Research Progress on the Application of Blue Light Irradiation Combined with Oral Probiotics in Neonatal Jaundice

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Abstract. The incidence rate of NNJ in the newborn population is quite high, which can cause serious consequences such as bilirubin encephalopathy when serious, and pose a serious threat to the health of newborns, so it has always been a research hotspot in the field of pediatrics. At present, methods such as phototherapy and drug therapy are widely used for the treatment of neonatal jaundice, and their efficacy and mechanisms have been explored by many scholars. The role of gut microbiota in the occurrence and development of NNJ has also gradually been emphasized. However, the specific mechanisms of action of different probiotic strains against NNJ are not fully understood. This article provides an in-depth analysis of the effects of various probiotic strains on the intestinal barrier function, bilirubin metabolism related enzyme activity, and immune regulation of NNJ children. It was found that specific probiotics can significantly enhance the intestinal barrier, regulate enzyme activity, and optimize immune status to improve symptoms. This study provides a useful reference for the precise selection of probiotics for the treatment of neonatal jaundice. However, the impact of differences in gut microbiota among newborns of different regions and races on the efficacy of probiotics is still unclear. Subsequent research can focus on the development of personalized probiotic treatment plans and the direction of large-scale multicenter clinical trials.

Keywords: Blue light exposure; Oral probiotics; Neonatal jaundice; Therapeutic effect; Intestinal flora.

1. Introduction

Neonatal jaundice (NNJ) refers to the abnormal metabolism of bilirubin in the neonatal period, which exceeds the metabolic capacity of the human body, causing the increase of the level of bilirubin in the body, resulting in yellowing of the skin, sclera and other organs. It is the most common clinical problem in newborns, with a high incidence rate. Bilirubin can absorb light, and under the action of light, lipophilic bilirubin is converted into a water-soluble isomer, which can be excreted from the body through bile and urine. A serum total bilirubin level exceeding 12.9mg/dL (221μmol/L) in full-term infants and 15mg/dL (256μmol/L) in premature infants may be diagnosed as NNJ. Excessive bilirubin levels may cause damage to the newborn's nervous system, making effective treatment of NNJ of great significance.

In China, the treatment of NNJ has always been a research hotspot. Traditional blue light irradiation therapy has been widely applied in clinical practice. Blue light irradiation causes photoisomerization of bilirubin, forming water-soluble isomers that are excreted from the body through bile and urine, thereby reducing serum bilirubin levels. Numerous studies have shown that blue light irradiation has a definite effect on reducing bilirubin, effectively alleviating jaundice symptoms and reducing the occurrence of serious complications such as bilirubin encephalopathy.

Meanwhile, in recent years, the application of oral probiotics in the treatment of NNJ has gradually received attention. Multiple studies have shown that probiotics can regulate the balance of gut microbiota in newborns, promote the establishment of normal gut microbiota, which helps reduce the enterohepatic circulation of bilirubin and increase its excretion. For example, some studies have found that probiotics of specific strains can enhance the hydrolysis of conjugated bilirubin in the intestine, thereby promoting the excretion of bilirubin.

The combination of blue light irradiation and oral probiotics for the treatment of NNJ has become a new research direction. This combination therapy is expected to have a synergistic effect, thereby further improving the therapeutic effect. At present, relevant research is attempting to explore the

safety, efficacy evaluation, and optimal solution of the combined application of the two. This study aims to further explore the effect of blue light irradiation combined with oral probiotics in the treatment of NNJ, providing a more scientific and effective basis for clinical treatment.

2. The Mechanism of Action of Probiotics on NNJ

Infants' liver function is relatively immature, leading to a decrease in bilirubin intake from the blood. One reason for this situation is the low concentration of ligands in infant liver cells. This protein is responsible for binding to bilirubin in the liver and its concentration only increases in the first few weeks of life. Another reason is that the activity of uridine diphosphate glucuronosyltransferase in liver cells is reduced, leading to a decrease in bilirubin binding in the liver. [1]

2.1. Regulating the Balance of Gut Microbiota

The gut microbiota of newborns has not yet been fully established, and probiotics can regulate the balance of gut microbiota by colonizing and reproducing in the intestine, inhibiting the growth of harmful baScteria and promoting the proliferation of beneficial bacteria. The improvement of gut microbiota balance contributes to the normal metabolism and excretion of bilirubin, reduces the hepatic intestinal circulation of bilirubin, and lowers serum bilirubin levels. In the study by Tsai ML et al. [2], NNJ caused red pigment metabolism and excretion problems due to immature liver, which were exacerbated by intestinal Escherichia coli. Beneficial Bifidobacterium subsp. lactis subsp. CP-9 can inhibit the growth of harmful bacteria such as E. coli, reduce the production of related enzymes, and lower the hepatic intestinal circulation of bilirubin. It can also promote the proliferation of beneficial bacteria in the intestine, regulate the balance of bacterial flora, and assist in the normal metabolism and excretion of bilirubin. When used in combination with phototherapy, it can cause a faster decrease in serum bilirubin in the experimental group and shorten the total phototherapy time.

