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Original Article

Dermal Progression of Neonatal Jaundice of Newborn Under 35 Weeks of Gestational Age

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ABSTRACT

Aim: To determine the dermal progression of neonatal jaundice in newborns under 35 weeks of gestational age and those risk factors which affect dermal progression.

Materials and Methods: We prospectively enrolled eighty-eight preterm newborns under 35 weeks of gestational age in neonatol intensive care unit of Dokuz Eylül University Hospital. It was a cross-sectional analytic case study. We measured capillary and transcutaneous bilirubin levels. Multiple sites of TcB measurement were performed.

Results: We observed that there is no significant difference between capillary and transcutaneous bilirubin measurements on preterm newborns under 35 weeks of gestational age (pearson's rho >75 and $p<0.05$). Additionally, we also observed that transcutaneous bilirubin measurements on preterm newborns under 35 weeks of gestational age (the first day taken on the back, the fourth day on the forehead and the remaining days on the chest) are higher than on the other sides (Friedman test). Therefore, for preterm newborns, jaundice progresses in a different way to cephalocaudal direction with progressive hyperbilirubinemia. We did not observe any association between the existence of cephalocaudal progression in preterm newborns and the laboratory data associated with the mother and baby (Mann-Whitney U test, $p>0.05$).

Conclusion: Transcutaneous bilirubin measurements can be used for neonatal jaundice of newborns under 35 weeks of gestational age. However, we need further studies for comprehensive descriptions of preterm newborns' jaundice progression.

Keywords: Dermal progression, neonatal jaundice, gestational age, transcutaneous bilirubin measurements, cephalocaudal progression

Introduction

Neonatal hyperbilirubinemia is the yellow color found in the sclera and skin of infants with increased bilirubin concentration in the plasma. It is one of the most common problems in the neonatal period, being the most frequent cause of hospitalization in the first two weeks of life. The frequency of jaundice is 60% in term and near term infants and 80% in preterm infants in the first week of life, although jaundice requiring treatment is only seen at a rate of 5-6% in newborns.

Neonatal jaundice first becomes visible on the face and forehead, then gradually becomes visible on the trunk and extremities as the level of serum bilirubin rises. This phenomenon is called the "cephalocaudal progression of jaundice". Kramer first described the cephalocaudal progression of jaundice in 1969 (1). Other investigators have confirmed his findings and demonstrated a direct relationship between plasma bilirubin concentrations and the cephalocaudal progression of jaundice (2-4). There are various theories to explain the cephalocaudal progression of jaundice. However, despite its long-time recognition, there has been no satisfactory explanation of how it occurs to date. Kramer suggested exposure to light may play a role (1). Other theories have indicated differences in the epidermis' surface lipid content and albumin's capillary permeability as

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explanations (3). More recently, one theory may explain the cephalocaudal color difference by conformational changes in the bilirubin-albumin complex in the blood (5,6) and differences in the skin temperature and capillary blood flow (7).

Spectrophotometric measurements of the yellow color of the skin and subcutaneous tissues (by transcutaneous bilirubin meter) were introduced in 1980 by Yamanouchi et al. (8) as an alternative to the determination of bilirubin in the serum of neonates.

The exact responsible mechanism for the color of jaundiced skin is unknown. It can show variations due to the skin's natural shade of bilirubin-albumin complexes in the extravascular space and the deposition of bilirubin acid in phospholipid membranes. In a state of equilibrium between plasma and dermal bilirubin concentrations, the intensity of the yellow color skin is related to three factors; plasma bilirubin concentration, the squared hydrogen ion concentration, and the reciprocal of the reverse albumin concentration (9).

In this study, we examined the cephalocaudal progression of jaundice and the effects of clinical and laboratory factors in neonates under 35 weeks of gestational age.

