

An Overview on Jaundice Assessment in Newborn: Types of Hyperbilirubinaemia, Kramel's rule and Optical Density Method

Open
Access

Asyraf Hakimi Abu Bakar^{1,*}, Najmuddin Mohd Hassan², Ammar Zakaria¹, Ahmad Ashraf Abdul Halim²

¹ School of Mechatronic Engineering, Universiti Malaysia Perlis (UniMAP), Pauh Putra Campus, 02600 Arau, Perlis, Malaysia

² Centre of Excellence for Advanced Sensor Technology (CEASTech), Universiti Malaysia Perlis (UniMAP), 02600 Arau, Perlis, Malaysia

ARTICLE INFO

ABSTRACT

Article history:

Received 18 August 2017

Received in revised form 4 October 2017

Accepted 2 December 2017

Available online 18 December 2017

Jaundice or neonatal jaundice is describes as yellow discoloration of the skin and other tissues of a newborn infant and normally it is conjunctiva due to the bilirubin. Jaundice clinically apparent when the level of serum bilirubin rises up to 5 mg/dL. Jaundice could cause abnormalities in the newborn infant when production of bilirubin exceeds the normal range. Formation of bilirubin starts from degradation of hemoglobin and haemoprotein, which is released from red blood cell. Jaundice can be classified into two types that is physiological jaundice and pathological jaundice. Current technique in evaluating jaundice of new born infant is based on Kramer's Rule, which is in non-invasive but unfortunately it is not very applicable to the babies with dark skin. Abdominal ultrasonography is categorized in non-invasive but the major disadvantage is that interpretation can be difficult to obese patients and commonly apply for adults. Therefore, Transcutaneous Bilirubinometer is one of the methods to measure the yellowness of the skin of a newborn baby. It is a non-invasive method and can avoid babies from getting a skin infection when a blood sample is drawn. This paper will go through short overview on jaundice types as well as its assessment.

Keywords:

Bilirubin, Kramer's rule, Abdominal ultrasonography, Transcutaneous Bilirubinometer

Copyright © 2017 PENERBIT AKADEMIA BARU - All rights reserved

1. Introduction

Jaundice or neonatal jaundice is the yellow discoloration of the skin and other tissues of a newborn infant and normally it is conjunctiva due to the bilirubin [1]. Jaundice comes from the French word 'jaune' meaning yellow discoloration and shows common sign of liver disease [2]. This happen due to the organs and metabolism of the newborn just started to develop [3]. It is an important clinical sign reflecting the accumulation of bilirubin in blood. It can result from increased bilirubin production, inability of the liver to take up and/or conjugate bilirubin (in Gilbert's

* Corresponding author.

E-mail address: asyrafhakimi90@gmail.com (Asyraf Hakimi Abu Bakar)

syndrome or parenchymal liver disease), or failure to excrete bilirubin into biliary canaliculi and/or into the biliary tree (when the bile ducts are obstructed) [4].

Jaundice in the newborn or neonatal hyperbilirubinemia, is a common problem. A survey of government hospitals and health centres under the Ministry of Health Malaysia, found that about 75% of newborns were jaundiced in the first week of life [5]. Jaundice is apparent clinically when the level of bilirubin in the serum rises above $85\mu\text{mol/L}$ (5mg/dl). While in-utero, unconjugated bilirubin is cleared by the placenta, resulting in a cord serum bilirubin level usually of $35\mu\text{mol/L}$ (0-2mg/dl) [6].

Jaundice is a marker used to identify those infants who may be at risk for developing severe hyperbilirubinemia which can be toxic to the nervous system of infants, potentially causing brain damage [7]. Clinical examination usually reveals the degree of hyperbilirubinaemia. The earliest place to manifest jaundice is the sclera owing to the high elastin level in the scleral tissue and the affinity of bilirubin for it. Scleral icterus indicates a serum bilirubin of at least $50\mu\text{mol}$ [2].

In order to determine total serum bilirubin in newborn infants, invasive technique is used to acquire blood sample from babies. It is a common technique used by the medical staffs in department of pediatric and neonatal intensive care unit (NICU) to assess neonatal jaundice [8].

Certain volume of blood samples are taken from newborn infants for bilirubin level analysis. Unfortunately, this conventional technique is causing trauma and discomfort for both the babies and parents. Hence, the babies are exposed to skin infection due to small cuts on their skins [9]. Figure 1 shows skin and eyes of a baby that is yellowing due to excess amount of bilirubin in the blood. When the excess bilirubin moves from the bloodstream to brain tissue it could cause kernicterus to the baby.

