Predicting Significant Hyperbilirubinaemia and Early Discharge for Glucose-6-Phosphate Dehydrogenase Deficient Newborns

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Abstract

***Introduction:** This study aims to assess the usefulness of day 3 (49 to 72 hours) pre-phototherapy total serum bilirubin (TSB) in predicting subsequent significant hyperbilirubinaemia (SHB) and the feasibility of early discharge for term and near-term glucose-6-phosphate dehydrogenase (G6PD) deficient newborns. **Materials and Methods:** This prospective cohort study involved inborn G6PD deficient neonates who were >35 weeks and weighed >2000 g at birth. TSB levels and phototherapy requirements in their first two weeks of life were studied. Day 3 pre-phototherapy TSB in the subgroup weighing >2500 g at birth was analysed for its value in predicting subsequent SHB. **Results:** Of the 129 neonates, 58 (45%) required phototherapy in the first week. Of these, only 4 patients (3.1%) needed phototherapy to be restarted in the second week. Seventy-one (55%) neonates did not require phototherapy at all. In the absence of SHB in the first week, the probability of its development in the second week was zero (95% confidence interval, 0 to 0.057). In the subgroup weighing >2500 g at birth, day 3 pre-phototherapy TSB <154 umol/L predicted no measurable risk of subsequent SHB (sensitivity, 100%; 95% confidence interval, 91.4% to 100%; negative predictive value, 100%; 95% confidence interval, 86.7% to 100%). **Conclusions:** G6PD deficient newborns without SHB in their first week of life were at no measurable risk of its development in the second week. Day 3 pre-phototherapy TSB in the subgroup weighing >2500 g was useful for predicting the risk of subsequent SHB. Low-risk infants, thus identified, may be eligible for discharge on or before day 7 of life. Evidence-based early discharge can decrease the social and financial burden of G6PD deficiency in Singapore.*

***Ann Acad Med Singapore* 2003; 32:257-61**

***Key words:** Day 3 pre-phototherapy total serum bilirubin, Evidence-based, Financial, Social, Term and near-term*

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency occurs in 2.5% of Singapore's population, and affected newborns are at risk for severe neonatal hyperbilirubinaemia and kernicterus.[1] In the past four decades, neonatology units in local restructured hospitals have hospitalised all affected newborns for at least 14 days after birth because of this risk. This practice is unique to Singapore and originated from the Kernicterus Surveillance Programme.[2] Started in 1965, the programme also involved universal screening of newborns for G6PD deficiency and a nationwide campaign to educate the public on hyperbilirubinaemia and kernicterus prevention. Its success led to the virtual disappearance of kernicterus in Singapore for the last 20 years.[3] (personal communication – Singapore Immigration and Registration) However, with escalating healthcare cost and easily accessible primary health services, local paediatricians have begun to question the necessity of this prolonged hospitalisation.

Locally, Ho et al[4] reported that up to 42.6% of G6PD deficient babies never had significant hyperbilirubinaemia (SHB) at all. Tan et al[5] reported that SHB usually occurs in the first week of life only. However, it was not clear which factors were predictive of low risk for SHB, or on which day these infants can be safely discharged. Some local paediatricians have begun discharging G6PD deficient babies earlier at various postnatal ages. However, indiscriminate early discharge of all patients may lead to a resurgence of kernicterus. This has been reported in America,[6-11] Denmark[12] and Africa,[13] especially after the American Academy of Paediatrics introduced a more liberal guideline for the management of neonatal jaundice in 1994.[14]

Some authors have identified predictors for SHB. For the last few years in the United States, age-specific total serum bilirubin (TSB) has been used for the prediction of hyperbilirubinaemia in healthy-term and near-term newborns.[15-17] Kaplan et al[18] similarly demonstrated the

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usefulness of hour-specific (44 to 72 hours) serum bilirubin values in delineating G6PD deficient Sephardic Jewish newborns at low risk of hyperbilirubinaemia. The patients were found to be at low risk for SHB if their hour-specific TSB was <50th percentile for age. There is, however, no local data correlating age- or hour-specific TSB and the risk of hyper-bilirubinaemia. Our pilot study, therefore, aims to assess the predictive value of day 3 (49 to 72 hours) pre-phototherapy TSB for SHB, evaluate the feasibility of early discharge on or before day 7 of life, and henceforth propose an alternative discharge plan for G6PD deficient newborns.

