The Predictive Value of Day one Serum Bilirubin Extent for Subsequent Increase Substantial Hyperbilirubinemia in Well Full Term Neonate in Mukalla Maternity and Child Hospital, Hadhramout,Yemen

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Abstract

Background: Significant neonatal hyperbilirubinemia is a common cause of readmission following initial sending home from hospitals in healthy mature neonates.

Objective: To determine the predictive ability of first 24th hr entire serum bilirubin (TSB) levels for later development of important hyperbilirubinemia in well mature neonates at Mukalla Maternity and Child Hospital (MMCH) in Mukalla city, Hadhramaut Governorate, Yemen.

Patients and Methods: A cross sectional study of 150 well mature newborns was tracked with everyday serum total bilirubin detections for five days of life at Mukalla Maternity & Child Hospital between March 2019 and February 2020.

Results: It was observed that 10%, 10%, 13.3% and 66.7%% of newborns were corresponding to high, high intermediate, low intermediate, and low risk zones respectively, while7.3% of newborns had developed significant hyperbilirubinemia and needed phototherapy. The day one bilirubin value of 5mg/dl had a sensitivity of 100% and specificity of 72%, the positive predictive value of 22%, and a negative predictive value of 100% in forecasting the risk of developing significant jaundice.

Conclusion: A total serum bilirubin measurement may be applied as a useful screening test for each neonate at the first week of life, to foresee those at risk for later development of

significant neonatal hyperbilirubinemia and permit for a harmless discharge from the hospital.

Keywords: Jaundice; newborn; prediction; hyperbilirubinemia;Yemen

Introduction

Hyperbilirubinemia is common and usually a benign problem in newborns. Jaundice is detected during week one of life in nearly 60% of mature babies and 80% of immature babies [1]. Between 60%–80% of all term or late-term, healthy newborns exhibit idiopathic jaundice [2]. A significant hyperbilirubinemia occurs in about 5%–10% of healthy term neonates [3]. About 4% of mature babies who were readmitted to the NCU during week one of life, about 85% of them are readmitted for hyperbilirubinemia [4]. Prompt discharge of well mature babies has become a public rehearsal to avoid hospital infections, persuasion of early maternal-baby attachment and also lesser price [5]. Because of the increasing number of early discharged newborns, there is a corresponding danger of failing to diagnose severe hyperbilirubinemia .Timed TSB measurements (at discharge between 18 hours and 72 hours) can be used to predict the chances of developing severe hyperbilirubinemia [6].

Initial recognition of frightening bilirubin values allow commencement of phototherapy and avoids greater risk and a great rate of exchange transfusion or kernicterus also hour-specific bilirubin nomogram and TSB measurement can be used for predicting the subsequent need for phototherapy [7-9] .The American Academy of Pediatrics (AAP) clinical practice guideline endorses that all newborn infants should be assessed before discharge for the risk of developing significant neonatal hyperbilirubinemia [3].

The present study was carried out to determine the predictive ability of first 24thhr TSB levels for later development of substantial hyperbilirubinemia in well mature babies at Mukalla Maternity and Child Hospital.

Patients and Methods

A cross-sectional observational study of 150 well mature babies was tracked with everyday TSB detections for the initial five days of life at Mukalla Maternity & Child Hospital in Mukalla city, Hadhramaut Governorate, Yemen, between March 2019 to February 2020.

Inclusion Criteria: Included babies were well mature neonates with body weight ≥ 2500 grams and maturity of ≥37 /52 and delivered vaginally or cesarean deliveries after ordinary pregnancy, with smooth delivery .

Exclusion criteria: Were prematurity, post-term, congenital anomalies, Rh or major ABO incompatibility, Infants presented with delayed meconium passage (> 24 hours), birth weight less than 2500. Low blood sugar, low body temperature, cephalhematoma, skin bruising, bleeding tendency of the newborn (vitamin K deficiency), birth asphyxia, renal system infection, and doubted neonatal infection were also omitted.

Sample size: According to the available prevalence of significant hyperbilirubinaemia among neonates 11% [8]. The necessary sample size was 150. A systemic random sampling procedure was used, and we selected every 3rd newborn baby delivered in the hospital after considering the inclusion and exclusion criteria.

