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Review Article

TREATMENT OF JAUNDICE IN NEWBORN RECENT PROGRESS

Yu-Jie Li[1*], Upendra Yadav[2], Xiao-Fang Zhu[3], Jian-Hong Liu[3], Hui Liu[3] and Xiao-Qian Yi[3]

[1]Yangtze University,1 Nan huan Road Jing zhou Hubei 434023, PR China

[2,3]Department of Pediatrics, The Second Clinical Medical College of Yangtze University, Jingzhou Central Hospital, Jingzhou, Hubei Province, PR China

ABSTRACT

Neonatal jaundice, also known as neonatal hyperbilirubinemia, is the most common clinical manifestation in neonatal period. It is an increase in bilirubin levels caused by bilirubin metabolism disorders in the body in the early stage of neonate of its own and disease, resulting in changes in skin, mucosa, and scleral yellow stains. When the concentration of bilirubin in the body is too high, it can cause bilirubin encephalopathy through the blood-brain barrier, causing neurological dysfunction. Improper treatment can cause permanent damage to central nervous system (CNS) or even death. In order to avoid serious CNS involvement and to reduce the morbidity and mortality rate of children, this article will mainly elaborate on the treatment status of neonatal jaundice.

Keywords: neonatal, jaundice, hyperbilirubinemia, treatment

INTRODUCTION

Neonatal jaundice is the most common clinical manifestation in neonatal period. According to statistics, the incidence of neonatal jaundice in China is as high as 48.2%[1] More than 60% of full-term infants and 80% of premature babies will have varying degrees of jaundice in about a week [2, 3]. Children with bilirubin encephalopathy can account for 4.8% of the total number of children admitted to hospitals[4]. A recent study to analyze neurodevelopment and neurosensory results of survivors of acute bilirubin encephalopathy [5] More than 50% to 75% of children with treated acute bilirubin encephalopathy have cerebral palsy and sensory neurological hearing loss in childhood; however, compared with language and general development, Children's cognitive function is better protected. Therefore, the treatment and management of neonatal jaundice is particularly important. Classical treatment methods may have some disadvantages, and new treatments and standardized nursing and missionary follow-up after discharge have also attracted attention. This article reviews the researches progress in the treatment of neonatal jaundice.

1. Appropriate Interventions for Physiological Jaundice:

Physiological jaundice does not require specific treatment, and usually subside spontaneously, but during this period, need to be bask in the sun frequently, breastfeed adequately and closely observe the baby's physical condition. Adequate breastfeeding is conducive to the normal establishment of neonatal intestinal flora and the promotion of neonatal physical growth and development. Su-hong Zhang [6]and other studies have shown that touching care combined with early swimming can effectively alleviate the clinical symptoms of neonatal jaundice reduce serum indirect bilirubin, and facilitate the growth and development of newborns. Swimming and touching can promote the increase of intestinal peristalsis and the frequency of defecation in newborns increase bilirubin excretion through feces hence circulating bilirubin is less absorbed by liver and intestines. And the early excretion of fetal stool is more conducive to the increase of the number of suckings in infants, so as to get an adequate nutritional supply. In addition, some studies [7]has confirmed that early comprehensive care interventions such as early sucking and early contact, neonatal touching, swimming, guardian health education and other measures can reduce the occurrence of neonatal physiological jaundice and reduce the degree of neonatal jaundice. Therefore, it is necessary to strengthen nursing during neonatal life.

2. Treatment of Pathological Jaundice:

2.1. Phototherapy:

Phototherapy is the most common clinical method to reduce serum unbound bilirubin. In the skin and subcutaneous circulation, the unbound bilirubin IXaZ type changes to a non-toxic water-soluble isomer IXaE type through light oxidation and isomerization, which easily excreted through bile and urine hence unbound bilirubin reduces from serum bilirubin concentration in the body. Clinically, the light source is mainly blue light (wavelength 425-475 nm) and green light (wavelength 510~530 nm), or white light (wavelength 550~600 nm). And there are two methods: continuous irradiation and intermittent irradiation. A randomized controlled

