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Review Article

YELLOWNESS IS A THREAT TO NEWBORN - A REVIEW

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ABSTRACT

Jaundice is a very well-known disease found worldwide. Jaundice comes from the French word "Jaune" - which means yellow. In medical term, jaundice is known as icterus which is a Greek word. This is a very common disease in the population, which causes the yellowish or greenish pigmentation in the skin and whiteness in the eyes. This is a condition of hyperbilirubinemia in which the amount of bilirubin increases in the blood. In this case, the high amount of bilirubin is found in blood, and the disruption of the movement of bilirubin into the liver and out of the body causes jaundice. Different symptoms seen in this case are yellow skin, yellow/white eyes, dark or reddish urine, loss of appetite, bitter taste of tongue, pale faces, nausea, itching in skin, anfd slow pulse rate. Jaundice may be mild to severe. Different types of jaundice are seen like normal jaundice in newborn, hepatic jaundice, and post-hepatic Jaundice.

Keywords: Neonatal jaundice, Hyperbilirubinemia, Kernicterus, Glucuronosyltransferase, Biliverdin, Cephalohematoma, Phototherapy.

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INTRODUCTION

Hemoglobin is a very important protein in our body which is otherwise known as respiratory element. Its main function is to carry oxygen in our body. There are two types of hemoglobin, i.e., fetal hemoglobin and adult hemoglobin, which are quite different from each other with respect to the availability of oxygen [1]. However, in both cases, bilirubin is the by-product produce after the death of red blood cell (RBC), and the heme group is released from the RBC and associates with the formation of new red cells [2]. These bilirubin pigments are released from our body through stool with the help of the liver. However, in case of newborn, the bilirubin usually causes the yellowness in them [3]. Although it is not seen in all babies, maximum infants have this disease called as neonatal jaundice. Lifespan of fetal hemoglobin is 80–90 days, so just after the birth of neonate, the hemoglobin changes from fetal hemoglobin to adult hemoglobin and rapid degradation of fetal hemoglobin takes place, and hence, more amount of bilirubin is formed [4]. However, the immature liver of the newborn is not capable to detoxify that amount of bilirubin so the bilirubin level is increased in the body and deposited in different parts such as skin and mucous membrane, along with the eyes becoming white [5]. Neonatal jaundice is not fatal in most of the cases, but still proper treatment and care is needed. Sometimes, this form of jaundice will lead to neurological problems called as kernicterus which is mostly fatal [6]. Neonatal jaundice may cause several disorders such as neurological problems, liver diseases, infections, hemolysis, and metabolic disorders and also may cause blood group incompatibility between mother and fetus [7,8]. In some cases, gflucose-6-phosphate dehydrogenase an antioxidant causes neonatal jaundice [9]. Bilirubin (unconjugated) may be found to be bound to albumin as it circulates to the liverg and some bilirubin pigments are in free form which can enter into brain causing kernicterus and is more toxic [10]. The unconjugated bilirubin is toxic and can be detoxified by metabolism in the liver and produce conjugated bilirubin, which is then removed through the stool. Among full-term babies, 50–70% babies have this disease, and in premature babies, it is above 80% [11,12]. Another type of unconjugated hyperbilirubinemia is breast milk jaundice, which is not seen just after birth but is seen in the baby of 3–4 weeks old. Breastfeeding jaundice is another type and also different from the first one and is caused just after birth. The hyperbilirubinemia is unconjugated jaundice so harmless. However, if the amount of unconjugated bilirubin level increases very high, then it crosses the blood-brain barrier and causes bilirubin encephalopathy or kernicterus. Many medicinal plants can be used for neonatal jaundice in addition to physiotherapy and intravenous immunoglobulin (IVIG) [13,14]. The bilirubin is formed from the heme part of the erythrocyte which has central role in bilirubin production [15]. Heme is an integral part of various proteins such as hemoglobin, myoglobin, and some enzymes which contain an iron-porphyrin ring and it is seen that 80% of bilirubin is formed in the liver, spleen, and reticuloendothelial cells. The metabolism of bilirubin takes place in three phases, i.e., pre-hepatic phase, intrahepatic phase, and post-hepatic phase. Any disturbance in any of the phases can lead to neonatal jaundice [16,17]. Although neonatal jaundice is not fatal, most of the cases and treatment is also there still several neonants die because of lack of treatment in developing countries.

