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Research Article

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Frequency of Hyperbilirubinemia at 72 Hours of Life in Term Newborns with a High-Intermediate Risk Serum Bilirubin Level At 48 Hours of Life

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Abstract

Neonatal jaundice is common in newborns affecting over half (50-60%) of all babies in the first week of life. Severe jaundice can result into significant morbidity in the form of kernicterus. Early screening along with, quick treatment of neonatal jaundice helps to reduce the risk of developing severe hyperbilirubinemia, hence Kernicterus. There is strong evidence that screening newborns with hour-specific serum bilirubin level measurements can help in identifying risk of developing hyperbilirubinemia in newborns. There is insufficient data from developing countries regarding hyperbilirubinemia and newborns with and without underlying risk factors for hyperbilirubinemia. This cross sectional study will help the physician to anticipate and manage newborns with high-intermediate zone total serum bilirubin (TSB) and will also help to established specific management guideline for these newborns to prevent bilirubin induced neurological damage (BIND). All term newborns of either gender (fulfilling inclusion criteria) with TSB level at high-intermediate risk zone at 48 hours of life, born at Aga Khan University Hospital were included in this study. Their demographics were recorded in structured proforma. Results were collected and analyzed by SPSS software, version 20.0.

A total of 173 newborns were enrolled. There was a female predilection 56.6% (n=98). One-third of the newborns having TSB in high-intermediate risk zone at 48 hours of life progressed to level of significant hyperbilirubinemia requiring treatment (31.2%; n=54). Those who required phototherapy had the mean rate of rise of 5.00 mg/dL/day (0.20 mg/dL/hr). For future implementations we recommended that early recognition, monitoring and early treatment of neonatal hyperbilirubinemia may help in reducing morbidity. Neonates with high-intermediate risk serum bilirubin level should be followed at 24 hours interval for assessment and possible treatment.

Keywords: Neonatal Hyperbilirubinemia, Neonatal Jaundice, Jaundice in Term Healthy Newborn

Introduction

Neonatal jaundice is common in newborns affecting over half (50-60%) of all babies in the first week of life [1]. Severe jaundice can result into significant morbidity in the form of Kernicterus [2]. Early screening along with, quick treatment of neonatal jaundice helps to reduce the risk of developing severe hyperbilirubinemia, hence Kernicterus [3]. There is strong evidence that screening newborns with hour-specific serum bilirubin level measurements can help in identifying, risk of developing hyperbilirubinemia in newborns. In a study conducted at Pennsylvania Hospital, 12.5% of the study population (356/2840) had total serum bilirubin (TSB) values in the high-intermediate risk zone (between 75th and 95th percentile) at 18 to 72 hours; of these, 12.9% (46/356) progressed into high risk zone within 24-48 hours post-discharge [4].

There are studies available from developed countries regarding hyperbilirubinemia and newborns with underlying risk factors for hyperbilirubinemia However, there is insufficient data from developing countries [5]. A study done at National Institute of Child Health Karachi, which included all newborns admitted in Neonatal ICU, showed the incidence of the neonatal hyperbilirubinemia as 13.15% but there is no data available for significant hyperbilirubinemia in term healthy newborns [6].

In 2004, American Academy of Pediatrics (AAP) published guideline for the management of hyperbilirubinemia which recommends that every newborn be assessed for the risk of developing severe hyperbilirubinemia, by using pre-discharge TSB or transcutaneous bilirubin (TcB) measurements and/or assessment of clinical risk factors before discharge [7]. In contrast, a recommendation statement from the US Preventive Services Task Force (USPSTF) concludes that evidence is insufficient to make that recommendation [8]. This creates ambiguity whether to screen newborns for hyperbilirubinemia or not.

Newborns are usually screened for hyperbilirubinemia at 48 hours of life at some private sector hospitals in city. Those falling within high-risk zone and requiring intervention are usually admitted and treated accordingly. While newborns falling within high-intermediate

risk zone or with borderline TSB level are usually followed clinically and TSB repeated later; but we do not know how many out of those require readmission or intervention.

Based on a previous study, 12.9% of newborns with high-intermediate risk zone TSB level between 18 to 72 hours of life progressed to high risk zone, resulting in readmission for the treatment of neonatal hyperbilirubinemia [9].

