An analysis on treatment effect of blue light phototherapy combined with Bifico in treating neonatal hemolytic jaundice

YAN JIAO, YUTING JIN, HUANHUAN MENG and MEIZHANG WEN

Department of Neonatology, People's Hospital of Rizhao, Rizhao, Shandong 276826, P.R. China

Received December 26, 2017; Accepted June 13, 2018

DOI: 10.3892/etm.2018.6340

Abstract. This study aimed to discuss and evaluate the clinical effect of blue light phototherapy combined with bifico in treating neonatal hemolytic jaundice. One hundred and twenty cases with neonatal hemolytic jaundice were randomly divided into treatment group and control group, 60 cases in each group. Neonatal patients in the control group were treated with traditional treatment, including administration of enzyme inducer phenobarbital and blue light phototherapy for 8 consecutive hours every day. Neonatal patients in the treatment group received bifico orally based on traditional treatment. Clinical effects of the two groups were observed after one course of treatment (7 days as one course). During the first course, serum bilirubin level in the treatment group treated with blue light phototherapy combined with bifico declined more rapidly ($P<0.01$) and more significantly ($P<0.01$) than that in the control group, and the mean time for eliminating jaundice was significantly reduced ($P<0.05$). The total effective rate was 91.67% in the treatment group, while that was 85.00% in the control group, which suggested that the treatment effect of the treatment group was better than that of the control group and the difference between the two groups was statistically significant ($P<0.05$). Compared with traditional treatment, the treatment effect of blue light phototherapy combined with bifico in treating neonatal hemolytic jaundice is significantly improved and the speed of eliminating jaundice is also higher. Thus, it is worthy to be applied in clinical practice.

Introduction

Neonatal hemolytic jaundice is one of the most common diseases during the neonatal period (1), mainly resulting from the antibodies produced by the blood of mother and infant. At present, the most common reason for this disease is ABO hemolysis and the incidence rate of ABO hemolysis in neonates is 11.7%. Jaundice is commonly seen in patients with liver and gallbladder dysfunctions and its occurrence is closely related to the bilirubin functional metabolism in neonatal patients. As bilirubin derives mainly from hemoglobin, the rise of bilirubin level in neonatal patients is caused by the breakdown of hemoglobin, thus resulting in a series of clinical symptoms (2) in neonatal patients such as skin yellowness and an increase in jaundice index. If the neonate is not treated in time, the jaundice index will gradually increase, thus resulting in kernicterus which usually leads to hypoxic ischemic encephalopathy because of a large amount of hemolysis. As hypoxic ischemic encephalopathy brings damage to the brain tissue and cranial nerves or even become life-threatening, it does severe harm to neonates (3). Bifico, also called bifid-triple viable capsule, is a drug for acute and chronic diarrhea caused by intestinal flora and plays a role in stabilizing and regulating the intestinal flora. At present, neonatal hemolytic jaundice is often treated with blue light irradiation in clinic (4). In this study, the neonatal patients with hemolytic jaundice selected from the Department of Neonatology of our Hospital (Rizhao, China) were treated with oral bifico on the basis of enzyme inducer phenobarbital and blue light phototherapy to investigate the clinical effect. This study aims to find a more effective treatment for neonatal hemolytic jaundice than the traditional blue light phototherapy. It is now reported as follows.

Materials and methods

General clinical data. A total of 120 neonatal patients with neonatal hemolytic jaundice treated in the Department of Neonatology of our Hospital (Rizhao, China) from April 2014 to June 2016 were collected and randomly divided into the treatment group and control group, 60 cases in each group. All neonatal patients conformed to the diagnostic criteria of neonatal hemolytic jaundice described in Pediatrics (8th edition) (5). The neonatal patients in the treatment group were: 28 males and 32 females; postnatal days ≤4 days (n=6), 5 days ≤ postnatal days ≤8 days (n=16), 8 days < postnatal days ≤14 days (n=23), postnatal days >14 days (n=17); the average age was 13.26±3.7 days, and the average weight was 3518±893 g. The neonatal patients in the control group were: 34 males and 26 females; postnatal days ≤4 days (n=4), 5 days ≤ postnatal days ≤8 days (n=11), 8 days < postnatal days ≤14 days (n=30), postnatal days >14 days (n=15); the

Correspondence to: Dr Meizhang Wen, Department of Neonatology, People's Hospital of Rizhao, 126 Taian Road, Rizhao, Shandong 276826, P.R. China
E-mail: w782sn@163.com

Key words: blue light phototherapy, bifico, neonatal hemolytic jaundice, serum bilirubin, jaundice

average age was 14.26±5.32 days and the average weight was 3320±970 g.

