeded 320 μmol/L.

2.3 Clinical biochemical index detection

Before treatment as well as 3 d and 7 d after treatment, 1-2 mL of peripheral venous blood was collected from two groups of children and centrifuged to separate serum, automatic biochemical analyzer was used to determine TBIL, ALT, AST, GGT and TBA contents, and enzyme-linked immunosorbent assay kit was used to detect CK-MB, cTnT, MYO, HBDH, NSE, S100B and GFAP levels.

2.4 Statistical methods

SPSS 20.0 software was used to input and analyze data, the measurement data analysis between two groups were by t test and $P<0.05$ meant statistical significance in differences in test results.

3. Results

3.1 Serum bilirubin before and after treatment

Before treatment as well as 3 d and 7 d after treatment, serum TBIL levels of SAMe group were (452.31±65.29) μmol/L, (102.11±14.95) μmol/L and (26.52±3.51) μmol/L respectively; serum TBIL levels of control group were (455.13±67.24) μmol/L, (205.35±31.76) μmol/L and (89.15±10.89) μmol/L respectively. Serum TBIL levels were not significantly different between two groups of children before treatment; serum TBIL levels of both groups of children decreased 3 d and 7 d after treatment, and serum TBIL levels of SAMe group were lower than those of control group after treatment.

3.2 Serum nerve injury indexes before and after treatment

Before treatment as well as 3 d and 7 d after treatment, analysis of serum nerve injury indexes NSE (ng/mL), S100B (pg/mL) and GFAP (ng/mL) levels between two groups of children was as follows: serum NSE, S100B and GFAP levels were not significantly different between two groups of children before treatment; serum NSE, S100B and GFAP levels of both groups decreased 3 d and 7 d after treatment, and serum NSE, S100B and GFAP levels of SAMe group were lower than those of control group 3 d and 7 d after treatment.

3.3 Serum myocardial injury indexes before and after treatment

Before treatment as well as 3 d and 7 d after treatment, analysis of serum myocardial injury indexes CK-MB (ng/mL), cTnT (ng/mL), MYO (ng/mL) and HBDH (U/L) levels between two groups

Table 1.

Analysis of serum nerve injury indexes before and after treatment.

Groups	n	Time	NSE	S100B	GFAP
SAMe group	34	Before treatment	38.59±5.92	3.20±0.62	37.68±5.96
		3 d after treatment	14.21±1.87^{*a}	1.56±0.21^{*a}	20.12±3.35^{*a}
		7 d after treatment	9.39±1.03^{*ab}	0.92±0.12^{*ab}	15.54±1.88^{*ab}
Control group	34	Before treatment	39.11±6.24	3.31±0.58	38.12±5.47
		3 d after treatment	28.46±4.29^{a}	2.33±0.35^{a}	28.59±3.41^{a}
		7 d after treatment	17.45±2.03^{ab}	1.41±0.19^{ab}	22.12±2.93^{ab}

*: comparison between SAMe group and control group, $P<0.05$; ^{a}: compared with before treatment, $P<0.05$; ^{b}: compared with 3 d after treatment, $P<0.05$.

Table 2.

Analysis of serum myocardial injury indexes before and after treatment.

Groups	n	Time	CK-MB	cTnT	MYO	HBDH
SAMe group	34	Before treatment	9.12±1.15	0.25±0.05	41.52±5.96	472.41±66.94
		3 d after treatment	3.58±0.56^{*a}	0.13±0.02^{*a}	20.24±3.26^{*a}	203.51±28.96^{*a}
		7 d after treatment	1.77±0.25^{*ab}	0.08±0.01^{*ab}	13.12±1.85^{*ab}	146.61±19.35^{*ab}
Control group	34	Before treatment	9.22±1.09	0.28±0.04	42.31±6.23	480.12±69.22
		3 d after treatment	5.42±0.77^{a}	0.20±0.03^{a}	30.25±4.58^{a}	314.52±44.57^{a}
		7 d after treatment	2.94±0.36^{ab}	0.15±0.02^{ab}	22.35±3.59^{ab}	246.41±33.57^{ab}

*: comparison between SAMe group and control group, $P<0.05$; ^{a}: compared with before treatment, $P<0.05$; ^{b}: compared with 3 d after treatment, $P<0.05$.

Table 3.

Analysis of serum liver injury indexes before and after treatment.