This study will help the physician to anticipate and manage newborns with high-intermediate zone TSB and will also help to established specific management guideline for these newborns to prevent bilirubin induced neurological damage.

Operational Definitions

High risk zone serum bilirubin level

TSB level greater than 95th percentiles for age in hours based on normogram for an hour specific serum bilirubin concentration designed by American Academy of Pediatrics.

High-intermediate risk zone serum bilirubin level

TSB level between 75th and 95th percentiles for age in hours based on normogram for an hour specific serum bilirubin concentration designed by American Academy of Pediatrics.

Hyperbilirubinemia

Level of bilirubin ≥15 mg/dL at 72 hours of life, falling at or above the intermediate risk zone as plotted on bilirubin "Phototherapy Management Chart" (attached below as Figure 4)

Material & Methods

Setting: This study was conducted at the Well Baby Unit at Aga Khan University Hospital Karachi.
Duration of Study: The study was carried out over six months between January 1st 2015 and June 30th 2015.
Study Design: This was a cross-sectional study.
Sampling Technique: Non-probability consecutive sampling

Sample Size

Assuming a progression of 12.9 %(9) of high-intermediate risk newborns to high risk zone, a sample size of 173 newborns was needed to have an estimate that falls within 5 % of the true proportion with 95% confidence. For the sample size WHO "Sample Size Determination in Health Studies" software was used.

Inclusion Criteria

All term newborns of either gender with TSB level at high-intermediate risk zone at 48 hours of life, born at Aga Khan University Hospital.

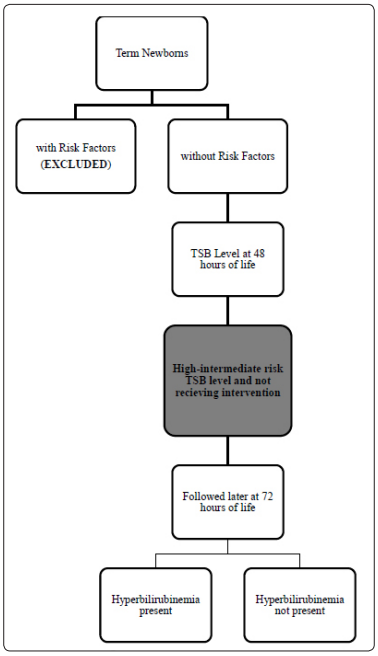
Exclusion Criteria

- Jaundice observed in the first 24 hrs.
- Newborn with high risk, low-intermediate risk, low risk or requiring intervention was excluded. Gestational age < 37 weeks or > 42 weeks
- History of previous sibling received phototherapy
- Significant bruising or Cephalhematoma (collection of blood between the skull and the periosteum of a newborn baby secondary to rupture of blood vessels crossing the periosteum and does not cross suture line)
- Poor Apgar score (<3 at 10th minute)
- Infant of diabetic mother
- Sepsis: (lethargy, temperature instability, respiratory rate >2 SD normal for age)
- Lost to follow up

Data collection

All term newborns delivered at Aga Khan University Hospital whose TSB level was done at 48 hours of life were approached. Subjects fulfilling the inclusion and exclusion criteria were enrolled in the study after acquiring parental consent. Confidentiality of participants was ensured by keeping all data in lock & key. Result of TSB was communicated to parents and caregivers only. Data was collected on a proforma and included basic demographic information, including gestational age, birth weight, and gender, baby and mother blood group. The study population was followed till 72 hours of life to determine the repeat TSB level. The outcome variable; hyperbilirubinemia was recorded as per operational definition and approved proforma. (Equation 1)

Equation 1: Data Collection steps.



Data analysis

Data was analyzed using statistical package for social sciences (SPSS) version 20.0. Mean ± standard deviation was calculated for age. Frequency and percentages was calculated for gender of the baby, mother and baby blood group and hyperbilirubinemia. Data was stratified with respect to age, gender, baby and mother blood group to look for confounding factors.

Results

During my study period, a total of 1807 term newborn babies were born in my hospital. Amongst them, first 173 term newborns fulfilling my inclusion criteria were enrolled and their demographics were documented on the preset proforma. Out of the total sample; 56.6% (n=98) were females, whereas 43.4% (n=75) were males. The mean birth weight was 3.08 kg with standard deviation (SD) of ±0.367. The mean gestational age was 38.49 ±1.12 SD weeks and median and mode of 38 weeks.