Inclusion and exclusion criteria. Inclusion criteria were: neonatal patients diagnosed with hemolytic jaundice; neonatal patients whose skin was stained yellow in different degrees; neonatal patients hospitalized within 24 h after onset and not receiving treatment before admission. Exclusion criteria were: neonates with pneumonia; neonates with hepatitis; neonates with infectious diseases; neonates with congenital metabolic disease. The families of all the neonatal patients with hemolytic jaundice selected in this study were informed and signed informed consent. The study was approved by the Ethics Committee of People's Hospital of Rizhao (Rizhao, China).

Instruments and reagents. Blue light therapeutic apparatus for jaundice was purchased from Wuhan Maixin Medical Equipment Co., Ltd. (Wuhan, China); bifico was purchased from Shanghai Sinepharm Co., Ltd. (NMPN S03100952) (Shanghai, China); BS-220 Mindray automatic biochemical analyzer and the serum bilirubin kit were purchased from Nanjing Vedeng Medical Co., Ltd. (Nanjing, China).

Methods. The selected 120 neonatal patients in the treatment and control groups received effective nursing measures after admission, including feeding, fluid infusion and infection prevention, and were treated with oral administration of enzyme inducer phenobarbital and blue light phototherapy in a phototherapy warmer at 31˚C with the relative humidity of 57%. Detailed methods: Naked neonatal patients with hemolytic jaundice were put into a phototherapy warmer with eyeshades, and the scrotum of male patients and the perineum of female patients were covered with black cotton cloth for protection. All neonatal patients received enzyme inducer phenobarbital orally and blue light irradiation in phototherapy warmer (the distance between light and neonatal patients was 26 cm, total skin irradiation, phototherapy for 8 consecutive hours every day). On this basis, the treatment group received 1 pill of bifico for combined therapy orally every day (1 pill in the morning, afternoon and evening, three times a day). The clinical effects of the treatment and control groups were observed after one course of treatment (7 days as one course). During the treatment, the conditions of the neonatal patients in the treatment and control groups at the time of phototherapy were carefully observed and the following matters were noted: an adequate water supply was ensured; changes in body temperature were monitored; neonatal patients' skin was well-protected; lacrimation, vomiting, feces and urine were recorded. The serum bilirubin level was detected by immunoturbidimetry and operation was performed in strict accordance with instructions.

Evaluation criteria of treatment effect. After 1 course of treatment, the treatment conditions of neonatal patients with hemolytic jaundice in the treatment and control groups were compared, and changes of the serum bilirubin level in the neonatal patients before and after treatment and regression status of clinical symptoms such as skin yellowness, serum bilirubin and jaundice were observed. With reference to the study of Lee *et al* (6), the evaluation criteria of the clinical effects are as follows: ineffective: Skin yellowness did not change, jaundice was not relieved and the serum bilirubin level did not decline; remission: Skin yellowness apparently disappeared, jaundice was obviously relieved and the serum bilirubin level evidently declined; effective: Skin yellowness disappeared, jaundice was relieved, the serum bilirubin level declined, urine and face colors were normal and each clinical examination index was consistent with that of the healthy neonates.

Statistical analysis. Statistical Product and Service Solutions (SPSS) 22.0 software (Tianjin Ruankewang Technology Co., Ltd., Tianjin, China) was used for the statistical analysis of data. Measurement data were presented as (mean ± SD), t-test was used for the comparison of measurement data between the two groups, Chi-square test was used for the comparison of rate. $P<0.01$ suggested that there was a significant difference and $P<0.05$ suggested that there was a difference, and both situations were considered as statistical difference.

Results

Clinical data of neonates in the treatment and control groups. Sex, gestational age, weight, delivery mode, family residence, serum sodium and serum calcium of the neonatal patients in the treatment and control groups had no influence on this experimental study. The differences were not statistically significant ($P>0.05$) (Table I).

