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Prolonged Jaundice in Newborn

Erhan Aygün and Seda Yılmaz Semerci

Abstract

Prolonged jaundice is defined as a serum bilirubin level higher than 85 $\mu\text{mol/L}$ (5 mg/dl), which persists at postnatal 14 days in term infants and 21 days following the birth in preterm infants. It affects 2–15% of all newborns and 40% of breastfed infants. Although underlying cause can not be found in the majority of prolonged jaundice cases, this may also be the first sign of a serious causative pathology. Tests performed to determine the underlying cause and failure to determine the etiology cause anxiety for both families and physicians. The most important point is to determine whether prolonged jaundice is of a benign cause or is due to a substantial disease. For this reason, health care providers should not take unnecessary tests in normal infants, but should also recognize infants with a causative pathology. Neonatal jaundice still maintains its importance in neonatal clinical practice, since early diagnosis and treatment is feasible.

Keywords: Hyperbilirubinemia, prolonged jaundice, newborn

1. Introduction

Prolonged jaundice is defined as a serum bilirubin level higher than 85 $\mu\text{mol/L}$ (5 mg/dl), which persists at postnatal 14 days in term infants and 21 days following the birth in preterm infants. It affects 2–15% of all newborns and 40% of breastfed infants [1].

Although underlying cause can not be found in the majority of prolonged jaundice cases, this may also be the first sign of a serious causative pathology [2]. The most important point is to determine whether prolonged jaundice is of a benign cause or is due to a substantial disease. For this reason, health care providers should not take unnecessary tests in normal infants, but should also recognize infants with a causative pathology. The timing of initial investigations should be between two and four weeks in order to reduce the associated mortality and morbidity. Neonatal jaundice still maintains its importance in neonatal clinical practice, since early diagnosis and treatment is feasible [3–6].

Although jaundice in early infancy is predominantly caused by indirect hyperbilirubinemia, it can also be seen as direct hyperbilirubinemia. Distinguishing between these types of jaundice is crucial in determining the etiology of prolonged jaundice.

To date, the most common cause of prolonged jaundice of indirect hyperbilirubinemia has been identified as breastmilk jaundice. It is known that breastmilk jaundice is seen at a rate of 1.3% in newborn infants and 2.4–25% in infants fed with breastmilk [7–9]. Besides, breastmilk jaundice may extend up to the twelfth week of life [10]. However, the diagnosis of breast milk jaundice is made by excluding other causes. Other possible causes of indirect hyperbilirubinemia include dehydration,

hemolysis, infection, congenital hypothyroidism, inborn diseases of metabolism, and pyloric stenosis [2, 11]. Delayed diagnosis of these causes may increase morbidity.

Despite the jaundiced appearance, newborns with breast milk jaundice appear healthy, grow up in a normal way, and have no signs of an underlying disease. However, the presence of abnormalities in laboratory tests consistent with hepatobiliary dysfunction, such as elevation of aminotransferases and/or γ -glutamyl transpeptidase (GGT), warrants investigating pathological causes [12].

Direct hyperbilirubinemia is defined as serum direct bilirubin $>20 \mu\text{mol/L}$ ($>1.2 \text{ mg/dl}$) or direct bilirubin $>20\%$ of total bilirubin. Although rare, it usually indicates an underlying pathological cause and requires immediate investigation and prompt intervention. Direct hyperbilirubinemia (cholestatic jaundice) is never physiological. It affects 1/2500 live births and should be suspected in all jaundiced infants with light coloured stools and/or dark urine [4]. Delayed presentation of cholestatic newborns is still an important issue. For the early diagnosis of cholestasis, it is recommended to measure the serum total bilirubin (STB) and direct bilirubin levels of each newborn with prolonged jaundice [13].