Birth weight was categorized into two categories; 2.5-3.0 kg (n=86: 49.7%) and 3.1-4.0 kg (n=87: 50.3%). Serum bilirubin at 48 hours

was categorized into; 11-12 mg/dL (n=111: 64.2%) and 12-13 mg/dL (n=62: 35.8%). Of total 173 newborns, 66 (38.2%) babies" mother blood group was B positive, while 59 (34.1%) babies" mother blood group was O positive, 2 (1.2%) babies" mother blood group was O negative, 30 (17.3%) babies" mother blood group was A positive, 3 (1.7%) babies" mother blood group was A negative, 13 (7.5%) babies" mother blood group was AB positive. Amongst the newborns, 75 (43.4%) babies had blood group B positive, 32 (18.5%) babies had blood group O positive, 3 (1.7%) babies had blood group O negative, 30 (17.3%) babies had blood group A positive, 1 (0.6%) baby had blood group A negative, 1 (0.6%) baby had blood group B negative, 29 (16.8%) babies had blood group AB positive & 2 (1.2%) babies had blood group AB negative.

Out of 173 terms newborns having TSB within high-intermediate risk zone; 31.2% (n=54) progressed to level of significant hyperbilirubinemia requiring treatment (Figure 1Figure 1). Whereas 68.8 % (n=119) did not progress above the threshold level. The mean rise in TSB over the preceding 24 hours for the complete cohort was 1.89mg/dL/day ±2.86 SD. Comparing the two groups, the group that did not require phototherapy had the mean rate of rise of 0.47 mg/dL/day (0.019 mg/dL/hr.) with ±1.88 SD, while the group that required phototherapy had the mean rate of rise of 5.00 mg/dL/day (0.20 mg/dL/hr) ±2.09 SD. The maximum rise of 10.1 mg/dL while the maximum fall of 5 mg/dL was observed over 24 hours.

Out of those babies who required phototherapy, 53.7% (n=29) were females while 46.3% (n=25) were male babies. The mean birth weight was 3.15kg ±0.355 SD. Majority of the newborns (57.4%: n=31) had birth weight between 3.1 – 4.0 kg while 42.6% (n=23) had birth weight between 2.5 – 3.0 kg. Of the babies requiring phototherapy, 22 (40.7%) babies" mother blood groups was O positive, 12 (22.2%) babies" mother blood group was A positive, 12 (22.2%) babies" mother blood group was group B positive & 8 (14.8%) babies" mother blood group was AB positive. Amongst the newborns that required phototherapy, 22 (40.7%) babies had blood group B positive, 14 (25.9%) babies had blood group A positive, 9 (16.7%) babies had blood group O positive, 7 (13.0%) babies had blood group AB positive & 2 (3.7%) babies had blood group O negative. Gestational age of 37 weeks was found in 19 babies (35.2%), 38 weeks in 8 babies (14.8%), 39 weeks in 16 babies (29.6%), 40 weeks in 10 babies (18.5%) & 41 weeks of gestation was found in 1 baby (1.9%). Among the study population, 53.7% (n=29) of the babies had 48 hours serum bilirubin between 11-12 mg/dL while 46.3% (n=25) had 48 hours serum bilirubin between 12-13 mg/dL.

Table 1: Frequency of newborns progressing to significant hyperbilirubinemia at 72 hours of life

Hyperbilirubinemia	Frequency	Percent
No	119	68.8
Yes	54	31.2
Total	173	100.0

Table 2: Distribution of newborns developing significant hyperbilirubinemia according to gender (n=54)

Gender	Frequency	Percent
Male	25	46.3
Female	29	53.7
Total	54	100.0

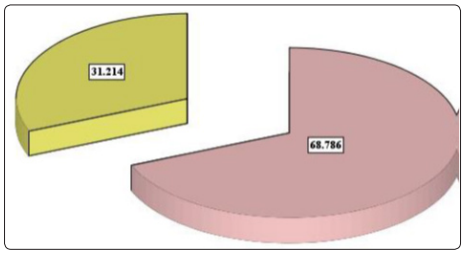


Figure 1: Graphical representation of term newborns developing significant hyperbilirubinemia at 72 hours of life

