Noninvasive Estimation of Serum Bilirubin

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ABSTRACT. Objective. The aim of this study was to evaluate the accuracy and clinical usefulness of a new computer-driven, hand-held device (Chromatics Colormate III) to estimate serum bilirubin from skin-reflectance (skin color) of neonates.

Study Design. A total of 2441 infants (both term and premature) at two hospitals had repeated measurements of transcutaneous bilirubin. Of these infants, 900 had one or more laboratory determinations of serum bilirubin. Many of the infants had early measurements of skin color before the onset of jaundice. A visual estimate of the degree of jaundice was made by a health care worker when the laboratory study was drawn. A subgroup of 61 infants was also studied while undergoing phototherapy with a total of 284 comparisons obtained. The reproducibility of the instrument was assessed separately using standardized color tiles and repeated measurements by multiple operators.

Results. The range of serum bilirubin measurements that had concurrent skin color measurements was 3.22 to 338.1 μmol/L (0.2 to 21 mg/dL). The linear regression indicated an r = 0.956, and 95% of the skin color measurements were within 32.2 μmol/L (2.0 mg/dL). There was no interference with the accuracy of the device because of infant race or weight, or because of the use of phototherapy. The device provided reproducible information when infants were tested repeatedly over 30 minutes; the coefficient of variation for the transcutaneous bilirubin measurement was 3.1% around a mean estimate of 135.32 μmol/L (8.4 mg/dL).

Conclusion. The Chromatics Colormate III allows for a clinically useful estimate of serum bilirubin in a wide variety of infants. By using a color discrimination algorithm and obtaining a skin measurement before the onset of icterus, this instrument can provide valuable clinical information that obviates the need for serum bilirubin determinations. Its use in newborn nurseries may allow physicians to shorten length of stay more safely and decrease the use of invasive blood tests. Pediatrics 1998; 102(3). URL: http://www.pediatrics.org/cgi/content/full/102/3/e28; jaundice, newborn, transcutaneous.

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Throughout the conception and performance of the studies reported, we were neither financially affiliated with nor received any remuneration from Chromatics Color Sciences, Inc. The maker of the colorimeter did supply both technicians, who were responsible for performing many of the clinical measurements, and the colorimeters that were used in the studies. At present, Dr Ian R. Holzman is a member of the Medical Advisory Board of Chromatics Color Sciences, Inc.

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T he ability to assess bilirubin simply, rapidly, and cost-effectively has taken on increased importance with the advent of managed care, capitation, and brief postpartum hospitalization. Concerns about the reappearance of kernicterus have been published as physicians attempt to respond to seemingly conflicting forces. Although a number of noninvasive methods are available to screen for significant jaundice (or the risk of developing jaundice), none have achieved widespread acceptance. We undertook an extensive evaluation of a new transcutaneous bilirubinometer that appeared to offer advantages over methodologies described previously. The study involved infants receiving routine care in two large inpatient facilities and was designed to determine whether the device could provide clinically useful information on the concentration of serum bilirubin in a diverse group of hospitalized newborns. These infants were to include both full-term and premature infants of multiple races, as well as infants receiving phototherapy. We also included in the study the visual estimates of the degree of icterus by the clinical caretakers to assess further the utility of the device. The overall goal of the project was to provide health care workers with a tool to eliminate the majority of serum bilirubin determinations presently obtained.

METHODS

From November 1988 to July 1997, a total of 2441 infants at Mount Sinai Medical Center and the City Hospital Center at Elmhurst, both in New York City, were enrolled in this study. As many patients as possible were sequentially enrolled in the study from both the well-baby nurseries and the neonatal intensive care units of both institutions. They were excluded only if their medical condition precluded any extraneous handling, if there was a family psychosocial barrier to inclusion, or if the family refused participation. The large number of study patients and the extensive time to complete the study were required to obtain a significant sample of infants who went on to need a measurement of serum bilirubin concentration.

After obtaining institutional review board-approved informed consent, each infant had an initial set of skin color measurements made within the first 30 hours of life (this time reflects the actual latest time an infant had a first measurement). These measurements were obtained with the Colormate III (Chromatics Color Sciences International, Inc, New York, NY), which is a hand-held colorimeter containing a Xenon flash tube and light sensors connected to a portable computer. Data are processed by the computer and reported as standard color coordinates (luminosity, redness, and yellowness). The instrument measures over a band of wavelengths from 400 to 700 nm with specific filters used to assess the reflectance of light for specific wave lengths. The algorithm incorporated into the device has been designed to examine the luminosity or lightness of the skin as a stable component (luminosity is the color science term for the actual light being emitted and is distinguished from the specific color of the light). The algorithm also incorporates the underlying color of normal
skin and can account for that in the baseline evaluation. Changes in the yellow component of the spectrum can be observed separately and used as a bilirubin estimate. In effect, a mathematical adjustment is made to the value of yellow that takes into account the underlying lightness of the skin. An integral part of the measurement process includes the computer analysis of the stability of luminosity. The software program requires that measurements be made on three of the following four sites (right or left cheek, back, forehead, chest), that at least the right or left cheek and the back or chest be measured, and that the sites used initially be used for subsequent measurements. These sites were chosen after extensive pilot investigations designed to improve the utility of the machine. The actual study protocol involved an initial color tile calibration followed by five measurements taken in rapid sequence on each of five sites (forehead, both cheeks, chest, back). This entire process took <5 minutes. No alterations were made in the actual measurement device (other than the addition of battery power capability) over the long period of the study.