Intrahepatic or extrahepatic biliary obstructions, viral infections, inborn diseases of metabolism and endocrine disorders can lead to hyperbilirubinemia [13]. Extrahepatic biliary atresia is rare. It has been reported to occur at a rate of 1 per 21,000 live births in the UK and 9 per 14,000 live births in New Zealand [14]. Biliary atresia is the most common cause of neonatal cholestasis, and affected infants may appear healthy for a considerable time [15]. Kasai hepatoportenterostomy should be performed in the first 45 days of life to restore bile flow and reduce further damage to the liver [16]. Early diagnosis of biliary atresia is the most important predictive factor in operated newborns [17].

Various conditions such as intrauterine infections, bacterial sepsis, galactosemia, aminoacidemias, and congenital hypopituitarism can occur with a mixture of increased direct and indirect bilirubin [18].

When severe jaundice goes untreated for too long, it can cause a condition called kernicterus. Kernicterus, or bilirubin encephalopathy, is bilirubin-induced neurologic damage, typically in infants. It can cause athetoid cerebral palsy and hearing loss. Kernicterus also causes problems with vision and teeth and sometimes can cause intellectual disabilities. Early detection and management of jaundice can prevent kernicterus.

2. Diagnosis

A global protocol for investigating prolonged jaundice is not defined yet. The incidence of conditions that play a role in prolonged jaundice in terms of etiology varies between countries. This difference is the main reason for the various protocols. The cost of the examinations in cases with prolonged jaundice and the differences in healthcare systems between countries also contribute to this situation. The fact that prolonged jaundice can persist up to 3 months in most of the breastfed newborns and that prolonged jaundice in some newborns can be caused by serious underlying pathologies, even which may lead to liver transplantation, makes the current situation more difficult [19, 20].

The cause of prolonged jaundice seen in 15–40% of newborns is breastfeeding [21]. Breast milk jaundice is highly prevalent among the etiologies of prolonged jaundice. However, the diagnosis of breast milk jaundice is a diagnosis of exclusion. In neonatal prolonged jaundice, at the first step, direct hyperbilirubinemia and indirect hyperbilirubinemia should be differentiated, promptly. This requires

getting a detailed history of the patient and a meticulous physical examination. Especially in the history, stool color and urine color should be questioned. Whether the urine and stool color is normal, the following initial tests should be performed.

2.1 Initial tests in patients with prolonged jaundice

1. Direct and indirect bilirubin level and liver function tests, in case of direct bilirubin level is increased	4. Glucose 6 phosphate dehydrogenase (G6PD) enzyme level
2. Complete blood count, peripheral blood smear	5. TSH, fT4
3. Maternal blood group, infant blood group, Direct Coombs test	6. Urinalysis, urine culture

If there is no direct bilirubin elevation in the initial tests, these tests are sufficient for the follow-up and treatment of neonatal prolonged jaundice [22]. However, if increased direct bilirubin level is observed, the infant should be examined for cholestasis and specific tests to some cholestatic liver diseases should be done [23].

These examinations are;

Tests for cholestatic liver disease	
1. ALT, AST, ALP, GGT, PT, APTT	6. Serology for TORCH-S infections
2. Abdominal and hepatobiliary ultrasonography	7. Reducing substance in the urine
3. Urine organic acids and blood amino acids	8. Alpha feto protein
4. Serum bile acids	9. Sweat test
5. Alpha-1 antitrypsin level	

3. Etiology

Albeit most of the causes of prolonged jaundice other than breast milk are rare, congenital hypothyroidism and direct hyperbilirubinemia, which require urgent diagnosis (recognition) and treatment, should also be excluded [6]. Determining whether jaundice is hemolytic is important in order to identify the initial approach [2]. The causes of indirect hyperbilirubinemia and direct hyperbilirubinemia regarding etiological investigation in neonatal prolonged jaundice are classified as follows:

Causes of direct hyperbilirubinemia in neonatal prolonged jaundice [24]:

• Biliary atresia
• Sepsis,
• TORCH-S infections
• Neonatal hepatitis syndromes,
• Choledochal cyst,
• Galactosemia
• Alpha-1 antitrypsin deficiency
• Hereditary bile acid synthesis disorders.