Comparison of clinical effect between the treatment and control groups. After one course of treatment, it is evident that the total effective rate of the neonatal patients in the treatment group was significantly higher than that in the control group ($P<0.05$). The remission rate in the treatment group was higher than that in the control group ($P<0.05$). The effective rate in the treatment group was higher than that in the control group ($P<0.05$). The ineffective rate in the treatment group was lower than that in the control group ($P<0.05$) (Table II).

Comparison of serum bilirubin level between the two groups. After treatment, the serum bilirubin level in the treatment group was significantly decreased compared with that before treatment ($P<0.01$). The serum bilirubin level in the treatment group was lower than that in the control group ($P<0.05$) (Table III).

Comparison of recovery condition of the clinical symptoms and indexes between the treatment and control groups. Through comparisons of the recovery condition of the clinical symptoms and indexes between the two groups, the results showed that the recovery time of skin yellowness, jaundice and serum bilirubin and hospital stay were all superior to those in the control group ($P<0.05$) (Table IV).

Discussion

Neonatal hemolytic jaundice is one of the most common diseases during the neonatal period, usually resulting from maternal-fetal blood group incompatibility (7). The serum bilirubin level of the neonatal patient with hemolytic jaundice rapidly increases and patients have symptoms such as cardiac

Table I. Clinical data of neonatal patients in the treatment and control groups [n (%)].

Items	Treatment group	Control group	χ^2/t-test	P-value
Sex	χ^2=3.208	0.326		
Male	28 (46.67)	34 (56.67)		
Female	32 (53.33)	26 (43.33)		
Gestational age			χ^2=2.264	0.431
≤38 weeks	23 (38.33)	28 (46.67)		
>38 weeks	37 (61.67)	32 (53.33)		
Weight			χ^2=3.681	0.201
≤3400 g	37 (61.67)	33 (55.00)		
>3400 g	23 (38.33)	27 (45.00)		
Age (years)	χ^2=3.051	0.289		
≤16 days	36 (60.00)	39 (65.00)		
>16 days	24 (40.00)	21 (35.00)		
Delivery mode	χ^2=3.161	0.243		
Eutocia	43 (71.67)	47 (78.33)		
Cesarean	17 (28.33)	13 (21.67)		
Family address	χ^2=2.930	0.304		
Urban area	49 (81.67)	41 (68.33)		
Rural area	11 (18.33)	19 (31.67)		
Serum sodium (mmol/l)	135.16±6.12	133.26±5.37	t=5.316	0.159
Serum calcium (mmol/l)	2.20±0.49	2.35±0.24	t=4.161	0.198

Table II. Comparison of treatment effect between neonatal patients in the treatment and control groups [n (%)].

Groups	n	Remission rate	Effective rate	Ineffective rate	Total effective rate
Treatment group	60	44 (73.34)	11 (18.33)	5 (8.33)	55 (91.67)
Control group	60	43 (71.67)	8 (13.33)	9 (15.00)	51 (85.00)
χ^2 test	-	2.760	2.928	3.862	4.062
P-value	-	0.047	0.045	0.43	0.031

Table III. Comparison of serum bilirubin level between the two groups before and after treatment (mean ± SD, μmol/l).

Groups	n	Before treatment	After treatment	t-test	P-value
Treatment group	60	306.16±42.36	99.38±18.26[a]	2.893	0.003
Control group	60	316.67±39.75	153.68±26.46	1.156	0.007

In the comparison between the treatment and control groups at 7 days after treatment, [a]t=7.628, P=0.037.

Table IV. Comparison of the recovery condition of clinical symptoms and indexes between the treatment and control groups (mean ± SD, days).

Groups	n	Disappearance time of yellowness	Disappearance time of jaundice	Recovery time of serum bilirubin	Hospital stay
Treatment group	60	2.63±1.09	3.63±1.63	4.63±1.06	4.89±2.96
Control group	60	4.46±2.16	5.37±3.02	6.82±2.46	8.63±3.07
t-test	-	6.065	7.963	7.164	10.268
P-value	-	0.041	0.031	0.035	0.026

failure and anasarca, or even have hepatosplenomegaly in severe cases. If the disease is not treated effectively in time, it may result in death of the nerve cells and thus cause lesions, or even kernicterus (8). According to statistics of relevant reports, the mortality rate of the neonatal patients in the acute phase of kernicterus worldwide is as high as 50-70%, and the neonatal patients who survive have a 70-90% chance of exhibiting neurological sequelae caused by the lesions of nerve cells (9). Therefore, it is very important to treat neonatal hemolytic jaundice at its early stage. At present, neonatal patients with hemolytic jaundice are mainly treated with blue light irradiation in clinic (10).

