Original Article Efficacy of adenosylmethionine combined with Si Mo Tang in treatment of neonatal jaundice

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Abstract: Objective: To investigate the efficacy of S-adenosylmethionine (SAM-e) combined with Si Mo Tang in the treatment of neonatal jaundice and its effect on liver function, cardiac enzymes, immune function, serum transferrin (TRF) and C-reactive protein (CRP) levels. Methods: The clinical data of 149 infants with neonatal jaundice were collected retrospectively. The infants were grouped according to the treatment methods. All neonates were treated with blue light phototherapy. Besides, group A was treated with SAM-e, group B was treated with Si Mo Tang, and group C was treated with SAM-e combined with Si Mo Tang. The treatment efficacy, serum bilirubin level, neonatal behavioral neurological assessment (NBNA) score, liver function, cardiac enzymes, immune function, serum TRF and CRP level were compared among the three groups before and after treatment. Results: The total effective rate of treatment in group C was 96.00%, which was higher than group A (73.47%) and group B (78.00%) (P < 0.05), but no significant difference was observed between groups A and B (P > 0.05). Compared with groups A and B, group C had higher NBNA scores, lower serum bilirubin levels, and lower serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK) and creatine kinase-MB (CK-MB) levels (all P < 0.05); however, there was no statistical differences in NBNA scores, serum bilirubin levels, serum AST and ALT, LDH, CK and CK-MB levels between group A and group B (all P > 0.05). Compared with groups A and B, group C showed higher CD4⁺, CD4⁺/CD8⁺, TRF levels and lower serum CRP levels (P < 0.05), while there was no statistical differences in CD4⁺, CD4⁺/CD8⁺, CD8⁺, TRF levels and serum CRP levels between group A and group B (all P > 0.05). Conclusion: SAM-e combined with Si Mo Tang promoted the regression of jaundice, improved liver function, neurodevelopmental conditions and the myocardial enzyme spectrum, reduced the level of inflammation, and improved the immunity of newborns with neonatal jaundice.

Keywords: Adenosylmethionine, Si Mo Tang, neonatal jaundice, liver function, cardiac enzymes, immune function, transferrin, C-reactive protein

Introduction

Neonatal jaundice is a disorder commonly seen in infants, characterized by abnormal bilirubin metabolism and significantly elevated serum bilirubin level, resulting in yellowing of the sclera, mucous membranes, and skin [1, 2]. There are two types of jaundice: pathological jaundice and physiological jaundice. Physiological jaundice is related to bilirubin metabolism, including increased enterohepatic circulation, abnormal bilirubin metabolism or excretion, insufficient uptake of bilirubin by hepatocytes, and excessive bilirubin production [3, 4]. Pathological jaundice is mainly related to increased bilirubin production, impaired hepatic bilirubin metabolism or bile excretion [5]. Mild neonatal jaundice can be improved after treatment, while severe cases may damage the nervous system, affecting the intellectual development of the newborn, and may even cause neonatal death [6].

Currently, blue light phototherapy is a clinical treatment for neonatal jaundice approved by Food and Drug Administration. However, some neonates have low tolerance and are prone to rash, fever, diarrhea and other adverse symptoms [7]. Studies have shown that Ademetionine 1,4-Butanedisulfonate Enteric Coated Tablets can reduce the serum bilirubin level in neonatal jaundice and promote bile excretion of bilirubin, which leads to the improvement of bilirubin enterohepatic circulation, and reduction of skin yellowing, but the efficacy of the drug alone needs to be further improved [8, 9]. Traditional Chinese medicine has gradually emerged for the treatment of neonatal jaundice due to its good efficacy and high safety. Si Mo Tang is one of the orally administered herbal medicines, which promotes the movement of Qi, descends rebellious Qi, expands the chest, and dissipates stagnation [10]. The main components of Si Mo Tang include fructus aurantii, semen arecae, radix aucklandiae and radix linderae. "Si Mo" refers to the method of grinding the four herbs into thick juice and then decocting them with water. At present, Si Mo Tang is commonly used to treat emphysema, bronchial asthma and other Qi stagnation and inverse Qi.

Although there are various clinical methods for the treatment of neonatal jaundice, there are few studies on S-adenosylmethionine (SAM-e) combined with the oral administration of the traditional Chinese medicine Si Mo Tang. Therefore, SAM-e combined with Si Mo Tang was used for the treatment of neonatal jaundice in this study to explore its effect on improving liver function, cardiac enzymes, immune function, serum transferrin (TRF) and C-reactive protein (CRP) levels.