Materials and Methods

Subjects

The study was conducted in the KK Women's and Children's Hospital (KKWCH) between 8 October 2001 and 31 March 2002. The population studied consisted of G6PD deficient neonates born in the hospital with gestation >35 weeks and birth weight >2000 g.

Cord or venous blood of the neonates was screened for G6PD deficiency, followed by G6PD quantitative analysis. A newborn was deemed deficient if the cord or venous enzyme activity was <12.6 IU/gHb or <6.0 IU/gHb, respectively.

Data Collection

In line with the current hospital policy, subjects were hospitalised till day 14 of life. During this period, they were observed visually for the development of jaundice and TSB was performed when clinically indicated. However, only day 3 pre-phototherapy (between 49 and 72 hours of life) TSB in newborns weighing >2500 g was used for prediction analysis.

SHB was defined as neonatal jaundice that required phototherapy. In accordance with our department's guideline, phototherapy was initiated when TSB was >190 umol/L for those weighing between 2000 and 2499 g, and >230 umol/L for those >2500 g, if the baby was >24 hours old. Exchange transfusion was performed if TSB was persistently >300 umol/L for those weighing between 2000 and 2499 g, and >340 umol/L for those >2500 g, despite intensive phototherapy for at least 4 hours. Blood group typing and Direct Coombs' test were done if phototherapy was required, or if the parents were agreeable. Breastfeeding was encouraged, although nursing mothers were warned to avoid food or drugs known to cause hemolysis in G6PD deficiency.

In the event of discharge against medical advice before day 14, telephone interviews were conducted to obtain the history of phototherapy requirement and outpatient TSB measurements between discharge and day 14. If follow-up post-discharge was inadequate and phototherapy requirement could not be clearly determined, the case was considered a defaulter and excluded from analysis.

Clinical and demographic risk factors for hyper-bilirubinaemia were recorded. Demographic factors included birth weight, gestation, race, gender, G6PD quantitative level, delivery mode, family history of G6PD deficiency and SHB, maternal drug history and blood group. Clinical factors were maternal diabetes during pregnancy, blood culture proven sepsis, cephalohematoma, hypothyroidism requiring thyroxine replacement, major dysmorphic syndrome, polycythemia, need for full intravenous drip >72 hours and type of milk feeds used.

Laboratory Analysis

G6PD screening was performed using a fluorescent visualisation method (Roche diagnostics G6PD deficiency screening test) in the hospital's biochemistry laboratory. If the result was suggestive of G6PD deficiency, a blood sample was sent to the Department of Pathology in Singapore General Hospital for G6PD quantitative analysis using spectrophotometry (Roche Diagnostics MPR 1 G6PDH).

TSB was measured by direct spectrophotometry (Creichert-Jung Unistat Bilirubinometer, Model 10310C/ 10311, Leica) in the hospital's laboratory. Only heel-prick capillary samples were used, with precautions taken to avoid their exposure to phototherapy light during collection and transport. For day 3 TSB, only measurements performed in the hospital laboratory were used for data analysis. Blood group determination and direct Coombs' test were performed by routine laboratory techniques in our hospital.

Data Analysis

The incidence of SHB and its 95% confidence interval (CI) were determined using the formula by Agnesti and Coull.[19]

Predictive characteristics of day 3 TSB were assessed based on the frequency of SHB. The outcome was binary, i.e. SHB was either "present" or "absent". The quartiles and 60th percentile of day 3 TSB were calculated. Predictive characteristics (sensitivity, specificity, positive and negative predictive values) of day 3 TSB in relation to these percentiles were computed and the receiver operating characteristic curves presented. The 95% CIs of significant predictive characteristics were derived using the Confidence Interval Analysis Program.[20]

Categorical variables were compared using chi-square (χ^2) analysis, and Student's *t*-test for continuous variables. Statistical significance was defined as P <0.05. Analysis was done using SPSS for Windows (version 10.0.1), unless otherwise specified.

