

# health technology assessment



## EXECUTIVE SUMMARY

### MANAGEMENT OF NEONATAL JAUNDICE

HEALTH TECHNOLOGY ASSESSMENT UNIT  
MEDICAL DEVELOPMENT DIVISION  
MINISTRY OF HEALTH  
MOH/PAK? 11/2002 (TR)

## EXECUTIVE SUMMARY

Jaundice in the newborn or neonatal hyperbilirubinemia, is a common problem. It encompasses neonates with physiological jaundice, breast milk jaundice and non-physiological jaundice. In the United States, for example, 65% of all newborn infants appear jaundiced during the first week of life. A survey of government hospitals and health centres under the Ministry of Health Malaysia in 1998, found that about 75% of newborns were jaundiced in the first week of life.

Increased levels of serum bilirubin will cause unconjugated bilirubin to enter nerve cells and kill these cells, leading to brain damage, this being termed as kernicterus. Severe kernicterus has a high mortality. Even survivors usually suffer sequelae including athetoid cerebral palsy, high frequency hearing loss, paralysis of upward gaze and dental dysplasia

Direct visual estimate of jaundice is unreliable, and carries the risk of underestimating significant neonatal jaundice. The most common method of assessing neonatal jaundice was through serum bilirubin determinations. Later hand-held spectrophotometers called bilirubinometers were developed.

In the management of neonatal hyperbilirubinemia, the major issues are to establish the level of serum bilirubin at which there should be intervention, and also the serum levels for the various treatment options. Intervention is either by phototherapy, drug treatment or by exchange transfusion. The aim of phototherapy is to prevent potentially dangerous bilirubin levels and to decrease the need for exchange transfusion. Exchange transfusion refers to the procedure where the baby's blood is replaced with other compatible blood. Drugs that have been used in the past to treat neonatal hyperbilirubinemia include phenobarbitone, cholestyramine, agar that prevents the reabsorption of unconjugated bilirubin from the intestines into the blood, and vitamin E. The newer drugs are the metalloporphyrins like tin porphyrin.

Jaundice can be divided into three major groups – physiological jaundice, breast milk jaundice, and non-physiological jaundice. *Physiological jaundice* is when a neonate has elevated serum bilirubin concentration up less than  $210 \mu\text{mol/l}$  (12mg%) by the 3<sup>rd</sup> day of life. *Breast milk jaundice* is the most common type of jaundice requiring phototherapy in breast fed infants in whom no cause for the jaundice could be determined. *Non physiological jaundice* is “pathological” jaundice due to haemolytic disease or sepsis.

The laboratory diagnosis of bilirubin can be conventionally carried out by spectrophotometric, diazo and enzymatic methods, as well as by newer methods like breath carbon dioxide measurement. *Bilirubin species* like unconjugated, monoconjugated, and diconjugated bilirubins are diagnosed by *high performance liquid chromatography* (HPLC). Transcutaneous bilirubinometers are the newer instruments and locally only two brands, Minolta-Air Shields Jaundice Meter (RM 14,000) and the BiliCheck (RM 18,000) are available.

In the treatment of hyperbilirubinemia, phototherapy works by using the light energy to change bilirubin into a more soluble form to be excreted in the bile or urine. There are various types of phototherapy available. Conventional phototherapy provide light in the 425-475 nm wavelength band corresponding to the peak absorption of light by bilirubin, the usual light intensity being 6-12  $\mu\text{watt}/\text{cm}^2$  per nm. There have been modifications of the traditional phototherapy in the number and configurations of phototherapy bulbs, the source of light (fluorescent vs. halogen bulb) and the colour of bulbs (white, blue, or green). *Fibre Optic Phototherapy* uses a fiberoptic cable, containing about 2000 – 2400 individual acrylic fibres, to deliver light from a tungsten halogen lamp to a light pad where the fibres are woven together. The pad, which remains cool, is inserted into a disposable paper jacket to avoid soiling of the pad and allowing it to be held securely to the infant's back. The baby can be dressed and wrapped normally thus enhancing his postural and autonomic stability, and can be nursed by the mother without interruption of phototherapy during breast-feeding. The Biliblanket (Ohmeda, Columbia, M D, USA) is a more sophisticated system containing a greater number of fibres with more points of light and an intensity of 35  $\mu\text{w}/\text{cm}^2/\text{nm}$ . *Intensified Phototherapy* provides an increased irradiance of 26 - 40  $\mu\text{w}/\text{cm}^2/\text{nm}$ , as compared to the irradiance of 7-16  $\mu\text{w}/\text{cm}^2/\text{nm}$  in conventional phototherapy through seven daylight fluorescent tubes placed close under the floor of the crib with the sides and top of the crib covered with a reflecting film, using high intensity blue lights with seven overhead lamps and four lamps placed below the infant, or by using a standard phototherapy unit close to the floor of the bassinet and conventional phototherapy given from above.