Materials and methods

Baseline data

The clinical data of 149 infants with neonatal jaundice in our hospital were collected retrospectively, and the infants were grouped according to the treatment methods. All the groups were treated with blue light phototherapy. Group A (n = 49) was treated with SAM-e alone, group B (n = 50) was treated with Si Mo Tang alone, and group C (n = 50) was treated with SAM-e with SAM-e combined with Si Mo Tang.

Inclusion criteria: infants with no contraindications for treatment; infants with pathological jaundice; full-term neonates; and infants with complete clinical data.

Exclusion criteria: infants whose parents withdrew them from the study; infants with co-infection of neonatal hemolytic disease; infants with low body mass index (BMI); infants with concomitant biliary tract disease; infants with concomitant severe congenital disease; or infants with obstructive jaundice caused by biliary tract and liver malformations. This study obtained approval from the Ethics Committee of Xingtai People's Hospital (approval number 2020[018]), and the family of each newborn provided written informed consent.

Methods

After admission, each group was treated with conventional blue light phototherapy, and the neonates were placed in a jaundice treatment box (manufacturer: Ningbo Dawei Medical Equipment Co., Ltd.) with eyes and genitals covered with black cloth. The single-sided phototherapy was initiated. The distance between the lamp and the newborn was 35 cm, and continuous irradiation treatment was performed for 12 h every day. The treatment continued for 10 days.

Group A was additionally treated with Ademetionine 1,4-Butanedisulfonate Enteric Coated Tablets (Zhejiang Hisun Pharmaceutical Co., Ltd., Approval No. H20133197, Specification: 0.5 g * 20 tablets) which were ground into powders and fed to newborns 3 times a day for continuous 10 days.

Group B was administrated with Si Mo Tang Oral Liquid (Hunan Hansen Pharmaceutical Co., Ltd., Approval No. Z20025044, Specification: 10 mL * 8 pcs), t.i.d 5 mL a day, with 5 days as one course, and two courses of treatment was given in total.

Group C was treated with SAM-e combined with Si Mo Tang, with the medication method the same as that of groups A and B.

Outcome measurements

(1) Efficacy criteria [11]. Cure: jaundice completely disappeared and laboratory indices returned to normal; markedly effective: jaundice obviously improved and laboratory indices basically returned to normal; effective: jaundice and laboratory indices were improved; if the above criteria were not met, it was deemed to be ineffective. The total effective rate was the sum of effective, markedly effective and cure.

(2) Serum bilirubin levels and neonatal behavioral neurological assessment (NBNA) scores [12, 13]. Before and after treatment, 2 mL of fasting venous blood was drawn from each group and centrifuged for 15 min at 3200 r/ min. Serum bilirubin levels were determined by automatic biochemical analyzer (lot no.: 2400296; manufacturer: Pointe (Nanjing) Co., Ltd.). The NBNA scale was used to evaluate the neurodevelopment of newborns in each group before and after treatment, including active and passive muscle tone, general assessment, behavioral ability and primitive reflexes. NBNA scores < 35 were regarded as abnormal neurodevelopment.

(3) Liver function. Before and after treatment, 2 mL of fasting venous blood was drawn from each group and centrifuged for 15 min at 3200 r/min. The serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured by automatic biochemical analyzer (lot no.: 20191110; manufacturer: Beijing Leadman Biochemistry Co., Ltd.) before and after treatment in three groups, respectively. A 96-well plate was used to set control well and sample well according to the instruction, each with three replicate wells. Matrix solution (20 µL) was added to each well. The sample well was added with 5 µL of sample, followed by adding 20 µL of color developing solution to each well after standing for 30 min at 37°C in the incubator. The control well was added with 5 µL of sample, and after reacting for 20 min at 37°C in the incubator, the stop solution (200 µL) was added to each well. After reacting for 15 min at room temperature, the 96-well plate was placed in a microplate reader (510 nm wavelength) to measure the OD value (absorbance) of each well. The values were calculated according to the standard curve.

(4) Cardiac enzymes. Before and after treatment, 2 mL of fasting venous blood was taken from each group in the morning, and centrifuged for 15 min at a speed of 3200 r/min. The serum lactate dehydrogenase (LDH), creatine kinase (CK) and creatine kinase-MB (CK-MB) levels of the three groups were measured by automatic biochemical analyzer (lot no.: M250-82; manufacturer: Jinan Tongxin Biotechnology Co., Ltd.) before and after treatment in strict accordance with the kit instructions. The kit lot number is.