Results

In this study, the incidence of G6PD deficiency was 25 per 1000 live births (140 of 5647). Only 134 were >35 weeks and weighed >2000 g at birth, with 125 weighing >2500 g.

Eighty-four per cent of enrolled subjects were male and 16% were female. They were racially diverse (64.9% Chinese, 22.4% Malay, 3% Indian, 9.7% others/mixed). The mean birth weight was 3132 g (range, 2220 to 4405 g) and mean gestation was 38.7 weeks (range, 35 to 41 weeks).

Five patients defaulted (3.7%) follow-up, leaving 129 patients with known outcomes. Fifty-eight subjects (45%) developed SHB, and all received their first session of phototherapy within the first week of life. Twelve patients (9.3%) started phototherapy < 48 hours of life. Ten required a repeat session of phototherapy (7.8%). Six of them were re-started on phototherapy in their first week of life, and only 4 were re-started in the second week (3.1%). None required an exchange transfusion.

On the other hand, 71 (55%) patients did not have SHB at all in both the first and second weeks of life. Therefore, if there was no SHB in the first week of life, the probability of its development in the second week was zero (95% CI, 0 to 0.057).

On comparing the demographics and clinical risk factors between groups with and without SHB, there was a statistically significant increase in the proportion of Chinese subjects (P = 0.008) and premature babies (gestation <37 weeks, P = 0.011) in the group with SHB. No significant differences were found in terms of gender, birth weight, G6PD quantitative level, delivery mode, presence of ABO incompatibility, maternal use of medications and traditional medicine during pregnancy, positive family history of G6PD deficiency and SHB, maternal diabetes and supplementation with breast milk.

Of the 125 subjects who were >2500 g at birth, 108 had valid day 3 TSB for computation of the percentiles. Twelve patients had phototherapy before day 3, and another 5 had no TSB done. Also, with 3 defaulters, only TSB measurements from 105 patients (day 3 TSB available and known outcome) were used for calculation of predictive characteristics. Day 3 TSB levels ranged from 71 to 357 umol/L (mean, 185 umol/L). The 25th, 60th and 75th percentiles correspond to 154 umol/L, 202 umol/L and 225 umol/L, respectively. The predictive characteristics of day 3 TSB levels for these percentiles are shown in Table I, and the receiver operating characteristic curve of day 3 TSB is shown in Figure 2.

Day 3 TSB level <154 umol/L predicted no measurable risk of SHB, with a negative predictive value of 100% and sensitivity of 100% (95% CI, 86.7% to 100% for negative predictive value, and 91.4% to 100% for sensitivity). Conversely, day 3 TSB >225 umol/L predicted a high risk for SHB, with a specificity of 100% and positive predictive value 100% (95% CI, 94.3% to 100% for specificity and 87.5% to 100% for positive predictive value).

In terms of clinical and demographic risk factors, there were significantly more non-Chinese among those with day 3 TSB <154 umol/L compared to those with day 3 TSB >154 umol/L (P = 0.006). There were also significantly more patients with a positive family history of SHB in those with day 3 TSB >225 umol/L compared to those with day 3 TSB <225 umol/L (P = 0.035). The other risk factors were not significantly different among the groups.

Discussion

The absence of SHB in the first week of life predicted that the baby would not require phototherapy subsequently. These babies may be eligible for discharge at day 7 of life.