Discussion

Clinical experience based on assessment and recent reports suggest an increased occurrence of kernicterus (Bilirubin induced neurologic dysfunction {BIND}) in otherwise healthy newborns. Strategies to prevent BIND need to be practical, safe, effective, and based on risk assessment. Recognizing this as a matter of public health concern, in developed healthcare systems, the emphasis is on identifying the first day jaundice as a marker of significant hemolysis (unconjugated hyperbilirubinemia) and on prolonged jaundice as a sign of obstructive jaundice (conjugated hyperbilirubinemia), in particular biliary atresia. Additionally, in most of healthy term newborns that developed kernicterus, significant jaundice was almost certainly present before the first hospital discharge, (judging from the level of TSB for age in hours at readmission). Either the early icterus had not been noted or its pathologic intensity for postnatal age was not appreciated. Hour specific bilirubin levels provide an estimation of potential toxicity of bilirubin. It is in the context of identifying such newborns before dangerous levels are reached that a universal TSB screen, before discharge, is recommended as a more specific predictive vector than clinically recognized jaundice.

Bhutani et al. in 1999 described the importance of pre-discharge hour-specific serum bilirubin. An hour-specific TSB before hospital discharge can predict which newborn is at high, intermediate or low risk for developing clinically significant hyperbilirubinemia.

They obtained total serum bilirubin (TSB) levels at the time of the routine metabolic screen in all term and near-term newborns cared for in the Pennsylvania Hospital Well Baby Nursery (n= 13003). Postnatal age (in hours) at the time of TSB measurement was recorded. A percentile-based bilirubin nomogram for the first week was constructed from hour-specific pre-discharge and post-discharge TSB values of newborns. Although effective when implemented as intended, clinical use of the guidelines has been limited by the absence of a prospective risk assessment and by dependence on visual assessment of jaundice [4].

Risk stratification was done on the basis of ABO blood types and serial TSB level monitoring was done; and it was found that in newborns having TSB values >95th centile, majority had mother blood group type O positive. These all were term newborns and appropriate for gestational age.

When comparing these findings with my study, my study showed 31.2% newborns in high-intermediate risk zone progressing to significant hyperbilirubinemia, while in their study 12.9% progressed to significant hyperbilirubinemia.

William Cashore in 2010 emphasized that a rate of increase > 0.25 mg/dL/hr should be followed with repeat determinations until stable or responding to ordered treatment [10]. In my study the group that progressed to significant hyperbilirubinemia had the rate of rise of 0.20 mg/dL/hr.

Kalakheti et al. in 2009 confirms the striking association between ABO-incompatibility and neonatal hyperbilirubinemia through a prospective cohort study [11]. The chance of developing hyperbilirubinemia within 72 hours was 2.6 times higher in the babies with other blood group than the "O" Positive, and showed 18.5% newborns born to blood type O positive mothers developing hyperbilirubinemia while my results showed 37.3%.

Excluding hemolytic disease, hyperbilirubinemia in the newborn is essentially a condition of infants of subnormal weight. The same tendency is expressed, in a minor way, in infants of normal weight, as per results in my study babies belonging to higher birth weight category had higher incidence of hyperbilirubinemia, for which one of the confounding could be in decrease frequency of feeding.

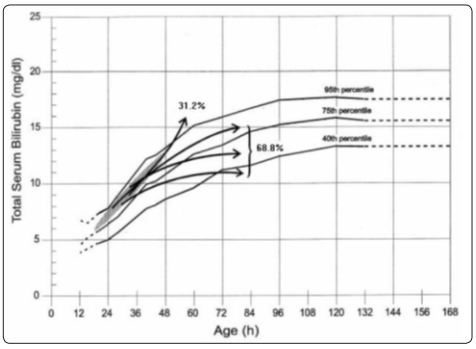


Figure 2: Outcome of newborns in high-intermediate risk zone (n=173)