(5) Immune function. Before and after treatment, 2 mL of fasting venous blood was drawn from each group and centrifuged for 15 min at 3200 r/min. CD4+, CD8+, CD4+/CD8+ were measured by flow cytometry (lot no.: 20190019; manufacturer: Saibai'ao (Beijing) Technology Co., Ltd.) before and after treatment in three groups, respectively. The specific method is as follows: 100 µL of anticoagulant whole blood was added vertically to the bottom of the counting tube, and 20 µL of CD4 and CD8 fluorescent labeled antibodies were added and mixed. After 15 min of incubation at room temperature in dark, 500 µL of hemolysin was added and mixed well by shaking, followed by 10-15 min of incubation at room temperature in dark. PBS (500 µL) was added to each tube, and the sample was shaken and mixed for detection. The percentage of CD4⁺ and CD8⁺ T cells was detected with the combination of light scattering and CD3⁺ cells as gating, and with CD4 and CD8 as horizontal and vertical coordinates respectively.

(6) Serum TRF and CRP levels. Before and after treatment, 2 mL of fasting venous blood was drawn from each group and centrifuged for 15 min at 3200 r/min. Serum TRF and CRP levels of the three groups were measured by enzymelinked immunosorbent assay (lot no.: 2019-1012; kit supplied by Thermo Fisher Scientific, Waltham, USA) before and after treatment. The specific steps were as follows: (i) According to the experimental requirements, blank well, standard well and sample well were set. The standard and sample dilutions were added to the blank wells, the standard solution was added to the standard wells, and the appropriate amount of sample was added to the sample well, followed by storing at the appropriate temperature for 90 min; (ii) The sample was removed from the incubator in step (i), the liquid was discarded, and 100 µL of biotin antibody working solution was add to each well without washing the wells, while coating each well and incubating at 37°C for 1 h; (iii) The liquid was discarded, and the plate wells were cleaned, followed by air dry, and the procedures were repeated three times; (iv) 100 µL of enzyme conjugate working solution was added to the washed plate well, and then covered with

Baseline data		Group A (n = 49)	Group B (n = 50)	Group C (n = 50)	t/X^2	Р
Gender (cases)	Male	31 (63.27)	35 (70.00)	33 (66.00)	0.0596	0.458
	Female	18 (36.73)	15 (30.00)	17 (34.00)		
Gestational age (weeks)		39.19 ± 2.13	39.29 ± 2.05	39.22 ± 2.15	0.963	0.785
Age (d)		13.25 ± 1.08	13.31 ± 1.02	13.29 ± 1.05	0.628	0.759
Body mass at birth (kg)		3.15 ± 0.12	3.22 ± 0.13	3.18 ± 0.11	1.326	0.269
Duration of jaundice (d)		11.85 ± 1.08	11.91 ± 1.02	11.89 ± 1.06	0.852	0.638

Table 1. Comparison of baseline data $[n (\%)]/(\overline{x}\pm s)$

Table 2. Comparison of efficacy

Group	Number of cases	Cured		Markedly effective		Effective		Ineffective		Total effective rate	
		Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%
Group A	49	18	36.73	11	22.45	7	14.29	13	26.53	36	73.47
Group B	50	20	40.00	12	24.00	7	14.00	11	22.00	39	78.00
Group C	50	22	44.00	15	30.00	11	22.00	2	4.00	48	96.00*,#
X ²		-	-	-	-	-	-	-	-	-	18.596
Р		-	-	-	-	-	-	-	-	-	0.019

Note: *P < 0.05 compared with group A; *P < 0.05 compared with group B.

film and incubated for 30 min; (v) The liquid was discarded, and the plate was washed for five times, followed by air dry; (vi) 90 μ L of color developing agent (TMB) was added to wash the plate well, and then covered the film and incubated for 15 min; (vii) 50 μ L of termination solution was added to each well to stop all reactions, and the liquid color was changed from blue to yellow; (viii) The density of each well of the plate was measured with a microplate reader at 450 nm wavelength; (ix) After completing the above steps and the experiment, the excess reagents were put into a suitable environment.

Statistical methods

SPSS22.0 was used as the analytical tool. Measurement data were expressed by mean \pm standard deviation (mean \pm SD). The *t* test was performed for comparing the data conforming to a normal distribution, and the Mann-Whitney U test was performed for data not conforming to a normal distribution. Count data [n (%)] were compared by X^2 test between groups. P < 0.05 suggested statistical significance.

Results

Comparison of baseline data

No statistical significance was found in baseline data such as gender, age, gestational age, birth mass, and time to onset among the three groups (P > 0.05) (**Table 1**).

