The value of transcutaneous method of bilirubin measurement in newborn population with the risk of ABO hemolytic disease

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Key words: newborn; transcutaneous bilirubin; ABO blood group incompatibility; hemolytic disease.

Summary. Objective of the study. To evaluate the correlation between total serum bilirubin (TSB) and transcutaneous bilirubin (TcB) levels in newborn infants at risk of ABO hemolytic disease.

Material and methods. During a prospective study, 130 full-term (≥37 weeks of gestation) newborn infants with diagnosed ABO blood group incompatibility were examined. TSB level was measured at the age of 6 hours; further measurements were performed at 24, 48, and 72 hours following the first measurement. Blood samples were collected from the peripheral veins. In clinical laboratory, total serum bilirubin level was measured using Jendrassik-Grof method. TcB level in the forehead was measured using a noninvasive bilirubinometer BiliCheck (SpectRX Inc, Norcross, GA) according to the manufacturer’s instructions within ±30 min after getting a blood sample.

Results. During the study, 387 double tests were performed to measure TSB and TcB levels. TSB level (114.83 ± 62.85 µmol/L) closely correlated with TcB level (111.51 ± 61.31 µmol/L) (r=0.92, P<0.001). The strongest correlation was reported at the age of 54 hours (r=0.873, P<0.001), the weakest – at the age of 6 hours (r=0.729, P<0.001). TSB and TcB levels showed a strong correlation; the difference between these values was significant (95% CI, 0.70; 5.93; P<0.05). The greatest difference between TSB and TcB levels was detected at the age of 6 hours (5.58 ± 17.46 µmol/L, 95% CI, 2.55; 8.61; P<0.001). No significant difference was reported at the age of 30, 54, and 78 hours. Using linear regression analysis, it was established that correlation of TSB and TcB was described by equation y = 14.13+0.903x. Transcutaneously measured bilirubin level underestimated serum bilirubin level. When at the age of 6 hours TcB level is ≥98 µmol/L, ABO hemolytic disease in newborns may be diagnosed with 100% sensitivity and 98% specificity; positive predictive value was 62% and negative predictive value was 100%. While a newborn’s age increases, TcB sensitivity and specificity for diagnosing ABO hemolytic disease decrease.

Conclusion. While evaluating bilirubin level transcutaneously according to nomograms of serum bilirubin level, the results should be considered with caution, especially for newborns with a risk of ABO hemolytic disease. The hour-specific nomograms of transcutaneous bilirubin level should be used to evaluate hyperbilirubinemia using only a noninvasive method.

Introduction
During recent years, because of the changes in medical, economic, and social conditions, more and more newborn infants are discharged during the first 24–48 hours. Newborn infants with ABO blood group incompatibility have a risk of developing hyperbilirubinemia. Hemolytic disease, caused by blood group incompatibility, manifests as jaundice during the first 24–48 hours. Physiological jaundice in newborns occurs on days 2–3 of life and reaches its peak on days 4–5. Jaundice is the most common condition that requires staying in hospital or hospital readmission (1). Yellow sclera and skin occur because of the collected amount of unconjugated bilirubin. In most cases, unconjugated hyperbilirubinemia reflects a normal physiological phenomenon. However, some infants have tendency to collect bilirubin too intensively. This brings risk of developing bilirubin encephalopathy or kernicterus. Kernicterus is a neurologic syndrome resulting from the deposition of unconjugated bilirubin in the basal ganglia and brainstem nuclei. This may lead to spastic paralysis, deafness, and disability. The mortality from kernicterus accounts for approximately 5%, and residual phenomena remain in 88% of survi-
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The increased bilirubin level in blood is collected in the skin and subcutaneously. This causes jaundice, i.e. yellow shade of the skin and mucous membranes. The relation between plasma bilirubin level and the intensity of jaundice is well known. This was first described by Ylppö (3) in 1913, and since then, it has been the most common way to evaluate the severity of jaundice, while observing a newborn infant. Kramer (1969) suggested a scheme in which the body of a newborn is divided into separate zones where each zone reflects certain serum bilirubin level. Hanemann (1979) and others reported the results of the study, which suggested that the bilirubin level in blood might be predicted by measuring the intensity of yellow light reflected from a light ray pointed at the skin. However, the suggested measurement device was too complicated for daily use. Japan scientist Yamanouch et al. (1980) introduced a simple transcutaneous bilirubinometer (4), which is a noninvasive analyzer of bilirubin level. This device is used for measuring the levels of cutaneous bilirubin without a blood test. A transcutaneous bilirubinometer points a light beam directly at newborn’s skin and measures the intensity of the length of reflected waves. When the spectral structure of skin components is known, it is possible to eliminate accessory components in order to determine the level of bilirubin. The analyzer inside the device performs this analysis. The results are obtained without a trauma for a patient and without a risk of infection. Scientists and clinicians were interested and still are interested in the reliability of transcutaneous analysis results. When no other methods were used simultaneously, some studies demonstrated a significant correlation between plasma bilirubin and cutaneous bilirubin levels, which not necessarily corresponded to the skin color, gestation, or the newborn’s sickness (5–8). However, other studies show that bilirubin level depends on the gestation, sex, or illnesses (6). The following devices are used for the transcutaneous bilirubin measurement in newborn infants: Minolta/ Hill-Room Air Shields JM-103 (Draeger Medical) and Bilischeck (SpectRX Inc, Norcross, GA).

