Improving the Management of Hyperbilirubinemia in a Limited-Resource Area

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Summary

The aim of this thesis is to understand why the incidence of hyperbilirubinemia, a more physiological increased level of bilirubin in blood of newborn infants is higher in Low-Middle income countries (LMICs) like Indonesia compared to high income countries (HICs) and to find ways to decrease this high incidence in a LMIC, including Indonesia. Hyperbilirubinemia might result in brain damage in newborn infants. Symptoms due to brain damage may occur in the period soon after birth, but also in later life. It is therefore important to try to prevent hyperbilirubinemia, and when present to treat as soon and effective as possible.

In chapter 1, a general overview of the bilirubin metabolism is given. Bilirubin is a degradation product of heme, an important constituent of red blood cells. After partial degradation in peripheral tissues, it is metabolized in the liver from a water-insoluble to a more water-soluble compound which is excreted with bile into the gastro-intestinal tract. Increased bilirubin levels, called jaundice (1, 2, 3), are found in the first days after birth in (60-80)% of all newborn infants (4). This is due to a high breakdown of fetal red cells after birth and an immaturity of the excretion of bilirubin by the liver (5). Severe hyperbilirubinemia a level of bilirubin level higher than accepted, safe levels, levels that can cause encephalopathy and temporal or persistent

brain damage, is seen more frequently in LMICs like Indonesia compared to HICs (6).

In chapter 2 we investigated how health care workers in Indonesia (midwives, general practitioners, and pediatricians) diagnose, monitor, and treat newborn infants with jaundice and hyperbilirubinemia. We send out questionnaires to these three groups of professionals asking them how they diagnose, monitor, and treat jaundice and hyperbilirubinemia. We asked if and how they measure bilirubin levels and how they conclude if an infant has hyperbilirubinemia and might need treatment. We specifically asked if they used guidelines for diagnosing and treating hyperbilirubinemia.

This study showed that 46 % of midwives use clinical observation as method to determine the bilirubin level, although studies have convincingly shown that this method is unreliable. Secondly, the three groups of professionals used different guidelines on how and when to measure the bilirubin level and when to treat an infant with hyperbilirubinemia. Twenty-nine percent of the midwives and 23 % of the general practitioners were unaware of the existence of guidelines. Forty-eight percent of the pediatricians indicated to have problems in getting access to the guidelines. Only 54 % of the midwives, 46 % of the GP's and 84 % of the pediatricians indicated to use the guidelines. The answers given indicate that guidelines were often not followed (7).

From this study we conclude that there is a great need to improve methods to determine the bilirubin level in newborn infants. Secondly, there is a great need to develop one guideline for the diagnosis and treatment of jaundice and hyperbilirubinemia that can be used by all groups of health care workers. Finally, in order to improve the adherence to the guidelines are systems needed that are user-friendly with easy access (7).

In chapter 3 we investigated the knowledge of and clinical practice of residents in pediatrics regarding jaundice and hyperbilirubinemia in newborns. We sent questionnaires to residents in the five largest teaching hospitals in Indonesia. We focused on pediatric residents as they are the pediatricians of tomorrow. The results show that the knowledge of residents regarding diagnosing and treating jaundice and hyperbilirubinemia is limited. Although all residents indicated to follow the guideline of the American Academy of Pediatrics, the guideline advised by the Indonesian Society of Pediatrics, the answers showed that in practice a significant

number of residents did not follow these guidelines (8, 9, 10). Seventy-six percent of the residents used the clinical evaluation of the infant to diagnose hyperbilirubinemia, while this method is unreliable according to the guideline. Secondly, residents indicated to use this guideline also for preterm infants, while in the guideline it is stated clearly that the guideline is only applicable for infants born after 35 weeks and more. Third, from the answers it was clear that the majority did not use the guideline to determine if patients needed treatment for their jaundice or hyperbilirubinemia or not. Finally, the residents indicated to use medication like ursode-oxycholic acid and phenobarbital as well as sunlight to reduce the bilirubin level, while these practices are not advised in the guidelines.

We conclude from this survey that, unfortunately, the pediatricians of tomorrow are not well trained how to diagnose and treat jaundice and hyperbilirubinemia in newborn infants. This lack of knowledge is dangerous and needs to be improved.

A cornerstone in the prevention and treatment of hyperbilirubinemia is the use of phototherapy (PT). Blue light with a wave length of 400-500 nm converts unconjugated, water insoluble bilirubin into a form of bilirubin that is more water soluble and can be excreted by the infant without being conjugated in the lever (11, 12). PT has shown to be able to prevent, in almost all infants, when started at the appropriate moment, hyperbilirubinemia as well as to reduce dangerous bilirubin levels to levels that are not dangerous (13,14).

In collaboration with the Indonesian Pediatric Society and Ministry of Health, we designed an Indonesian guideline for the diagnosis and treatment of hyperbilirubinemia. This guideline is aimed to be followed also by midwives and general practitioners. Introducing a guideline is not the same as implementing the guideline in daily practice. As written in chapter 2 seem pediatricians and other health care workers in Indonesia not to be inclined to follow national guidelines. To assist health care workers to use and follow the new national guideline, we developed a web-based application, to be used with a smart phone. In chapter 4 we describe the application and give the results of a pilot study on its use. After opening the app on the smart phone, the practitioner must fill in a few data: date and time of birth, gestational age and birthweight and date and time of bilirubin measurement. The presence or absence of risk factors for both developing a fast increase in bilirubin and

for an increased risk for brain damage also needs to be filled in. The program then provides information if the bilirubin level exceeds a treatment level and gives advise on how to treat the infant. Advises about the follow-up of the infant are also given.