study by Monica[8]et al showed that for children with moderate jaundice, intermittent phototherapy groups (12 hours of exposure and 12 hours of holding) decreased bilirubin faster, shorter phototherapy duration and lower cost. However, for children with severe jaundice, continuous light should be selected. However, recent studies [9]have found that phototherapy can increase the fatality rate of very low birth weight infants through oxidative stress, DNA damage and other mechanisms, and is associated with childhood tumors, melanin moles, allergic diseases, epilepsy and other diseases. In order to reduce the harm of phototherapy to newborns, studies[10] have proved that the safest and most effective spectrum may be in the blue-green region (475-490 nm). At the same irradiation level, 490nm blue-green fluorescent lamps can reduce bilirubin levels in premature infants more effectively than 452 nm blue fluorescent lamps.[11]In addition, bilirubin has a competitive advantage in light absorption in the blue-green spectrum region than in blue light. Blue-green light has longer wavelengths and lower photochemical energy, which can reduce oxidative stress response[12]. Compared with traditional phototherapy equipment, LED lamps have lower thermal output and lower oxidative stress response[13]. In addition, studies [14]show that phototherapy combined with abdominal massage can significantly improve serum PON1 levels and reduce oxidative stress levels. Attention should be paid to the homeostasis of the neonatal environment during phototherapy. Electrolyte disorders and dehydration are common adverse reactions in phototherapy. Therefore, breast milk or formula feeding and rehydration should continue in the phototherapy process[15]. Timely rehydration during phototherapy can also reduce the blood exchange rate and phototherapy time[16].

2.2 Blood Exchange Therapy:

Blood exchange therapy is often used to treat children with severe hemolysis, and is also the most effective method to treat severe neonatal hyperbilirubinemia that may impend to bilirubin induced encephalopathy. Bilirubin induced encephalopathy is the most serious complication of neonatal jaundice. When the concentration of unbound bilirubin in the blood reaches a certain level, it can pass through the blood brain barrier which causes the oxidation of brain cells and lead brain damage. Moreover, the blood-brain barrier of children in neonatal period is not well developed. At this time, free bilirubin is more likely to cause damage to the central nervous system through the blood-brain barrier, and in serious cases, it can lead to the death of children. Blood exchange therapy mainly removes free bilirubin, free antibodies and allergic red blood cells in the blood circulation, which can effectively reduce bilirubin levels[17]. Clinically, peripheral arterio-venous double-tube synchronous and fully automatic blood exchange therapy is commonly used. Compared with traditional blood exchange therapy, simultaneous blood exchange of peripheral arteriovenous reduces the probability of infection and reduces the trauma[18]. After blood exchange, the blood routine and blood biochemical indicators of newborns have been significantly improved, correcting children's anemia to a certain extent, which has a good effect[19]. However, as invasive therapy, there are certain risks. The adverse reactions related to it include thrombocytopenia, hyperkalemia, etc.[20]. However, most of them are only abnormal laboratory indicators without obvious clinical symptoms. There is limited research on whether there are long-term adverse reactions in hemotherapy, and further research is needed.

2.3 Drug Treatment:

2.3.1 Intravenous Injection of Gamma Globulin:

Intravenous injection of gamma globulin is mainly used for the treatment of severe hyperbilirubinemia caused by neonatal hemolytic diseases. It can reduce the destruction of antigen coated red blood cells by combining Fc receptors on mononuclear macrophages, thus reducing bilirubin production. The results of the study[21]showed that intravenous injection of gamma globulin combined with phototherapy for hemolytic jaundice can effectively reduce the blood exchange rate, shorten the duration of phototherapy, and have good safety. However, Louis[22]et al. believe that intravenous injection of gamma globulin for Rh hemolysis and ABO hemolysis has a high bias risk. The results of the study on the high risk of bias shows that intravenous injection of gamma globulin can effectively reduce the blood exchange rate, while the systematic evaluation of the study of low bias risk shows that the blood exchange rate of gamma globulin received and the non-accepted gamma globulin in children with severe cases caused by Rh hemolysis is not unified. Significance of planning (P< 0. 0 5), this may be related to the pathogenesis of Rh hemolysis and ABO hemolysis. Moreover, intravenous injection of gamma globulin for severe neonatal hyperbilirubinemia can also lead to serious adverse reactions. Meta[23]analysis of intravenous gamma globulin can significantly increase the risk of necrotizing enterocolitis, but does not increase the final mortality rate of children. Therefore, the efficacy and safety of intravenous injection of gamma globulin in the treatment of severe jaundice in newborns still need further study.