Measurements were repeated on each enrolled infant at 6- to 8-hour intervals until discharge. This range was chosen as a way to balance the practicality of performing the study with the need to capture significant changes in jaundice. The physicians caring for the infants determined whether a serum bilirubin determination was required at any point. No health care worker had access to the results of the skin color measurements. When a serum bilirubin sample was sent to the clinical laboratory, the nurse or physician caring for the infant was asked to estimate the total serum bilirubin based on visual icterus. This was not always convenient, and fewer visual estimates were recorded than actual laboratory bilirubin measurements obtained. When a serum sample was to be obtained, a corresponding skin color measurement was made to compare both the laboratory value and the visual estimate. Infants received phototherapy as clinically indicated, and skin color measurements continued while infants were under single or double phototherapy lights.

The laboratory measurement of bilirubin was performed in the clinical laboratories of both institutions using standard methodologies (Beckman CX7, Beckman Instruments, Brea, CA; AO Unistat, Cambridge Instruments, Buffalo, NY; IL Monarch, Instrumentation Laboratory Company, Lexington, MA; or Bayer Chem-1, Technicon Instruments Corporation, Tarrytown, NY). The coefficient of variation for these laboratory measurements is between 3% and 6%. The data reported use the total serum bilirubin concentration for each infant because this is the clinical measurement commonly obtained. During the period of investigation, none of the infants studied were readmitted to either institution for direct hyperbilirubinemia. The influence of small quantities of either conjugated or delta bilirubin on the reported results cannot be estimated from this study.

A separate study to assess interoperator reproducibility also was performed in which three different technicians repetitively performed five measurements on standardized skin color tiles. Three different operators also made sequential measurements over 30 minutes on seven infants of four different ethnic groups.

RESULTS

Of the 2441 infants enrolled in the study, 900 had one or more laboratory determinations of total serum bilirubin during hospitalization and 1600 separate evaluations of skin color with the jaundice meter. This group of 900 patients is reported in this study. This population consisted of 72 African-American infants, 110 Caucasians, 615 Hispanics, and 103 Asians. Of the group, 455 infants were male and 445 female. The average birth weight of the infants was 3135 g (SD = ±612), with 53 of the infants weighing <2000 g and 11 weighing <1500 g. A total of 61 infants required phototherapy. Of these infants, 19 weighed ≤2000 g. The group included 15 Caucasian infants, 31 Hispanic infants, 11 African-American infants, and 4 Asian infants.

The average time at which the first skin color measurement was obtained for the 900 infants was 11.9 (SD = ±0.9) hours after birth, with the earliest sample obtained at 1 hour. At one of the institutions (Elmhurst Hospital), it was routine to obtain an early laboratory measurement of bilirubin before the onset of clinical icterus. This knowledge of the contribution of clinically not apparent “icterus” to the baseline skin color of the infant allowed for an improvement in the mathematical algorithm that converts the “physical” skin color characteristics to a bilirubin number. The range of serum bilirubin measurements that had concurrent skin color measurements was 3.22 to 338.1 μmol/L (0.2 mg/dL to 21 mg/dL). Because it was not possible to obtain many of the skin color measurements at the exact time a blood sample was obtained, there is a range of times around the blood study when the skin color was assessed. The transcutaneous reading was done, on
average, within a 40-minute (SD = ±31) period of the laboratory measurement. Figure 1 presents the linear regression data for the entire population of 900 infants who had both skin color measurements and serum total bilirubin analyses (r = 0.956). When an initial baseline skin color measurement is not performed, the correlation coefficient drops to ~0.85. An examination of all the data points comparing a laboratory bilirubin measurement and a skin color measurement reveals that 95% of the skin color measurements were within 32.2 μmol/L (2.0 mg/dL) of the laboratory number. There were only seven measurements in which the skin color estimate of bilirubin was >193.32 μmol/L (12.0 mg/dL) and the laboratory measurement was <177.21 μmol/L (11.0 mg/dL). Similarly, there were only eight measurements in which the skin color indicated a number >193.32 μmol/L (12.0 mg/dL) and the laboratory measurement was <177.21 μmol/L (11.0 mg/dL). A comparison was made of the results by infant race, and there was no difference in the ability of the transcutaneous bilirubinometer to assess bilirubin regardless of the race of the infant (r values: Caucasian = 0.94; African-American = 0.92; Hispanic = 0.94; Asian = 0.94). Figure 2 presents the linear regression for the comparison of the health care worker’s estimate of the serum bilirubin to that obtained by the laboratory analysis (r = 0.748). A separate analysis of the relationship of the colorimeter skin measurement and the laboratory bilirubin value was performed for those infants who underwent phototherapy. A total of 284 comparisons were available for this group of 61 patients. The linear regression for this comparison (r = 0.921) is shown in Fig 3.