Blue light phototherapy is one of the main therapies for neonatal hemolytic jaundice and its wave length is as long as 420-470 nm. Blue light phototherapy can effectively lower the serum bilirubin level of neonatal patients (11,12). The mechanism of blue light phototherapy is that irradiation to skin can facilitate the serum bilirubin in neonatal patients translating into water soluble derivatives which can be excreted from body through intestine in the manner of urine. Thus, it can effectively lower the serum bilirubin level and avoid aggravation of the disease and occurrence of kernicterus (13). Blue light phototherapy is easy to be operated and is an effective therapy (14) at present as long as the exposure time can be well-controlled to avoid the adverse reaction caused by long term exposure. A combined treatment of oral bifico based on blue light therapy was applied and the clinical effect was observed in this study. Bifico can be used to adjust alterations in the intestinal flora caused by intestinal function disorder, exerts biological antagonistic effects on *Staphylococcus* aureus and *Escherichia coli* as well as certain inhibitory effects on *Shigella* and *Salmonella*. Thus, it can assist neonates effectively restore intestinal balance and prevent neonatal patients from diarrhea (1,15). In this study, the serum bilirubin level in the treatment group declined more rapidly ($P<0.01$) and more significantly ($P<0.01$) than that in the control group, and the mean time for eliminating jaundice was significantly reduced ($P<0.05$). Thus, the analysis indicated that bifico can make the intestinal tract of neonatal patients produce more organic acid. With the effect of organic acid, the PH value of intestinal tract tends to be acidic, which can maintain the intestinal tract in an acidic environment, reduce the activity of intestinal β-glucuronidase, increase bacterial colonization and serum bilirubin resorption in the intestinal tract. With the combined effect of bifico and blue light phototherapy, the water secretion in the intestinal tract is increased, which can effectively prompt intestinal peristalsis and excretion of bilirubin, reduce the abnormal absorption of bilirubin in the intestinal wall, thus relieving jaundice (10,16,17). The total effective rate of phototherapy combined with bifico in treating neonatal jaundice was 91.67% while the total effective rate in the control group was 85.00%. The result suggested that the treatment effect of the treatment group was superior to that of the control group ($P<0.05$). Thus, the clinical symptoms of the neonatal patients with hemolytic jaundice treated with blue light phototherapy combined with bifico were improved and their recovery time was shortened. The study of Shen *et al* (18) revealed that blue light phototherapy for neonatal hemolytic jaundice can treat neonatal patients effectively, which is similar to the conclusion of this study. In this study, bifocal was administrated orally on the basis of blue light phototherapy and the results showed that it can treat neonatal hemolytic jaundice rapidly and effectively.

The neonatal patients in this study were selected in strict accordance with the inclusion and exclusion criteria, thus, improving the reliability of the results in this study. Blue light phototherapy is a traditional treatment for neonatal hemolytic jaundice and its side effects on neonatal patients can be negligible. Bifico is a kind of non-prescription drug having a stabilizing effect on the gastrointestinal function and is harmless to the human body in general. However, it may result in drug dependence if taken regularly over a long period of time. Although the treatment effect of neonatal hemolytic jaundice was improved in this study, there were still some neonatal patients whose jaundice could not be relieved and clinical symptoms were still abnormal after receiving this combined treatment. Therefore, it is hoped that more effective treatment means can be found in future research.