2.3.2 Albumin

Albumin binds to free bilirubin present in plasma helps to reduce serum total bilirubin levels in severe hyperbilirubinemia. After binding the albumin to free bilirubin, its molecular weight becomes large enough to prevent penetrating to blood-brain barrier, effectively reducing the neurotoxic effect of bilirubin. Now some studies have proved that albumin combined with blue light phototherapy and can reduce bilirubin levels more effectively. First, liposoluble bilirubin is changed into water-soluble bilirubin through the oxidative isomerization of phototherapy. However, at this time, water-soluble bilirubin is quite unstable and can reversely change back to liposoluble bilirubin. At this time, albumin can be combined with water-soluble bilirubin. Combine to increase its stability and prevent its reverse transformation, thus promoting the excretion of bilirubin through bile or feces and urine[24].

2.3.3 Yinzhihuang:

The main ingredients of Chinese patent medicine Yinzhihuang are Yinchen, Gardenia, Scutellaria, etc., which have the functions of protecting the liver, promoting gallbladder, and de-yellow. In recent years, the efficacy and safety of Yinzhihuang in the treatment of neonatal hyperbilirubinemia has also been a research hotspot. Meta analysis[25]shows that Yinzhihuang oral liquid combined with other treatments can improve the cure rate of jaundice, significantly shorten the subsidence time of jaundice and is safer. Existing studies have shown that neonatal jaundice is associated with hypothyroidism. In hypothyroidism, body's basal metabolic rate is reduced, resulting in liver metabolic bilirubin dysfunction, resulting in increased bilirubin levels. A randomized controlled trial by Liu Lei[26]proved that Yinzhihuang combined with microecological biological

preparations can not only reduce the subsidence time of jaundice, but also regulate thyroid function and promote the growth and development of newborns.

2.3.4 Phenobarbital:

Phenobarbital is antiepileptic drug with hepatic enzyme inducer. It can improve the liver's ability to deal with bilirubin by inducing the activity of uridine diphosphoglucuronyl transferase (UDPGT) in hepatocytes, enhancing the ability to bind unbound bilirubin to glucuronic acid, accelerate the process of bilirubin metabolism, and thus reducing bilirubin levels. At the same time, it can also increase the clearance rate of the kidneys, increase urinary bilirubin excretion, and reduce the duration of jaundice. Due to the slow action time of phenobarbital, the effect should not begin until 3 days after taking the medicine, so it should be given as soon as possible[27]. Now research[28]has proved that phenobarbital combined with other treatments can effectively reduce bilirubin levels and reduce the occurrence of bilirubin encephalopathy, with remarkable results. In addition, it should be noted that phenobarbital is a central inhibitor, and a few children may have drug withdrawal effect.

2.3.5 Antomin/Clofibrate:

Antomin is a peroxidase receptor agonist, which is mainly used for lipid-lowering therapy. But at the same time, Antomin also has another function, which is to enhance the activity of liver UTT and accelerate the metabolism of bilirubin. Meta analysis[29]shows that the treatment of neonatal hyperbilirubinemia with Antomin can reduce the level and duration of serum bilirubin, and reduce the duration of phototherapy and the chance of exchange transfusion. However, the dosage of Antomin needs to be adjusted based on the gestational age. For children with gestational age of 31-33 weeks, the dose is > 100 mg/kg; for children with gestational age of 34-36 weeks, the dosage is 100mg/kg, and during treatment, the changes of children's condition need to be closely monitored.