Comparison of the efficacy

After treatment, 18 cases in group A were cured, 11 cases were markedly effective, 7 cases were effective, and 13 cases were ineffective, with a total effective rate of 73.47%. In group B, 20 cases were cured, 12 cases were markedly effective, 7 cases were effective, and 11 cases were ineffective, with a total effective rate of 78.00%. Group C had 22 cases which were cured, 15 cases were markedly effective, 11 cases were effective, and 2 cases were ineffective, with a total effective rate of 96,00%. The total effective rate in group C was significantly higher than that of groups A and B (P < 0.05), while there was no statistical difference in total effective rate between group A and group B (P > 0.05) (**Table 2**).

Comparison of serum bilirubin levels and NBNA scores

No significant difference was found in serum bilirubin levels and NBNA scores among the three groups before treatment (P > 0.05). Compared with before treatment, NBNA scores were increased and serum bilirubin levels were decreased in the three groups after treat-



Figure 1. Comparison of serum bilirubin levels and NBNA scores. A: Serum bilirubin levels; B: NBNA scores. *P < 0.05 compared with group A; *P < 0.05 compared with group B.



Figure 2. Comparison of liver function. A: Serum AST; B: Serum ALT level. *P < 0.05 compared with group A; *P < 0.05 compared with group B.

ment (P < 0.05). Compared with groups A and B, group C showed significantly higher NBNA scores and significantly lower serum bilirubin levels after treatment (P < 0.05), while there was no statistical differences in NBNA scores and serum bilirubin levels between group A and group B (P > 0.05) (**Figure 1**).

Comparison of liver function

No significant difference was found in serum AST and ALT levels among the three groups before treatment (P > 0.05). Serum AST and ALT levels were decreased in the three groups after treatment (P < 0.05). Compared with groups A and B, group C showed significantly lower serum AST and ALT levels after treatment (P < 0.05), while there was no statistical differences in serum AST and ALT levels between group A and group B (P > 0.05) (**Figure 2**).

Comparison of cardiac enzyme

Serum LDH, CK and CK-MB levels showed no significant difference among the three groups before treatment (P > 0.05). Compared with before treatment, serum LDH, CK and CK-MB levels were decreased in the three groups after treatment (P < 0.05). Compared with groups A and B, group C showed significantly lower serum LDH, CK and CK-MB levels after treatment (P < 0.05), while there was no statistical differences in serum LDH, CK and CK-MB levels between group A and group B (P > 0.05) (**Figure 3**).

Comparison of immune function

No significant difference was found in CD4⁺, CD8⁺, CD4⁺/CD8⁺ levels among the three groups before treatment (P > 0.05). Compared with before treatment, CD4⁺ and CD4⁺/CD8⁺





Figure 3. Comparison of cardiac enzymes. A: Serum LDH; B: Serum CK; C: Serum CK-MB. $^{+}P < 0.05$ compared with group A; $^{+}P < 0.05$ compared with group B.

levels were increased, and CD8⁺ levels were decreased in the three groups after treatment (P < 0.05). Compared with groups A and B, group C showed significantly higher CD4⁺, CD4⁺/CD8⁺ and significantly lower CD8⁺ (P < 0.05), while there was no statistical differences in CD4⁺, CD4⁺/CD8⁺ and CD8⁺ between group A and group B (P > 0.05) (**Figure 4**).

Comparison of serum TRF and CRP levels

No significant difference was found in serum TRF and CRP levels among the three groups before treatment (P > 0.05). Compared with before treatment, serum TRF levels were increased and serum CRP levels were decreased in the three groups after treatment (P < 0.05). Compared with groups A and B, group C showed significantly higher serum TRF levels and significantly lower serum CRP levels after treatment (P < 0.05), while there was no statistical differences in serum TRF and CRP levels between group A and group B (P > 0.05) (**Figure 5**).

Discussion

Blue light phototherapy is a common method for clinical treatment of neonatal jaundice, which can promote the transformation of unconjugated bilirubin into water-soluble isomers

after light exposure and excretion from urine and bile, ultimately achieving the purpose of reducing the serum bilirubin levels [14, 15]. Although this method can achieve certain efficacy in the treatment of neonatal jaundice, it may also cause adverse reactions such as dermatitis, abdominal distension, vomiting and fever, limiting its clinical application [16, 17]. In view of this, this study combined SAM-e with Si Mo Tang on the basis of conventional treatment, and the results showed that the total effective rate in group C was higher than that of groups A and B. After treatment, NBNA scores were higher and serum bilirubin level, AST and ALT levels were lower in group C than in groups A and B (P < 0.05), suggesting that the efficacy of SAM-e combined with Si Mo Tang could better promote the regression of jaundice and improve liver function. This may be due to the fact that SAM-e is mainly composed of methionine and adenosine triphosphate, which can promote the stability of cell membrane structure and minimize harmful effect of bilirubin on cell membrane structure, thus reducing the serum bilirubin level and promoting the remission of jaundice [18, 19]. Neonatal jaundice was classified as "fetal jaundice" and "fetal yellow" in traditional Chinese medicine, and was believed to be caused by inactivation of spleen

