MANAGEMENT OF NEONATAL JAUNDICE IN NIGERIA

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ABSTRACT

Jaundice is yellowish discolouration of the skin, sclera and mucous membranes.[1] Neonatal jaundice (NNJ) is so common that it can be regarded as a normal physiologic adaptation of the newborn infant to extrauterine life. However, it may also be a symptom or sign of an underlying disease. Neonatal jaundice is due to increased serum levels of bilirubin, a pigment derived mainly from the breakdown of haemoglobin. It becomes clinically visible when serum bilirubin level exceeds 5 mg/dL. Worldwide NNJ is an obsession of neonatologists because of the association between raised unconjugated bilirubin levels and permanent neurological damage.[2-6] Newborns produce bilirubin at a rate of 6-8 mg/kg/ day which is more than twice the production rate in adults.[7,8] This is due to relatively large red cell mass, shorter red cell life span causing increased red cell turn-over in neonates.[9] Bilirubin production in neonates however declines to adult level within 10 to 14 days after delivery.[7] The prevalence of neonatal jaundice in clinical practice range between 23–60%.[1] Jaundice is noticed during the first week of life in about 60% of term infants and 80% of preterm infants with only a few signifying underlying disease.[7,

BILIRUBIN METABOLISM

Bilirubin is the end product of haem catabolism.[8] Haem is derived mainly from circulating haemoglobin; 1g of haemoglobin yields 35mg of bilirubin when catabolised.[7,8] The remaining 25% of haem is derived is derived from tissue proteins e.g. cytochromes, catalase, muscle myoglobin and ineffective erythropoiesis.[7,8] Two enzymes are involved in the oxidation-reduction reaction that result in the formation of bilirubin from haem.[1] The first enzyme is haem oxygenase that catalyse the conversion of haem to biliverdin while the second enzyme is biliverdin reductase, a NADP-dependent enzyme which catalyses the reduction of biliverdin to bilirubin. The reaction takes place in the reticuloendothelial system. The bilirubin that is released is insoluble in plasma and so it binds tightly to albumin with which it is transported to the liver. When it gets to the liver, selective uptake occurs by the aid of ligandins (Y-protein). Thereafter, conjugation takes place and the unconjugated bilirubin is converted to the water-soluble conjugated bilirubin. The process is catalysed by Uridine diphosphate glucuronyl transferase (UDPGT) and the end product is bilirubin diglucuronide, which is the readily excretable form.

Conjugated bilirubin is rapidly excreted into the bile from where it gets to the gastrointestinal tract and some of it is excreted in the faeces as stercobilin and a fraction is hydrolysed back to the unconjugated form and is reabsorbed into the plasma through the enterohepatic circulation.

However in the neonatal period, some defects in the above process are responsible for the jaundice. These include:

- Increased bilirubin load from red blood cell turnover.
- Reduction in the level of ligandin, which affects hepatic bilirubin uptake.
- Reduction in the activity of Uridine diphosphate glucuronyl transferase (UDPGT). At birth, the UDPGT activity level is only 0.1 to 1% that of the adult.[8,9] Its activity however increases over time but takes about 6-14 weeks after birth to reach adult level.
- Defective excretion.

CLASSIFICATION OF NEONATAL JAUNDICE

Neonatal jaundice can be classified as physiological or pathological based on the time of onset of the jaundice, the clinical course, resolution, and rate of rise and total serum bilirubin levels. It can also be classified as unconjugated (indirect reacting) or conjugated (direct reacting) hyperbilirubinaemia based on the reaction in the van der Bergh reaction. It can also be a mixed form. Most cases of neonatal jaundice seen in developing world are the unconjugated form[11] and the clinical significance of this is its ability to cause kernicterus.[8]

AETIOLOGY OF NEONATAL JAUNDICE

The causes of neonatal jaundice could either be physiological or pathological. Physiological jaundice of the newborn is the most common cause of neonatal jaundice. It is a diagnosis of exclusion and its diagnosis is based on the following criteria:

- It does not appear until the 36th hour of life
- The serum bilirubin level does not rise above 12mg/dL in term neonates or 15mg/dL in preterms
- It does not persist beyond 7 days in term infants and 14 days in preterm infants
- The rate of rise must not be greater than 5mg/dL per day or 0.5mg/dL per hour
- The conjugated bilirubin must not be higher than 2mg/dL at any time

Physiological jaundice of the newborn require no active treatment other than reassuring the parents but in our environment where it can readily merge with pathological jaundice, the patient may benefit from treatment pending when the diagnosis is made conclusively.

Pathological causes of jaundice will include:

Prematurity: Because of reduced red blood cell life span, immature hepatocyte conjugating system, increased bilirubin load and increased enterohepatic circulation.

Blood Group Incompatibility: ABO incompatibility is the most common form in our environment and the mother always has blood group O while the baby's blood group may be A, B or AB. Rhesus isoimmunisation is another form of blood group incompatibility.

Neonatal Septicaemia

Glucose-6-Phosphate Dehydrogenase deficiency: This is the most important factor associated with severe neonatal jaundice and kernicterus in Nigeria.[12] It follows exposure of the individual to oxidant agents such as sulphonamides, camphor balls, menthol, aspirin etc.[13,14]

Extravasated blood: Examples are cephalhaematoma and intraventricular haemorrhage

Polcythaemia: This may be due to twin-twin transfusion, small for gestational age babies etc

Breastfeeding or Breast Milk jaundice

In-born errors of metabolism

Hypothyroidism

Congenital malformations: Biliary atresia, choledochal cyst, annular pancreas

Conjugated hyperbilirubinaemia is not a common finding in clinical practice and it is defined as direct or conjugated bilirubin fraction greater than 15 or 20% of the total serum bilirubin. It may be due to hepatic disorders or disorder of the excretory system. It may lead to liver damage.

MANAGEMENT OF NEONATAL JAUNDICE

The management of neonatal jaundice has two guiding principles, which are: identifying the underlying aetiology that requires immediate treatment and determining the severity of the jaundice. Neonatal jaundice is an emergency as severe unconjugated hyperbilirubinaemia could cause kernicterus which can result in neonatal death and chronic handicapping conditions such as cerebral palsy[15], deafness, speech disorders, learning disability and mental retardation.[7,8]

Management starts with full evaluation of the baby and this will include a detailed history of the antenatal and delivery period, time when jaundice was first noticed, the activity and feeding of the baby, fever; history of jaundice in the elder siblings as well as use of icterogenic agents and mothers blood group if known.

Thorough physical examination should be done to check for pallor, hepatosplenomegaly, extent of the jaundice bearing in mind the cephalocaudal progression of jaundice which was first described by Kramer in which the body is divided into 5 zones and serum bilirubin range is associated with the zones.[16] This method is however inaccurate and may be unreliable because of inter-observer variability especially in dark skinned infants. Neurological assessment should also be done.

Important investigations will include:

Haematocrit: Low PCV or decreasing PCV values may suggest haemolysis while PCV value greater than 65% may suggest polycythaemia as the possible aetiology.

Reticulocyte count: If high will suggest bone marrow response to anaemia which can be due to either haemolysis or haemorrhage.

White cell count: If elevated or markedly low may suggest infection as the cause of the jaundice.

Peripheral blood smear examination: The presence of spherocytes or elliptocytes may suggest aetiology such as hereditary spherocytosis or elliptocytosis. Also the presence of numerous immature white cells or neutrophils with toxic granulations within them may suggest infection as the cause of the jaundice. Presence of spherocytes on blood smear may suggest ABO

incompatibility, while nucleated red cells may suggest rhesus isoimmunisation

Blood Group for the baby and the mother: If maternal blood group is O and baby's blood group is either A or B, this may suggest ABO incompatibility.