The aim of this study was to evaluate the correlation between transcutaneous bilirubin and serum bilirubin levels in newborn infants at risk of ABO hemolytic disease.

Material and methods

The study included healthy, full-term (≥37 weeks) newborn infants with ABO incompatibility born at the Clinic of Obstetric and Gynecology of the Hospital of Kaunas University of Medicine from February 2006 to July 2006. Full-term infants of the mothers with RhD antibodies were excluded from the study. Serum bilirubin levels were measured at the age of 6 hours and at hours 24, 48, and 78 following the first sampling (9). Total serum bilirubin level was evaluated by the guidelines (2004) of the American Academy of Pediatrics for the management of hyperbilirubinemia in a newborn infant (10). ABO hemolytic disease was diagnosed when Hct was <45%; reticulocytes amount, >4.5%; and hyperbilirubinemia was present (11). Blood samples for tests were collected from the peripheral vein. Jendrassik-Grof method was used for measuring total serum bilirubin (TSB) level in a clinical laboratory. Forehead skin bilirubin level was measured using a noninvasive bilirubinometer BiliCheck (SpectRX Inc, Norcross, GA) following the manufacturer’s instructions within ±30 min after getting a blood sample. Once hyperbilirubinemia was diagnosed and a subsequent medical care was provided, the further pair tests were not performed.

Regional Ethics Committee for Biomedical Research approved the study protocol (No. BE-2-44).

Statistical analysis

The results were collected into the database. Statistical analysis was performed using the SPSS 13.0 software package. The descriptive analysis was performed, and the difference between averages was examined. For statistical hypothesis testing, the level of significance was 0.05. For comparing the averages between two groups, two-sample Student t test was used. To find the relation between the symptoms, the coefficients of correlation were evaluated. To evaluate the cutoff values, the analysis of receiver operating characteristic (ROC) was used. The formula was used for calculating sensitivity and specificity of the examined features.

Results

A total of 130 newborn infants were included into the study; 94 (72.4%) were born in a natural way; 36 (27%) by caesarean section. O-B incompatibility was found in 44 (33.6%) and O-A in 86 (66.1%) infants. ABO hemolytic disease was diagnosed in 6 (4.8%) newborn infants, hyperbilirubinemia was reported in 12 (9.5%) cases, and 108 (85.7%) infants had physiological jaundice. The demographic data had no significant influence on the results of this study.

During the study, 387 double measurements were performed for 130 infants. TSB and TcB levels were
We found that TSB level (114.83 ±62.85 µmol/L) significantly correlated with TcB level (111.51 ±61.31 µmol/L) (r=0.92, P<0.001). The strongest correlation (r=0.873, P<0.001) was noticed at 54 hours of age, and the weakest one (r=0.720, P<0.001) at 6 hours of age. TSB and TcB levels showed a strong correlation, and we found the significant difference between these values (95% CI [0.70; 5.93], P<0.05) (Table 2).

The greatest difference between serum bilirubin and transcutaneous bilirubin levels was found at the age of 6 hours (5.58 ±2.55; 8.61 µmol/L; 95% PI, 2.55; 8.61; P<0.001). No significant differences were reported at the age of 30, 54, and 78 hours. Linear regression analysis showed that the correlation of TSB and TcB level could be expressed by the formula y=14.13+0.903x. The 2004 guidelines of the American Academy of Pediatrics for the management of hyperbilirubinemia in newborn infants recommends initiating the treatment when in case of ABO hemolytic disease, TSB level is ≥102 µmol/L at the age of 6 hours, ≥187 µmol/L at the age of 30 hours, and ≥238 µmol/L at the age of 54 hours (10). The ROC curve was used for searching TcB cutoff value with the help of which it is possible to recognize ABO hemolytic disease. At the age of 6 hours, this cutoff value was ≥98 µmol/L (the area under the curve, 0.99), ≥172 µmol/L (the area under the curve, 0.82) at the age of 30 hours, and ≥218 µmol/L (the area under the curve, 0.83) at the age of 54 hours (Fig.).

When at the age of 6 hours TcB level is ≥98 µmol/L, ABO hemolytic disease in newborns may be diagnosed with a sensitivity of 100% and a specificity of 98%; the positive predictive value (PPV) and negative predictive value (NPV) were 62% and 100%, respectively. While a newborn’s age increases, TcB sensitivity and specificity for diagnosing ABO HL decrease (Table 3).