2.2. Regulating Immune Function

Probiotics can stimulate the development and maturation of the intestinal immune system, enhance the body's immune defense ability, and reduce the occurrence of infections and inflammatory reactions. At the same time, it can also regulate the activity of immune cells and the secretion of cytokines, reducing the impact of inflammatory reactions on bilirubin metabolism. Studies [3] have shown that probiotics can promote the development and differentiation of immune cells in intestinal related lymphoid tissues. Lactic acid bacteria strains such as Lactobacillus acidophilus and Bifidobacterium can induce dendritic cell maturation, thereby constructing intestinal immune defenses, reducing infections, and indirectly ensuring bilirubin metabolism; It can also regulate the balance of cytokine secretion, stimulate the production of anti-inflammatory cytokines, inhibit the overexpression of pro-inflammatory cytokines to alleviate inflammatory reactions, maintain intestinal epithelial barrier function, reduce intestinal permeability, and facilitate normal metabolism of bilirubin.

2.3. Promote Intestinal Peristalsis

Probiotics can stimulate the intestinal nerve plexus, promote the contraction of intestinal smooth muscle, accelerate intestinal peristalsis, shorten the residence time of bilirubin in the intestine, reduce the reabsorption of bilirubin, and promote the excretion of bilirubin with feces. Probiotics have a positive impact on the prevention of neonatal hyperbilirubinemia by promoting intestinal peristalsis, which effectively reduces the reabsorption of bilirubin in the intestine and provides strong support for reducing the risk of NNJ [4]. Ling, et al. discovered that this mechanism of action was further clarified, emphasizing that probiotics stimulate the intestinal nerve plexus, promote smooth muscle contraction, and accelerate the process of intestinal peristalsis, which can shorten the residence time of bilirubin in the intestine and promote its excretion with feces [5].

3. Applications of Combination Therapy

3.1. Application of Blue Light Irradiation Combined with Oral Probiotics to Enhance the Therapeutic Effect of NNJ

Due to the incomplete development of various functions in newborns, complications that may occur in severe cases include neurological damage and bilirubin encephalopathy, which can affect the child's hearing, vision, intelligence, and growth and development. Gong, et al. randomly divided 40 full-term NNJ patients into a control group and an observation group, with 20 cases in each group. It was found that multiple intermittent blue light irradiation combined with oral administration of Bacillus licheniformis granules was used for treatment [6]. After 3-4 days of continuous treatment, the clinical efficacy of the two groups was compared, and it was found that the total effective number of patients in the observation group was 5 more than that in the control group. $P<0.05$ indicates statistical significance of the difference. After 48 hours of treatment, the average bilirubin level in the blue light therapy group was 180.70 ± 31.53 μ mol/L, while the average bilirubin level in the combination therapy group was 158.45 ± 25.92 μ mol/L. Moreover, the jaundice resolution time in this group was shorter, about 0.65 days. This indicates that the combination of blue light irradiation and oral probiotics therapy can quickly and effectively reduce serum bilirubin levels, accelerate the resolution of jaundice, promote the recovery of children, and improve their quality of life. The problem with this study is that the sample size is too small, which may result in a lack of representativeness of the data, and its conclusions may only reflect the situation of a small number of individuals, making it difficult to generalize to the entire target population. Moreover, a small sample size can lead to unstable statistical results, which are greatly affected by accidental factors and cannot guarantee the reliability of the study. In the experiment conducted by Jiao, et al. 120 neonatal jaundice patients were selected and randomly divided into a treatment group and a control group, with 60 cases in each group [7]. The control group was treated with enzyme inducer phenobarbital and 8-hour daily blue light irradiation, while the treatment group was given Bifico triple active bacterial capsules on this basis. The serum bilirubin level in the treatment group decreased faster and more significantly, and the average time for jaundice to subside was significantly shortened. The total effective rate reached 91.67%, which was higher than the control group's 85.00%. From this, it can be seen that the combination of blue light irradiation and Bifico treatment significantly improves the effect of NNJ and is more conducive to the resolution of jaundice.

