

Determining the Correlation and Accuracy of Three Methods of Measuring Neonatal Bilirubin Concentration

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Abstract

Objective: There are different methods for measuring bilirubin concentration; however, it is quite important for practitioners to know which method should be used in certain clinical situations. The present prospective study aimed to compare three different methods for measuring neonatal bilirubin concentrations.

Methods: All full term neonates who were either brought into emergency departments or admitted to the neonatal wards in Kerman city in 2011 were recruited (n=428). The correlation coefficients were estimated for the routine ways of bilirubin concentrations including "Capillary", "Cutaneous" and "Laboratory" methods.

Findings: Of 428 recruited neonates, 178 were female. Mean age \pm SD was 178 ± 71 hours. The correlation coefficient for "David Ictrometer" vs "JM103" was 0.91, while the corresponding coefficient for "David Ictrometer" vs "Capillary" was 0.96. It was also equivalent to 0.85 for correlation between "JM103" and "Capillary" methods. The David Ictrometer measured an average of 2.36 mg/dl levels of bilirubin concentration compared to the JM103 method. The Capillary method showed a lower bilirubin level than the venous concentration (0.91 mg/dl on average). Compared with the "Capillary", the "JM103" measured a slightly higher level of bilirubin with an average 0.57 mg/dl.

Conclusion: Due to low difference (less than 1 mg/dl) between "JM103" and the "Capillary methods" for measurement of neonatal bilirubin concentration, these two methods could alternatively be used instead of usual laboratory method.

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Key Words: Capillary Bilirubinometer; Neonate; Bilirubin; David Ictrometer

Introduction

Jaundice is one of the most prevalent clinical problems during neonatal period which requires interventional treatment^[1]. It affects 60% of healthy term neonates during the first week of life^[1,2]. Despite the fact that most icteric neonates have not any other disorders, physicians are worried about the toxic effects of bilirubin on neural cells and the subsequent appearance of

kernicterus which is a chronic, degenerative and debilitating disease^[2,3]. Due to socioeconomic reasons, there is a global agreement on the early discharge of healthy neonates from hospitals and if neonatal hyperbilirubinemia was not predicted at this stage, the early discharge of these neonates will be leading to an increase in the incidence of kernicterus^[5,6].

Different methods of measuring the serum levels of bilirubin are currently used which can be

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categorized into three groups of "Cutaneous" (A non-invasive method of measuring bilirubin precipitated in the layers of skin by relevant apparatus, "Capillary" (Bilirubin measurement using a spectrophotometer) and "Laboratory" (The typical method of serum bilirubin measurement using chemical reactions).

There are only a few studies investigating the correlations between the popular and the new laboratory methods as alternative methods for bilirubin measurement^[7]. The apparatus for cutaneous and capillary measurements are currently presented in Iran.

By achieving this study, the correlation rate of these apparatuses has been clearly defined and there is a chance to test the "JM103" (Draeger Medical System, Inc, Telford, PA) setting and to clarify the functions of the "Capillary" and "Cutaneous" methods of bilirubin measurement in different levels for the first time, in Iran. In addition, this study suggests replacing the ordinary laboratory systems with the "capillary" and "cutaneous" methods as a practical and reliable method to minimize the pain and discomfort during blood sampling in neonates.

Subjects and Methods

This prospective non-blind randomized clinical trial study was performed in 3 steps and in 3 different locations. Term healthy icteric neonates without sepsis or hemolysis enrolled the study. Infants with Rh or ABO isoimmunisation, major congenital malformations, hemoglobinopathies, evidence of liver disease or receiving phototherapy 12 hours before study were excluded from the study (Fig. 1).

The first step: 120 term healthy infants without sepsis or hemolysis were enrolled to determine the correlation and measurement accuracy of bilirubin serum level by the 2 methods "laboratory" and "capillary": All the icteric neonates who were brought into the Emergency Department of Afzalipour Hospital of Kerman University of Medical Sciences and all the icteric neonates admitted to the neonatal ward of this hospital entered this study. To determine the serum bilirubin level, 2 cc venous blood was taken

from each neonate. The samples were sent to the hospital laboratory. After several minutes, 2 capillary samples were taken in capillary tubes from the baby's heel and bilirubin measured by a bilirubinometer apparatus after centrifugation. The average value of the 2 samples was recorded as the capillary bilirubin level.

