Risk Factor Analysis for Late-onset Neonatal Hyperbilirubinemia in Taiwanese Infants

Mi-Shu Huang1,2, Ming-Chih Lin1,3, Hsiu-Hsi Chen3, Kuo-Liong Chien3, Chao-Huei Chen1*

1Department of Pediatrics, Taichung Veterans General Hospital, Taichung, Taiwan
2Nursing department, Taichung Veterans General Hospital, Taichung, Taiwan
3Institute of Preventive Medicine, National Taiwan University, Taipei, Taiwan

Received: Dec 17, 2007
Revised: Dec 23, 2008
Accepted: Feb 6, 2009

KEY WORDS:
late-onset hyperbilirubinemia; newborn

Background: Neonatal hyperbilirubinemia is a recognized health risk for newborns. It can cause kernicterus and hearing impairment. Certain groups of infants who do not have significant jaundice during the first few days of life develop hyperbilirubinemia later. Because early discharge is a worldwide trend, prompt identification of this group of infants is of paramount importance in preventing complications.

Methods: The data used were derived from a medical center. A total of 523 term or near-term infants were enrolled in this study. All infants were scheduled for follow-up visits. In this study, late-onset neonatal hyperbilirubinemia was defined as a total bilirubin level greater than 15 mg/dL, or receiving phototherapy at 5–7 days. Newborns that had clinically significant jaundice within 96 hours of life were excluded from analysis. Univariate and multivariate logistic regressions were applied for statistical analysis.

Results: One hundred and eighty infants were included for data analysis. Thirty-nine (21.7%) had late onset hyperbilirubinemia. Exclusive breast-feeding and less body weight loss during the 1st day of life were both significant risk factors for late onset hyperbilirubinemia. However, early discharge was not associated with late-onset hyperbilirubinemia.

Conclusion: Thirty-nine (21.7%) infants develop late hyperbilirubinemia at the age of one week. Exclusive breast-feeding and less body weight loss were significant risk factors. Follow-up visits are recommended for all infants, especially for those who have these risk factors.

1. Introduction

Neonatal hyperbilirubinemia is a health risk for newborns.1 Approximately 60% of newborn infants (2.4 million) develop clinical jaundice every year in the United States.2 It is one of most common reasons for neonatal readmission3–6 and has been the focus of attention in recent years for two reasons. First, cases of kernicterus have been occasionally reported in the United States7,8 and Europe,9 although the American Academy of Pediatrics (AAP) provided practical guidelines for neonatal hyperbilirubinemia in 1994.2 Second, other minor neurological abnormalities have been reported among infants with
hyperbilirubinema. The sequelae of hyperbilirubinema include kernicterus, permanent brain damage, and hearing impairment. These complications can be prevented by phototherapy (blue light) or blood exchange transfusion if hyperbilirubinema is detected early.

Currently, early discharge—even within 24 hours of birth—is a worldwide trend in obstetric care. However, there are certain groups of infants who do not have significant jaundice in the first several days of life but develop it later. Therefore, the AAP recommends that all infants discharged before the age of 48 hours should be followed up within 2–3 days after discharge. The follow-up rate has been reported to be low even in the United States. Early identification of these groups of infants is of paramount importance in preventing complication. This study was designed to analyze the risk factors for infants who develop late-onset neonatal hyperbilirubinema.

2. Materials and Methods

The study subjects were neonates in the well-baby nursery of a medical center located in central Taiwan. According to the regulations of the National Health Insurance (NHI) of Taiwan, newborn infants are observed in the hospital for 3 days if they are born by vaginal delivery, and for 5 days if by cesarean section. Breast-feeding is encouraged in this medical center. Mothers receive information and care from the staff during the whole peripartum stay. Infant formula was not given unless requested by parents or prescribed by pediatricians under certain medical circumstances.

This study included 639 infants who were born at the medical center between October 2003 and April 2004. Of these, 531 were term or near-term and were cared for at the well-baby nursery. Term or near-term infants with gestational age > 35 weeks and birth weight >2000g were enrolled. Sick infants who were transferred to the intensive care unit or sick baby nursery were excluded. Newborns with significant jaundice, defined as having a bilirubin level higher than the 95 percentile on the nomogram, plotted by continuous monitoring of the 639 infants in our nursery, or receiving phototherapy within 96 hours after birth, were not included. Gender, G6PD deficiency, pregnancy history, delivery pattern, feeding pattern, birth weight, blood type, maternal age, and body weight were collected for risk factor analysis.

All parents received a card on which the follow-up date and the reason for follow-up were written. During follow-up visits, all infants received complete physical examinations, their medical history was briefly recorded, and transcutaneous bilirubin (TcB) measurements were taken using a BiliCheck device (American Laubscher Corporation, Farmingdale, NY, USA). If the bilirubin level was over 15 mg/dL, total serum bilirubin was rechecked for confirmation. Late-onset neonatal hyperbilirubinema was defined as having a TcB level greater than 15 mg/dL or receiving phototherapy at 5–7 days.