3.2. Application of Blue Light Irradiation Combined with Oral Probiotics in Reducing Adverse Reactions in NNJ Patients

In Yin Tingting's study, 90 children with NNJ were selected as research subjects and divided into two groups according to different treatment methods: the experimental group (oral administration of Bifidobacterium triple active powder+blue light therapy) and the control group (oral administration of Bifidobacterium triple active powder only), with 45 cases in each group. This study compared the levels of indirect bilirubin (IBIL) and total bilirubin (TBIL) in NNJ patients who received different treatment methods. The results showed that compared to probiotic treatment, the combination of probiotics and blue light therapy can significantly reduce the incidence of treatment adverse reactions, such as diarrhea, rash, fever, and bronze syndrome. The application of combination therapy can reduce the incidence of adverse reactions from 31.11% to 4.44%. If this combination therapy can be used for treatment, it can significantly reduce serum bilirubin levels while avoiding adverse reactions, thereby ensuring improved prognosis and healthy growth for NNJ patients. In the study by Chen Z et al., they searched multiple databases for randomized controlled trials up to December 2016, using the following main search terms and MESH titles: "probiotics" or "lactic acid bacteria" or "bifidobacteria" or "bla yeast" or "yogurt" and "neonatal jaundice" or "neonatal hyperbilirubinemia" [8,9]. A total of 13 studies involving 1067 cases of NNJ were included, and the results showed that probiotic supplementation therapy was effective and safe. Blue light irradiation combined with oral probiotics could reduce adverse reactions in NNJ patients and improve treatment safety.

3.3. Positive Effects of Blue Light Irradiation Combined with Oral Probiotics on the Nutritional Status of NNJ Patients

In the clinical treatment of NNJ, conventional phototherapy intervention is not ideal and cannot fully ensure the therapeutic effect. Chen Fangfang conducted a study on 98 newborns with pathological jaundice who were randomly divided into two groups: a control group and an observation group, with 49 cases in each group [10]. The control group only received double-sided blue light irradiation treatment box irradiation, while the observation group was given Bifidobacterium lactis triple active bacterial powder on the basis of blue light irradiation treatment. The research results showed that the daily milk intake and body weight increase of the observation group were (356 00 ± 49.00) ml, (159 70 ± 24.30) g were all higher than the control group, indicating the advantage of improving the nutritional status of the children. Jiang Bao'an randomly divided 84 newborns with NNJ into two groups: the control group received only blue light irradiation, while the observation group received blue light irradiation combined with probiotic treatment [11]. The results showed that the total effective rate of the observation group was 97.62%, which was higher than the 73.81% of the control group; The serum bilirubin level was (119.27 ± 25.42) μ mol/L, lower than the control group; The average daily milk intake (356.00 ± 49.00) ml and body weight gain (159.70 ± 24.40) g were both higher than the control group, and the incidence of adverse reactions was 4.76% lower than 21.43% in the control group. This indicates that the combination of blue light irradiation and probiotics in the treatment of neonatal jaundice can effectively reduce bilirubin levels, significantly improve the nutritional status of children, and the efficacy is safe and reliable.

3.4. The Preventive Effect of Oral Probiotics on NNJ

Early intervention is the key to preventing severe neonatal hyperbilirubinemia and bilirubin encephalopathy. In the study by GAO Yan Et Al., 1000 full-term newborns were included as research subjects and randomly divided into an experimental group and a control group, with 500 cases in each group [12]. The experimental group received oral probiotics, while the control group received oral placebo. The research results showed that in healthy full-term newborns, prophylactic oral probiotics were used to compare the incidence of bilirubinemia. The incidence rate of the placebo group was 17.60%, while the incidence rate of the probiotic group was as low as 9.00%. A study randomly divided 60 newborns into a placebo group and a probiotic group. The probiotic group was given Lactobacillus rhamnosus GG. Measure TBIL levels at multiple specific time points and record the duration of phototherapy, the need for repeat phototherapy, and daily bowel movements [13]. The results showed that at 36 hours, the average levels of TBIL and rebound water in the probiotic group were lower than those in the placebo group, and the probiotic group had more frequent bowel movements on the second and third day after birth. From this, it can be concluded that probiotics can reduce bilirubin levels by decreasing enterohepatic circulation 36 hours after NNJ, and have a certain preventive effect on NNJ caused by homologous immunity.

4. Discussion

In the current research field of NNJ, some existing studies have certain limitations. For example, in the application of blue light irradiation combined with probiotics in the treatment of NNJ, it has been found that some studies have small sample sizes, making it difficult to comprehensively and accurately reflect the true effects of combination therapy. Meanwhile, the blue light irradiation equipment used by medical institutions in different regions varies in many aspects. If the blue light irradiation equipment used in China is a specific model of a certain brand, the wavelength of the light source is mainly concentrated in 427-475nm, with a temperature range of 30-33 ℃, while another brand of equipment is used in China, the wavelength of the light source is between 420-470nm, with a temperature range of 28-30 ℃. In addition, the selection of probiotic strains varies in different regions, with most using bifidobacteria and a few experiments using other types. There is also a lack of unified standards for dosage, which may affect the universality and accuracy of research results.