### Table 1. Mean values of TSB and TcB level at different newborn’s age

| Newborn’s age (hours) | N  | Mean value of bilirubin level ±SD (µmol/L) | r     | P      |
|-----------------------|----|------------------------------------------|-------|--------|
|                       |    | TSB                                      |       |        |
| 6                     | 130| 65.00±20.01                              | 0.72  | <0.001 |
| 30                    | 119| 128.13±40.48                              | 0.77  | <0.001 |
| 54                    | 103| 174.55±48.54                              | 0.87  | <0.001 |
| 78                    | 35 | 225.46±54.99                              | 0.83  | <0.001 |
| 6–78                  | 387| 114.83±62.85                              | 0.92  | <0.001 |
|                       |    | TcB                                      |       |        |
| 6                     | 130| 59.42±24.99                               |       |        |
| 30                    | 119| 126.94±40.01                              |       |        |
| 54                    | 103| 171.63±51.60                              |       |        |
| 78                    | 35 | 218.09±50.93                              |       |        |
| 6–78                  | 387| 111.51±61.31                              |       |        |

### Table 2. Mean values of TSB and TcB differences at different newborn’s age

| Newborn’s age (hours) | N  | Difference of TSB and TcB level (µmol/L) | Mean value [95% CI] | P      |
|-----------------------|----|------------------------------------------|---------------------|--------|
| 6                     | 130| 5.58 [2.55; 8.61]                        |                     | <0.001 |
| 30                    | 119| 1.19 [–3.68; 6.06]                       |                     | NS     |
| 54                    | 103| 2.92 [–2.04; 7.89]                       |                     | NS     |
| 78                    | 35 | 7.37 [–3.30; 18.04]                      |                     | NS     |
| 6–78                  | 387| 3.31 [0.70; 5.93]                        |                     | <0.05  |

### Table 3. TcB cutoff value corresponding to diagnostic TSB with the highest sensitivity and specificity, positive predictive and negative predictive value

| Threshold of TSB (µmol/L) | Cutoff TcB (µmol/L) | Sensitivity % | Specificity % | PPV % | NPV % |
|---------------------------|---------------------|---------------|---------------|-------|-------|
| ≥102                      | ≥98                 | 100           | 98            | 65    | 100   |
| ≥187                      | ≥172                | 70            | 91            | 41    | 97    |
| ≥238                      | ≥218                | 64            | 90            | 50    | 94    |
Discussion

The American Academy of Pediatrics recommends examining the TSB level in every newborn infant every 8–12 hours (10). Jaundice that is visible in the first 24 hours of life is always caused by pathological reasons, such as AB0, Rh hemolytic disease. Hyperbilirubinemia in newborns has become a very acute issue in recent years. It is closely related to early hospital discharge, breastfeeding, and the fact that observation and evaluation of adaptation of newborn infants have become a duty of family physicians, not neonatologists. Noninvasive bilirubin level measurement is a few skill-demanding, comfortable, fast, and painless method; but is it a reliable method for diagnosing hyperbilirubinemia? During the last 10 years, many studies have been carried out on examining the correlation between cutaneous bilirubin level measured by noninvasive method and plasma bilirubin level. Maisels et al. performed double tests for 840 newborn infants and found a strong correlation ($r=0.949$) between TcB level and TSB level (20). However, the correlation coefficient does not provide information about clinical significance of a diagnostic test. It was found that when TSB level increases, the difference between values of TSB and TcB increases as well. Other authors provide similar data that TcB level is lower than TSB level (6, 14, 17, 18). Data of our study shows not only strong correlation between TSB level and TcB level, but also the fact that the difference between these values is especially significant in diagnosing hyperbilirubinemia at early age (6 hours).

The correlation can be described by an equation (15, 20); however, in clinical practice it is more useful to know cutaneous bilirubin level, which corresponds to cutoff value for serum bilirubin level, or to use transcutaneous bilirubin nomograms (21).