Kernicterus is often seen in sick newborns because their liver and kidneys aren't fully developed and cannot quickly remove extra bilirubin. Babies become excessively lethargic when they have too much bilirubin or kernicterus. They are abnormally sleepy, and they are difficult to arouse [10]. Figure 1 shows the jaundice condition on newborn.

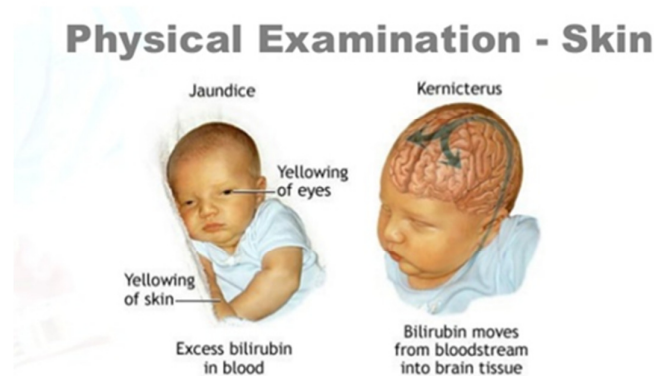


Fig. 1. Jaundice in newborn infant [11]

2. Literature Review

2.1 Type of Jaundice

Jaundice is a common problem in the first week of life to the newborn infants. This phenomenal increase in the anxiety of the parents. Jaundice has two different types which are physiological jaundice and pathological jaundice [12].

By definition, physiological jaundice appears between 24 to 72 hours of age, peaks by 4 to 5 days in the term and 7th day in preterm neonates. Then, disappears by 10 to 14 days of life. Approximately, the level of bilirubin of newborn infants does not exceed 15 mg/dL but in some cases, if the newborn infants have 17 to 18 mg/dL of serum bilirubin, they still considered as healthy newborn [12]. Sometimes, this type of jaundice disappears without going through any treatment.

Pathological or also known as non-physiological jaundice appears in the first 24 hours and serum bilirubin is rising beyond 5 mg/dL per day. The peak level might be greater than the expected normal range [13]. The phenomena of pathological jaundice is difficult to distinguish from physiological jaundice but can be identified from the illness that faced by the infants or the symptoms that might be appear to the newborn infant such as vomiting, poor feeding, excessive weight loss, lethargy and temperature instability [13].

2.2 Bilirubin

Bilirubin is one of the bile pigments in human body and it is a tetrapyrrolic yellowish pigment compound in blood serum and a water-soluble which require enzyme-mediated glucuronidation in the liver for biliary excretion [14]. Production of bilirubin is originated from degradation of haemoglobin and other haemoproteins where 75 % to 80 % of it is structured and discharged from red blood cell [15-17].

In a healthy person daily bilirubin production averages about 0.5 μmol (250–300 mg). About 80% of this bilirubin is derived from breakdown of haemoglobin from senescent red blood cell in the reticuloendothelial system, 15% from ineffective erythropoiesis in the bone marrow, and 5% from turnover of haem proteins such as myoglobin, catalases and the cytochrome enzyme system elsewhere in the body [2].

Bilirubin is likely to be toxic to newborn infant and possibly can lead babies to suffer irreversible brain damage [18]. Production of bilirubin starts from releasing of heme which degraded in human body and associated to the heme oxygenase (HO), where this element changes over heme to biliverdin IX [14]. In this regard, biliverdin represent hydrophilic compound which act as biliverdin reductase into hydrophobic compound bilirubin. After that, heme ring is opened by heme oxygenase (HO) catalase an oxidase because to converts one of the bridge carbons to carbon monoxide. Thus, iron is discharged from the linear tetrapyrrole yielding biliverdin. Finally, enzyme of biliverdin reductase will reduce the double bond on nitrogen which inside one of four of the pyrrole rings then prompts to development of bilirubin [14] as in Figure 2.

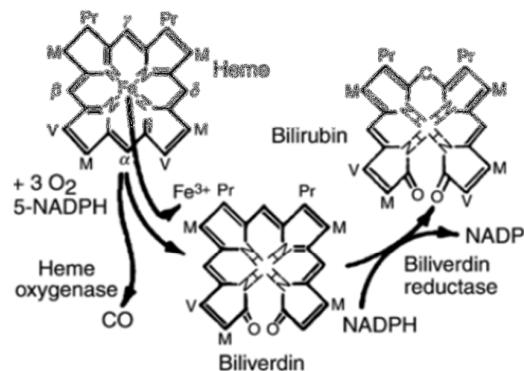


Fig. 2. Bilirubin formation [19]

2.3 Type of Hyperbilirubinaemia

Discovering whether accumulated serum bilirubin is not helping to identify the underlying cause of jaundice and is therefore an important first step. The presence of bile in the urine indicates jaundice due to conjugated hyperbilirubinaemia. A more quantitative analysis can be obtained by measurement of conjugated (direct) and unconjugated (indirect) bilirubin in the blood [4].

