Well Neonate Due For Discharge In Low Resource Setting Must Be Screened For Significant Hyperbilirubinemia

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Abstract

Introduction: Due to inadequacy of postnatal care in low resource settings, neonates with significant hyperbilirubinemia are likely to be discharged home only to develop complications of hyperbilirubinemia.

Objective: To determine the prevalence of significant hyperbilirubinemia among well neonates due for discharged, factors associated with it and performance of transcutaneous bilirubin (TCB) compared to visual inspection in identifying these neonates.

Methods: We conducted a cross sectional study involving 235 neonates in the postnatal ward of Mulago Hospital. Relevant data were captured. Neonates with significant hyperbilirubinemia were referred for treatment. Data was entered in to Epi-data version 3.0 then exported to STAT 14.0 software and analyzed. P-value of <0.05 was considered significant with confidence interval of 95%.

Results: Thirty two (13.6%) participants had significant hyperbilirubinemia and 3 (1.3%) were above exchange transfusion threshold. Eleven (34.3%) of these neonates had ABO/Rhesus discordancy and eight (25%) had high CRP. Significant hyperbilirubinemia was independently associated with CRP ≥ 10mg/dl (AOR 3.96, CI 1.23-12.73, p 0.021), ABO discordance (AOR 3.67, CI 1.28-10.49, p 0.015), jaundice in previous baby (AOR 3.565, CI 1.10-11.51, p 0.034) and Time of initiation of feeds > 1 hour (AOR 2.74, CI 1.10-6.90, p 0.007). The sensitivity, specificity, positive and negative predictive values of TCB were 96.5%, 84.6%, 47.5% and 99.4% respectively compared to 31.2%, 98.5%, 76.9% and 90% respectively for visual assessment.

Conclusions: Well neonates prior to discharge must be screened for significant hyperbilirubinemia preferably using transcutaneous bilirubinometer. Early initiation of feeding should be promoted. Screening for sepsis in neonates with significant hyperbilirubinemia should be emphasized.

Introduction

Jaundice affects 60–80% of all neonates and without any underlying exacerbating factors, it should disappear with no intervention (1–3). In the presence of underlying factors like sepsis, blood group incompatibility, G6PD deficiency, inadequate feeding among others some neonates develop severe neonatal jaundice (SNJ) warrantying hospital readmission. Severe neonatal jaundice is a leading cause for hospitalization in the first week of life (4).

If SNJ is not identified early and managed promptly it can cause brain dysfunction (acute bilirubin encephalopathy (ABE)) and death. Survivors of ABE are at increased risk of disability (5, 6). It is estimated globally 481000 term/ near term neonates are affected by SNJ annually of whom 114000 die and 63000 survive with disability (7). The majority of neonates affected by SNJ are in Low and Middle income countries (LMICS)(1, 4, 7, 8).

Neonates with SNJ need urgent phototherapy while those with signs of brain dysfunction need exchange transfusion at the shortest time possible to prevent disability and death. The highest burden of neonates needing exchange transfusion and mortality associated with neonatal jaundice are in the LMICs which have been attributed to health system challenges in these setting (1)(8).

Available evidence shows that risk factor assessment along with carefully timed estimation of bilirubin levels with prompt intervention has significantly reduced hospital readmissions, the occurrence of severe jaundice, need for exchange transfusion as well as associated disability in the developed countries (9, 10).

The WHO recommends 24 hour hospital stay after uncomplicated delivery, assessing for jaundice prior to discharge, follow up review within 72 hours and again within the first week (11); implementation of these recommendation in LMICS has been challenging.

At Mulago National referral hospital, stable babies are not screened for jaundice and are discharged early. The prevalence of significant hyperbilirubinemia (SHB) among these neonates and associated factors are not known. We conduct this study to determine how prevalent SHB was among these babies, factors associated with it and how transcutaneous bilirubinometer performed in identification of such neonates compared to visual inspection.