Groups	*n*	Time	ALT	AST	GGT	TBA
SAMe group	34	Before treatment	74.02±9.35	81.69±11.28	142.93±17.63	40.21±6.95
		3 d after treatment	32.13±4.56^{*a}	37.62±6.93^{*a}	66.43±9.23^{*a}	19.28±2.66^{*a}
		7 d after treatment	20.33±3.58^{*ab}	19.25±2.46^{*ab}	38.79±5.49^{*ab}	12.13±1.76^{*ab}
Control group	34	Before treatment	74.59±9.18	82.12±10.93	141.39±17.86	40.88±6.39
		3 d after treatment	40.39±6.48^{a}	50.31±7.58^{a}	92.31±11.29^{a}	27.64±3.58^{a}
		7 d after treatment	27.64±4.16^{ab}	33.46±4.29^{ab}	68.48±8.94^{ab}	21.25±3.29^{ab}

*: comparison between SAMe group and control group, $P<0.05$; ^{a}: compared with before treatment, $P<0.05$; ^{b}: compared with 3 d after treatment, $P<0.05$.

of children was as follows: serum CK-MB, cTnT, MYO and HBDH levels were not significantly different between two groups of children before treatment; serum CK-MB, cTnT, MYO and HBDH levels of both groups decreased 3 d and 7 d after treatment, and serum CK-MB, cTnT, MYO and HBDH levels of SAMe group were lower than those of control group 3d and 7d after treatment.

3.4 Serum liver injury indexes before and after treatment

Before treatment as well as 3 d and 7 d after treatment, analysis of serum liver injury indexes ALT (U/L), AST (U/L), GGT (U/L) and TBA (μmol/L) levels between two groups of children was as follows: serum ALT, AST, GGT and TBA levels were not significantly different between two groups of children before treatment; serum ALT, AST, GGT and TBA levels of both groups decreased 3 d and 7 d after treatment, and serum ALT, AST, GGT and TBA levels of SAMe group were lower than those of control group 3 d and 7 d after treatment.

4. Discussion

Jaundice is a common disease in neonatal period, part of physiological jaundice can fade on its own, but the condition will continue to progress and the bilirubin levels will continue to rise in some children, which will seriously threaten the children′s lives. Blue ray irradiation is a normal therapy for neonatal jaundice, but its velocity to lower bilirubin levels shows the trend of fast followed by slow, and it is unable to effectively reduce the bilirubin levels in children with severe hyperbilirubinemia[4]. The S- adenosine -L-methionine in the body is the compound synthesized by methionine and triphosadenine under the catalysis of ademetionine enzyme, which can be used as the methyl donor and sulphur donor to participate in the methyl transition and sulphur transition in the process of amino acid metabolism[5]. Exogenous supplement of S-adenosine-L-methionine can guarantee the smooth completion of the methyl transition and sulphur transition of amino acids, generate glutathione, taurine, CoA, etc., and protect the viscera[6,7]. In addition, S-adenosine -L-methionine can also regulate the activity of Na+-K+-ATP enzyme in cell membrane, stabilize cell membrane structure, and reduce the bilirubin damage to cell membrane structure[8,9]. In the study, ademetionine was used for auxiliary treatment on the basis of the blue ray irradiation, and analysis of the change in bilirubin metabolism before and after treatment showed that serum TBIL levels of both groups of children decreased after treatment, and serum TBIL levels of SAMe group were lower than those of control group. This indicates that the adjuvant ademetionine therapy based on blue ray irradiation could improve bilirubin metabolism and more effectively reduce TBIL content.

Hyperbilirubinemia has clear neurotoxicity, and the rising unconjugated bilirubin, in particular, can cause the neuron and glial cell damage in central nervous system, which is not only characterized by cell morphology swelling and mitochondrial dysfunction, but can also lead to the destruction of the cellular structure[10,11]. Bilirubin encephalopathy is a serious complication of patients with pathological jaundice, which can cause nerve damage if not treated in time[12]. When hyperbilirubinemia damages the neurons and glial cells, a variety of specific molecules in cells will be released into the blood circulation and become the marker molecules that reflect the degree of nerve injury. NSE participates in the regulation of glycolysis process within neurons, S100B is involved in the regulation of calcium-related biological processes in neurons and a variety of glial cells, and GFAP participates in the regulation of astrocyte skeleton structure. The analysis of the changes in nerve injury indexes between the two groups before and after treatment showed that serum NSE, S100B and GFAP levels of both groups decreased after treatment, and serum NSE, S100B and GFAP levels of SAMe group were lower than those of control group. This means that both blue ray irradiation alone and blue ray irradiation combined with adjuvant ademetionine therapy can relieve the toxic effects of hyperbilirubinemia on the central nervous system, and blue ray irradiation combined with adjuvant ademetionine therapy is better than blue ray irradiation alone in reducing the central nervous system damage.

The persistent hyperbilirubinemia in neonatal jaundice is not only neurotoxic, but can also cause damage to other organs in the body. The myocardium and the liver are the common target organs involved in neonatal jaundice duration, the elevated bilirubin level can cause myocardial cell and liver cell membrane structure damage, and a variety of specific molecules in cells are released into the blood

circulation[13]. CK-MB, cTnT, MYO and HBDH are the biochemical indicators closely related to myocardial injury, CK-MB and HBDH participate in the catalysis of biological conversion process in myocardial cells, and the cTnT and MYO are closely related to the integrity of myocardial cell structure and function[14]. ALT, AST, GGT and TBA are the biochemical indicators closely related to liver injury, ALT, AST and GGT are the metabolic enzymes that catalyze the transamination process in liver cells, and TBA is the metabolite discharged through the liver[15]. The analysis of the changes in myocardial injury indexes between the two groups of children before and after treatment showed that serum CK-MB, cTnT, MYO, HBDH, ALT, AST, GGT and TBA levels of both groups decreased after treatment, and serum CK-MB, cTnT, MYO, HBDH, ALT, AST, GGT and TBA levels of SAMe group were lower than those of control group. It means that both blue ray irradiation alone and blue ray irradiation combined with adjuvant ademetionine therapy can reduce hyperbilirubinemia damage to the myocardium and the liver, and blue ray irradiation combined with adjuvant ademetionine therapy is better than blue ray irradiation alone in reducing the myocardial and liver injury.