The use of day 3 TSB <154 umol/L had a high negative predictive value in predicting SHB. It was, therefore, highly unlikely that a newborn would require phototherapy if his/her serum bilirubin was <154 umol/L on day 3. This newborn may be eligible for earlier discharge, possibly at day 3 of life. On the contrary, day 3 TSB >225 umol/L had

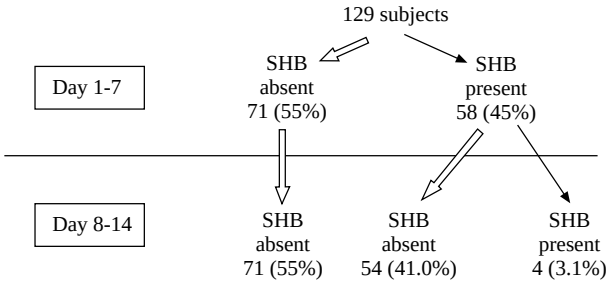

Fig 1. Incidence of significant hyperbilirubinaemia (SHB)

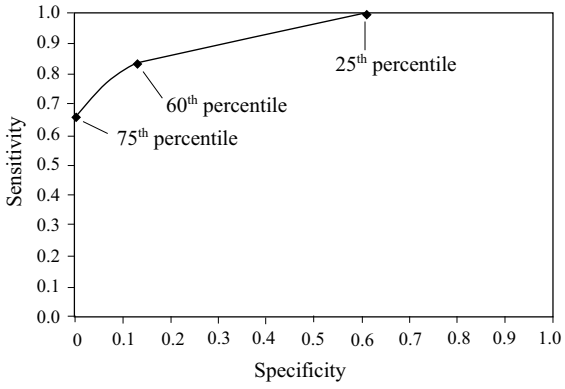

Fig. 2. Receiver operating characteristic curve of pre-phototherapy day 3 total serum bilirubin.

TABLE I: PREDICTIVE CHARACTERISTICS OF PRE-PHOTOTHERAPY DAY 3 TOTAL SERUM BILIRUBIN (TSB)

Day 3 TSB (umol/L)*	Number of newborns	Significant hyperbilirubinaemia		Predictive characteristic (%)			
		Present	Absent	PPV	NPV	Sensitivity	Specificity
<154	25	0	25	51.3	100	100	39.1
>154	80	41	39				
<202	63	7	56	81.0	88.9	82.9	87.5
>202	42	34	8				
<225	78	14	64	100	82.0	65.9	100
>225	27	27	0				

* 25^{th} percentile = 154 umol/L; 60^{th} percentile = 202 umol/L; 75^{th} percentile = 225 umol/L
** PPV: positive predictive value; NPV: negative predictive value

a high positive predictive value (100%) for SHB. This indicated that a newborn with day 3 TSB >225 umol/L was at extremely high risk of developing SHB and should be closely monitored for hyperbilirubinaemia.

Previous studies have indicated the usefulness of day 3 TSB as a predictor for SHB.[15,18] Using day 3 TSB as a predictive factor also has several advantages. Firstly, TSB of most G6PD deficient babies peak on day 3 to 4 of life. Sampling at this age would potentially give the best predictive values. Secondly, our facilities dictated that confirmed G6PD quantitative result was available only after 48 hours of life. Measuring the serum bilirubin levels on day 3 would, therefore, minimise unnecessary blood sampling in these babies.

For prediction analysis, only infants weighing >2500g were chosen because they constituted the largest number of deficient newborns, who were otherwise well, with the potential for early discharge. They also had the same criteria for initiation of phototherapy, which was necessary for prediction analysis.

It has been our department's policy to initiate phototherapy for G6PD deficient newborns at TSB >230 umol/L or >190 umol/L, if they weighed >2500 g or between 2000 and 2499 g respectively. We have chosen to maintain this practice in our study. The definition of SHB has been controversial,[3,21] with levels at TSB >256 umol/L,[18,22-24] or TSB >95^{th} percentile for age[14] being the more commonly used definitions. Using a stricter criterion for SHB, our study may *underestimate* the potential number of newborns who may be discharged at an earlier date.