Methodology

Study Setting: This study was conducted at the postnatal ward of Mulago National Referral Hospital. This Hospital is Uganda's National Referral Hospital and training hospital for Makerere College of Health Sciences. The hospital records 31000 deliveries annually.

After delivery stable neonates are kept by the mother's side in the post natal ward where they spend 6–12 hours for normal and 72 hours for cesarean deliveries. In the post natal ward the neonates are assessed by midwives and if there is any concern then a doctor is notifies; unwell neonates are transferred to the special care baby unit. Sick neonates are admitted to the Special Care Baby Unit (SCBU).

Exclusive breast feeding is encouraged. Once newborn and mother are thought to be stable by midwife then they are discharged. The postnatal ward does not have structured protocol on the review on the newborn while with the mother or once due for discharge.

Study Population: well neonates 24 to 72 hours of age due for discharge.

Sample size: The sample size for prevalence was calculated using Kish Leslie formula for cross sectional studies $N = Z\alpha^2P(1-P)/W^2$ assuming expected prevalence for severe neonatal jaundice of 34% (12), as observed among neonates admitted in Kenya; the sample size needed to determine prevalence of significant hyperbilirubinemia with 95% level of confidence was 227. The sample size of 220 was needed to determine factors associated with SHB was computed using open-Epi calculator for unmatched case control using a two sided confidence interval of 95% and power of 80% assuming 19% risk for septicemia

among neonates with jaundice(13). We used the larger sample size and assuming a 3.5% for incompleteness of data our final sample size was 235.

Study Procedure

Parents or primary care givers of the neonates who meet study criteria were given information about the study and informed consent obtained by the principal investigator/ research assistants. Data capturing sheet was used to enter relevant information.
History was taken and study neonates were examined by the principal investigator or research assistant. Gestational age was determined using mother's records if available and the New Ballad Score (14). Mother's documented blood group was ascertained and test done for those with no record.

Study neonates were assessed for jaundice by visual inspection and graded as per the Kramer rule (15), Transcutaneous Bilirubin (TCB) determined over the sternum using Draeger JM103 transcutaneous bilirubinometer after calibration and Total Serum Bilirubin (TSB) using blood samples collected from by heel prick. The blood collection site was cleaned with 70% alcohol and allowed to air dry. A minimum of 2 ml of blood was drawn, dispensed into an EDTA free container and transported within one hour to Mulago chemistry laboratory. Blood group and C-reactive protein were done on all neonates.

Total serum bilirubin was determined through High Performance Liquid Chromatography.

Study neonates found to have SHB i.e any level 20 µmol/l within threshold or greater on the age specific bilirubin nomogram (Using the neonatal academic hospitals' consensus guidelines for South African hospitals and primary care facilities) (16) were referred to SCBU.

Data management and analysis

Information captured in the data sheet was checked by the principle investigator for completeness and accuracy. The data sheets were stored in a locker.
Data were entered into the computer using Epi-data version 3.0 and thereafter exported into STATA version 14.0 for analysis with the help of a Bio-statistician. Data was checked for errors, cleaned and coded before analysis. Baseline characteristic of study participants were summarized in a table. The prevalence of SHB was computed as a ratio of neonates with total serum bilirubin warranting treatment to total number of study neonates. Univariate analysis was conducted for continuous variables. Multivariate analysis for factors associated with SHB were determine in a stepwise manner.

P values of < 0.05 were considered significant and confidence interval of 95% was used. Though a 2×2 table; the performance of transcutaneous bilirubinometer and visual assessment were determine. The sensitivity, specificity, positive and negative predictive values were computed. Results were summarized in tables.

Results

Between March 2017 and May 2017 a total of 235 neonates were enrolled. The average age of the neonates was 49 (± 14.4) hours. Majority were on exclusive breast feeding (96%) and 18.3% had clinical jaundice.