In conclusion, the treatment of neonatal hemolytic jaundice with blue light phototherapy combined with bifico is worthy of clinical application and promotion, as it may enhance the total effective treatment rate, reduce the disappearance time of yellowness and jaundice as well as shorten the recovery time of serum bilirubin and hospital stay.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YaJ, YuJ and MW conceived and designed the study. YaJ, YuJ and HM were responsible for the collection and analysis of the experimental data. YaJ and YuJ interpreted the data and drafted the manuscript. HM and MW revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of People's Hospital of Rizhao (Rizhao, China). Signed informed consents were obtained from the patients and/or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Menon M, Sreejyothi G and Raveendranath K: Incidence of early neonatal hyperbilirubinemia in ABO incompatibility and cord bilirubin as a predictor for phototherapy. Pediatric Review. Int J Pediatr Res 3: 2016.
2. Wang G, Wang J, Huang N and Yu F: The study on clinical value of the detection about serum and Unconjugated Bilirubin in diagnosis of neonatal jaundice. Pak J Pharm Sci 29 (Suppl 1): 339-341, 2016.
3. Wong RJ, Bhutani VK and Stevenson DK: The importance of hemolysis and its clinical detection in neonates with hyperbilirubinemia. Curr Pediatr Rev: Aug 7, 2017 (Epub ahead of print). doi: 10.2174/1573396313666170807121444.
4. Olusanya BO, Iskander IF, Slusher TM and Wennberg RP: A decision-making tool for exchange transfusions in infants with severe hyperbilirubinemia in resource-limited settings. J Perinatol 36: 338-341, 2016.
5. Ramy N, Ghany EA, Alsharany W, Nada A, Darwish RK, Rabie WA and Aly H: Jaundice, phototherapy and DNA damage in full-term neonates. J Perinatol 36: 132-136, 2016.
6. Lee BK, Le Ray I, Sun JY, Wikman A, Reilly M and Johansson S: Haemolytic and nonhaemolytic neonatal jaundice have different risk factor profiles. Acta Paediatr 105: 1444-1450, 2016.
7. Chen M, Zeng Y and Chen X: Effects of maternal serum IgG anti-A (B) and neonatal direct anti globulin red blood cell antibody expression on the occurrence and development of neonatal ABO haemolysis. Biomed Res 28: 1855-1858, 2017.
8. van Toorn R, Brink P, Smith J, Ackermann C and Solomons R: Bilirubin-induced neurological dysfunction: A clinico-radiological-neurophysiological correlation in 30 consecutive children. J Child Neurol 31: 1579-1583, 2016.
9. Babu TA, Bhat BV and Joseph NM: Neurobehavior of term neonates with neonatal hyperbilirubinemia. J Pediatr Neurosci 8: 11-14, 2013.
10. Mreihil K, Benth JS, Stensvold HJ, Nakstad B and Hansen TW; Norwegian NICU Phototherapy Study Group; and the Norwegian Neonatal Network: Phototherapy is commonly used for neonatal jaundice but greater control is needed to avoid toxicity in the most vulnerable infants. Acta Paediatr: Nov 8, 2017 (Epub ahead of print. doi: 10.1111/apa.14141.
11. Waterham M, Bhatia R, Donath S, Molesworth C, Tan K and Stewart M: Phototherapy in transport for neonates with unconjugated hyperbilirubinaemia. J Paediatr Child Health 52: 67-71, 2016.
12. Woodgate P and Jardine LA: Neonatal jaundice: phototherapy. BMJ Clin Evid 2015: 0319, 2015.
13. Slusher TM, Vreman HJ, Olusanya BO, Wong RJ, Brearley AM, Vaucher YE and Stevenson DK: Safety and efficacy of filtered sunlight in treatment of jaundice in African neonates. Pediatrics 133: e1568-e1574, 2014.
14. Edris AA, Ghany EA, Razek AR and Zahran AM: The role of intensive phototherapy in decreasing the need for exchange transfusion in neonatal jaundice. J Pak Med Assoc 64: 5-8, 2014.
15. Christensen RD, Yaish HM, Nussenzveig RH, Reading NS, Agarwal AM, Eggert LD and Prchal JT: Acute kernicterus in a neonate with O/B blood group incompatibility and a mutation in SLC4A1. Pediatrics 132: e531-e534, 2013.
16. Kaplan M, Bromiker R and Hammerman C: Hyperbilirubinemia, hemolysis, and increased bilirubin neurotoxicity. Semin Perinatol 38: 429-437, 2014.
17. Olusanya BO, Osibanjo FB and Slusher TM: Risk factors for severe neonatal hyperbilirubinemia in low and middle-income countries: A systematic review and meta-analysis. PLoS One 10: e0117229, 2015.
18. Shen L, Wang H and Guo Y: Retrospective analysis of the pathogeny and treatment for hyperbilirubinemia in 162 newborns. Int J Pathol Clin Med 33: 2013. doi: 10.3969/j.issn.1673-2588.2013.02.008.