Patients and Methods

This prospective cross-sectional analytical case study was performed between June, 2012 and May, 2013 at the Neonatal Intensive Care Unit (NICU) of Dokuz Eylül University Hospital and it was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (date: 17.05.2012, approval no: 2012/18-18). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or the National Research Committee and within the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to the prospective nature of this study, informed consent was obtained.

During the study period, newborns under 35 weeks of gestational age were included after parental consent. Eighty-eight newborns admitted to the NICU for various causes were included in this study.

In the inclusion of neonates in this study, the yellow skin color (TcB) measurements were taken at six different sites; forehead (TcBf), sternum (TcBs), abdomen (level of the umbilicus) (TcBa), back (interscapular area) (TcBb), knee (TcBk), and foot (TcBf). TcB was measured daily between the postnatal first and tenth days at these six different sites. We took two readings at each site, and used the average value in the calculation. We did not include those newborns who were already receiving phototherapy or had received phototherapy 24 hours prior to the measurement. We measured TcB with a Minolta Jaundice Mater 103 (Konica Minolta Sensing Inc., Osaka, Japon). TcB color difference measurements (between the highest and lowest value) were made simultaneously on the same day with the same baby.

If we observed jaundice through a blood sample by heel prick, the bilirubin level was determined by a standard direct spectroscopic method using Wako's bilirubin tester.

All values are given as the mean ± standard deviation (Figure 1).

We used the SPSS 17.0 program for statistical analysis. In comparisons between groups, if parametric conditions

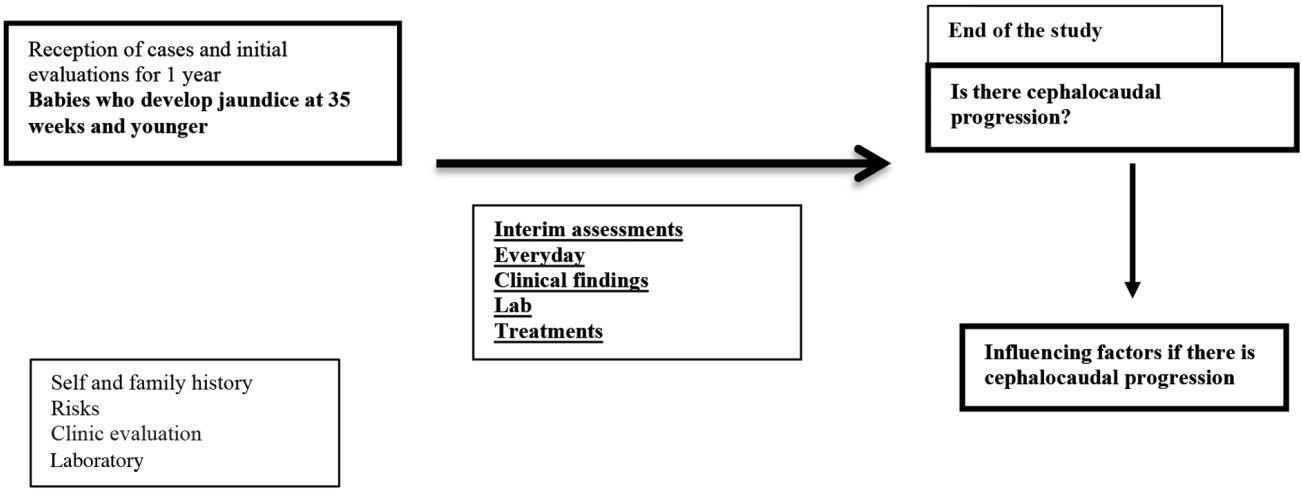

Figure 1. Research design (cross-sectional follow-up and evaluation of infants)

are met, the t-test was employed; if not, the Mann-Whitney U test was used. A statistical significance value of $p<0.05$ was chosen.

Results

Demographic information is given in Table I. The mean gestational age was 30.7±3.3 weeks. The mean gestational weight was 1,617±672 grams. Sixty point two percent of infants were male.