NORMAL JAUNDICE IN NEWBORN

This is a common disease found in most of the newborns within 24 h of birth. This usually occurs when the two conditions such as pre-hepatic and hepatic source of bilirubin result in the same time [18]. The higher bilirubin amount is normal due to stress birth in newborns causing the deposition of the yellow pigment in the skin. The normal bilirubin in newborns should be under 0.3–1.0 mg/dl within 24 h of birth, but the amount rises up to 5 mg/dl after a few hours of birth and remains as such for a few days [19]. Although, for several cases, this is mild and causes no harm, in some, this can cause a form of brain damage called kernicterus [20,21].

BILIRUBIN

In the newborn jaundice, it is seen in most of the cases and the bilirubin level is very high in the blood leading to yellowness in skin and eyes. Bilirubin is a yellow substance produced by everybody when the red blood cells (RBCs) die by the action of the liver. This bilirubin is deposited in bile and then removed from the body through stool and urine. Bilirubin formation starts in the form of hemoglobin in the bone marrow. Hemoglobin is of two types, i.e., fetal hemoglobin and adult hemoglobin [22]. During fetal stage, the hemoglobin is of fetal type

as they take oxygen from the mother's body at low level, but just after parturition, the fetal hemoglobin is converted into the adult hemoglobin as they breathe through their lungs. As the process goes on the fetal, hemoglobin gets degraded forming biliverdin followed by bilirubin. This process takes place rapidly releasing out the bilirubin through the liver. However, the newborn liver was not properly ready to release all the bilirubin formed by the degradation of the fetal hemoglobin. Hence, the level of the bilirubin increases in the blood of the newborn causing yellowness of skin, eye, and red urine formation (Fig. 1). The liver takes 1–2 weeks for the total removal of all the billirubin from the blood, so the jaundice remains for 1–2 weeks [23]. This results in the overproduction of bilirubin forming a shortening of the lifespan of RBC and increases the circulating red cell mass and the decreased excretion of bilirubin forming a low concentration of the hepatic binding protein, increased internal hepatic circulation, and low activity of glucuronosyltransferase. In normal case, serum bilirubin lasts for 10 days with a rapid rise of it up to 204 μmol/L. In premature infants, the amount rises up to 255 μmol/l [24].

Jaundice is found in most of the newborns, and this is most frequently seen in the premature babies. Usually, two types of jaundice are seen in the newborns, i.e., breastfed but both of them are harmless. Breastfeeding jaundice - the breastfed babies have this jaundice during the 1st week of birth. Breast milk jaundice is different from breastfed jaundice type [25]. In this case, the elements come from the mother's milk affecting the breakdown of the bilirubin in the liver (Figure. 2). This usually occurs after 7 days and peaks at 2–3 weeks of lactation and lowers after a month. Sometimes, more high level of bilirubin can cause severe effects such as abnormal shapes of RBC, Rh incompatibility between mother and baby, cephalohematoma caused by delivery difficulty, infections, and kernicterus (most dangerous). Kernicterus condition is not found frequently but is very severe of untreated neonatal jaundice [26].

This is usually caused when the excess level of bilirubin in blood damages the brain and other parts of CNS. In hyperbilirubinemia cases, the increased level of bilirubin can cross the blood-brain barrier, a thin layer of tissues separating the blood and brain. If the brain is damaged by the bilirubin, then encephalopathy occurs which is a threat to a life. Studies reveal that this condition is extremely rare. Jaundice in newborn may be mild or severe [27]. Mild neonate jaundice may disappear in 2–3 weeks on its own, but if that is severe, then the baby needs to be admitted to hospital with intense care. The primary treatment is phototherapy or light treatment to reduce the amount of bilirubin from the blood of the baby. The most widely used therapies in infants having neonatal jaundice are phototherapy, IVIG, and exchange transfusion. Although neonatal jaundice is frequent, still there are countries which lack phototherapy. On one side in countries like the USA, neonatal jaundice death rate is almost unknown, on the other side in the places like Myanmar and West Africa, lacking phototherapy with most of the death cases found [28,29]. About 60% of newborns are found to have neonatal jaundice worldwide, but still one in ten requires phototherapy treatment to prevent the severity like kernicterus. Each year 5.7 millions of newborn babies in South Asia and Africa are having this disease and deprived of this therapy [30], so newborns are still found dead due to this jaundice in these countries. Death of a newborn may also take place in the mother having jaundice during pregnancy due to any liver disorder.