All participants were exposed to the subsequent standard valuation for each baby by history, clinical assessment and laboratory tests. Interrogation included gender, mode of birth, thorough prenatal and natal history, gestational age, blood groups and Rh , and family history of newborn jaundice. The clinical assessment comprised APGAR score, anthropometric dimensions, cutaneous color, the existence of bruises or cephalohematoma, valuation of GA (agreeing to New Ballard Score), [10], and reflexes (Moro and suckling). Serum total bilirubin determination was firstly made within 24hours of life and was repetitive daily for the next 4 days, 24 hours apart.

A percentile based neonates were divided in 4 risk zones using nomogram organized by Tiberi [11], the nomogram has 4 risk zones:
Neonates had their 24th hr TSB < 40th percentile corresponding to the low risk zone.
Neonates had their 24th hr TSB level between 40th–95th percentile consistent to intermediate risk zone and sub divided into two groups:
Neonates s had their 24th hr TSB level between 40th – 75th percentile equivalent to low intermediate risk -zone.
Neonates had their 24th hr TSB level between 76th – 95th percentile equivalent to high intermediate risk zone.
Neonates had their 24th hr TSB level > 95th centile percentile corresponding to high risk zone.
Significant neonatal hyperbilirubinemia was classified according to AAP [3] after 72 hours of life into:
Group I: Babies developing significant hyperbilirubinemia (serum bilirubin ≥17 mg.) after the third day of life.
Group II: Babies developing non-significant hyperbilirubinemia (serum bilirubin <17 mg)) after the third day of life.

The research protocol and the questionnaires were conducted according to the principles of the Declaration of Helsinki. Verbal consents was also taken from the parents and caregivers of children involved in the study.

Statistical analysis

The data were veiled, tabularized, and statistically evaluated using SPSS package version 17. Data were abridged using range, mean, standard deviation, and percentages for quantitative variables or frequency and percentage for qualitative ones. Appraisal between groups was achieved using Mann-Whitney test for quantitative variables while appraisal for qualitative variables was made through Chi-square or Fisher's exact test. The specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPP) for the gained cut-offs were designed. $P< 0.05$ was considered important.

Results

150 babies were included in the study and TSB detection was firstly made within the initial 24hours of life (mean:19±3.6 hours) and were repetitive daily for the subsequent 4 days, acting each detection just 24 hours after

the preceding measurement. Table (1) shows a significant association between male babies who had a TSB of <5 mg/dL and of ≥ 5 mg/dL in the first 24 hours of life. There were also non-significant differences between the other clinical characteristics of the cases who had a TSB of <5 mg/dL and of, ≥ 5 mg/dL in the first 24 hours of life.

Table (1): Demographic features of babies who had TSB level of <5 mg/dL and ≥5 mg/dL in the day of life

Variable	Babies with TSB of <5mg/dL (*n* 5= 100)	Babies with a TSB of ≥5 mg/dL (*n*= 50)	P-value
Sex Boys Girls	 87 (87%) 13 (13%)	 35 (70%) 15 (30%)	0.01
Gestational age (weeks) mean ± SD	38.3±1.23	38.6±1.25	0.16
Birth weight (grams) mean ± SD	2873±392	2793±192	0.17
Mode of delivery Vaginal delivery Cesarean delivery	 60 (60%) 40(40%)	 26 (52%) 24(48%)	0.35
Neonatal jaundice in previous sibling Yes No	 47 (47%) 53(53%)	 20 (40%) 30(60%)	0.41
Oxytocin drug use Yes No	 16(16%) 84(84%)	 7 (14%) 43(86%)	0.74
Type of feeding Breast feeding Bottle feeding Mixed feeding	 16(16%) 25(25%) 59(59%)	 7(14%) 10(20%) 33(66%)	0.74

Table (2) shows a significant association between the clinical features of babies who did and who did not develop important hyperbilirubinemia (≥17 mg/dL) after 72 hours of life with respect to various factors such as male sex, neonatal jaundice in previous sibling and oxytocin drug use. None of the other maternal and neonatal characteristics were associated with the development of significant hyperbilirubinemia.