The average and variation values of TcB measurements from the six body sites are shown in Table II. We evaluated TcB measurements from the different body sites with the Friedman test; the highest values were detected on the first day on the back, the fourth day on the forehead, and on the other days on the chest. For each day, the TcB measurement values from different body parts differed, and the ranking in TcB values varied depending on the day, compared by the Friedman test. The highest TcB measurement for each day is marked with an asterisk (*). Day 1 TcB and serum bilirubin measurement were not included in the evaluation because there was no correlation.

The order of TcB measurement values "HIGHEST and LOWEST" from the 6 different body regions for each day are given in Table III.

There was no difference between the ratio of the decrease in TCB values in the knees and the foot and the decrease in the TCB values in the chest 1.-10. between days (Figure 2).

Table IV shows the mean and standard deviation values of the TcB difference variable (the highest-lowest TcB difference for that day) according to the days.

We compared the difference values of all days in pairs with the paired test and applied Bonferroni correction to these results. When the course of the mean of the TcB difference variable according to the days was examined with regression curve estimation models, the averages showed a cubic function, and the model was significant ($p<0.009$) (Figure 3) (When the R2 value of the regression model was examined, it was 0.83, and the explanatory power of the model was 83.7%).

As can be seen in Figure 3, the bilirubin difference persists (Y=5.725X+(-1.037)X2 +0.054 X3).

Concerning the TcB color difference, we reported the highest value on day 3. Regression curve models investigated difference averages by day, and as a result, standards have cubic functions (R^2: 0.83) (Figure 3). When we compared the difference values of all days with the paired test, day three was statistically significant compared to days one, two, and seven. We found the differences between the highest and lowest transcutaneous measurements on the same day in infants continued significantly on day ten, in a similar manner to the other days ($p<0.001$).

The mean value of the difference of TcB in this study (highest measurement-lowest measurement) simultaneously on the same day between the same baby's regions continued meaningfully on day ten, in a similar manner to all other days ($p<0.001$).

Regarding the infants included in this study; 10 (11.4%) had rhesus (Rh) isoimmunization, 3 (3.4%) had ABO blood group incompatibility, 3 (3.4%) had polycythemia, and 1 (1.1%) had a double-volume exchange transfusion. None of the infants had G6PD deficiency, acute bilirubin encephalopathy, cephalohematoma, significant bruising from birth trauma, positive Coombs test, or positive thyroid function tests. We used the hour-specific phototherapy treatment thresholds from the American

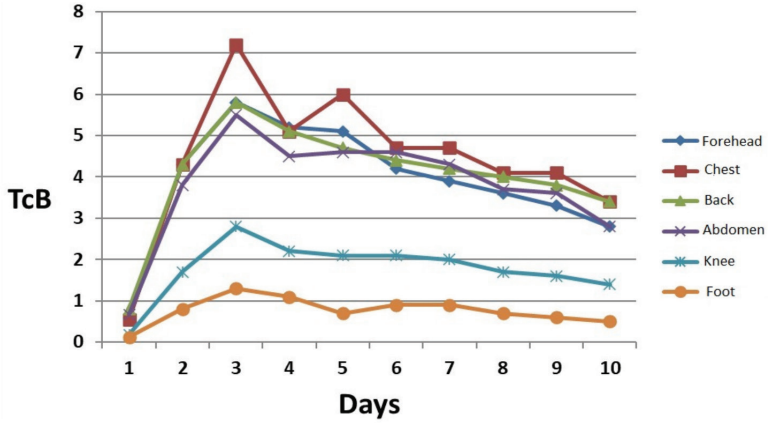

Figure 2. Average values of transcutaneous bilirubin measurements made from six different regions according to days