Causes of indirect hyperbilirubinemia in neonatal prolonged jaundice [24]:

• Breast milk jaundice
• Sepsis
• Hemolytic diseases
• Congenital hypothyroidism
• Urinary tract infection
• Extravascular blood collection
• Pyloric stenosis
• Gilbert syndrome
• Crigler najjar syndrome

3.1 Hemolytic diseases

The reason for isoimmunization in the mother and the formation of IgG antibodies is the passage of fetal erythrocytes into the maternal circulation. The basis of hemolytic disease in the newborn is the breakdown of fetal erythrocytes by antibodies passing through the placenta [25, 26].

Hemolytic diseases are classified in two groups as immune and nonimmune. Rh, ABO and minor blood group incompatibilities are in the immune group. In the nonimmune hemolytic group, erythrocyte enzyme defects, erythrocyte structural defects, infection, polycythemia and sequestration exist. Rh and ABO incompatibilities are the most common causes of immune hemolytic diseases [27, 28].

3.1.1 Rhesus incompatibility

Rh incompatibility occurs in 30–35% of cases of prolonged jaundice which goes with hemolysis [29, 30]. Rh is a large protein with many antigenic sites. Common antigens are D, C, c, and E antigens. All antigens cause their specific antibody responses. In fact, 90% of this response is against the D antigen [31]. Therefore, a response to the D antigen is required for the diagnosis of Rh positivity [32]. Since the Rh antigen is only present on the erythrocyte membrane, severe hemolysis can be met in the event of Rh compatibility [33]. Rh system genes are located in the short arm of chromosome 1. The presence of the Rh gene can be learned in the first trimester by polymerase chain reaction (PCR) method via amniocentesis. Alloimmunization occurs when as little as 0.1 ml of blood from the Rh (D) positive fetus passes through the placenta into the circulation of the Rh negative mother [28, 30, 34]. The level of antibodies developed in the mother determines the degree of hemolytic disease. Hemolysis is caused by IgG type antibodies. The level of these antibodies indicates that the mother is sensitized.

In order to prevent the risk of Rh hemolytic disease and maternal sensitization, Rh (–) women whose spouses are Rh (+) should be routinely administered 300 µg anti-D immunoglobulin (Rhogam), whether the indirect Coombs test result is (–) at 28 weeks of pregnancy. This dose provides a prophylaxis for Rhesus disease in the vast majority of deliveries. The risk increases gradually in pregnancies after maternal sensitization [35]. The increase in serum bilirubin level during follow-up determines the severity of the hemolytic event [36].

Prolonged jaundice can be seen in Rh incompatibility. Rh incompatibility should not be forgotten in patients with prolonged jaundice which goes with hemolysis.

3.1.2 ABO incompatibility

The most common blood group incompatibility is the ABO group incompatibility. It does not cause serious problems generally, although it is the most common reason. Unlike Rh incompatibility, the mother does not need to be sensitized beforehand in this entity [37]. Hemolytic disease due to ABO incompatibility is seen in cases where the mother's blood type is O and the infant has A or B blood type. Although ABO incompatibility is seen in 20–25% of pregnancies, fetal sensitization findings (direct Coombs positivity) vary between 3 and 4% [38, 39].

Unlike Rh incompatibility, most of the maternal antibodies for ABO incompatibility are in the IgM form. Therefore, those antibodies do not have the ability of crossing the placenta. In addition, A and B antigens are not only found on erythrocytes, they are also found on different tissue cells. Consequently, not all antibodies passed to the fetus are retained by erythrocytes, but by other tissue cell antigens as well. These situations described, are the main reasons why ABO incompatibility does not cause serious problems compared to Rh incompatibility [40].