Table 1

Baseline characteristics and Factors associated with significant hyperbilirubinemia

VARIABLES	Significant hyperbilirubinemia		OR(95%CI)	p-value
	No (203)	Yes (32)		
Sex				
Male	108(85.7)	18(14.3)	1.13(0.53-2,39)	0.748
Female	95(87.1)	14(12.9)		
Gestational age				
≤ 37	28(80.0)	7(20.0)	1.85(0.73–4.67)	0.193
38–39	102(87.9)	14(12.1)		
≥ 40	83(88.3)	11(11.7)		
Birth weight				
< 2.5 kg	14(82.4)	3(17.6)	1.39(0.37–5.15)	0.616
2.5–3.9 kg	179(87.7)	25(12.3)		
≥ 4 kg	10(71.4)	4(28.6)	2.75(0.80–9.39)	0.105
Jaundiced in previous baby				
Yes	15(68.2)	7(31.8)	3.50(1.30–9.44)	0.013
No	188(88.3)	25(11.7)		
Time of initiation of first feed				
≤ 1 hour	126(90.0)	14(10.0)		
> 1 hours	72(80.0)	18(20.0)	2.25(1.05–4.79)	0.036
Rupture of membrane (ROM)				
≥ 18hrs	11(91.7)	1(8.3)	0.56(0.07–4.51)	0.589
< 18hrs	192(86.1)	31(13.9)		
Mother-infant ABO discordancy				
Yes	21(70.0)	9(30.0)	3.17(1.27–7.87)	0.013
No	148(88.1)	20(11.9)		
Mother-infant Rh discordancy				
Yes	4(66.7)	2(33.3)	3.05(0.53–17.5)	0.22

VARIABLES	Significant hyperbilirubinemia		OR(95%CI)	p-value
	No (203)	Yes (32)		
No	165(86.0)	27(14.0)		
C-reactive protein				
< 10	151(87.3)	22(12.7)		
≥ 10	14(63.6)	8(36.4)	3.92(1.47–10.42)	< 0.006
Mode of delivery				
Caesarean section	141	27	2.14(0.78–5.85)	0.136
Vaginal velivery	56	5		

Table 2
factors independently associated with significant hyperbilirubinemia

Variables	Adjusted Odds Ratio	95% Conf. Interval	P-value
Jaundice in previous baby			
No	1		
Yes	3.565	(1.10-11.51)	0.034
TTF < 1hr			
No	2.74	(1.10–6.90)	0.007
Yes	1		
CRP			
< 10	1		
≥ 10	3.962	(1.23–12.73)	0.021
ABO Incompatibility			
No	1		
Yes	3.670	(1.28–10.49)	0.015

All factors with p-value less than 0.2 at bivariate analysis were for the multivariate analysis and then using some the background method some were dropped.

Table 3: Sensitivity and Specificity of TCB (TSB as Gold standard)

SHB No SHB

True positive 28	**False positive 31**
False negative 1	True negative 171
Sensitivity = 96.5%	

Specificity = 84.6%

PPV = 47.5%
NPV = 99.4%

Sensitivity And Specificity Of Kramer (tsb As Gold Standard)

True positive 10	**False positive 3**
False negative 22	True negative 200

SHB No SHB

Sensitivity = 31.2%

Specificity = 98.5%

PPV = 76.9% NPV = 90.0%

Discussion

The prevalence of significant hyperbilirubinemia among neonates due for discharge in this study was high 13.6% with 1.3% of study participant having serum bilirubin levels at/above exchange transfusion threshold. This high prevalence seen compared to those observed in other studies (3, 4) might be because we used the South African neonatal guidelines whose intervention threshold are slightly lower as compared to the other guidelines.

Considering the challenges of post natal follow up in LMICs we decided to use the South African guidelines whose treatment threshold is relatively lower hence minimizing the risk associated with late return for follow up and heightened risk for exchange transfusion.