Elevation of a predominantly unconjugated bilirubin can result from overproduction of bilirubin, impaired bilirubin uptake by the liver, or abnormalities of bilirubin conjugation. Increased of bilirubin production will caused extravascular haemolysis, intravascular haemolysis, haematoma, and dyserythropoiesis. Impaired hepatic bilirubin will caused hepatic failure, portosystemic shunts, medications, and congestive cardiac failure. Impaired bilirubin conjugation will caused Gilbert's syndrome, Criglar-Najjar syndrome, Neonates, Advanced cirrhosis, and hyperthyroidism [4].

Causes of conjugated hyperbilirubinaemia can be divided into hepatocellular injury, intrahepatic cholestasis, and biliary obstruction. Hepatocellular injury will caused viral hepatitis, Alcoholic hepatitis and Neoplasia. Intrehepatic will caused primary biliary cirrhosis whereas extrahepatic cholestasis will caused chronic pancreatitis and benign strictures [4].

2.4 Jaundice Assessment

2.4.1 Kramer's rule

Kramer's Rule is one of the technique used to evaluate baby that have experienced in jaundice. Kramer's Rule is similar to visual assesment. Regarding on Kramer's Rule, observation in newborn infant for jaundice begin from head of the baby then broadens towards the feet when the level rises [6][20][13]. Always assess jaundice in good light by blanching the baby's skin with a finger and observing the underlying skin colour [21]. Two clinical features of increasing severity of neonatal jaundice dominate the visual assessment:

- 1) The underlying skin colour changes from a lemon yellow to a deeper orange yellow.
- 2) The jaundice also progresses caudally from the face with a progression to the trunk and extremities, following Kramer's rule. If the feet or hands are visibly yellow, the TSB is likely to be above 250 $\mu\text{mol/L}$.

Rather than estimating the level of jaundice by simply observing the baby's skin colour, one can utilize the cephalocaudal progression of jaundice. Kramer drew attention to the observation that jaundice starts on the head, and extends towards the feet as the level rises. This is useful in deciding whether or not a baby needs to have the SBR measured [21]. Kramer divided the infant into 5 zones as shown in the Figure 3, and the SBR range associated with progression to the zones is shown in Table 1.



Fig. 3. Zones of Kramer's Rule [21]

Table 1
Serum bilirubin (SBR) range [13]

Zone	1	2	3	4	5
SBR ($\mu\text{mol/L}$)	100	150	200	250	>250

Unfortunately, Kramer's Rule is not beneficial if the baby have dark skin. There are limits to the accuracy of visual estimation of TSB levels, and, if there is any doubt clinically, TcB or TSB measurement should be performed [21]. Most hospitals in Malaysia using invasive method, by taking a specific amount of infant's blood and test it in the laboratory [3]. Thereby, the blood test need to be taken from the baby's heel onto a blood spot card [22] as shown in Figure 4. Then, the sample of blood will store in the dark because to prevent from the light exposure and immediately sent to the chemistry laboratory to determine the total serum bilirubin (TSB) level. The measurement takes around 30 minutes where it's measured by spectrophotometry by using two different of wavelengths, 455 nm and 575 nm. Unfortunately, invasive jaundice measurement has some drawbacks which is painful for the infants, occasionally dangerous and time consuming [23]. Besides that, discharging time for the mother and the infant is delay when the blood sample is needed to identify the bilirubin level in the infant. The result obtained from the central clinical laboratory is often slow, thereby health care cost will increasing [1].

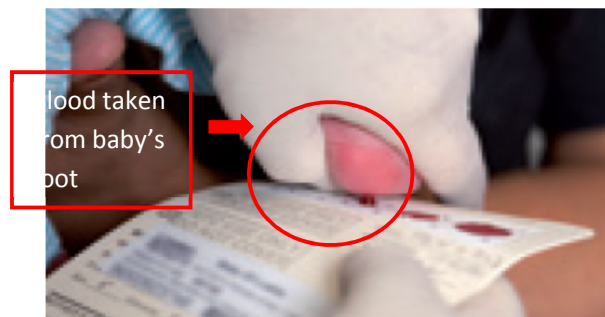


Fig. 4. Blood sample [22]

2.4.2 Abdominal ultrasonography

Abdominal ultrasonography is the initial imaging of choice to obtain information about the hepatic parenchyma and the intrahepatic and extrahepatic biliary tree. It is non-invasive and reproducible. However, there is an element of interobserver variation in real-time ultrasonography. A major disadvantage is that interpretation can be difficult in obese patients, and periampullary lesions and distal common bile duct pathology cannot be easily made out because of obscuring bowel gas. The sensitivity and specificity of detecting biliary obstruction in jaundiced patients vary from 55 to 91%, and 82 to 95% respectively, depending on the site of obstruction and radiographer's experience [24].