In the future, not only should larger sample size long-term follow-up studies be conducted to further verify the long-term efficacy and safety of the treatment regimen of blue light irradiation combined with probiotics, but more innovative methods can also be explored. For example, based on gene editing technology, therapies targeting key genes regulating bilirubin metabolism can be developed to treat NNJ by precisely intervening in the synthesis, transport, and metabolism processes of bilirubin; Or develop intelligent wearable devices to monitor real-time changes in neonatal bilirubin levels, in order to adjust treatment strategies in a timely manner and achieve personalized medicine; Exploring the combined application of traditional Chinese medicine extracts with existing treatment methods, fully leveraging the advantages of multi-target and holistic regulation of traditional Chinese medicine, and opening up new paths for the treatment of NNJ, providing more diversified and efficient solutions.

5. Conclusion

NNJ, as a common disease in the neonatal period, can cause bilirubin encephalopathy in severe cases, posing a significant threat to the health of newborns. This study summarized the research progress of blue light irradiation combined with oral probiotics in NNJ through comprehensive analysis of relevant literature.

The core findings include: firstly, the synergistic effect of blue light and probiotics is significant. Blue light irradiation can promote the photoisomerization of bilirubin, reducing its level in the body, while probiotics can regulate the intestinal microbiota and reduce the enterohepatic circulation of bilirubin. The synergistic effect of the two can accelerate the resolution of jaundice, improve the clinical symptoms of children, and play a good preventive role. Secondly, combination therapy has good safety, with a lower incidence of adverse reactions compared to some traditional treatment methods. This provides doctors with a safer and more reliable treatment plan, while also reducing medical disputes caused by treatment side effects.

However, this review still has certain limitations, such as the small sample size of some studies analyzed in this study, differences in blue light irradiation equipment and probiotic strain types and doses used by medical institutions in different regions, which may affect the universality of the results, and the lack of long-term follow-up statistics on growth and development indicators of pediatric patients. These still need to be supplemented and improved in the future.

References

[1] Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008; 371(9606):64-74.

[2] Tsai ML, Lin WY, Chen YT, et al. Adjuvant probiotic Bifidobacterium animalis subsp. lactis CP-9 improve phototherapeutic treatment outcomes in neonatal jaundice among full-term newborns: A randomized double-blind clinical study. Medicine (Baltimore). 2022; 101(45):e31030.

[3] Yan F, Polk DB. Probiotics and immune health. Curr Opin Gastroenterol. 2011; 27(6):496-501.

[4] Teran CG, Grandy G, Walker-Pizarro N. The role of probiotics in preventing neonatal hyperbilirubinemia. J Clin Neonatol. 2021; 10(3):178-181.

[5] Yaojun L, Jun L. Research progress on the mechanism of probiotics-assisted treatment of neonatal jaundice. Shandong Med J. 2017; 57(33):107-110.

[6] Gong XQ, Luo SH, Liu YP. The effect of multiple intermittent blue light irradiation combined with probiotic therapy on the recovery process and quality of life of neonatal jaundice. Presented at: The First South China Precision Medicine Forum and Academic Exchange on Modern Clinical and Nursing Research Progress; 2022; Guangzhou, China.

[7] Jiao Y, Jin Y, Meng H, Wen M. An analysis on treatment effect of blue light phototherapy combined with Bifico in treating neonatal hemolytic jaundice. Exp Ther Med. 2018; 16(2):1360-1364.

[8] Yin T. The effect and prognosis evaluation of probiotics combined with blue light therapy for neonatal jaundice. Chin Foreign Med Res. 2019; 17(5):129-130.

[9] Chen Z, Zhang L, Zeng L, et al. Probiotics supplementation therapy for pathological neonatal jaundice: A systematic review and meta-analysis. Front Pharmacol. 2017; 8: 432.

[10] Chen FF, Li CS, Ni WP. The clinical effect of probiotics combined with blue light irradiation on neonatal jaundice and its improvement on the nutritional status of children. China Matern Child Health Care. 2022; 37(6):1012-1014.

[11] Jiang BA. Clinical effect of blue light irradiation combined with probiotics in the treatment of neonatal jaundice. Chin Foreign Women's Health Res. 2024 ;(3):94-96.

[12] Gao Y, Peng F, Wang J, et al. Study on the preventive effect and tolerance of probiotics on neonatal jaundice. China Matern Child Health Care. 2015; 30(35):6229-6231.

[13] Mutlu M, Aslan Y, Kader Ş, Acar FA. Preventive effects of probiotic supplementation on neonatal hyperbilirubinemia caused by isoimmunization. Am J Perinatol. 2020; 37(11):1173-1176.