The second step: 160 infants involved in evaluating the accuracy and correlation rates of the bilirubin level measured by cutaneous measurement apparatuses: Healthy neonates brought into the clinic to be checked for any possible jaundice were investigated by 2 cutaneous measurement apparatuses, simultaneously over chest skin, to measure the level of bilirubin.

The third step: 148 infants enrolled in determining the correlation and measurement accuracy of bilirubin level by the 2 methods "cutaneous" and "capillary": This step of the study was performed at the Imam Hassan Mojtaba Health Center. A blood sample, from the samples taken for thyroid screening purposes, was prepared in a capillary tube and was immediately centrifuged and analyzed by a bilirubinometer. The bilirubin level was then measured over the thorax of the neonates by cutaneous measurement apparatus. The apparatuses were correlated at this stage in each working shift according to the manufacturer's guidelines. The neonates, who experienced home phototherapy, were excluded from the study. We acquired informed consent from parents before entering neonates into our study. The research was approved by Ethics Committee of Kerman University of Medical Sciences.

Considering a maximum of 5% as the first type error, 20% as the second type error and 4% as the minimum valuable correlation, the sample size was estimated to be 65 for the present study. By comparing the three methods, the estimated figure was multiplied by the square root of 2, according to which, a sample size of 90 was estimated for calculating simple correlations. For eliminating the effects of at least 2 confounding variables such as skin color, 20% was added to the estimated sample size and the final figure of 108 was estimated as the study sample size.

Data was analyzed using Pearson's correlation. The correlation rate of the results of the two other methods and the method of measurement by

The first step:

- * 120 full term healthy infants without sepsis or hemolysis
- * 2 cc venous blood samples were taken from each neonate. After several minutes, 2 capillary samples were taken in capillary tubes from the baby's heel and were entered into a bilirubinometer apparatus after centrifugation.

The second step:

- * 160 infants involved for the accuracy of bilirubin level (by cutaneous apparatuses)
- * Healthy neonates, who were brought into the clinic to be checked for any possible jaundice, were investigated by 2 coetaneous measurement apparatuses, simultaneously at their chest, to measure the level of bilirubin.

The third step:

- * 148 infants for determination the accuracy of bilirubin level by the two methods of "cutaneous" and "capillary"
- * Blood samples for thyroid screening analyzed by a bilirubinometer apparatus
- * Measurement of bilirubin level from the thoracic part of the neonates by cutaneous measurement apparatuses

Fig. 1: Randomized Controlled Diagram (RCT)

venous sample (standardized chemical analysis) was then calculated using the linear regression method. In this study the correlation coefficient of higher than 0.8 and *P* value of less than 0.05 was considered statistically significant.

Findings

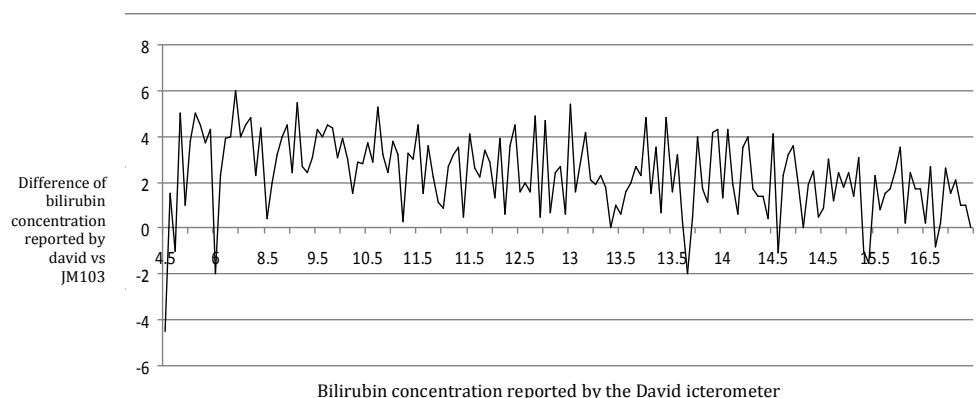
Of 428 recruited neonates, 178 were female. Mean age \pm SD was 178 ± 71 hours. There was no statistically significant difference between the three groups of study regarding the age and sex at entrance.