2.4.3 Transcutaneous Bilirubinometer

A large number of studies have demonstrated the possibility of prediction of serum bilirubin in neonates by measuring the yellowness of the skin in the jaundiced neonate using transcutaneous bilirubinometers. These meters work by directing light into the skin of the neonate and measuring the intensity of specific wavelength that is returned. The meter analyzes the spectrum of optical signal reflected from the neonate's subcutaneous tissues. These optical signals are converted to

electrical signal by a photocell. These are analyzed by a microprocessor to generate a serum bilirubin value [25].

A latest non-invasive product named Bilicheck (Specter, Inc) is developed as it can performs a spectral analysis at more than 100 different wavelengths. It displays the results in clinically appropriate units: mg/dl or $\mu\text{mol/L}$ [25].

The basic operating procedure for bilirubinometer explains that the optic head of the meter is gently pressed against the neonate's skin (usually forehead or upper part of sternum). For correct measurement, the optic head should make full contact with the skin and there should be no gaps between the head and the skin. This should be achieved by gentle pressure.

To take a measurement using the BiliChek, the device is calibrated prior to each measurement; the disposable probe (BiliCal) is applied on the forehead level below the hairline and five readings are used to generate one measurement that is displayed in $\mu\text{mol/L}$ [26]. When correct pressure is applied a green light alerts the operator to take a reading, if a faulty measure is taken an error message is displayed and the last reading must be repeated [26]. Figure 5 shows the Bilicheck device.



Fig. 5. Bilicheck device [26]

Bilicheck differs from the other meters, in that, each time, 5 values are recorded at different sites in a neonate and then the result gets displayed [25]. By comparing Bilicheck to the other bilirubinometers, it has come out with some advantages, such as:

- 1) The measurements are accurate for newborn of all races and ages
- 2) It is optimized for measuring bilirubin in the venous plexus.
- 3) The results are displayed in clinically appropriate unit mg/dl or $\mu\text{mol/L}$.

Eventhought it has a lot of advantages, Bilicheck's tip (Bili-Cal) need to be changed for each measurement, where it will adds to the cost of operation, This shows the disadvantage of using Bilicheck.

3. Conclusion

Jaundice is a common problem that faced by every newborn infant. Ministry of Health Malaysia have found that about 75% of newborns were jaundiced in the first week of life. It is an important clinical sign reflecting the accumulation of bilirubin in blood. There are several types of method or assessment to investigate the jaundice level which is Kramer's rule, Abdominal Ultrasonography, and Transcutaneous Bilirubinometer. Kramer's rule is not really suitable for baby that has dark skin, so blood test need to be done and this categorized it in invasive method. Abdominal ultrasonography is categorized in non-invasive but the major disadvantage is that interpretation can be difficult to obese patients. Therefore, Transcutaneous Bilirubinometer is one of the methods to measure the yellowness of the skin of a newborn baby. Transcutaneous Bilirubinometer is a non-

invasive method and can avoid babies from getting a skin infection when a blood sample is drawn. This method should be explored and studied.