Rhesus factor: Rhesus negative mother with rhesus positive infant with positive Coomb's test shows rhesus isoimmunisation as the cause.

Coomb's test (**nonagglutinating antibody level**)**:** Positive direct Coomb's test may suggest blood group incompatibility although may be weakly positive in ABO incompatibility.

Total and conjugated serum bilirubin concentration: For objective assessment of the severity of the hyperbilirubinaemia, the result of which will aid decision on the most appropriate treatment.

Glucose-6-phosphate dehydrogenase screening: This will be carried out to determine the G-6-PD status of the patient. Babies who are deficient are at risk of severe neonatal jaundice especially if exposed to precipitating factors including septicaemia. This is more important in male infants of African, Asian or Mediterranean descent.

Blood culture and sensitivity: When indicated helps in identifying the offending organism particularly in patients who are at risk for septicaemia.

Urinalysis particularly for reducing substance: This may give a clue in patients with Galactosaemia.

Urinalysis for bilirubin: If positive, suggests conjugated hyperbilirubinaemia

Hepatitis B and anti-HCV screening

Total serum protein and Albumin level

Abdominal ultrasound

Other investigations will depend on the history obtained.

TREATMENT OF NEONATAL JAUNDICE

The treatment of unconjugated hyperbilirubinaemia will be guided by the aetiology and severity of the jaundice. Treatment of unconjugated hyperbilirubinaemia is directed at reducing the bilirubin level and preventing central nervous system toxicity.

Modalities of treatment of neonatal jaundice will include:

PHOTOTHERAPY

Phototherapy is the most widely used treatment for unconjugated hyperbilirubinaemia, and it is both safe and effective. It was first demonstrated by Cremer *et al* in 1958 in England. It uses light energy to bring about a reduction in serum bilirubin concentration. If started early, it will modify the course of hyperbilirubinaemia in haemolytic disease and reduce the need for exchange blood transfusion.[1]

Indications for phototherapy include:

Treatment of moderate hyperbilirubinaemia

Prevention of hyperbilirubinaemia in preterm low birth weight infants in which case it can be used prophylactically although some reports have shown it has no beneficial effect

Post-exchange transfusion to accelerate excretion and prevent rebound hyperbilirubinaemia

The exact mode of action of phototherapy is largely unknown but it is thought to act through 3 mechanisms which are:

Photooxidation in which bilirubin is bleached by the action of light. It is however a slow process.

Configurational isomerization in which the intramolecular bonds are opened and a water soluble isomer is formed. It is a rapid process and the formed isomer make up about 20% of the circulating bilirubin few hours after commencement of phototherapy.

Structural isomerization, which consists of intramolecular cyclization between adjacent pyrole, rings leading to lumirubin formation. This may constitute 2-6% of the total serum bilirubin concentration and it is rapidly eliminated from the body. The photoisomers of bilirubin are excreted in bile, and to some extent, in urine.

Various kinds of light sources have been used for phototherapy ranging from the white fluorescent light to sunlight (early morning sun), blue light and green light. Green light has been shown theoretically to have better skin penetrance but has not been proven to be more effective than white or blue light. Green light also makes the babies look sick and it is unpleasant to work in thus making it to be unacceptable widely. However in clinical

practice in Nigeria, the white and blue lights have gained wide acceptance.

There are principles guiding the use of phototherapy and these include:

Wavelength: The wavelength of the light should range between 420-460nm as bilirubin absorbs light maximally within this range. Light with longer wavelength penetrate the skin better.

Irradiance: A direct relationship exists between the efficacy of the phototherapy and the irradiance of the light used. The irradiance should be in the range of 30-40μW/cm^2/nm for maximum efficiency.

Distance: The distance between the light infant and the light source should not be greater than 50cm and can be less (down to 10cm) provided the infant's temperature is monitored.