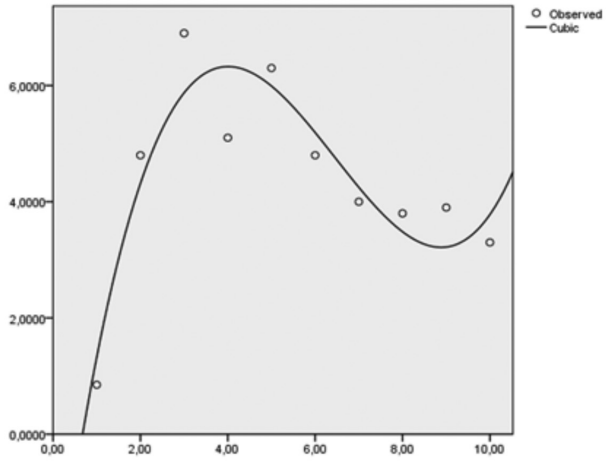

Figure 3. The change in the mean difference of the group of 10 days

Table I. Clinical characteristics of the study group

Features	Number (n=88)	%
Gender		
Male	53	60.2
Female	35	39.8
Birth weight		
1,000>	21	23.9
1,000-1,500	20	22.7
1,500-2,500	40	45.5
+2,500 gr	7	7.7
Average: 1,617±672 gr		
Birth week		
28>	18	20.5
28-32	23	26.1
32-35	47	53.4
Average: 30.7±3.3 week		

Academy of Pediatrics Clinical Practice Guideline on neonatal hyperbilirubinemia management.

We observed no significant difference between capillary and transcutaneous bilirubin measurements (Pearson's rho >75 and p<0.05) (Table V). These findings are consistent with the literature. Studies have shown that TcB and TSB measurements show a perfect correlation (r=0.87-0.96) and a linear relationship between them. In our study, the correlation was weak in the first days with lower bilirubin values. The best correlation was obtained in those measurements from the forehead and chest area.

We evaluated the mean value of the difference of TcB in this study (the highest measurement minus the lowest measurement) on the same day between the same baby's regions non-parametrically by Mann-Whitney U test. It was unrelated to abnormalities in albumin. This is shown in Table VI.

On the 3rd day, the relationship between the average difference and blood gas (with the result of univariate linear regression analysis with blood gas value as the independent variable, and the mean difference on the 3rd day as the result variable), we noted that it was related with blood gas increases. In other words, as the pH increased, the difference increased (p<0.05). However, when we examined the R2 value of the regression model (0.18), it was seen that the explanatory power of the model was low, and this model could only explain 18% of the variation in the difference values. The TcB difference variable was shown not to be affected by plasma albumin level, hematocrit (htc) value, maternal or child disease, Rh incompatibility or ABO incompatibility.

Table II. TcB measurements mean and SD values for daily

Day	n	Forehead (TcBf)	Sternum (TcBs)	Back (TcBb)	Abdomen (TcBa)	Knee (TcBk)	Foot (TcBf)
1	80	0.58±1.4	0.55±1.3	0.8±1.6	0.67±1.6	0.18±0.6	0.12±0.5
2	55	4.3±2.5	4.3±2.8	4.3±2.3	3.8±2.7	1.7±1.7	0.8±1.1
3	44	5.8±8.0	7.2±8.0	5.8±2.4	5.5±2.4	2.8±1.8	1.3±1.5
4	30	5.2±3.0	5.1±3.2	5.1±2.4	4.5±3.0	2.2±2.0	1.1±1.5
5	28	5.1±3.3	6.0±6.1	4.7±2.4	4.6±2.7	2.1±1.8	0.7±1.1
6	39	4.2±2.7	4.7±2.7	4.4±2.4	4.6±2.8	2.1±1.7	0.9±1.2
7	38	3,9±2.9	4.7±3.3	4.2±3.0	4.3±3.3	2.0±1.8	0.9±1.5
8	48	3.6±2.9	4.1±3.2	4.0±3.1	3.7±3.0	1.7±1.8	0.7±1.1
9	44	3.3±3.1	4.1±3.5	3.8±3.0	3.6±3.1	1.6±1.8	0.6±1.4
10	40	2.8±3.0	3.4±3.1	3.4±3.1	2.8±2.9	1.4±1.9	0.5±0.9