Both univariate and multivariate logistic regression models were applied. The risks were presented as odds ratios with 95% confidence intervals. The stepwise method was adapted in variable selection for multivariable logistic regression. The entry criterion was set at 0.2 and the stay criterion at 0.1. The body weight loss percentage between groups was compared by non-parametric (Mann-Whitney U) tests. Statistical significance was defined as p < 0.05.

3. Results

Eight infants were excluded: four had a birth weight ≤ 2000g; the other four, who were suspected of having hemolytic diseases, received phototherapy within 48 hours after birth. A total of 523 infants were enrolled in this study. Among them, 231 infants had available bilirubin data at one week either from the follow-up clinic or well-baby nursery records. The demographic data of the follow-up and the non-follow-up groups were compared and are summarized in Table 1. Infants having gestational age less than 37 weeks, born by cesarean section, or not exclusively breastfed were more likely to be followed-up. Among these 231 infants, 51 with significant jaundice within 96 hours post-birth were excluded. Of the remaining 180 infants, 39 (21.7%) were diagnosed as having late-onset hyperbilirubinema. The study cohort is summarized in Figure 1. The results of univariate and multivariate logistic regression for risk factor analysis are shown in Table 2. In univariate analysis, exclusive breast-feeding at the end of the first week, vaginal delivery, and body weight loss during the first day of life were significant variables. We further analyzed these three risk factors in a multivariate logistic regression model by stepwise selection of variance. Only exclusive breast-feeding and less body weight loss during the first day of life were considered significant. Early discharge within 72 hours was not a risk factor either in the univariate or multivariate models. Because infants with more body weight loss during the first day had less late-onset neonatal hyperbilirubinema, we further analyzed the correlation by a scatter plot in regression analysis, and the
Late-onset neonatal hyperbilirubinemia

4. Discussion

In this study, we found that some infants who had no significant jaundice during the 3-day well-baby nursery stay developed jaundice later. We defined this phenomenon as late-onset neonatal hyperbilirubinemia and tried to analyze the risk factors involved.

Phototherapy is indicated where bilirubin levels exceed 15 mg/dL, according to the Bureau of National Health Insurance, Taiwan. Choosing 15 mg/dL as the cut-off point may lead to lower specificity but may reduce false negative cases. If the cutoff point was set at 18 mg/dL, there would only be seven cases of late-onset hyperbilirubinemia in our study. Using multivariate logistic regression, we found that exclusive breastfeeding until 7 days is a significant risk factor for late-onset neonatal hyperbilirubinemia. It is compatible with previous epidemiological findings that show breastfed infants have higher bilirubin levels and longer periods of jaundice.16−19

Some infants who were discharged within 72 hours after birth developed hyperbilirubinemia at the 4th day after birth and were considered as cases of late-onset hyperbilirubinemia. This result may lead to outcome measure misclassification. We do not think this is a major limitation because the aim of this study was to determine risk factors for infants who should be followed-up after discharge. Furthermore, this kind of misclassification is non-differential and can lead the results toward the null value. It may also move the risk factors further from significance in statistical analysis.

In the regression model, we found that infants with greater body weight loss during the 1st day had less late-onset neonatal hyperbilirubinemia. This is in contrast to the calorie-deprivation theory suggested in previous studies.20,21 Our study does not enable the elucidation of the cause of this phenomenon. The body weight discrepancy was not significant at follow-up.

Whether early discharge is a risk factor for late-onset neonatal hyperbilirubinemia and neonatal

Table 1 Comparison of demographic data of infants who were followed-up at 1 week and those who were not

<table>
<thead>
<tr>
<th></th>
<th>Followed up (n=231)</th>
<th>Not followed up (n=292)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>53.9%</td>
<td>51.6%</td>
<td>0.619</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>0%</td>
<td>2%</td>
<td>0.102</td>
</tr>
<tr>
<td>First pregnancy</td>
<td>39.3%</td>
<td>32.8%</td>
<td>0.142</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>47.8%</td>
<td>26.0%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Exclusive breast-feeding</td>
<td>32.2%</td>
<td>42.5%</td>
<td>0.022*</td>
</tr>
<tr>
<td>Birth weight &gt;3500 g</td>
<td>18.3%</td>
<td>17.2%</td>
<td>0.747</td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>15.5%</td>
<td>13.8%</td>
<td>0.613</td>
</tr>
<tr>
<td>Maternal age &gt;35 yr</td>
<td>24.4%</td>
<td>21.9%</td>
<td>0.504</td>
</tr>
<tr>
<td>Preterm (GA 35−37 wk)</td>
<td>17.3%</td>
<td>7.6%</td>
<td>0.001*</td>
</tr>
<tr>
<td>Birth body weight (g)</td>
<td>3106±34</td>
<td>3157±21</td>
<td>0.171</td>
</tr>
</tbody>
</table>

*pStatistically significant by Pearson’s $\chi^2$ test. G6PD = glucose-6-phosphate dehydrogenase; GA = gestational age.