Surface area: The efficiency of phototherapy also depends on the amount of bilirubin irradiated and this has to do with the surface area exposed. Thus, the larger the exposed area, the more effective the phototherapy.

Protection: The eyes and gonads should be shielded from direct light.

Monitoring: The patient's activity, temperature and fluid balance should be strictly monitored.

Fibreoptic light can also be used and this has the advantages of delivering a high energy, low risk of overheating the infant, no need for eye shield, promotes infant- mother bonding, can be used at home and can be combined with the conventional overhead phototherapy to achieve double or triple phototherapy. Its drawbacks are that it delivers light to a small surface area, the noise from the fan in the light source and decrease in the amount of energy delivered with aging or breakage of the optic fibers. This is however not yet available in many centers in Nigeria.

Phototherapy is a relatively safe and effective procedure but it has some complications that may follow its use. These will include temporary separation of mother and baby if the overhead type is used, maculo-papular rash, hyperpyrexia or hypothermia, dehydration from increased insensible fluid loss or diarrhoea, retinal damage, bronze baby syndrome, damage to the gonads, accidents from the electrical appliances[1] including burns and hypocalcaemia, patent ductus arteriosus.[8]

Phototherapy in Nigeria may not be as effective as expected not because the equipments are not available but because of the erratic power supply reduces the effectiveness of this treatment modality.

EXCHANGE BLOOD TRANSFUSION

This is the most effective way of reducing serum bilirubin concentration. Exchange blood transfusion achieves a rapid reduction of the serum bilirubin level and it requires a great deal of expertise and asepsis.[17] It is done when phototherapy fails to control the rising bilirubin levels. In severe unconjugated hyperbilirubinaemia, factors such as the age of the infant, birthweight, gestational age, rate of rise of bilirubin, presence or absence of factors that increase the risk of bilirubin encephalopathy (hypoxia, hypoglycaemia, acidosis, hypoalbuminaemia, asphyxia, prematurity etc) are taken into account in deciding when to perform an exchange blood transfusion in a patient.[1] In haemolytic disease, the indication for exchange blood transfusion is:

- Serum bilirubin level of 10mg/dL (170mmol/L) within 24 hours of life,
- 15mg/dL (255mmol/L) by 48 hours of life,
- 20mg/dL (340mmol/L) at any age, also known as virgintiphobia
- Rate of rise of serum bilirubin more than 5mg/dL/24 hours or >1mg/dL/hour
- Cord blood bilirubin of > 5mg/dL
- Cord blood packed cell volume < 36% or Hb < 12g/dL indicating significant anaemia.

Exchange blood transfusion helps in removing bilirubin-laden blood from the circulation and replacing it with a fresh donor blood. It also helps in removing antibody coated red blood cells, corrects anaemia, removes maternal antibody and other toxins within the circulation in patients with haemolytic disease.[8] Double volume exchange transfusion is done in most cases of neonatal jaundice and this removes about 85% of the infant's red blood cells but only 25–50% of the total serum bilirubin is removed.[18] The technique still being used in our environment mostly is the push-pull method using the umbilical vessels, however the automated method can be use if the facilities are available. The procedure is done over 60 to 90 minutes and fresh whole blood is used i.e. blood not older than 4 days. The blood can be preserved with either of these anticoagulants, Heparin, Acid-citrate-dextrose (ACD), Citrate-Phosphate-dextrose-adenine (CPDA). Blood is exchanged in aliquots, the volume depending on the weight and the patient's blood volume. The infant can be primed before the procedure by infusing 1mg/kg of salt poor albumin a few hours before the

procedure in order to increase efficiency.[1] During the procedure, the baby's vital signs should be monitored, the blood should be mixed at intervals and accurate documentation of volume of blood exchanged at each cycle should be made. The procedure is not without its complications and these may include:

Complications of catheter placement: Perforation of the peritoneum, wrong positioning of the catheter tip causing cardiac arrhythmia, necrotizing enterocolitis and liver cirrhosis

Complications of blood transfusion: Transmission of infections (malaria, hepatitis B or C, HIV) and blood transfusion reactions

Complications of the procedure: Haemodynamic changes (hypovolaemia or hypervolaemia), electrolytes changes (hyperkalaemia, hypocalcaemia, hypomagnesaemia), acid-base imbalance- acidosis

Others: Rebound hypoglycaemia (from the large amount of glucose in the anticoagulant), Hypothermia, Anaemia, Thromboembolism (air or clot), Portal vein thrombosis, Portal abscess, and Bowel perforation.

PHARMACOTHERAPY

This has to do with the use of drugs in the treatment of neonatal jaundice and drugs that have been shown to be of benefit include:

Phenobarbitone, Clofibrate, Flumecinolone: These drugs act by augmenting the hepatic uptake of bilirubin and increasing the activity of the glucuronyl transferase enzyme. By these mechanisms, they stimulate bilirubin conjugation and eventual excretion. Phenobarbitone use is however limited because of its slow onset of action (48-72 hours) and the sedative effect it may have on the infant which may affect the feeding of the baby, thus increasing the gut transit time, hence enterohepatic circulation.

The metalloporphyrins or mesoporphyrins: These drugs act by inhibiting the cytosomal enzyme haem oxygenase that catalyses the conversion of heme to biliverdin thus preventing bilirubin formation. Examples include tin mesoporphyrin.

Intravenous immunoglobulin has been found to be useful in patients with jaundice due to immune mediated haemolysis.

Anti D immunoglobulin (Rhogam) in rhesus negative mothers following delivery has reduced the incidence of rhesus isoimmunization as a cause of neonatal jaundice.

Antibiotics are important in patients with neonatal jaundice due to septicaemia.

L-thyroxine will be important in patients with hypothyroidism.

Hydration: This can be in form of increased oral intake of breastmilk or formula administration. This helps by improving hepatic bilirubin uptake as hepatic blood flow increases and also reduces enterohepatic circulation, as the baby is able to move bowel regularly. Adequate hydration also improves the renal blood flow as some lumirubin is excreted in the urine.[8] Adequate hydration improves the efficiency of phototherapy.

DIET MODIFICATION

Infants with breast milk jaundice may benefit from interruption of breastfeeding for 24-48 hours and recommencing afterwards. Increasing the frequency of breastfeeding will be of help in patients with breastfeeding jaundice.

Casein rich formula can be used as it helps in inhibiting beta glucuronidase that deconjugates conjugated bilirubin thereby reducing the risk of increased enterohepatic circulation.Agar or Activated charcoal can be used. These act by binding bilirubin in the gut, thus reducing enterohepatic circulation.

Babies with galactosaemia will benefit from galactose-free diet.

SURGERY

This is indicated in infants in whom jaundice is caused by bowel or external bile duct atresia or obstruction.

CONCLUSION

Neonatal jaundice in Nigeria continues to hold the potential threat of complications from bilirubin encephalopathy and kernicterus. Careful assessment of risk factors, detailed patient evaluation, appropriate laboratory monitoring, judicious use of phototherapy with stable electricity supply and specific treatment of other disorders e.g. septicaemia are essential for the optimal management of neonatal jaundice.

There are a lot of challenges limiting optimal management of neonatal jaundice in Nigeria and these include poverty which results in late presentation, failure to attend antenatal clinic, unsupervised delivery and inability to purchase drugs in case of infections; ignorance about the identification of jaundice in the

newborn, causes and effect of neonatal jaundice among women of reproductive age group, cultural factors such as cord fomentation and use of camphor balls to preserve the baby's clothing; erratic power supply and lack of modern facilities for effective treatment. Addressing these issues will go a long way in further improving the outcome of neonatal jaundice in Nigeria.

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