Exchange transfusion can be carried out by the automated method or the classical push-pull technique, via the umbilical or peripheral vessels, and takes about 1.5 to 2 hours. As for drug treatment Phenobarbitone is not routinely recommended. Cholestyramine has side effects include long-term steatorrhea, deficiency of fat soluble vitamins and folic acid, flatulence and constipation and even intestinal obstruction. Agar is a dried hydrophilic colloidal substance obtained from various species of algae. Vitamin E deficiency increases red cell hemolysis. Tin protoporphyrin and tin mesoporphyrin competitively inhibit the activity of heme oxygenase, the rate-limiting enzyme in heme catabolism, which reduces the production of bilirubin and can substantially diminish plasma level of the bile pigment.

The objective is to assess the safety, efficacy and effectiveness, and cost implications of management of neonatal hyperbilirubinemia

With respect to laboratory diagnosis the gold standard is estimation of carbon monoxide in breath, while high performance liquid chromatography is the gold standard for measurement of bilirubin fractions. There is significant variability in bilirubin measurements due to various factors like problems with standardisation and quality control. Cord serum has not been found to be a useful predictor of hyperbilirubinemia in comparison to other methods of measurement. Transcutaneous bilirubinometry is a cheap, reliable, easy-to-use, non-invasive method of serum bilirubin estimation. It correlates well with serum bilirubin measurements over the ranges of bilirubin that are considered significant to initiate phototherapy, and is thus an effective screening tool in determining

significant neonatal jaundice. However, transcutaneous bilirubinometry rapidly loses its reliability once phototherapy is initiated. In addition, the reliability of transcutaneous bilirubinometry in a multi-ethnic population of babies (as in Malaysia) with varying cutaneous pigmentation remains unresolved.

With respect to the treatment of hyperbilirubinemia, there is no consistent serum bilirubin level to commence phototherapy. The general trend is that phototherapy should be considered at serum bilirubin levels of 222-260  $\mu\text{mol/l}$  in healthy normal babies and at lower levels for pre-term and ill babies. Blue light phototherapy is the most effective, followed by white, with green light being the least effective. *Fibreoptic phototherapy* is as effective as conventional phototherapy in pre-term babies, but there is insufficient evidence of its efficacy for term babies. There is evidence of the efficacy of *Intensified phototherapy* in infants with rapidly increasing serum bilirubin, or with very high levels of serum bilirubin not responding to conventional phototherapy. Eye-shielding using a modified light-proof head-box can reduce the dangers due to prolonged illumination including eye infections. The evidence on other effects of phototherapy is inconclusive. A cost analysis of the various types of phototherapy indicated that white light phototherapy is the cheapest, especially using the wooden photolight manufactured locally. Overall, phototherapy is an effective tool for treating neonatal jaundice with acceptable side effects, which can be minimised with special precautions.

For *Exchange transfusion*, apart from serum bilirubin levels, the bilirubin/albumin ratio can also be used as criteria for decisions on the need for exchange transfusion. For babies at risk, other factors like low Apgar score, low birth weight, hemolysis, clinical condition and the like have to be considered. There is a degree of morbidity and mortality associated with exchange transfusions, mortality ranging from 0.4 - 10.6%, and morbidity ranging from 6.7 - 20.4%.

With respect to drug treatment, there is limited evidence on the effectiveness of tin mesoporphyrin.

It is recommended for laboratory diagnosis, the laboratory should select the appropriate method based on needs and availability of technical resources. Quality control programmes and other measures need to be instituted to increase the accuracy of results. Transcutaneous bilirubinometry should be carried out on a selective basis. Periodic instrument calibration and generation of individualised correlation curves (institutional or regional) between transcutaneous bilirubinometer indices and serum bilirubin levels should be instituted. Local data on the reliability of transcutaneous bilirubinometry in a multi-ethnic population with varying intensities of skin pigmentation, as well as its cost effectiveness is needed. More data is also needed with respect to laboratory diagnosis like the indications for use of the non-invasive end tidal carbon monoxide excretion (ETCOc) technique and the best method of bilirubin determination for identifying the infant at risk for kernicterus.

In the treatment of hyperbilirubinemia, phototherapy should be considered at serum bilirubin levels of 222-260 $\mu\text{mol/l}$  taking into account other clinical factors. White light

phototherapy is recommended, using intensive or blue light phototherapy only if serum bilirubin levels are high and it does not respond to conventional phototherapy.

In using exchange transfusions, serum bilirubin levels, bilirubin/albumin ratio and other clinical factors should be taken into consideration. All necessary precautions should be taken to limit morbidity and mortality.

Drug treatment is not recommended at present, until more evidence on efficacy is available.