The clinical course resulting from hemolysis due to ABO incompatibility is generally mild in many cases and jaundice is observed as the only clinical finding. Jaundice usually develops on the first day and is often kept under control with phototherapy [38]. However, severe hemolysis due to ABO incompatibility is considerably rare [41].

Since it is the most common condition in patients with prolonged jaundice with hemolysis, it should definitely be investigated.

3.1.3 Subgroup incompatibility

Minor blood group incompatibility accounts for as low as 3% of neonatal hemolytic disease cases. Duffy, Kidd and MNS antigens are responsible for this hemolysis. The pathophysiology of hemolysis is similar to Rh and ABO incompatibilities. Minor blood group incompatibilities can usually cause subclinical hemolysis as well as possible severe hemolysis and worsen pictures [30, 34].

Since it usually goes with subclinical hemolysis, it may cause milder manifestations such as prolonged jaundice [42].

3.1.4 Erythrocyte enzyme deficiencies

The most common enzyme defects are; Glucose 6 phosphate dehydrogenase deficiency is a deficiency of 5' nucleotidase and pyruvate kinase.

3.1.5 Glucose 6 phosphate dehydrogenase deficiency (G6PD)

The most common enzyme deficiency is glucose 6 phosphate dehydrogenase deficiency. The G6PD enzyme acts as a catalyst and helps to reduce oxidative products in erythrocytes.

Due to the X-linked recessive inheritance, it is more common in male. Numerous mutations of the G6PD gene have been detected on the X chromosome. Because of having so many variants of the enzyme, hemolysis caused by G6PD can be present in different scenarios [43, 44]. In infants with G6PD in the neonatal period, hemolysis develops in case of exposure to oxidant stress or infection, and jaundice occurs as a result. Jaundice usually develops within 24–72 hours of life. In newborns with G6PD enzyme deficiency, bilirubin conjugation is much lower than in infants with normal G6PD enzyme. In fact, there are newborns with kernicterus caused by G6PD deficiency in the literature [45, 46]. The rate of G6PD deficiency in the

etiology of prolonged jaundice varies according to populations. Various studies reported the rate of G6PD deficiency between 3.8% and 24% [47, 48].

Since prolonged jaundice may be the first sign of G6PD deficiency, the enzyme level should be checked in newborns diagnosed with prolonged jaundice.

3.1.6 Pyruvate kinase enzyme deficiency

It is inherited autosomal recessively. It is less common than G6PD deficiency. Unlike G6PD deficiency, signs of hyperbilirubinemia, anemia and reticulocytosis are present from the very beginning. Pyruvate kinase enzyme deficiency should be considered in infants with negative Coombs test and hemolytic anemia, in case of prolonged jaundice without erythrocyte membrane defect [49].

3.1.7 Erythrocyte membrane defects

Hereditary spherocytosis, elliptocytosis, stomatocytosis and infantile pycnocy-tosis, which are erythrocyte membrane defects, can elicit hemolysis in the neonatal period. Hereditary spherocytosis is common in this group, while hereditary elliptocy-tosis and stomatocytosis are the other rare causes of hemolysis in newborn infants.

3.1.7.1 Hereditary spherocytosis

It has an autosomal dominant inheritance. Transforming spherocytic erythro-cytes, which are more fragile than normal ones, under osmotic stress, is the char-acteristic of hereditary spherocytosis. The diagnosis of hereditary spherocytosis is made by detecting spherocytes in the peripheral smear and by osmotic fragility test. ABO incompatibility can be confused with hemolytic disease. Because microspher-ocytes can also be seen in the peripheral blood smear in ABO hemolytic disease. The distinction between these two diseases is made with the direct Coombs test [49].

Kocabay et al. found the rate of hereditary spherocytosis to be 0.1% in neonatal jaundice cases. Hyperbilirubinemia occurs in approximately half of newborn infants with hereditary spherocytosis, but this jaundice is usually considered as physiological, and may be overlooked. It can also be a reason for prolonged jaundice in a minority of the newborn infants [50].