In the studies that were performed following the guidelines of the American Academy of Pediatrics (2000) for diagnostics and treatment of hyperbilirubinemia, to compare transcutaneous bilirubin level and serum bilirubin level, cutoff values of 171 $\mu$mol/L (24 hours of age) and 256.5 $\mu$mol/L (25–48 hours of age) were chosen, because at this time treatment of hyperbilirubinemia was initiated. The sensitivity of transcutaneous bilirubin level that corresponds to these cutoff values, the same as in our study, was 61.9–100% and specificity was 56–100% (5, 13–16). The American Academy of Pediatrics (2004) recommends evaluating the bilirubin level in newborns according to hour-specific bilirubin nomograms (10). However, there are no data published about any studies that evaluated the reliability of transcutaneous measurement of bilirubin level in newborn infants at high risk of ABO hemolytic disease, especially at an early age. In the course of our study, TcB cutoff value corresponding to diagnostic TSB value for ABO hemolytic disease at the age of 6, 30, and 54 hours was established. And though at the age of 6 hours, out of 8 newborns with TcB $\geq$98 $\mu$mol/L only 5 exceeded diagnostic limit (PPV, 62%), in none of 122 newborns with TcB <98 $\mu$mol/L, serum bilirubin level exceeded diagnostic value (NPV, 100%). However, at the age of 30 hours, out of 107 newborns with TcB level lower than cutoff value in 3 newborns, TSB level exceeded age limits (NPV, 97%), and 10 newborns out of 17 had wrong diagnosis of hyperbilirubinemia (PPV, 41.2%).

Fig. Transcutaneous bilirubin cutoff value for diagnosing ABO hemolytic disease using receiver operating characteristic (ROC) curves

ROC curve of transcutaneously measured bilirubin level at the age of 6 hours (area under the curve, 0.99; $P<0.000$), TSB=102 $\mu$mol/L.

ROC curve of transcutaneously measured bilirubin level at the age of 30 hours (area under the curve, 0.82; $P=0.001$), TSB=187 $\mu$mol/L.

ROC curve of transcutaneously measured bilirubin level at the age of 54 hours (area under the curve, 0.83; $P<0.001$), TSB=238 $\mu$mol/L.

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At the age of 54 hours, this index was even lower: NPV was 94% (9 of 99) and PPV was 50% (9 of 14).

For physicians caring for neonates, it is essential to know the TcB values up to which they can trust the skin test device and avoid TSB measurements without missing a newborn in need of therapeutic intervention. Therefore, based on the results of this study, we state that not in every case an increase in serum bilirubin level should be evaluated with care especially in newborns at risk of developing ABO hemolytic disease, when cutaneous bilirubin level is interpreted using nomograms of serum bilirubin levels. In diagnosis of hyperbilirubinemia using only a non-invasive method, hour-specific nomograms of cutaneous bilirubin level should be used.

Transkutaninio bilirubino kiekio nustatymo vertė, esant naujagimų ABO hemolizės ligos rizikai

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Conclusions
Transcutaneous bilirubin level closely correlates with serum bilirubin level (r=0.92, P<0.001), and there is a significant difference between these values. Test results should be considered with caution especially in newborns at risk of developing ABO hemolytic disease, when cutaneous bilirubin level is interpreted using nomograms of serum bilirubin levels. In diagnosis of hyperbilirubinemia using only a non-invasive method, hour-specific nomograms of cutaneous bilirubin level should be used.

Raktažodžiai: naujagimis, transkutaninis bilirubinas, ABO kraujo grupių nesutapimas, hemolizinė liga.

Santrauka. Tyrimo tikslas. Ivertinti bilirubino kiekio odoje ir serume koreliaciją naujagimiams, kuriems yra ABO hemolizės ligos rizika.

Tyrimo medžiaga ir metodai. Išvirta 130 išnešiotų, sveikų (≥23 savaicių nėštumo) naujagimų, kuriems nustatyta ABO kraujo grupių nesutapimas. Bilirubino kiekis kraujo serume matuotas šeštąją gyvenimo valandą, kiti matavimai atlikti 24, 48 ir 72 val. po pirmojo matavimo. Kraujo tyrimui imta iš periferinės kūno sodo. Klinikinėje laboratorijoje bilirubino kiekis kraujoje nustatytas Jendrassik–Grof analizės metodui. Bilirubino kiekis kaktos odoje matuotas neinvaziniu transkutaniniu bilirubino matuokliu „BiliCheck“ (SpectRX Inc, Norcross,GA) gamintojo nurodyta metodika per ±30 min. Ėmės kaujo mėginių.

Rezultatai. Nustatant bilirubinio kiekį kraujo serume ir odoje, atlikti 387 poriniai matavimai. Bilirubino kiekis kraujo serume 114,83 (62,85) µmol/l (95 proc. PI (2,55; 8,61), p<0,001). Didžiausias skirtumas nustatytas ABO kraujo grupių nesutapimuose, kurie yra ABO hemolizės ligos rizikai. Transkutaninio bilirubino kiekio nustatymo vertė, esant naujagimų ABO hemolizės ligos rizikai. Transcutaneous bilirubin level closely correlates with serum bilirubin level (r=0.92, P<0.001), and there is a significant difference between these values. Test results should be considered with caution especially in newborns at risk of developing ABO hemolytic disease, when cutaneous bilirubin level is interpreted using nomograms of serum bilirubin levels. In diagnosis of hyperbilirubinemia using only a non-invasive method, hour-specific nomograms of cutaneous bilirubin level should be used.

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