A total of 73 neonates were excluded from the study because of the hemolysis of their capillary blood samples. The range of bilirubin level measured in the first, second and the third stage of

the study was 1-30 mg/dl, 1-30 mg/dl and 1-18 mg/dl, respectively.

Fig. 2 illustrates that the David Icterometer apparatus has measured the bilirubin concentration averagely 2.36 mg/dl more than that measured by the JM103 apparatus. This difference is statistically significant ($P < 0.001$)^[1]. The correlation coefficient between the concentrations reported by these two tools is 0.91 which is also statistically significant. The figure also shows that the difference in the concentration of bilirubin measured by these two apparatuses is seen in almost all ranges of bilirubin concentration.

Fig. 3 shows that the bilirubin concentration in capillary blood sample is averagely 0.91 mg/dl lower than that measured in venous sample. This difference is statistically significant ($P < 0.001$). The correlation coefficient between the concentrations reported by these two tools is obtained as 0.96

**Fig. 2:** Comparing the measured bilirubin level by two cutaneous apparatuses

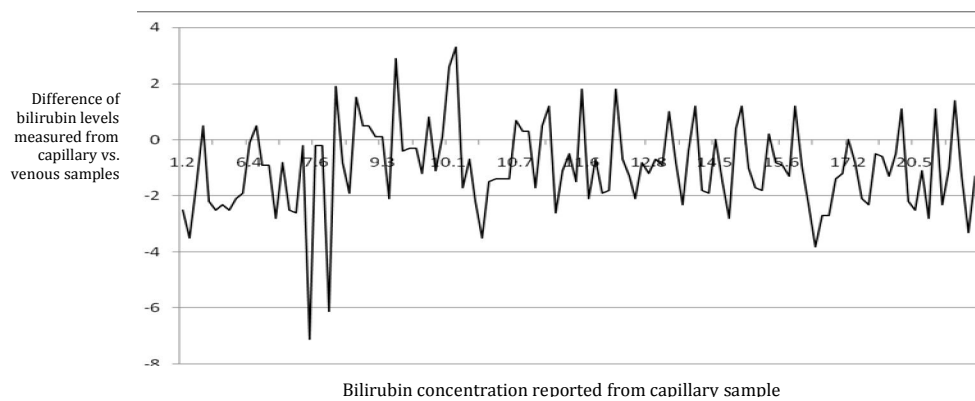


Fig. 3: Comparing the measured bilirubin levels by the capillary and laboratory methods

which is also statistically significant. In addition, this figure shows that the difference in the concentration of bilirubin by the two tools is almost seen in all the ranges of bilirubin concentration reported.

Fig. 4 indicates that David Icterometer apparatus has measured the bilirubin concentration 3.1 mg/dl more than the capillary samples on average. This difference is statistically significant ($P < 0.001$). The correlation coefficient between the concentrations reported by these two tools is 0.85. This difference is more obvious at lower concentrations of bilirubin whilst it is not detected above the bilirubin concentration of 9 mg/dl, and at this level of bilirubin shows a better correlation with the capillary method.

Fig 5 indicates also that the JM103 apparatus has measured the bilirubin level averagely 0.57 mg/dl more than the capillary samples. This difference is statistically significant ($P < 0.001$). The correlation coefficient between the concentrations reported by these two tools is 0.89

but the difference pattern among different concentrations of bilirubin is almost constant.