References

- [1] Kudavelly, Srinivas, Payal Keswarpu, and S. Balakrishnan. "A simple and accurate method for estimating bilirubin from blood." In *Instrumentation and Measurement Technology Conference (I2MTC), 2011 IEEE*, pp. 1-4. IEEE, 2011.
- [2] Ramappa, Vidyasagar, and Guruprasad P. Aithal. "Jaundice: applying lessons from physiology." *Surgery (Oxford)* 32, no. 12 (2014): 627-634.
- [3] Osman, Zulfadhli, Afandi Ahmad, and Azlan Muharam. "Rapid prototyping of neonatal jaundice detector using skin optics theory." In *Biomedical Engineering and Sciences (IECBES), 2014 IEEE Conference on*, pp. 328-331. IEEE, 2014.
- [4] Houlihan, Diarmaid D., Matthew J. Armstrong, and Philip N. Newsome. "Investigation of jaundice." *Medicine* 39, no. 9 (2011): 518-522.
- [5] C. M. Lewandowski, "Management of Neonatal Jaundice," *Eff. Br. Mindfulness Interv. Acute pain Exp. An Exam. Individ. Differ*, vol. 1, pp. 1689-1699, 2015.
- [6] M. of H. M. Medical Development Division Ministry, "Clinical Practice Guidelines, Management of Jaundice in Healthy Term Newborns," *Minist. Heal. Malaysia, Acad. Med.*, vol. 3, no. February, 2003.
- [7] Mansor, M. N., S. Yaacob, M. Hariharan, S. N. Basah, SHFS Ahmad Jamil, ML Mohd Khidir, M. N. Rejab et al. "Jaundice in newborn monitoring using color detection method." *Procedia Engineering* 29 (2012): 1631-1635.
- [8] "Assessment Health," *Minist. Heal. Malaysia, Acad. Med.*, 2002.
- [9] Zakaria, Z., J. Abd Jalil, S. Sarkawi, I. Balkhis, M. Aliff, A. Rahim, and N. Mustafa. "A Short Review on Kramel's Rule and Magnetic Induction Spectroscopy." *vol 6* (2015): 103-106.
- [10] R. & Walsh, "Kernicterus," 2010. [Online]. Available: <http://www.abclawcenters.com/frequently-asked-questions/can-jaundice-cause-cerebral-palsy/>. [Accessed: 27-Nov-2015].
- [11] H. H. NICU, "Newborn Assessment," Neonatology Resident Al Hadi Hospital, 2013. [Online]. Available: <http://www.slideshare.net/shajuedamana/newborn-assessment-by-hadi-hospital-nicu>.
- [12] Zulkarnay, Z., A. J. Jurimah, B. Ibrahim, S. Shazwani, E. M. Cheng, A. R. Ruzairi, and MAK Abdul Nasir. "An overview on jaundice measurement and application in biomedical: The potential of non-invasive method." In *Biomedical Engineering (ICoBE), 2015 2nd International Conference on*, pp. 1-6. IEEE, 2015.
- [13] D. Simkiss and R. Martin, "Neonatal jaundice," *J. Trop. Pediatr.*, vol. 58, no. 5, pp. 339-340, 2012.
- [14] Friel, James K., Russell W. Friesen, and B. Sc. "Bilirubin: Friend or Foe?." (2003): 1-21.
- [15] Nag, N., S. Halder, R. Chaudhuri, S. Adhikary, and S. Mazumder. "Role of bilirubin as antioxidant in neonatal jaundice and effect of ethanolic extract of sweet lime peel on experimentally induced jaundice in rat." (2009).
- [16] Wang, Xia, Jayanta Roy Chowdhury, and Namita Roy Chowdhury. "Bilirubin metabolism: applied physiology." *Current Paediatrics* 16, no. 1 (2006): 70-74.
- [17] L. Fialová and M. Vejražka, "Bile pigments Porphyrins General Medicine," 2013.
- [18] Tenhunen, Raimo, Harvey S. Marver, and Rudi Schmid. "The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase." *Proceedings of the National Academy of Sciences* 61, no. 2 (1968): 748-755.
- [19] Fevery, Johan. "Bilirubin in clinical practice: a review." *Liver International* 28, no. 5 (2008): 592-605.
- [20] British Columbia Reproductive Care Program, "Jaundice in the healthy term newborn," *Newborn Guidel.* 4, no. April, pp. 1-20, 2004.
- [21] PROTOCOL, SMALL BABY. "RPA Newborn Care Guidelines."
- [22] N. S. U. of the M. of Health, "The Newborn Metabolic Screening Programme," *Newborn Screen. Free Heal checks your baby*, pp. 1-8, 2010.
- [23] Szabo, Peter, Martin Wolf, Hans Ulrich Bucher, Jean-Claude Fauchere, Daniel Haensse, and Romaine Arlettaz. "Detection of hyperbilirubinaemia in jaundiced full-term neonates by eye or by bilirubinometer?." *European journal of pediatrics* 163, no. 12 (2004): 722-727.
- [24] Baron, R. L., R. J. Stanley, J. K. Lee, R. E. Koehler, G. Leland Melson, D. M. Balfe, and P. J. Weyman. "A prospective comparison of the evaluation of biliary obstruction using computed tomography and ultrasonography." *Radiology* 145, no. 1 (1982): 91-98.
- [25] D. of N. WHO-CC Department of Pediatrics, "Transcutaneous Bilirubinometer," 2006.
- [26] T. Bilirubinometers, "Transcutaneous Bilirubinometers Use of Transcutaneous Bilirubinometers (TcBs) Serum bilirubin blood test (SBRs) Indications for SBR blood tests Risk factors for jaundice in the term infant TcB Measurements," 2006.