TREATMENT

Various methods applied for the treatment of neonatal jaundice are described as follows.

Phototherapy

Drugs are usually not used for the neonatal jaundice treatment, so phototherapy is the primary treatment and is most commonly used. This therapy was first discovered in London and is now used worldwide. Phototherapy is very effective as bilirubin shows three reactions when exposed to light. Bilirubin is bleached through the action of light; photooxidation takes place in bilirubin, making the polymers water-soluble colorless by-product removed through urine. Intermolecular cyclization of bilirubin results in the formation of lumirubin, which have only 6% of total serum bilirubin concentration. This process is increased by increasing light therapy. Lumirubin can be excreted out through urine and bile. Configurationally, isomerization takes place when bilirubin is exposed to light by converting some of its predominant isomers [31]. Hence, the amount of the predominant isomers decreases greatly after treatment with light, and this is dependent on the intensity of light rather on the type of light. Bilirubin can absorb light at a wavelength of 450-460nm. Although longer wavelengths penetrate the skin better, still the capacity of the skin to intake the light inside the body is important [32]. Hence, light of higher wavelength such as white, blue, turquoise, and green is used frequently for this purpose. Nowadays, LED bulbs are also used for phototherapy. Phototherapy may have some adverse effects which are as follows:

- Intense water loss may occur.
- This may be associated with loose stools.
- Increases the amount of water in faces.
- Retina may be damaged.
- Sometimes, hyperbilirubinemia and phototherapy can lead to DNA strand breakages and other effects on genetic materials.
- Hypocalcemia is found very frequently in premature infants under the light.

IVIG

IVIG has been used more frequently nowadays for several immunological conditions. Blood group incompatibilities may cause significant neonatal Jaundice, where the use of IVIG can reduce the need of transfusion exchange. IVIG is thought to decrease the hemolysis by blocking Fc receptor cites of reticuloendothelial cells by preventing lysis of nenonatal erythrocytes, which produces more bilirubin [33]. A new therapy process is under development in which there is inhibition of bilirubin production by blocking the heme oxygenase [34]. Heme is directly formed from the hemoglobin through bile, so the inhibition of heme oxygenase does not result in unprocessed heme accumulation. This may virtually eliminate the neonatal jaundice as a whole. Issues regarding the safety of this treatment should be cleared first before using this therapy in a wide scale.

Exchange transfusion

When other treatments are failed or not sufficient to eradicate the neonatal jaundice, then exchange transfusion is needed to avoid the bilirubin neurotoxicity. This is done if the infants have severe anemia, hydrops, or both, even in the absence of high serum bilirubin levels. This is usually done with Rh (−ve) isoimmunization in infants [35]. The numbers of infants are very rare requiring exchange transfusion. The presence of moderate anemia with rapid increase in the serum bilirubin level needs the early exchange transfusion. This is mostly used for the hemolytic jaundice [36]. The hemolytic jaundice has a great risk for neurotoxicity than the non-hemolytic jaundice. However. still the real reason is not known as the bilirubin rate is same in both cases.

Other therapies

Breast milk Jaundice having infants shout have interruption of breast feeding for 24-48 hours and feeding with breast milk substitutes helps to reduce the bilirubin levels. Oral bilirubin oxidase can also be used to reduce serum bilirubin levels which reduce the enterohepatic circulation [37,38].

Surgical care

This is not needed in infants in neonatal jaundice. This is done in infants where jaundice is caused by the external bile duct atresia [39].

Drugs

The infant having physiological neonatal jaundice does not need any medication usually. However, a drug phenobarbital has been used