Discussion

Because of the early discharge of neonates from hospitals, a worldwide concern appeared on the uncontrolled neonatal hyperbilirubinemia and its sequels. In July 2004, The American Academy of Pediatrics proposed a practical protocol to all neonatal surveillance centers as to examine any possible jaundice in the neonates above 35 weeks of age. It also notified that all neonatal wards must possess a practical instruction as to examine and pursue jaundice in neonates^[4]. Although this academy did not define any methods of bilirubin examination or measurement, measuring the serum bilirubin level is one of the most common laboratory tests carried out in neonates. This test

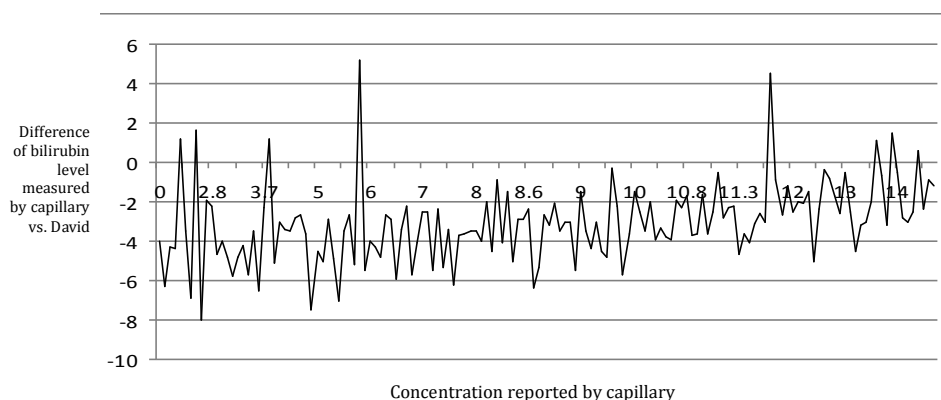


Fig. 4: Comparing the measured bilirubin level by the capillary and David Icterometer

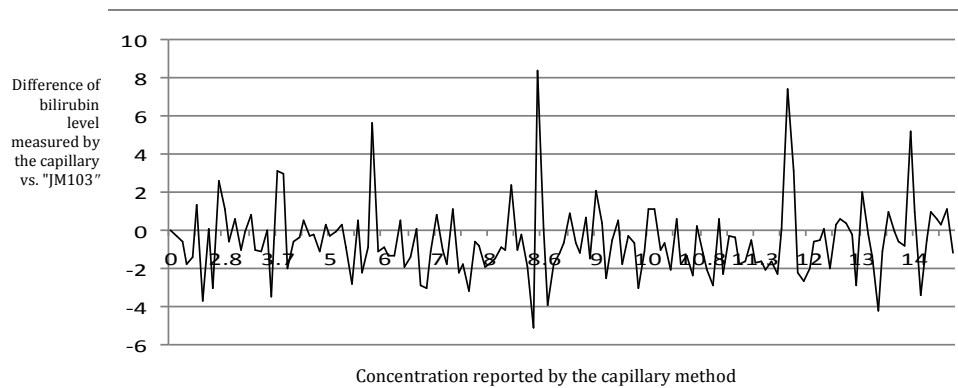


Fig. 5: Comparing the measured bilirubin level by the capillary and JM 103 apparatuses

is painful and can put the neonate at increased risk of sepsis. On the other hand, this test is stressful for both the neonate and parents and requires a lot of time and money. Therefore, a reduction in repeated blood sampling is very important which might be achieved by utilizing the new set of apparatuses, available on market, for cutaneous and capillary measurement of bilirubin concentration. Different studies have evaluated the sensitivity and accuracy of these tools, according to which different results have been obtained^[7-11].

According to the literature review concerning the role of cutaneous measurement apparatuses, it has been shown that the "JM103" tool has a good correlation with serum bilirubin level in neonates; however, because of its different error factors, it cannot predict the precise serum bilirubin concentration and therefore, the cutaneous bilirubin test, on its own, cannot be a reliable criterion for exchange transfusion or phototherapy in neonates^[12].

In another study, a comparison was made between the accuracy of the two cutaneous measurement apparatuses "JM103" and "Bilichcek" in measuring the serum bilirubin concentration. The accuracy of these two tools on estimating different levels of bilirubin was assessed and it was shown that a significant correlation and similarity existed between the serum and the cutaneous bilirubin concentration measured by these tools.

The difference between the level of serum bilirubin and the cutaneous bilirubin measured by "JM103" was 0.7 mg/dl which was also 0.7 mg/dl for the "Bilichcek" apparatus^[13].