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Figure 4. Comparison of immune function. A: Flow cytometry of CD4⁺, CD8⁺, and CD4⁺/CD8⁺; B1: Quantitative result of CD4⁺; B2: Quantitative result of CD4⁺; B2: Quantitative result of CD4⁺, CD8⁺: $^{*}P < 0.05$ compared with group A, $^{*}P < 0.05$ compared with group B.



Figure 5. Comparison of serum TRF and CRP levels. A: Serum TRF; B: Serum CRP. *P < 0.05 compared with group A; *P < 0.05 compared with group B.

yang, dampness and heat obstruction, and derangement of liver and gallbladder drainage. Therefore, the treatment modality should focus on protecting the liver and relieving dampness, clearing heat and reducing jaundice. The main components of Si Mo Tang include Aurantii Fructus, Areca catechu L, Radix Aucklandiae and Lindera aggregata. Aurantii Fructus can remove stagnation, eliminate distension, and promotes Qi circulation to alleviate middle energizer: Areca catechu L. can loosen the bowels to relieve constipation; Radix Aucklandiae can relieve dyspepsia and eliminate stagnation, and Lindera aggregata can disperse cold and relieve pain. The combination of various herbs in the prescription has the effects of relieving pain, promoting the movement of Qi and reducing adverse effects. The combination of SAM-e and Si Mo Tang in the treatment of neonatal jaundice can exert treatment effects from different mechanisms, promote the remission of jaundice and improve liver function [20, 21].

Neonatal immune dysfunction is also closely related to the development of jaundice [22]. Studies have shown that the immune function is generally low in newborns with jaundice compared to normal neonates [23]. A dynamic balance between CD4⁺, CD8⁺ should be maintained for stable immune function. High bilirubin levels in newborns with jaundice can leave T-lymphocyte subsets in a dysregulated state, leading to abnormalities in cytokine secretion and synthesis, further impairing immune function [24, 25]. In this study, group C showed higher CD4⁺ and CD4⁺/CD8⁺ and lower CD8⁺ after treatment compared with groups A and B (P < 0.05), suggesting that combined treatment with Si Mo Tang could improve the immune function. It is speculated that this may be re-

lated to the effective promotion of bilirubin metabolism. It was found that the myocardium is a commonly involved organ during the development of jaundice [26]. In neonatal jaundice, cardiomyocyte and hepatocyte membrane structures were damaged, and the release of LDH, CK and CK-MB was promoted, interfering with normal blood circulation [27]. In this study, LDH, CK and CK-MB levels in group C were lower than those in groups A and B after treatment, suggesting that SAM-e combined with Si Mo Tang may prevent myocardial damage. This may be because SAM-e can nourish the myocardium, so the myocardial enzyme levels are improved in neonates, which could be enhanced by Si Mo Tang. It has been found that TRF and CRP can be utilized clinically as physiological indicators for the differential diagnosis of neonatal jaundice, where TRF is transferrin and its level is correlated with liver metabolic function [28]. CRP is an acute chronotropic protein produced mainly by the liver, and it rises when hepatocytes are damaged or the organism is in an inflammatory state [29]. In this study, compared with groups A and B, group C showed higher serum TRF levels and lower serum CRP levels (P < 0.05), suggesting that SAM-e combined with Si MoTang can effectively improve liver metabolism and reduce the level of bilirubin in newborns. The reason may be that SAM-e can bind serum-conjugated bilirubin and promote its excretion, and also regulate the ecological balance of intestinal flora, which will reduce the degree of intestinal mucosal damage and reduce the level of inflammation, while Si Mo Tang can promote blood circulation, intestinal peristalsis, bile excretion and gallbladder contraction, and play a role in improving liver metabolism.

In conclusion, SAM-e combined with Si Mo Tang has a significant therapeutic effect on neonatal jaundice, which is beneficial to promote jaundice remission, improve the liver function, neurodevelopment and the myocardial enzyme spectrum, as well as reducing the level of inflammation and improving immunity.

Disclosure of conflict of interest

None.

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