SD: Standard deviation

Table III. Ordering of TcB measurements from different body parts by days

Days	
1.	-
2.	Sternum>forehead=back>abdomen>knee>***foot***
3.	Sternum>back=forehead>abdomen>knee>***foot***
4.	***Forehead***>sternum=back>abdomen>knee>***foot***
5.	Sternum>forehead>back>abdomen>knee> ***foot***
6.	Sternum>abdomen>back>forehead>knee>***foot***
7.	Sternum>abdomen>back>forehead>knee >***foot***
8.	Sternum>back>abdomen>forehead>knee>***foot***
9.	Sternum>back>abdomen>forehead>knee>***foot***
10.	Sternum>back>abdomen=forehead>knee>***foot***

Table IV. The difference between the highest and lowest bilirubin values measured transcutaneously

Days	TcB difference variable (Mean±SD)
1	0.85±1.6
2	4.8±2.3
3	6.9±7.8
4	5.1±2.5
5	6.3±5.7
6	4.8±2.4
7	4.0±2.7
8	3.8±2.6
9	3.9±2.9
10	3.3±2.6

SD: Standard deviation

Table V. Correlation levels between TcB measurements from the six different body regions and TSB measurements

Forehead (TcBh)	0.95***
Sternum (TcBs)	0.96***
Back (TcBb)	0.86***
Abdomen (TcBa)	0.85***
Knee (TcBk)	0.72**
Foot (TcBf)	0.74**

*Rho 25-50 and p<0.05, **Rho 50-75 and p<0.05, ***Rho >75 and p<0.05

Table VI. Comparison of transcutaneous bilirubin difference values according to albumin value groups

Albumin	3rd day difference average	
	Median (min.-max.)	**p***
Normal (n=20)	6.2 (1.7-9.1)	0.196
Low (n=5)	5.5 (3.4-6.6)	

Min.-max.: Minimum-maximum

These current findings suggest that the course of jaundice in neonates younger than 35 weeks was differentially centrifugal.

Discussion

Knudsen and Ebbesen (6) investigated the cephalocaudal progression of jaundice in 377 newborn babies. They made two transcutaneous measurements on the forehead, sternum, knee, and foot regions with a JM-101 device and evaluated the accompanying clinical and laboratory factors (6). Knudsen and Brodersen (9) suggested that bilirubin is transferred to the skin by two different mechanisms. The first of these pathways is the transition of bilirubin-albumin complexes from the plasma to the extravascular compartment. The second is the precipitation of bilirubin acid in phospholipid membranes. The bilirubin acid supersaturates the plasma of the newborn. *In vitro* studies have shown that pigment precipitates immediately on phospholipid membranes in contact with supersaturated bilirubin solution.

Bilirubin, which is present as a dianion in the bilirubin-albumin complex, combines with two hydrogen ions in the plasma, after which solid bilirubin acid accumulates on the capillary wall, and one molecule of albumin is released into the plasma (4-6). Various hypotheses have tried to explain the cephalocaudal progression of bilirubin; namely, regional skin vascularity differences, regional differences in epidermal lipid content, variations in skin temperature, capillary blood flow, and Knudsen's bilirubin-albumin binding time. The publications of Knudsen and Brodersen (9) cover young albumin-bilirubin complexes circulating in the blood and their conformational changes over time. In this study, the young complexes were separated and extravasated easily, and a tight connection occurred between the complex over time. More youthful complexes in proximal body parts are associated with cephalocaudal progression. The theory is that cephalocaudal progression increases with bilirubin concentration and decreases with albumin's affinity for bilirubin. However, the time for complexes to reach the most distal parts of the body is shorter than the tight junction formation time (the tight junction formation time between albumin and bilirubin starts in 30 seconds and ends in about 8 minutes. However, the blood travel time from the aorta to the foot in a newborn is 4.3 seconds, and blood travels at 1.1 m/sec. In other words, albumin-bilirubin complexes arrive at the foot without having formed a tight connection) (4-9,10).