2.3.6 Probiotics:

The main mechanism of probiotics in the treatment of neonatal jaundice is to promote the establishment of intestinal flora. Probiotics can not only change the pH value of the intestine but also it reduces the activity of β-glucuronidase in the intestine, and reduce the production of free bilirubin, but also promote intestinal peristalsis and accelerate the excretion of bilirubin. Among them, the most commonly used probiotic pharmaceutical in clinic is Bifidobacterium live bacteria tablets. Some studies believe that Bifidobacterium can promote the establishment of intestinal flora, reduce binding bilirubin in the intestine, and reduce bilirubin levels. Adding bifidobacterium to infant formula can effectively relieve neonatal jaundice symptoms and have a safe and effective effect[30].

2.3.7 Metal Porphyrin:

Metalloporphyrin can inhibit the production of bilirubin. It can inhibit the activity of heme oxygenase and prevent heme from changing to bilirubin, thus reducing the production of bilirubin[31]. At present, zinc

porphyrin and tin porphyrin are mainly used in clinical practice, but there are few clinical applications and it is unclear whether there are long-term adverse reactions to metal porphyrins, which need further research.

2.3.8 Vitamin D:

Neonatal hyperbilirubinemia can lead to multiple organ damage when it is serious. Vitamin D can not only regulate calcium and phosphorus balance, but also regulate the immune system and promote the repair of damaged tissue[32]. Some studies have proved that vitamin D deficiency can lead to an increase in serum bilirubin levels in the body, but the specific mechanism is unknown. However, vitamin D's antioxidant, anti-infection and effect that can reduce liver cell damage can indirectly affect serum bilirubin levels[33]. Meta analysis[34]proves that vitamin D is closely related to the development of hyperbilirubinemia. Vitamin D levels in children with hyperbilirubinemia are reduced, and vitamin D supplementation is conducive to the recovery of children. However, the specific mechanism has not been known and further research is needed.

2.3.9 Therapeutic Bile Acid:

Neonatal jaundice or hyperbilirubinemia is related to nuclear jaundice, which can lead to permanent nerve damage or death, while traditional phototherapy cannot effectively prevent neonatal hyperbilirubinemia. A recent study[5]found that therapeutic bile acids such as Ursodeoxycholic acid (UDCA) and Obelcholic acid (OCA) have the potential to prevent hyperbilirubinemia in newborns and can effectively reduce plasma and brain bilirubin. The main mechanism is to induce the expression of UDP - glucuronosyltransferase 1A1 (hUGT1A1) in the intestine and activate the Fanitol X receptor (FXR). In addition, it is also found that some of UDCA's effects on reducing bilirubin can't rely on the expression of hUGT1A1. It may be that UDCA reduces the reabsorption of intestinal bilirubin or stimulates intestinal bilirubin. After direct excretion or treatment, UDCA becomes the main component of the bile acid (BA) pool, thus affecting the composition of the liver and intestinal BA. Changes in the composition of intestinal BA can cause changes in liver and intestinal bilirubin metabolism, and the specific mechanism needs to be further studied. At present, therapeutic bile acid can prevent neonatal hyperbilirubinemia is only theoretically studied, and has not been clinically verified.

2.4 Touch and Swimming Therapy:

Touch and swimming therapy can promote the neurological and muscle development of children, increase intestinal peristalsis, reduce liver and intestinal circulation, and accelerate bilirubin metabolism. Studies[35]show that touching combined with early swimming can reduce serum bilirubin levels and is safer. In recent years, touching and swimming have become nursing and home-assisted treatment methods for children with hyperbilirubinemia, but they cannot be used alone.

CONCLUSION

Neonatal jaundice is the most common disease in neonatal period, and the incidence rate is increasing, which can cause infant death in severe cases. Therefore, the treatment of neonatal jaundice has always been a

research hotspot. The treatment of neonatal jaundice is a comprehensive treatment. On the basis of etiological treatment, combined with other conventional treatments, nursing is strengthened to ensure that the nutritional supply of newborns can avoid serious development of the disease to the period of bilirubin encephalopathy. Routine treatment of neonatal jaundice includes phototherapy and drug treatment, but these treatments have their own advantages and disadvantages, and suitable solutions should be selected according to the actual situation of the child. Among them, phototherapy is a common treatment for neonatal jaundice. However, in recent years, it has been found that the incidence of long-term adverse reactions in children caused by phototherapy is increasing. In order to achieve the most effective, minimal adverse reactions and minimal cost, further research is still needed.

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