3.2 Bilirubin uptake and conjugation disorders of the liver

3.2.1 Gilbert's syndrome

In Gilbert's syndrome, both hepatocytes' bilirubin uptake is decreased and UDPGT activity is decreased. It is inherited in autosomal dominant or autosomal recessive. It has a prevalence of 2–6%. Although it can cause neonatal hyperbili-rubinemia, the diagnosis is usually made at a later stage [25, 50]. It is thought that hyperbilirubinemia, which is observed in newborns with weight loss after insuf-ficient caloric intake, also has a similar etiologic mechanism to Gilbert's syndrome. Phenobarbital can be used as treatment in selected cases of Gilbert's syndrome [51].

Studies have shown that Gilbert syndrome either elicit neonatal prolonged jaundice.

3.2.2 Crigler Najjar syndrome type 1

Crigler-Najjar Syndrome type 1 is caused by the complete absence of the hepatic glucuronyl transferase enzyme and is inherited autosomal recessively. It is a chronic non-hemolytic indirect hyperbilirubinemia syndrome and has a severe clinical

course. In the homozygous form, severe indirect hyperbilirubinemia, which may progress to kernicterus, develops within the first three days of life, and bilirubin levels increase gradually, whether treatment is delayed. Diagnosis is made by percutaneous liver biopsy. UGT activity is measured in the biopsy sample/specimen. Phenobarbital is not an effective treatment of choice in Crigler-Najjar Syndrome type 1 syndrome [43, 52].

3.2.3 Crigler Najjar Syndrome type 2

Crigler Najjar Syndrome Type 2 is more common than Type 1. Besides, the clinical course is better. The reason for this is that the activity of the UDPGT enzyme is partially present in Type 2. It has an autosomal dominant inheritance. Although indirect bilirubin levels start to increase in the first days of life, they usually do not go above 20 mg/dl levels. Unlike type 1, Crigler-Najjar Syndrome responds to phenobarbital. Therefore, response to phenobarbital can be used as a distinguishing strategy for type 1 and type 2 disease [25, 53]. Crigler-Najjar syndrome is also an important reason for prolonged jaundice.

In Crigler-Najjar syndrome type II, UDPGT activity is reduced in the same way as is found in infants with prolonged jaundice due to Gilbert's syndrome [54]. Therefore, it is an etiology that should be kept in mind in newborns with prolonged jaundice.

3.2.4 Lucey Driscoll Syndrome

It is a rare disease of newborn, which goes with high bilirubin levels in the postnatal first two days of life. Bilirubin levels are above 20 mg/dl and may rise to levels that can require exchange transfusion. These high bilirubin levels can persist for longer than 14 days [40]. Most of these infants develop kernicterus, whether exchange transfusion is not performed.

3.3 Hypothyroidism

It is one of the substantial causes of neonatal prolonged jaundice. Prolonged jaundice is seen in approximately 10% of infants with congenital hypothyroidism. Decreased UGT activity is blamed for the pathophysiology of hyperbilirubinemia seen in congenital hypothyroidism. In this case, hyperbilirubinemia may persist for several months. Treatment with thyroid hormone leads rapid resolution of jaundice [55, 56].

3.4 Galactosemia

Galactosemia may present with hyperbilirubinemia in the neonatal period. In the clinical picture of the disease; there are findings such as vomiting, dehydration, hepatomegaly, splenomegaly. Diagnosis is made by detecting the reducing substance in urine, sugar chromatography and enzyme levels [30].

Galactosemia is one of the etiologies of prolonged conjugated hyperbilirubinemia as a hereditary and metabolic disease. In newborns with galactosemia, hyperbilirubinemia becomes evident in the first week of life and can proceed with prolonged jaundice in many patients [57].

3.5 Infections

In the neonatal period, infections can be accompanied by jaundice. Particularly, urinary tract infections, and sepsis are common causes of jaundice. Indirect hyperbilirubinemia can develop in sepsis due to hemolysis caused by endotoxins [44].