In our study, we found transcutaneous bilirubin measurements to be higher on the back on the first day, on the forehead on the fourth day, and on the chest on the other days in preterms under 35 weeks during the first ten days. Our study shows that, unlike term babies, the most significant elevation is on the chest region in transcutaneous bilirubin measurements in preterms under 35 weeks, and that jaundice progression follows a different spread, i.e. not from head to toe as in term babies. In this respect, our findings are not similar to the data in the literature (4,6). Our study suggests that jaundice progression in preterms under 35 weeks of age follows a different "centrifugal" spread, not from head to toe as in term babies. In our study, the course of jaundice in preterms may be associated with local factors, such as the lipid content of the skin, the basal skin color of the baby, differences in blood flow, differences in permeability of regional capillaries to albumin, skin perfusion and temperature, decreased capillary flow in the distal skin regions, increased bilirubin production, decreased bilirubin removal from the blood, and/or increased enterohepatic circulation (4,6,7).

TcB measurements on the chest area correlated very well with TSB measurements, suggesting that it would be appropriate to measure TcB on the chest area.

Whether the mother has a history of hypertension, preeclampsia, gestational DM, Rh incompatibility, or antenatal steroid use during pregnancy and whether the patient has a history of direct Coombs negativity, polycythemia, abnormalities in hemogram, biochemistry, or albumin levels, we analyzed the distribution in terms of transcutaneous bilirubin measurement differences, and no difference was found. No similar study was found in the literature (11,12-24). The change in bilirubin difference significantly affects the increase in blood gas. In other words, the difference increases as the pH increases (p-value<0.05). These results are consistent with the literature (5).

We found a statistically significant correlation between transcutaneous-capillary bilirubin measurements. We have shown that using the TcB measurement as a screening tool to determine the necessity of serum bilirubin measurement is reliable for preterm infants. Many studies in the literature have also shown that there is a correlation between TcB and TSB measurements (8,10-23).

Study Limitations

This study has some limitations. The most important limitation is the small sample size. Additionally, it is also possible that the cephalocaudal progression of icterus spreads slower in neonates born closer to term than our population of preterms under 35 weeks of gestational age, as seen in the population of the study of Kamphuis and Bekhof (25).

More studies are needed to better understand the dermal kinetics of bilirubin. A better understanding of bilirubin kinetics may offer new possibilities for preventing bilirubin encephalopathy.

Conclusion

We found a statistically significant correlation between transcutaneous-capillary bilirubin measurements. We have shown that using the TcB measurement as a screening tool to determine the necessity of serum bilirubin measurement is reliable for preterm infants. Many studies in the literature have also shown that there is a correlation between TcB and TSB measurements. And also, our study shows that, unlike term babies, the most significant elevation is on the chest region in transcutaneous bilirubin measurements in preterms under 35 weeks and that jaundice progression follows a different spread, not from head to toe as in term babies. In this respect, our findings are not similar to the data in the literature. Our study suggests that jaundice progression in preterms under 35 weeks of age follows a different "centrifugal" spread, not from head to toe as in term babies.

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Ethics

Ethics Committee Approval: This study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (date: 17.05.2012, approval no: 2012/18-18).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.Ç.K., B.İ., A.K., Concept: Ç.Ç.K., N.D., H.Ö., Design: Ç.Ç.K., H.Ö., A.K., Data Collection and/or Processing: B.İ., A.K., H.Ö., Analysis and/or Interpretation: B.İ., N.D., H.Ö., Literature Search: B.İ., N.D., H.Ö., A.K., Writing: Ç.Ç.K.

Conflict of Interest: All of the authors declare that they have no conflict of interest.

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