Significant hyperbilirubinemia was independently associated with ABO discordancy (AOR 3.6 CI 1.28–10.49 p 0.015). This finding suggests possibility of ABO associated hemolysis as one of the causes of

SHB in our study population. This finding is in line with those observed in other studies (17).

Among our study participants 22 (9.36%) had incidentally elevated CRP of ≥ 10 mg/dl suggesting infection. Compared to the other study participants, these with elevated CRP were 3.9 times more likely to have SHB. This finding is not surprising since sepsis in neonates tends to be associated with hemolysis and jaundice (17, 18). Our finding of seemingly well neonate due for discharge having elevated CRP is a phenomenon that needs further thought in to.

Neonates whose mothers have had previously infants with jaundice were more likely to have SHB 7/22 (AOR 3.5, CI 1.10–11.5, p 0.034), this can be explained by the other familial causes of neonatal jaundice including G6PD deficiency, hemoglobinopathies and enzymopathies among others (17). History of jaundice in previous infant is a known risk factor for jaundice in subsequent infant (2).

Adequate enteral feeding facilitates excretion of bilirubin while inadequate favors increased entero-hepatic circulation and jaundice. Study participants who were initiated early on breast feeding < 1hr were more unlikely to develop SHB 126/140 compared to those who delayed 18/90. This finding is similar to that observed in Zimbabwean study that looked at early initiation of breast feeding on jaundice (19). Early initiation of breast feeding cant not be over emphasized.

Transcutaneous bilirubin over the sternum identified majority of study participants with SHB 28/29 compared to visual inspection 10/32. Transcutaneous bilirubinometry is steadily being accepted as modality for screening term neonates for hyper bilirubinemia (2, 20). It has been found to yield results that highly correlate with serum levels even among black African infants (21, 22) yet short turn-around time.

Visual assessment for jaundice is a very well described process but its accuracy in determining the levels is very subjective that even specialist can wrongly estimate bilirubin level using the visual assessment (4, 20, 23). In low resource setting where transcutaneous bilirubinometer is not available this tool cannot be invaluable. In our study it had a good negative predictive value of 90% implying it can identify majority of neonate's not needing treatment.

Conclusion

Significant hyperbilirubinemia is prevalent among well neonates due for discharge. Transcutaneous bilirubinometry identifies majority of neonates with SHB. Delayed initiation of breast feeding is a risk factor for SHB. Well neonates with SHB may have concurrent sepsis.

Recommendation

All neonates due for discharge must be screening for significant hyperbilirubinemia if possible by use of transcutaneous bilirubinometer. Early initiation of breast feeding should be encouraged. Neonates with significant hyperbilirubinemia should be screened for sepsis.

Study limitation
majority of study participants were delivered by caesarian section hence our findings might not be very representative of neonates delivered vaginally. We could not do coombs test, blood cultures, film comment among others to confirm infection and hemolysis.
What is already known? Continued screening of all neonates for jaundice in necessary in order to identify those at risk. Transcutaneous bilirubinometry is a good screening tool for hyperbilirubinemia.
What this study adds? Visual assessment for jaundice might be good at ruling out but not in the need to treat jaundice. Concurrent sepsis is heightened among well neonates with significant hyperbilirubinemia.

Declarations

List of abbreviations:

Rh: Rhesus

ABO: Blood groups A, B and O

CRP: C-reactive protein

LMICs: Low and Middle Income Countries

SCBU: Special Care Baby Unit

SHR: Significant Hyperbilirubinemia

TCB: Transcutaneous Bilirubin

TSB: Total Serum Bilirubin

WHO: World Health Organization

Ethics approval and consent to participate: Ethical approval to conduct this study was obtained from the Makerere Colleague of Health Sciences Institution review board. Written informed consent was obtained from the parents.

Consent to publish:

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest: None of the authors have any conflict of interest to declare.

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Authors' contribution: N.C collected and entered the data, she along with Y.A reviewed literature and did the write up. K.C and M.J reviewed the literature, methodology and write up.

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