In our study, Chinese babies and those with a positive family history of SHB were at a higher risk of developing it. This suggests the presence of additional genetic factor(s) that increase the risk of SHB. Kaplan et al[25,26] reported a synergistic effect between variant promoter gene for uridine 5'-diphosphate glucuronosyltransferase 1 seen in Gilbert's syndrome with G6PD Mediterranean^{563T} mutation. In the presence of both mutations, newborns were at higher risk of SHB compared to the presence of either factor alone. Similar genetic interactions may explain our observations. Future local research should, therefore, be directed at identifying the prevalence of mutations associated with increased risk of SHB, the genetic variants of G6PD deficiency and interactions between these genes.

On the other hand, contrary to logical deduction, concurrent ABO incompatibility did not increase the risk of SHB. This was also reported in another study.[24] However, further studies with larger sample sizes may be required to examine the effect of this risk factor independently using logistic regression.

Our results have demonstrated that early discharge of low-risk G6PD-deficient newborns in Singapore may be possible. We have provided important predictive factors to help us formulate a new discharge plan for these babies. A possible alternative discharge plan based on current data is illustrated in Figure 3.

Using proportions and incidence rate derived from this study, an estimated 19.8% of patients may be eligible for discharge at day 3, 35.2% at day 7 and the rest (45%) at day 14 of life. This translates to potential savings of up to S$160,000 per year in hospital ward charges alone for the annual cohort of babies born in our hospital.

From the perspective of a healthcare organisation, our study results will enable administrators to better allocate healthcare expenditure and resources. Based on the alternative discharge plan, the average length of stay for a newborn with G6PD deficiency will be 9.36 days.

Other potential advantages of this alternative discharge plan exist as well. The current cumbersome 14-day hospitalisation policy will tend to discourage mothers from breast-feeding their newborns. In our study, none of the subjects were fully breastfed, and only 50% received partial breast-feeding or breast milk supplementation. This contrasts with a general figure of 11% total breast-feeding, and 79% partial breast-feeding or breast milk supplementation rate in babies born in KKWCH during the

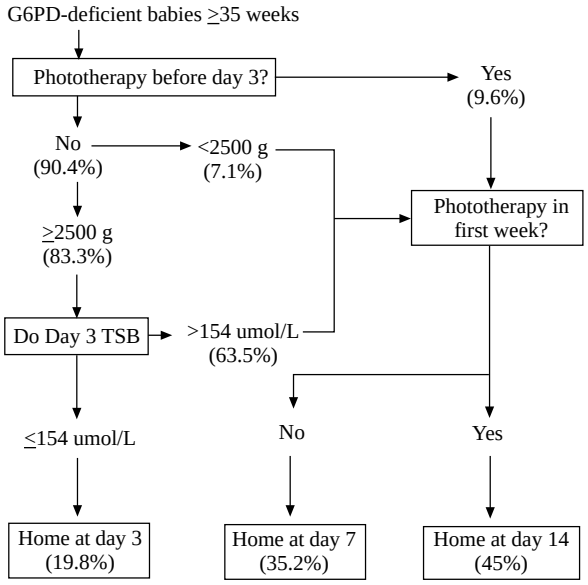

Fig. 3. Alternative discharge plan.

same period of time. Early discharge will certainly decrease interruption of breast-feeding and promote maternal-infant bonding.

Being a pilot study involving a small sample, we recognize its limitations. We were unable to perform logistic regression for all risk factors sensibly because of the small sample size. This will be possible with a larger study.

Though our results are promising, a larger sample size is again needed to validate them. This will improve the 95% CI for the predictive criteria and also provide information on their usefulness in other smaller group of infants, e.g. G6PD-deficient newborns <2500 g at birth. Meanwhile, our department has opted to continue our current management of G6PD deficient newborns until the above results are validated by a larger cohort study.

Our study involved newborns in a segregated environment devoid of any triggering factors for haemolysis and aggravating postnatal factors for hyperbilirubinaemia, e.g., dehydration. Therefore, care must be taken to educate parents on potential risks in the home environment in the event of early discharge.

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