The reproducibility evaluation consisted of two separate studies. The first examined five repeated measurements of a standardized color tile by three different operators. The coefficient of variation for the luminosity measurement was 0.019%. In the second study, three different operators made sequential measurements over ~30 minutes on seven infants. The coefficient of variation for the transcutaneous bilirubin measurement was 3.1% around a mean estimate of 135.32 μmol/L (8.4 mg/dL). It also has been possible to determine which individual readings of skin color represent technical error and should be repeated. Once the baseline skin color is established, an increase in the skin luminosity of greater than 5 represents an artifact attributable to a poor seal against the skin or moisture from an inadequately cleaned skin site.

**DISCUSSION**

The transcutaneous bilirubinometer has been evaluated in a number of studies and has been proposed as a valuable screening device that might aid in decreasing length of stay. Unfortunately, concerns exist regarding linearity of transcutaneous measurements. The literature also suggests a complex relationship between phototherapy and the measurement of transcutaneous bilirubin; it is unclear if it works reliably when phototherapy has been used.

The device described in this investigation has a sophisticated computer algorithm for assessing underlying skin color. The algorithm allows for the “mathematical” extraction of yellow color regardless of the underlying skin pigmentation or degree of erythema. The accuracy of the device, especially when phototherapy is used, is increased by an early determination of an infant’s underlying skin type before the onset of visual jaundice. This improved computer calculation obviates many of the difficulties noted previously with transcutaneous bilirubinometry. It also has been possible to determine which individual readings of skin color represent technical error and should be repeated.

Although the data are not presented, during the study we also examined both the cephalocaudal progression of jaundice and the efficacy of vari-
ous sites for measurement. We were able to confirm that there is a progression of jaundice from face to chest and back; however, once the serum bilirubin exceeds 193.32 \( \mu \text{mol/L} \) (12 mg/dL) additional cephalocaudad progression can no longer be assessed reliably by transcutaneous bilirubinometry. We also determined that it is essential for measurements to be made on either the right or the left cheek and either the chest or the back. It is assumed that this represents the known predilection of these sites to become visually icteric early in the progression of jaundice.

The present instrument allows for a way to evaluate the extent and progression of jaundice in newborn infants. Any device that purports to measure “jaundice” is, by necessity, compared with the clinical laboratory measurements of bilirubin presently available. This introduces a significant problem in evaluation because the coefficient of variation of the laboratory tests used have been reported to be anywhere from 3.4% to 17.2%.\(^{20-22}\) It has been suggested that the measurement of skin color could provide information more relevant to the risk of brain injury than what can be derived from blood bilirubin measurements. If some of the factors responsible for the transfer of bilirubin into brain also operate in the skin, skin icterus would be a more “physiologic” measurement.\(^{16}\)

It has long been known that the ability of health care workers to assess jaundice is quite limited. We have shown (Fig 2) in a wide variety of infant skin types and gestational ages how poor visual estimates truly can be. Infants were thought to be minimally jaundiced with serum bilirubin measurements in the 193.32 to 241.65 \( \mu \text{mol/L} \) (12 to 15 mg/dL) range. With the emphasis on early discharge of newborns, a greater number of infants may require blood tests before discharge or while at home as a response to the concerns about the recurrence of kernicterus.\(^{23}\) As Maisels has suggested,\(^{12}\) transcutaneous bilirubinometry offers a simple method to assess jaundice that can save money and needless testing.

It was not possible to obtain measurements of transcutaneous bilirubin on infants with serum bilirubin values >338.31 \( \mu \text{mol/L} \) (21 mg/dL), nor are there an adequate number of samples to assess the value of the device for serum bilirubin concentrations approaching 322.2 \( \mu \text{mol/L} \) (20 mg/dL). Although these data should become available with more experience using the bilirubinometer, we do not believe this affects the utility of this tool for screening; the majority of the decisions concerning phototherapy and discharge occur at values <322.2 \( \mu \text{mol/L} \) (20 mg/dL). An initial measurement made before the development of clinical icterus (preferably during the first 6 to 8 hours after birth), followed by measurements if an infant appears jaundiced or at the time of discharge, should eliminate the need for blood tests in the vast majority of infants. There were only eight occurrences in which the skin color measurement underestimated a serum bilirubin concentration \( >193.32 \mu \text{mol/L} \) (12.0 mg/dL). This cutoff was examined because it is unlikely that an unsensitized infant will become significantly jaundiced if a serum bilirubin is below this number at 48 hours of age. The device also can be used for home measurements or office measurements for those infants who are reported to have increasing clinical jaundice. Infants also can be tracked while undergoing phototherapy because the correlation is nearly as good for this group. Although the smaller infants in this study could not be distinguished from term infants in the ability of the bilirubinometer to estimate bilirubin, we did not have a large number of small sick infants. We also were unable to obtain many small infants with serum bilirubin concentrations \( >161.1 \mu \text{mol/L} \) (10 mg/dL) because of our routine care guidelines. We expect that greater experience with the machine in a large number of nursery settings should allow an even better estimate of its utility.
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