Figure 1  Summary of the study cohort. SBR = sick baby nursery; NICU = neonatal intensive care unit.

p value revealed statistical significance. However, when comparing birth weight and weight at 7 days, we did not find any significant difference between the jaundiced and non-jaundice groups.

We further analyzed the effect of exclusive breast-feeding by plotting the median TcB values for infants who were exclusively breastfed versus those who were not (Figure 2). Analysis revealed that breastfeeding infants did not have higher median TcB values in the first 4 days of life.
readmission is still a point of controversy in the United States.\(^3\)\(^4\)\(^6\) As we know, a substantial proportion of neonatal readmission can be attributed to hyperbilirubinemia.\(^3\)\(^6\) In this study, regular discharge within 72 hours after birth was not a significant risk factor for late-onset neonatal hyperbilirubinemia; this means observation for 2–3 or 4–5 days in the well-baby nursery made little difference in preventing late-onset hyperbilirubinemia. From the perspective of insurance policymaking, follow-up at clinics may be more important than keeping babies in the nursery for 1 or 2 more days.

Comparison of demographic data showed that infants of gestational age between 35–37 weeks, birth by cesarean section, or exclusively breast-fed babies were more likely to be followed-up. This is because both physicians and parents were more concerned when they observed that the infants had jaundice. As a risk factor, it may be over-presented because almost all of these babies were

### Table 2  Risk factor analysis for late-onset neonatal hyperbilirubinemia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Late-onset hyperbilirubinemia*</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=39)</td>
<td>No (n=141)</td>
</tr>
<tr>
<td>Male gender</td>
<td>61.5% (24/39)</td>
<td>51.8% (73/141)</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>0% (0/39)</td>
<td>0% (0/141)</td>
</tr>
<tr>
<td>First pregnancy</td>
<td>35.9% (14/39)</td>
<td>40.3% (56/139)</td>
</tr>
<tr>
<td>CS</td>
<td>33.3% (13/39)</td>
<td>51.8% (74/141)</td>
</tr>
<tr>
<td>Exclusive BF</td>
<td>41% (16/39)</td>
<td>29.8% (42/141)</td>
</tr>
<tr>
<td>Giant baby</td>
<td>28.2% (11/39)</td>
<td>15.6% (22/141)</td>
</tr>
<tr>
<td>ABO</td>
<td>15.4% (6/39)</td>
<td>15.6% (21/135)</td>
</tr>
<tr>
<td>Maternal age &gt; 35 yr</td>
<td>20.5% (8/39)</td>
<td>25.5% (36/141)</td>
</tr>
<tr>
<td>Preterm</td>
<td>23.7% (9/38)</td>
<td>15.6% (22/141)</td>
</tr>
<tr>
<td>Early discharge</td>
<td>46.2% (18/39)</td>
<td>34.8% (49/141)</td>
</tr>
<tr>
<td>Exclusive BF till 7 d</td>
<td>68.6% (24/35)</td>
<td>45.5% (61/134)</td>
</tr>
<tr>
<td>BW loss (%) in first 24 hr</td>
<td>3.02±0.13%</td>
<td>3.92±0.31%</td>
</tr>
<tr>
<td>BW change at age of 7 d</td>
<td>−3.26±6.14%</td>
<td>−2.94±6.02%</td>
</tr>
</tbody>
</table>

*Data from follow-up clinic for 89 infants and from daily nursery record for the other 91 infants. BF = breast-feeding; BW = body weight; CS = cesarean section; CI = confidence interval; G6PD = Glucose-6-phosphate dehydrogenase.

Figure 2  Median transcutaneous bilirubin (TcB) values for infants who were exclusively breast-fed vs. those who were not—there was no significant difference between the two groups.
followed up. Because most infants delivered by cesarean section were discharged at day 6 or day 7 after birth—according to National Health Insurance policy—there was a significantly higher follow-up rate for infants born by cesarean section. To control for possible confounding factors, we used multiple logistic regression analysis. Because exclusive breastfeeding was highly correlated with delivery type (48.1% exclusive breastfeeding rate for vaginal delivery vs. 20.6% for cesarean section), only the delivery type was chosen for multiple logistic regression to avoid co-linearity. We controlled for cesarean section and the two significant risk factors—exclusive breast-feeding until 7 days post-partum and less body weight loss during the first day. Both were evenly distributed between follow-up and non-follow-up groups; we therefore do not believe there is major selection bias in our study.

After comparing babies who were followed-up with those who were not, we found there were only differences in cesarean section rate, exclusive breast-feeding, and preterm infants. All three variables were controlled using multivariate regression models. We believe that bias caused by dropouts would be minor.

In summary, there are certain groups of infants who appeared normal in the well-baby nursery that developed jaundice at 1 week. Exclusive breastfeeding and less body weight loss during the first day of life are significant risk factors for developing late-onset neonatal hyperbilirubinemia. Follow-up visits should be recommended for all infants, especially for those who have the above risk factors.

References