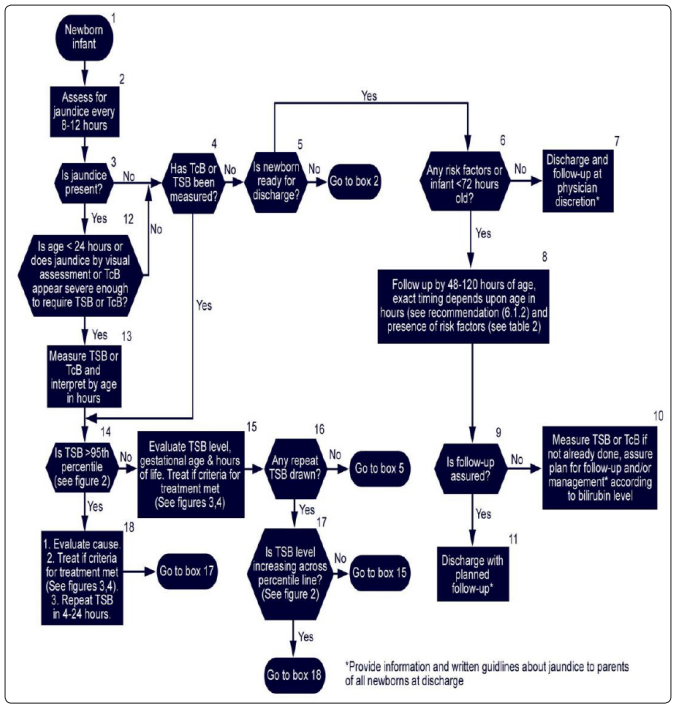


Figure 3: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation

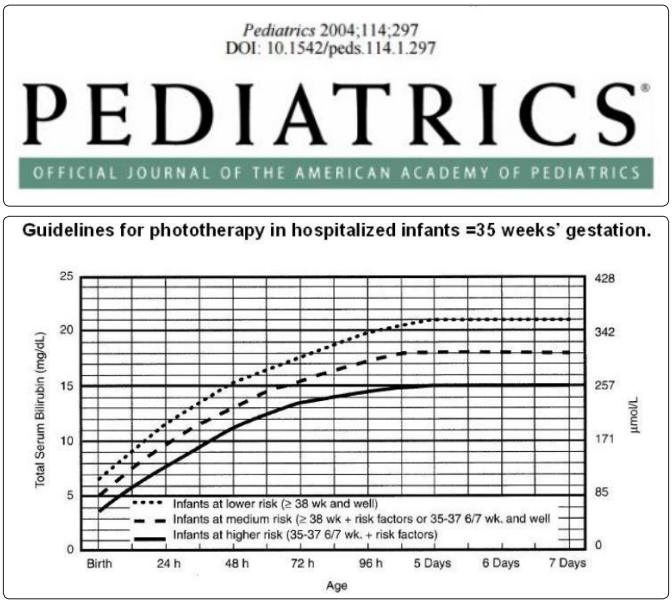


Figure 4: Bilirubin phototherapy management chart

Maisels M J et al. Pediatrics 2009;124:1193-1198

PEDIATRICS

Bilirubin Phototherapy Management Chart

Guidelines for phototherapy in hospitalized infant's ≥35 weeks" gestation. Note that these guidelines are based on limited evidence and that the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the TSB level exceeds the line indicated for each category.

Conclusion

Bilirubin is not only a waste product, but also a versatile molecule that has an essential role in cellular metabolism. It is one product of a catabolic pathway that is essential for life on this planet. More importantly, however, is the understanding of the beneficial effect of bilirubin as an antioxidant as well as its harmful effects. The earlier are known to occur, but the mechanisms involved are still being investigated. Any strategy to prevent such bilirubin induced injury must begin with a sound understanding of bilirubin physiology and clinical chemistry. Understanding the cellular biology of heme catabolism and defining the roles of this ancient and elegant set of reactions in other developmental and pathological circumstances remains a scientific challenge. In my study, One-third of the term newborns having serum bilirubin in high-intermediate zone progressed to high risk zone in next 24 hours requiring treatment. There was a slight female predilection. As the study was conducted on a small scale so it may not be a true reflection of the whole picture. For future implementations we recommended that early recognition, monitoring and early treatment of neonatal hyperbilirubinemia may help in reducing morbidity. We further recommend that studies should be conducted at regional, national and international level to establish universal guidelines for monitoring and management of neonatal hyperbilirubinemia.

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