COMPARING TRANSCUTANEOUS VS. SERUM BILIRUBIN AFTER PHOTOTHERAPY IN THE OUTPATIENT SETTING

A thesis submitted to the University of Arizona College of Medicine - Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Natasha Makarova
Class of 2017

Mentor: Shawn McMahon, MD, MPH

ABSTRACT

Currently few studies have investigated the accuracy of using transcutaneous bilirubinometry after phototherapy especially in the outpatient setting. The purpose of this study was to evaluate the accuracy of transcutaneous bilirubin measurements (TCB) after phototherapy for neonates with jaundice. At the Maricopa Integrated Health System, neonates who undergo phototherapy for hyperbilirubinemia come in for outpatient follow-up at the Comprehensive Health Center following their discharge. For those neonates, current protocol calls for serum bilirubin (TSB) to be measured to properly monitor bilirubin levels, however transcutaneous measurements were made and recorded as well. In this study, we compared the values of total serum bilirubin and transcutaneous bilirubin in jaundiced neonates who underwent phototherapy. From October 2013-April 2015, a total 67 healthy infants were seen in the Pediatric Clinic who had received phototherapy in our hospital, only 36 (54%) of those met minimum data criteria to be included in the study. The absolute difference between mean serum bilirubin and transcutaneous bilirubinometry in healthy outpatient newborns who received inpatient phototherapy was 0.4 and is clinically insignificant. The average time from hospital discharge to return to clinic was 47 hours. We conclude that for the outpatient physician, transcutaneous bilirubinometry can be used following phototherapy, which facilitates faster, more convenient, and painless follow-up visits.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

INTRODUCTION

Neonatal hyperbilirubinemia is common among newborns occurring in up to 60%, and evaluating the severity is crucial to the management[1]. The American Academy of Pediatrics recommends the initiation of phototherapy (PT) to reduce excessive bilirubin for neonates falling in the high-risk zones of hyperbilirubinemia, therefore severe hyperbilirubinemia [2]. The initiation of and duration of therapy is determined by a specific range of total bilirubin based on the patient's postnatal age and risk of toxicity. Therapy usually implies the use of high levels of irradiance in the 430 to 490nm band length, applied to as much of the patient's surface area as possible[3]. By exposing the infant's skin to this specific range of light, phototherapy can decrease total bilirubin through isomerization into a more soluble and excreted product[4]. The initial reaction for this reduction occurs in the skin and causes the exposed area of skin to become blanched during the process.[5]

The current gold standard of measuring the level of bilirubinemia is the determination of bilirubin in serum samples (total serum bilirubin [TSB])[6]. However, obtaining venous or heel stick samples are invasive and painful. Transcutaneous bilirubinometry (TCB) was introduced as a noninvasive method to provide an easy, safe, and convenient method of evaluating the severity of the hyperbilirubinemia[7]. This method relies on using multiwavelength spectral reflectance and light transport through neonatal skin by accounting for the role that bilirubin plays in skin color. Studies have established that TCB is clinically equivalent to the measurement of TSB[8]. Phototherapy however, due to its blanching effects, has been reported to adversely affect the correlation between TCB and TSB and prior studies have discouraged the use of TCB once phototherapy was initiated[9].

There have been several inpatient studies that have shown a higher correlation between TCB and TSB with increasing hours following phototherapy. For example, Tan et al evaluated the accuracy of TCB during and after phototherapy[10]. They had a group of 240 inpatient infants in a control group where they compared TCB to TSB. In another group, 70 infants were treated with

phototherapy. For the infants who were treated with phototherapy, TCB measurements were obtained on skin that was uncovered and exposed to the blanching effects of the therapy as well on skin that was covered for the duration and did not get blanched. Through the control group, Tan et al were further able to support that TCB and TSB values correlated and that TCB is an accurate method for detecting hyperbilirubinemia. Additionally, they demonstrated that phototherapy reduces the correlation between TSB and TCB values, but that the correlation is not fully eliminated. Upon the cessation of phototherapy, the correlation of TCB and TSB was closer to the control group by 18 -24 hours post therapy and that there was even more improvement by the second day.

In a similar study, Fonseca et al compared values of TCB on covered and exposed skin during phototherapy and looked at values 6 hours after the cessation of phototherapy.[11] They looked at a population of 39 infants and found that prior to phototherapy there was no significant difference between the TCB and TSB. During phototherapy, they also found that covered skin reported values of TCB to be much closer to TSB than exposed skin. After the cessation of phototherapy, the exposed skin TCB values were lower than serum and did not correlate after a six-hour mark. However, after 24 hours, but while still inpatient, they found that skin regained normal coloring and the measured bilirubin values showed that there was no longer a significant difference between TCB and TSB.