Another study compared the correlation between the bilirubin levels measured by 9 different methods (3 cutaneous measuring apparatuses, 3 photometric apparatuses, 3 chemical and laboratory analyses) and concluded that photometric apparatuses had good correlations with chemical and laboratory methods; however, when the serum level of bilirubin is high, the cutaneous measurement apparatuses show a lower bilirubin concentration^[14].

The present study showed that the "JM103" has a significant correlation with the laboratory and capillary methods and that the bilirubin concentration measured by this apparatus is averagely 0.57 mg/dl higher than the capillary method and 0.34 mg/dl lower than that measured by laboratory method (correlation coefficient 0.89). This study also showed that the sensitivity and accuracy of the "JM103" was constant among all the different levels of bilirubin and even on high concentrations of bilirubin, it is possible to decide reliably, based on the bilirubin level measured by this apparatus, on the procedures for pursuing the icteric neonates. The "JM103" can, with a high sensitivity, replace the ordinary laboratory methods of neonatal bilirubin measurements, even though the manufacture setting of this apparatus is set in a way that no more than 20 mg/dl of bilirubin concentration can be measured.

This study showed that the "David Icterometer" apparatus measured the bilirubin level averagely 3.1 mg/dl higher than the capillary method and about 2.2 mg/dl higher than the serum level in venous samples. This difference is statistically

significant ($P < 0.001$) and is more obvious in lower bilirubin levels. At bilirubin levels higher than 9 mg/dl, however, the results obtained showed a slight difference and had a better correlation with capillary method. Although the statistical results are indicative of a correlation between bilirubin levels measured by David Icterometer and capillary (correlation coefficient 0.85), however, during evaluation of neonatal hyperbilirubinemia, particularly at levels which need interventional treatment, this amount of difference in serum bilirubin level is not accepted and can lead to incorrect decisions on presuming jaundice in neonates.

This study showed that the capillary method has a significant correlation with the laboratory method and that the bilirubin level measured is averagely 0.9 mg/dl less than the serum level (correlation coefficient 0.96). This difference is constant among the different levels of bilirubin and is independent of its concentration. This study also showed that the capillary method can be used not only as a tool for pursuing jaundiced neonates, is also as a suitable alternative for laboratory methods. The capillary method, however, is influenced by many variables which, in turn, limit its application as a preliminary option in measuring neonatal bilirubin as well as its potential in becoming a suitable alternative for ordinary laboratory methods. This method, compared to venous blood sampling, is less invasive, causes less pain in the neonate and requires less talent and experience.

To avoid frequent and repetitive blood sampling, the capillary and JM103 methods can be used, with a high confidence, to measure the neonatal bilirubin level. The David Icterometer method, however, measures the bilirubin level averagely 2.2 mg/dl higher than the serum level which, from a clinical point of view, is a significant difference and, at higher bilirubin levels, can lead to wrong decisions in pursuing jaundiced neonates.

We had some limitations to our study. First of all, we excluded newborns that were exposed to phototherapy. Therefore, our results could not be used for newborns who received phototherapy. Second, we excluded neonates with prematurity, sepsis, hemolysis or liver disease. Therefore, our study could not be used for sick or preterm newborns.

Conclusion

The JM103 apparatus has a significant correlation with the serum bilirubin level without a notable difference between the apparatus-measured and the actual serum bilirubin level. Therefore, at bilirubin concentrations less than 20 mg/dl, this apparatus can be used both as a monitoring tool and as an alternative for routine laboratory methods of bilirubin measurement. The JM103 technique can be used as the primary method in assessing jaundice in neonates; however, at bilirubin levels higher than the limits of this apparatus or levels requiring interventional treatments such as phototherapy or exchange transfusion, the capillary method could, instead, be used as the first option in investigating jaundice in neonates.

Considering the fact that healthy neonates with normal peripheral perfusion were investigated in this study to assess the accuracy and sensitivity of cutaneous bilirubin measuring methods, it seems that the results of this study cannot be extrapolated to sick or premature neonates. Further studies on sick and premature neonates are, therefore, recommended.

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Conflict of Interest: None

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