In a pilot study described in chapter 4, we introduced the app to pediatricians in two university-based teaching hospitals in East Java and explained how to use the App. After they had time to work with the program in daily practice, we asked them their opinion about the program, if they used it and their experience with using it. We also conducted a retrospective chart review of all newborn infants cared for in these two hospitals in the period before and after the introduction of the app. We found in the retrospective chart review that proper treatment of hyperbilirubinemia increased from 38% before the introduction of the app to 51% thereafter. Undertreatment decreased from 14 to 10%, overtreatment from 34 to 32%. Still, 7% of infants were given PT without measuring the bilirubin level.

We conclude from this pilot study that the app is a valuable tool to improve the care for infants with jaundice/hyperbilirubinemia. Still, correct treatment was given only in half of the infants. Studies therefore are needed to identify why not all pediatricians adhere to the guideline.

A crucial part of the diagnosis and treatment of newborn infants with jaundice/hyperbilirubinemia is the measurement of the bilirubin level. The gold standard is measuring bilirubin in a blood sample (15). For this, it is needed to take blood, to transfer blood to a laboratory that is well equipped and can measure bilirubin accurately. Two important problems exist in rural parts of Indonesia. First, the transport of the blood samples to the laboratory, where it is important to keep the blood cool and shielded from light and secondly, the availability of a well-equipped laboratory. Transport is difficult and small local hospitals not always have the proper equipment to measure bilirubin in blood. Reliable bed-side methods to measure the bilirubin level therefore are needed. In chapter five, we discussed the results of a study where two bed-side methods for measuring bilirubin levels, the transcutaneous bilirubin measurement (TcB) and a point of care method, Bilistick® (BS), were compared with the bilirubin measurement in the laboratory (TSB) (16). One hundred t twenty six infants, mean gestational age 35.5±2 weeks and birthweight 2243± 610 g were included. We found a good correlation between the TSB and the TcB, r=0.785There was an

overestimation of the bilirubin level as measured by the TcB of 26 ± 30 μmol/L. The correlation of the Bilistick® with the TSB, was r= 0.738 The average Bilistick® level was 10.9±45.86 μmol/L lower than the TSB. A negative aspect of the Bilistick® are outliers. In the sample of 126 infants, ten infants showed an, unpredictable low value of which four of showed an extremely low value. The TcB identified all infants where, according to the TSB, PT was indicated. When using the Bilistick, four patients would be missed.

Crucial for the prevention and treatment of hyperbilirubinemia is the use of Phototherapy to decrease the bilirubin levels (14). As mentioned above, under the influence of mainly blue light, water insoluble, not conjugated bilirubin, is transformed into a form that is more water soluble and can be excreted without the need to be conjugated. PT can be given by lamps that emit blue light and, recently, by LED systems (1,2,3). How well the systems work is dependent on three factors, the intensity of the irradiation produced, the distance from the system to the infant and the amount of skin exposed to light. The intensity of the blue light bulbs decreases over time and hours used (14, 17, 18, 19). A study in the Netherlands showed that the intensity of irradiation is not seldom less than required (20). No study in Indonesia evaluated if insufficient irradiation by blue light bulbs might be present in Indonesia and thereby might be a factor in the high incidence of hyperbilirubinemia found in Indonesia. In chapter six we describe the results of our study on the intensity of systems for PT in Indonesia. We measured the irradiance levels of PT under the regular clinical situation in 17 hospitals in Indonesia, both teaching centers and local hospitals. The irradiance level was less than what is considered the minimum level for standard PT: < 10 μW/cm2/nm in nine hospitals. In 8 hospitals, irradiance failed to reach the levels for intensive PT : < 30 μW/cm2/nm, three hospitals provided very high irradiance levels : > 50 μW/cm2/nm. In half of the hospitals the distance between device and infant was greater than recommended, irradiance level was inversely correlated with distance. The effect of a curtain around the cot on irradiance levels was variable, ranging from – 6.15 to + 15.4 μW/cm2/nm, with a mean difference (SD) of 1.82 (3.81) μW/cm2/nm (P = 0.486)

A good method to prevent hyperbilirubinemia in newborn infants is daily measurement of the bilirubin level. This can be done using a transcutaneous bilirubin meter (21). An a situation with limited resources this might be

difficult to perform (22). The care for -preterm- newborn infants in Indonesia is often given in hospitals with limited resources or at home. There, it might be difficult to obtain daily bilirubin levels. We wandered if it might be possible to predict, based on the bilirubin level at 24 hours after birth, which infants are at risk to develop hyperbilirubinemia that needs intervention. We found that cumulatively 63 % of preterm infants with a birthweight of 1000-1500 gram showed hyperbilirubinemia at 48 hours after birth, while this was collectively 27% in infants with a birthweight of 1501-2000 g at 48 hours. We calculated that a TcB level measured at 24 hours after birth of 4.5 mg/dl predicted which infants weighing 1000 – 1499 g needed PT in the following days. A bilirubin level of 5.8 mg/dl measured at 24 hours after birth was predictive for the need of PT in infants 0f 1501-2000 g. These data might help to identify those infants where close monitoring of the bilirubin level is needed (23).

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