Most recently, a 2014 study by Grabenhenrich et al showed that the further out from phototherapy the difference between TCB and TSB approached pre-therapy levels. The study looked at 86 newborn infants, and the mean difference between TcB-TSB before phototherapy was -0.6mg/dL. Within the first 8 hours, the different between the two values was -2.4mg/dL. However, afterwards the difference decreased and by 24 hours it was -0.8mg/dL[12]. They concluded that although TCB initially underestimates TSB, especially in the first 8 hours, it can still be used to reduce the amount of venous or heel stick samples.

Inpatient studies have revealed higher correlation between TCB and TSB with increasing time post phototherapy and it is estimated that the blanching effects of phototherapy wear off around 18-24 hours. Currently, TCB is used before initiating phototherapy only and few studies have investigated the accuracy of using TCB after phototherapy in the outpatient setting. Our goal was to determine whether the outpatient physician can safely rely on TCB, allowing for a painless and time saving alternative to TSB.

METHODS

This was a retrospective study that looked at data from October 2013 to April 2015 at the Pediatric Clinic at Maricopa Medical Center. We looked at healthy neonates who received inpatient phototherapy and then followed up at the outpatient clinic. Each neonate who was treated with phototherapy obtained both transcutaneous (TCB) and serum bilirubin (TSB) measurements. TCB measurements were made on the forehead with BiliCheck and recorded by nursing staff, while all blood samples for TSB were run in the main hospital.

Phototherapy treatment:

The decision for phototherapy treatment was made by the attending physician in the neonatal unit per protocol in place at Maricopa Integrated Health System. Intensive phototherapy with overhead light and Biliblanket are standard of care. We recorded the start and stop time of the phototherapy as noted in the hospital record.

Subjects:

In this retrospective study, we used existing data from the Maricopa Integrated Health System from October 2013 to April 2015. We included neonates who required phototherapy for the management of neonatal hyperbilirubinemia. The Pediatric Clinic uses electronic health records and the data was available through the electronic health record. We excluded any neonates with skin discolorations (eg. Nevi, hemangiomas on the face), or any neonates who required intensive care.

Total Serum Bilirubin and Transcutaneous Bilirubin

Blood samples were collected during the first outpatient visit to the Pediatric Clinic. Additionally, at the time of the visits transcutaneous measurements on the forehead using BiliCheck were made. All blood samples were run at Maricopa Integrated Health System and all transcutaneous values were recorded by the nursing staff as per routine.

Data

Using the electronic health record, we recorded;

The phototherapy start and stop time, hours after phototherapy, age in days, TCB and TSB while in clinic, gestational age, birth weight, race/ethnicity, and Coombs test results.

Statistical Analysis

The difference in Bilirubin values was looked at by statistician, Napatkamon Ayutyanont, PhD via ROC values.

RESULTS

From October 2013-April 2015, a total of 67 healthy neonates had been seen in the Pediatric Clinic who had received phototherapy, however only 36 (54%) met complete inclusion criteria and minimum data to be included in the study. Results were based on these 36 infants. The study population consisted mainly of healthy neonates who had a gestational age of 35 or more weeks, 89% were born at or greater than 37 weeks gestation; and of spontaneous vaginal delivery (83%). Other demographics showed that 53% of the patients were female, and 66% of the patients were Hispanic (Table I).

For healthy outpatient newborns who received inpatient phototherapy the mean TSB measurement was 11.78mg/dL +/- 2.5 mg/dL, and the mean TCB value was 12.13mg/dL +/-2 mg/dL. The absolute difference between the TSB and TCB was 0.4 (range 0- 4.3, $p = 0.22$) (Table II). The correlation of serum versus transcutaneous bilirubin demonstrated a positive correlation with a r-value of 0.8 (Graph I). The mean length of phototherapy was 23 hours (range 9-41 hrs), and the mean length from the end of phototherapy and the outpatient visit was 47 hours (range 19-102 hrs). The results also demonstrated that 75% of infants had an absolute difference between TSB and TCB of less than or equal to 2. Additionally, only 8% of neonates returned to the outpatient clinic < 24 hours after receiving phototherapy, all had absolute difference of <2.