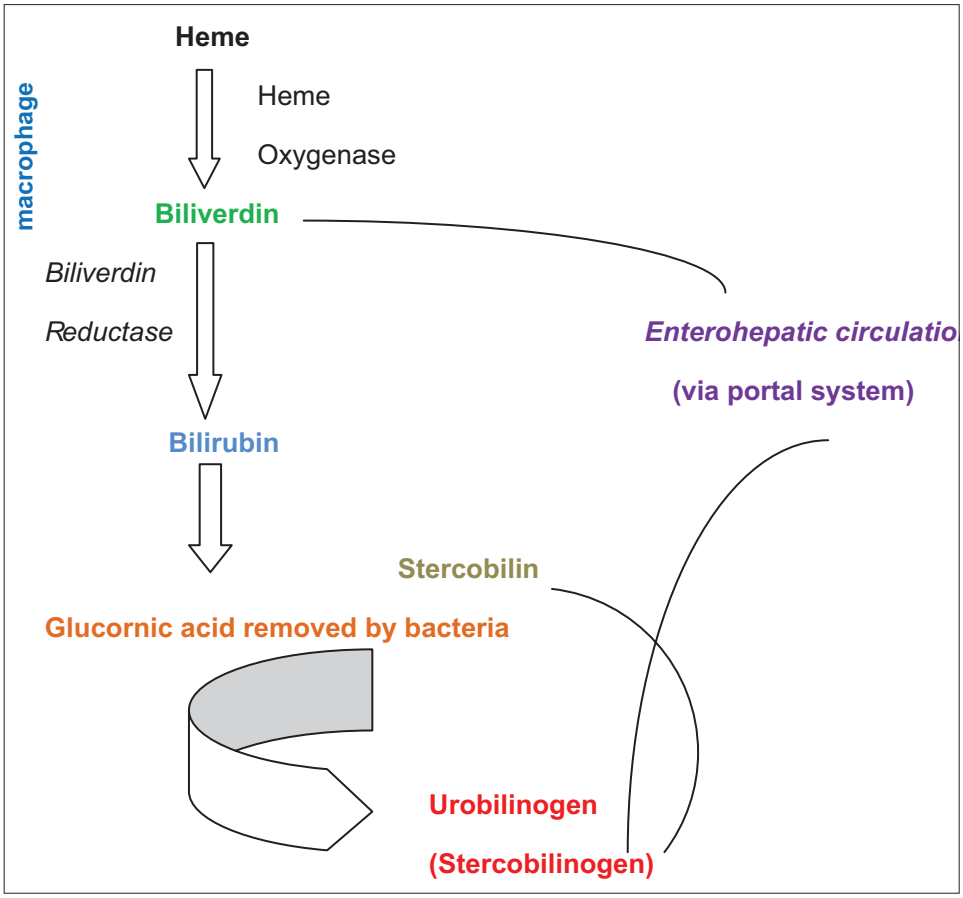

Fig. 1: The conversion of bilirubin

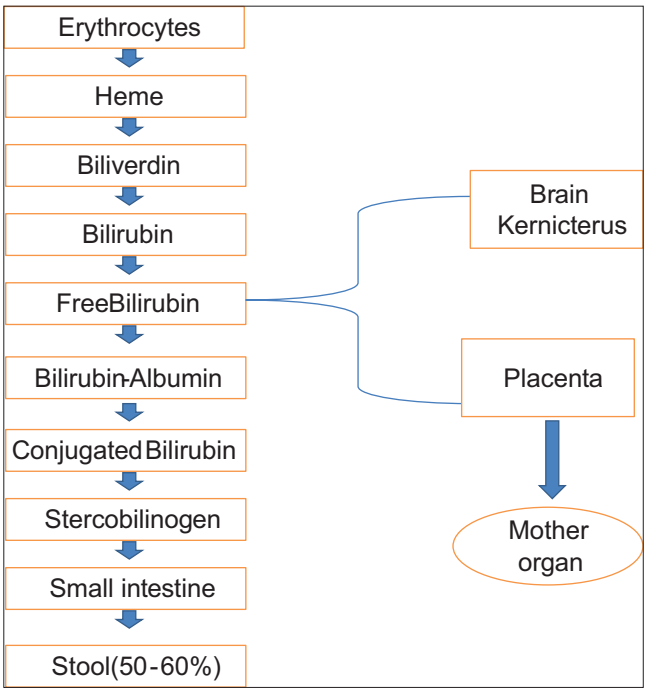

Fig. 2: The mechanism of bilirubin production

to enhance the bilirubin metabolism in the body of the newborn by inducing the hepatic bilirubin metabolism which reduces the bilirubin level in the blood as well as in the serum of the infant [40]. This medication is effective and is reducing the serum bilirubin values during the 1st week of life. This medicine can be used in two ways such as parentally in the mother and postnatal to the baby [41].