To sum up, it can be concluded that adjuvant ademetionine therapy on the basis of blue ray irradiation can be more effective than blue ray irradiation alone in improving the bilirubin metabolism of neonatal jaundice, and it can also relieve the damage to central nerve, myocardium and liver.

References

[1] Isa HM, Mohamed MS, Mohamed AM, Abdulla A, Abdulla F. Neonatal indirect hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency. *Korean J Pediatr* 2017; **60**(4): 106-111.

[2] Al-Omran A, Al-Abdi S, Al-Salam Z. Readmission for neonatal hyperbilirubinemia in an area with a high prevalence of glucose-6-phosphate dehydrogenase deficiency: A hospital-based retrospective study. *J Neonatal Perinatal Med* 2017; **10**(2): 181-189.

[3] Stebelova K, Kosnacova J, Zeman M. Intense blue light therapy during the night-time does not suppress the rhythmic melatonin biosynthesis in a young boy. *Endocr Regul* 2017; **51**(1): 31-34.

[4] Ebbesen F, Madsen PH, Vandborg PK, Jakobsen LH, Trydal T, Vreman HJ. Bilirubin isomer distribution in jaundiced neonates during phototherapy with LED light centered at 497 nm (turquoise) vs. 459 nm (blue). *Pediatr Res* 2016; **80**(4): 511-515.

[5] Gregoire S, Millecamps M, Naso L, Do Carmo S, Cuello AC, Szyf M, et al. Therapeutic benefits of the methyl donor S-adenosylmethionine on nerve injury-induced mechanical hypersensitivity and cognitive impairment in mice. *Pain* 2017; **158**(5): 802-810.

[6] King AL, Mantena SK, Andringa KK, Millender-Swain T, Dunham-Snary KJ, Oliva CR, et al. The methyl donor S-adenosylmethionine prevents liver hypoxia and dysregulation of mitochondrial bioenergetic function in a rat model of alcohol-induced fatty liver disease. *Redox Biol* 2016; **9**: 188-197.

[7] Lee SY, Ko KS. Effects of s-adenosylmethionine and its combinations with taurine and/or betaine on glutathione homeostasis in ethanol-induced acute hepatotoxicity. *J Cancer Prev* 2016; **21**(3): 164-172.

[8] Ding W, Smulan LJ, Hou NS, Taubert S, Watts JL, Walker AK. s-adenosylmethionine levels govern innate immunity through distinct methylation-dependent pathways. *Cell Metab* 2015; **22**(4): 633-645.

[9] Morgan TR, Osann K, Bottiglieri T, Pimstone N, Hoefs JC, Hu KQ, et al. A phase ii randomized, controlled trial of s-adenosylmethionine in reducing serum α -fetoprotein in patients with hepatitis c cirrhosis and elevated AFP. *Cancer Prev Res (Phila)* 2015; **8**(9): 864-872.

[10] Yuan J, Zhang Y, Wang X, Ma H. Exogenous brain-derived neurotrophic factor at a 50 ng/ml concentration has a significant protective effect on bilirubin-induced cerebral cortex neuronal injury. *Clin Lab* 2017; **63**(9): 1421-1429.

[11] Watchko JF, Spitzer AR, Clark RH. Prevalence of hypoalbuminemia and elevated bilirubin/albumin ratios in a large cohort of infants in the neonatal intensive care unit. *J Pediatr* 2017; **188**: 280-286.

[12] Stadem PS, Hilgers MV, Bengo D, Cusick SE, Ndidde S, Slusher TM, et al. Markers of oxidative stress in umbilical cord blood from G6PD deficient African newborns. *PLoS One* 2017; **12**(2): e0172980.

[13] Huidekoper HH, Vaz FM, Verrips A, Bosch AM. Hepatotoxicity due to chenodeoxycholic acid supplementation in an infant with cerebrotendinous xanthomatosis: implications for treatment. *Eur J Pediatr* 2016; **175**(1): 143-146.

[14] LIANG Jian-wei, ZHOU Wei, LI Wan-sha, SHAN Quan-zhong. The effect of liver and renal function as well as myocardial enzyme spectrum detection for neonatal hyperbilirubinemia. *Lab Med Clin* 2017; **14**(8): 1153-1155.

[15] Zhang Na, Yin Yue, Jia Mei. Impact of total bilirubin on the hepatic function, renal function and myocardial enzyme among neonate. *Chin J Clin* 2016; **10**(4): 517-520.