Table 1. Patient Demographics. Characteristics of Infants, n= 36, looked at sex, delivery method, gestational age, and ethnicity.

Sex	53% female	47% male
Delivery Method	83% vaginal births	17% Cesarean section
Gestational Age	89% $\geq$37 weeks	11% 35-36 weeks
Ethnicity	66% Hispanic	36% Other

Figure 1. Serum vs Transcutaneous Bilirubin.

R value of 0.8

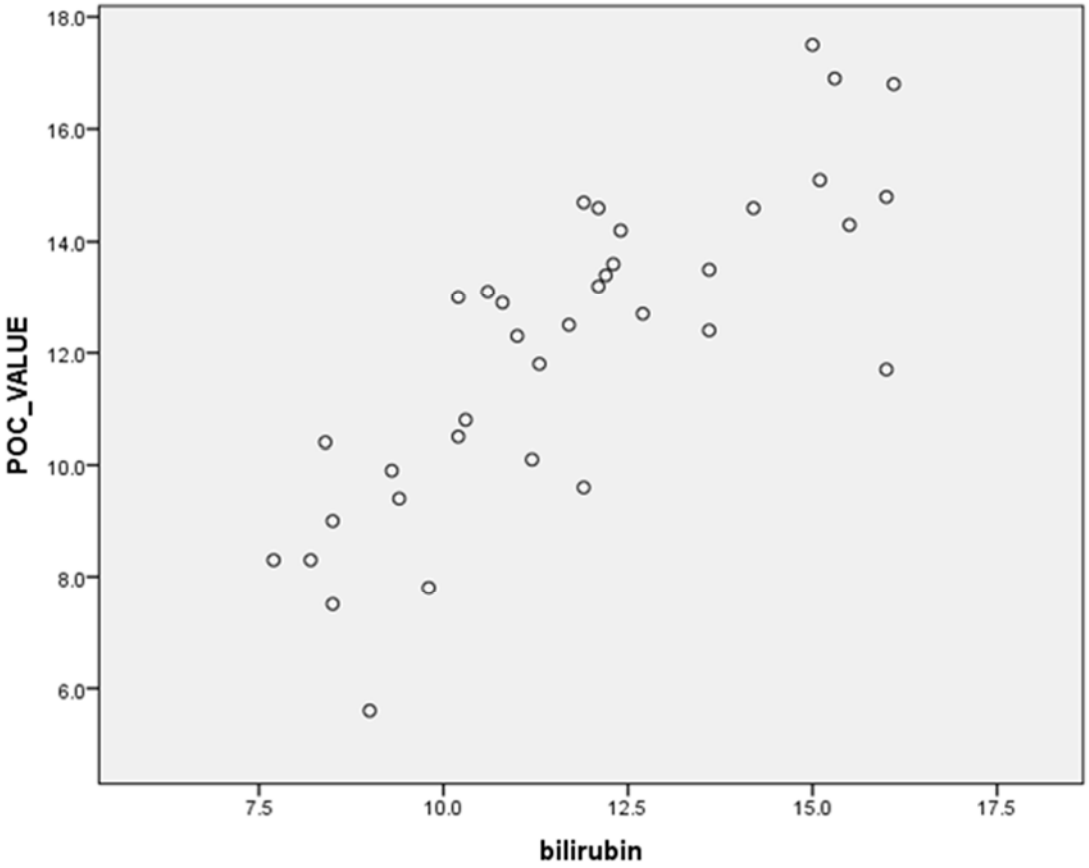

Table 2. Difference Between TCB and TSB levels by mean and absolute difference.

Category	Value
Mean length of PT	23 hrs, range (9- 41 hrs)
Mean length from end of PT to outpatient visit	47 hrs, range (19-102 hrs)
Mean serum bilirubin (TSB)	11.78 mg/dl +/- 2.5
Mean transcutaneous bilirubin (TCB)	12.13 mg/dl +/- 2.8
Absolute difference between TSB and TCB	0.4, range (0- 4.3) p= 0.22

DISCUSSION

The study demonstrated an absolute difference between mean TSB and TCB in healthy outpatient newborns who received inpatient phototherapy of 0.4, which is clinically insignificant. A correlation between TSB and TCB was seen after 1-2 days following phototherapy, and the average time to return to clinic was 47 hrs. Additionally, 75% of neonates had an absolute difference between TSB and TCB of less or equal to 2. Based on this data, we suggest that for the outpatient physician who typically sees patients 1-2 following phototherapy, TCB can be used safely. This would allow for the faster, more convenient, and painless follow up visits. This replacement of TSB by TCB could have a large impact in the outpatient setting, especially in the rural and underserved communities.