Direct and indirect hyperbilirubinemia is seen in congenital infections such as TORCH-S group infections [30].

The incidence of urinary tract infection in asymptomatic infants, under two months of age with jaundice, but without fever, has been shown to be 7.5%. Therefore, prolonged jaundice may be the unique finding in urinary tract infection [58]. In a study, the most common infection associated with jaundice in the neonatal period was found to be urinary tract infection [59].

3.6 Extravascular blood collection

Extravasation of blood in the body leads to increased bilirubin production by enhanced heme protein metabolism via destruction of erythrocytes. Accumulation of red blood cells in tissue layers surrounding the brain and skull (cephalo hematoma, subdural hematoma, subgaleal hematoma) or in any part of the body in traumatic deliveries can lead severe hyperbilirubinemia [60].

3.6.1 Cephal hematoma

Cephal hematoma defines a bleeding into the subperiosteal region and occurs in approximately 1–2% of all live births. Rupture of vessels results in a blood collection extending from the bone to the periosteum during labor [61]. Cephal hematoma can be causitive for jaundice due to the increase in bilirubin synthesis in the first 48–72 hours of life because of the destruction of erythrocytes in the extravasous blood collection [41].

4. Treatment of neonatal jaundice

The aim of the treatment is to reduce the increased bilirubin levels in order to prevent the damage to the central nervous system by the formation of kernicterus. Timely and prompt treatment is crucial to prevent the permanent effects of bilirubin toxicity such as kernicterus [62].

Whether the underlying cause of hyperbilirubinemia is known, treatment should be arranged according to that etiology. The most commonly used methods in the treatment of jaundice are: Phototherapy, intra venous immunoglobulin (IVIg) administration, exchange transfusion, and phenobarbital. Treatment indications vary according to the gestational week of the infant, postnatal age, bilirubin level, and the presence of hemolysis [63].

Treatment of Neonatal Jaundice	
1. Phototherapy	2. Phenobarbital
3. Intravenous Immunoglobulin	4. Metalloporphyrins
5. Exchange Transfusion	

It is appropriate to use the curves designed by American Academy of Pediatrics, which evaluate either the gestational week, and risk factors for infants whose gestational age is greater than 35 weeks. Instead, the tables include the cut-off bilirubin levels according to birth weight, for the infants whose gestational age is less than 35 weeks [64].

In case of a rapid rise in bilirubin levels within the first 24 hours, newborn infants should be evaluated for hemolysis. The ETCOc measurement directly indicates heme

catabolism and bilirubin production [65]. The hourly rate of increase in bilirubin levels is also an important indicator for hemolysis. An increase of 0.2–0.5 mg/dl per hour in the bilirubin level is thought as an indicator of hemolysis. With a positive direct Coombs test (+), higher reticulocyte count, a decrease in hemoglobin and hematocrit levels are laboratory findings supporting hemolysis [66].

4.1 Phototherapy

Phototherapy is used to reduce increased serum bilirubin level and reach a normal bilirubin level, to reduce the need for exchange transfusion and to prevent the development of kernicterus. Phototherapy lowers bilirubin levels by using certain wavelengths of light energy [67]. Blue light at a wavelength of 440–460 nm is the value at which bilirubin is best absorbed. In order for phototherapy to be effective, the energy must be a maximum of 5u/cm/nm. In order to obtain this energy, ideally, 440–460 nm, which is the best absorbed wavelength, and blue light should be used. The distance of the light should be adjusted to be 30–40 cm away from the infant. It should be given at the ideal wavelength and distance of 40 uw/cm/nm [68, 69]. In the same way, multidirectional administration of one-way phototherapy, from different angles enhances the success of the treatment [70].