PREVENTION

In some full-term babies, the fully matured liver can filter and eliminate bilirubin, but the immature livers of newborn cannot do this work properly, thus developing jaundice. There is no proper way to prevent jaundice completely still understanding the risk factor can help to determine what can be done to prevent and care for the newborn [42,43]. A blood test of mother can be done [44]. As the fetus inside the womb is directly connected with the mother's blood, so any incompatibility of fetus and mother's blood can cause more bilirubin production. Rh incompatibility and ABO incompatibility are having the highest risk factor. Glucose-6-phosphate dehydrogenase can also produce more bilirubin by destroying several blood cells having a higher risk of Jaundice [45]. The premature birth of the babies should be reduced. The babies delivered before 38 weeks have more risk factor to jaundice because the premature infant's liver is less developed than the full-term babies, creating more difficulty to eliminate bilirubin from the infant's body [46]. Breastfed babies have been seen to develop jaundice more likely, but after a few days of birth. Breast milk does not come as soon as the delivery occurs. As fast a nutrient dense, pre-milk substance called colostrum is secreted [47,48]. Some babies do not fed frequently as their digestive system is not ready to digest which can cause the production of more bilirubin. Breastfeeding immediately after delivery reduces the risk factor, and if they already have jaundice, then it is healed [49]. By frequent breastfeeding, more amount of colostrum enters into the newborn body promoting the babies' digestive system which leads to remove more amount of bilirubin [50]. Ultraviolet light reacts with bilirubin converting it into a product which does not need to pass through the liver and

eliminate. Hence, the baby should be exposed to sunlight every day to reduce the risk of jaundice. However, prolonged exposure can burn baby's body, so the time of exposure should be less [51,52].

Risk factors

The risk factors for neonatal jaundice are as follows:

Premature birth

Birth before 38 weeks has immature liver and less stool due to less feeding causing jaundice [53].

Significant bruising

Bruising of newborns from the time of delivery may have increased amount of bilirubin due to the breakdown of more RBC.

Blood type

If the blood type of mother and fetus is not compatible, then there is a chance of production of antibody in the mother and passing into the fetus causing the destruction of RBCs [54,55].

Breast feeding

Difficult breastfeeding and less lactation increase the chance of jaundice.

CONCLUSION

Although neonatal jaundice has not any severe effect on newborns, still proper care is mandatory. Newborns are extremely sensitive to external environment as they are new to this condition. Inside the mother's womb, they are safe but as they come out several physiological and biochemical changes take place inside their body causing several disorders. Neonatal jaundice is one of them, which is seen frequently in neonates, but this can be minimized by considering the risk factors, proper care, proper treatment, and regular breastfeeding. The production of more bilirubin may not be controlled easily but the removal of bilirubin from the body can be done. Many factors develop neonatal jaundice such as less breast milk, sickle cell anemia, premature birth, and blood incompatibility against mother's blood. Many other things cause this like unhygienic practices of mother and health workers, infections, use of camphor, Robb, mentholatum, and dusting powder on babies. Media should help the people by raising awareness in society about the prevention and early signs. The public should know that jaundice is a major infant killer. If jaundice is seen after a few days of birth, then the babies should be admitted to the hospital instead of doing home treatment. Several therapies such as phototherapy and IVIG are in use, but still newborns are dying due to the negligence of parents. Rh incompatibility and blood group incompatibility can cause maximum death in newborns, so mother's blood test in regular interval is important. Despite all these treatment, excess mother milk is best to help infants to get rid of jaundice. Phototherapy should be available in every developing country as the death rate is higher in these countries. As traditional methods have proven very helpful, all the times, so there are many plants which could be used for the treatment of jaundice. Several herbs can be useful for this; like *Asteraceae* and *Fabaceae* family are mostly used plants for the treatment of neonatal jaundice. Some plants such as Kutki, Giloy, and Indian *Aloe vera* are the best example of medicinal plants for neonatal jaundice. Besides, that sunlight can be proved very helpful to detoxify the bilirubin level. Neonatal jaundice is not mostly fatal, but due to illiteracy and negligence, this becomes fatal. Hence, the proper awareness among people and proper treatment is needed to minimize this problem. Developing countries should take proper steps to minimize this problem.

AUTHOR'S CONTRIBUTION

SSM and AD contributed in conceptualization and writing, MKJ contributed in conceptualization, and editing the manuscript.

CONFLICT OF INTEREST

There is no conflict of interest declared among the authors.

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