One of the limitations of this study was that the study population was smaller than anticipated. Out of the 67 neonates who received phototherapy, only 46 infants returned for follow-up visits between October 2013-April 2015. Further, 10 neonates did not meet minimum data criteria for the study leaving the n = 36. Ideally, the study population would have been larger, n=100-150. Perhaps with a larger sample size there could have been statistically significant results.

Of note, a portion of those who did not meet full study criteria for the study had originally received a TCB but had no laboratory follow-up. The patient population at Maricopa Medical Center includes many underserved patients and there are several variables that could be at play for no laboratory follow-up. For example, not all parents have the availability to wait for lab results following their appointments to determine whether the child has hyperbilirubinemia and/or is high-risk and needs therapy. This further illustrates the significance and utility of TCB, and being able to rely on it as a replacement for TSB.

FUTURE DIRECTIONS

Given the p-value and small population size of this study, continuing further studies or expanding further on this one would be highly advantageous. Being able to then re-analyze the results on a larger population would not only give more perspective but would revalidate our current results. Based on prior inpatient studies, we would expect that with a larger population the results would be similar, likely with similar correlation (r=0.8), however the power of the study would be greater and hopefully leading to statistically significant results.

Ideally, we would have liked to sub-stratify the results, which we were unable to do with the smaller sample size of patients who qualify. We hope that with sub-stratifying the results based on ethnicity, gestational age, age at time of presentation, and sex, they could reveal more information about the relationship between the transcutaneous and serum bilirubin levels.

CONCLUSIONS

At the onset of this study, our goal was to determine if outpatient providers could safely rely on transcutaneous bilirubinometry (TCB) over serum bilirubin (TSB) levels after patients have had phototherapy. The data demonstrated that a correlation between TCB and TSB does exist and 75% of the patients in the study had an absolute difference between bilirubin levels of less than or equal to 2. Therefore, we conclude that TCB can be used following phototherapy in the outpatient setting which would facilitate faster, more convenient, and painless follow-up visits. Further studies and sub-stratification of data will be needed to further validate results and explore the relationship between TSB and TCB more in deeply.

REFERENCES

[1] Bhutani V, Gourley G et al. Noninvasive Measurement of Total Serum Bilirubin in a Multiracial Predischarge Newborn Population to Assess the Risk of Severe Hyperbilirubinemia. Pediatrics 2000; 106: 1-9.

[2] Bhutani V, The Committee on Fetus and Newborn. Phototherapy to Prevent Severe Neonatal Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2011; 129: e1046-e1052.

[3] Bhutani V, The Committee on Fetus and Newborn. Phototherapy to Prevent Severe Neonatal Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2011; 129: e1046-e1052.

[4] Ennever JF, Costarino AT et al. Rapid clearance of a structural isomer of bilirubin during phototherapy. Journal of Clinical Investigation 1987; 79: 1674.

[5] Zecca E, Barone G et al. Skin bilirubin measurement during phototherapy in preterm and term newborn infants. Early Human Development 2009; 85: 537-540.

[6] Grabenhenrich J, Granbenhenrich L, et al. Transcutaneous Bilirubin After Phototherapy in Term and Preterm Infants. Pediatrics 2014; 123: 1324-1329.

[7] Zecca E, Barone G et al. Skin bilirubin measurement during phototherapy in preterm and term newborn infants. Early Human Development 2009; 85: 537-540.

[8] Bhutani V, Gourley G et al. Noninvasive Measurement of Total Serum Bilirubin in a Multiracial Predischarge Newborn Population to Assess the Risk of Severe Hyperbilirubinemia. Pediatrics 2000; 106: 1-9.

[9] Zecca E, Barone G et al. Skin bilirubin measurement during phototherapy in preterm and term newborn infants. Early Human Development 2009; 85: 537-540.

[10] Tan KL, Dong F.Transcutaneous bilirubinometry during and after phototherapy. Acta Paediatr 2003; 92: 327-331.

[11] Fonseca R, Kyralessa R. Covered skin transcutaneous bilirubin estimation is comparable with serum bilirubin during and after phototherapy. Journal of Perinatology 2012; 32: 129-131.

[12] Grabenhenrich J, Granbenhenrich L, et al. Transcutaneous Bilirubin After Phototherapy in Term and Preterm Infants. Pediatrics 2014; 123: 1324-1329.