In phototherapy, treatment decision was determined by bilirubin level, rate of increase in bilirubin level over time, birth weight, gestational age and postnatal age, and the presence of risk factors such as Rh, ABO and minor blood group incompatibility, G6PD enzyme deficiency, presence of asphyxia, hypothermia, acidosis, sepsis, and lower levels of albumin. Phototherapy is started when the serum bilirubin rises to a level that pose a risk for neurotoxicity. Phototherapy should be started in bilirubin values that exceed the determined limits. Risk factors that should be considered when determining the phototherapy limit are: Rh, ABO and minor blood group incompatibility, G6PD, albumin levels below 3 g/dl, presence of asphyxia, pronounced tendency to sleep, sepsis, hypothermia, presence of acidosis in blood gas analysis. In order for a newborn to be considered risk-free, all risk factors must be excluded, otherwise the newborn is considered as under risk. Decision of phototherapy, depends on the TSB.

Phototherapy is considered as safe. But it can have some undesirable effects. These side effects can be listed as follows: Retinal degeneration without an eye protective cover, fluid loss, bronze baby syndrome, rash, lactose intolerance, hypocalcemia, an increased risk of PDA particularly in preterm infants [40, 68]. There are studies showing that phototherapy increases the risk of conjunctivitis, and it predisposes to asthma and allergic rhinitis in long term [71].

4.2 Exchange transfusion

Exchange transfusion is a successful but risky treatment method used in severe neonatal hyperbilirubinemia [72]. When TSB exceeds the cut-off level that is determined for exchange transfusion, the procedure should be performed without a delay.

Whether the expected decrease is not reached in TSB level despite intensive phototherapy or in case of a gradual increase, or when the risk of kernicterus is greater than the risk of exchange transfusion, or whether kernicterus has developed and signs are present, transfusion should be performed quickly [73].

When albumin levels are low, more care should be taken in terms of exchange transfusion. Because the amount of free bilirubin that cannot be bound to albumin will increase and there will be a high amount of free bilirubin which can increase the risk of kernicterus. The bilirubin/albumin ratio does not make a decision for exchange transfusion, but is used to support the treatment decision in conjunction

with TSB levels in newborn infants. Albumin infusion is not recommended in patients with either hyperbilirubinemia and hypoalbuminemia [66].

A central catheter is placed before the patient for blood exchange. Then, blood collection from the newborn and replacement of the patient's own blood with whole blood or erythrocyte suspension mixed with plasma are performed through this catheter. Approximately twice of the blood volume of the infant, which corresponds to 160–170 ml/kg, is exchanged by this way. The volume of blood taken or given once during the exchange transfusion process should not exceed 5 ml/kg. Besides, the volume rate of blood given or taken in the exchange process should not be more than 2 mL/kg/min. The reason for this is that if this rate is exceeded, sudden changes in intracranial pressure can occur due to blood pressure fluctuation [74]. The exchange transfusion process ensures that the majority of the infant's sensitized erythrocytes are replaced by unsensitized erythrocytes. This change provides a significant decrease in serum bilirubin level.

Serum electrolytes, bilirubin and blood glucose level should be checked at regular intervals during exchange transfusion. Because hypocalcemia and hypoglycemia may occur depending on the content of the blood product used during the procedure.

Exchange transfusion is not an innocent procedure and complications may befall. During the procedure, the newborn can have apnea, blood pressure imbalances can be met, the heart rate can slow down, electrolyte disturbances may be observed, disturbances in blood glucose level can be observed, thrombocytopenia, coagulation disorders, disseminated intravascular coagulation, metabolic acidosis, thromboembolism, malnutrition, necrotizing enterocolitis, sepsis can also be observed. While the risk of death is 1% in healthy infants, it is 12% in infants with risk factors [75].

The use of exchange transfusion has greatly decreased due to the frequent and ideal use of phototherapy. This has also reduced the incidence of possible mortality and morbidity risk arising from the exchange transfusion procedure.

4.3 Pharmacological treatment

Agents used to treat neonatal jaundice can be classified according to their action of mechanism as follows; Inhibition of bilirubin (Tin protoporphyrin and mesoporphyrin, Zinc protoporphyrin and mesoporphyrin), accelerating bilirubin excretion process (Phenobarbital, Ethanol, Chloroquine, Antihistamines, Clofibrate, Antipyrine), inhibiting the enterohepatic circulation (Agar, Activated charcoal, Cholestyrylpyrron, bilirubin oxidase) and IVIG [75]. IVIG, phenobarbital, and metalloporphyrins are the most preferred ones in the treatment of hyperbilirubinemia.

4.3.1 Phenobarbital

Phenobarbital is a potent inducer of microsomal enzymes. It makes this strong induction by inducing the enzyme glucuronyl transferase. By this mechanism, it increases bilirubin conjugation, excretion and bile flow, which means that it affects all steps of bilirubin metabolism. In addition, phenobarbital is used in the diagnosis and treatment of Crigler Najjar disease [76]. It is recommended for use only in high-risk conditions.

4.3.2 Intravenous immunoglobulin

Intravenous immunoglobulin therapy can be used in Coombs test positive Rh or ABO incompatibility, minor blood group incompatibility, and newborn infants

who received intrauterine transfusion/s. IVIG should be given timely at a dose of 0.5–1 g/kg and within 2 hours, without delay, in newborn infants with hyperbilirubinemia that do not decrease despite intense phototherapy, and whose bilirubin level is close to the limits of exchange transfusion [77].

High-dose IVIG therapy in newborn infants, such as a dose of 0.5 g/kg, reduces the need for exchange transfusion. It does this by slowing the rate of bilirubin rise and lowering maximum bilirubin levels. IVIG is thought to prevent hemolysis by its mechanism of blocking reticuloendothelial Fc receptors [78, 79].

As a special case, the management of hemolytic disease due to Rh incompatibility is as follows; Preparation should be made before birth. First of all, preparation of the blood product to be given should be done. Since exchange transfusion can be required as soon as in the delivery room, equipment should be ready for use and IVIG should be kept, if needed. A staff experienced in neonatal resuscitation should be present. As soon as the infant is born; intensive phototherapy treatment is started and IVIG is given to the patient as a pharmacological treatment promptly. Hemoglobin (Hb) and STB levels are checked from the blood sample taken from the umbilical cord. Intensive phototherapy should be started in newborn infants born above 38 weeks, if the bilirubin level is above 6 mg/dL and/or the Hb value is less than 10 g/dL in the blood sample taken from the umbilical cord, as well as the preparation begins for exchange transfusion. In case of the STB increase is more than 0.5 mg/dL per hour despite intensive phototherapy and IVIG therapy, rapid exchange transfusion should be performed [80].

4.3.3 Metalloporphyrins

Metalloporphyrins, which competitively inhibit heme oxygenase enzyme, slow down bilirubin synthesis. The most effective metalloporphyrin is Tin (Sn) because it lowers bilirubin [81, 82]. A single dose of 6 $\mu\text{mol/kg}$ is used in the treatment of neonatal jaundice. It has been observed that Sn-mesoporphyrin applied together with phototherapy can elicit transient erythema in some of the newborn infants. Currently, metalloporphyrins are not a part of routine practice of treatment for neonatal jaundice [76].

5. Conclusion

Prolonged jaundice can become an intensive care problem, if not noticed early. Extreme hyperbilirubinemia (TB of 25 to 30 mg/dL) can cause bilirubin encephalopathy, Kernicterus, which is usually characterized by the deposition of unconjugated bilirubin in brain cells. Neuronal necrosis/damage occurs in the basal ganglia, hippocampus, hypothalamic nuclei as a bilirubin-phosphatidylcholine precipitate, diencephalon, midbrain, neurohumoral and electrolyte control, brainstem nuclei for oculomotor and auditory function, and in the cerebellum. Clinical manifestations include cerebral palsy, deafness, seizures, etc.

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