Table (2): Demographic characteristics of babies who had and who had not developed substantial hyperbilirubinemia (≥17 mg/dL) after third day of life

Variable	Babies with a TSBl of <17mg/dL (*n* = 139)	Babies with a TSB of ≥17 mg/dL (*n*= 11)	P-value
Sex Boys Girls	 114 (82%) 25 (18%)	 6 (54.5%) 5 (45.5%)	0.03
Gestational age (weeks) mean ± SD	38.1±1.42	38.7±2.12	0.83
Birth weight (grams) mean ± SD	2883±190	2793±221	0.12
Mode of delivery Vaginal delivery Cesarean section	 79 (56.8%) 60(43.2%)	 7 (63.6%) 4(36.4%)	0.66
Neonatal jaundice in previous sibling Yes No	 59(42.4%) 80 (57.6%)	 9(81.8%) 2 (18.2%)	0.02
Oxytocin drug use Yes No	 18(13%) 121(87%)	 5(45.5%) 6(54.5%)	0.008
Type of feeding Breast feeding Bottle feeding Mixed feeding	 21(15.1%) 32(23%) 86(61.9%)	 2(18.2%) 3(27.3%) 6(54.5%)	0.78

Table (3) illustrates 11 newborns (7.3%) from a total of 150 neonates enrolled in the study and followed for 5 days, had developed substantial hyperbilirubinemia with serum total bilirubin levels of ≥17 mg/dL compared to 139 (92.7%) who did not develop important hyperbilirubinemia with TSB of <17 mg/dL after 72 hours of life (p <0.05).

Table (3): First five days' bilirubin levels of the babies who had and who had not developed substantial hyperbilirubinemia (≥17 mg/dL) after 3rd day of age

Days	Insignificant hyperbilirubinemias (*n* = 139)	Significant hyperbilirubinemias (*n* = 11)	P-value
Day 1	4.96±1.88 (2.66 - 3.63)	6.34±1.79 (5.25 - 8.13)	0.02**
Day 2	6.92 ± 2.75 (6.62–7.08)	9.10 ±1.11 (9.32–10.25)	0.01*
Day 3	8.09±1.13 (7.49–9.56)8	12.4±1.61 (12.31–13.14)	P < 0.001***
Day 4	9.37 ± 1.72 (8.33–10.53)	17.16 ±1.23 (17.19–19.33)	P < 0.001
Day 5	10.56 ± 1.73 (9.85–10.87)	17.51 ±1.15 (18.14–19.13)	P < 0.001

In the Table (4) the data was evaluated for later risk of evolving hyperbilirubinemia, an eleven (7.3%) of babies developed important hyperbilirubinemia. Ten percent of babies (15/150) had TSB levels in the high-risk zone (>95th percentile) at the first 24 hours; of these, (7/15 or 46.7%) stayed in that zone, while (4/15 or 26.7%) moved downwards to intermediate high risk zone and (3/15 or 20% %) moved downwards to intermediate-low risk zone and (1/15 or 6.6%) moved downwards to low risk. Regarding the high-intermediate risk zone, (3/15 or 20%)of babies in the intermediate high risk zone moved upwards to high risk zone, while (5/15 or 33.3%) remained in same zone and (4/15 or 26.7%) moved down to low intermediate risk zone and (3/15 or 20%) moved down to low risk zone. On the other hand, low intermediate risk zone (8/20 or 40%) remained in the same zone, while (9/20 or 45%)moved down wards to low- risk zone and (2/20 or 10%)and (1/20 or 5%) moved upwards to intermediate high risk zone and high-risk zone respectively. While 66.7% of the newborns (100/150) were in the low-risk zone (<40th percentile) had no measurable risk for substantial hyperbilirubinemia.

Table (4): Subsequent risk categorization of study newborns after 72hrs of age

		Subsequent risk categorization of study population after 72hrs of age			
Risk zone	**Total number of newborns (N=150)**	**Low risk**	**Low Intermediate risk**	**High Intermediate risk**	**High risk**
Low- risk zone	100	100(100%)	0(00)	0(00)	0(00)
Low-intermediate risk zone	20	9(45%)	8(40%)	2(10%)	1(5%)
High-intermediate risk zone	15	3(20%)	4(26.7%)	5(33.3%)	3(20%)
High risk zone	15	1(6.6%)	3(20%)	4(26.7%)	7(46.7%)

In the Table (5) the predictive capacity of the 40th, 75th, and 95th percentile tracks as risk demarcates. A day-one bilirubin level of ≥5mg/dl had a sensitivity of 100% and specificity of 72%,the positive predictive value of 22% and a negative predictive value of 100% in expecting the risk of developing significant neonatal jaundice.

Table (5): Sensitivity, specificity, and positive and negative predictive values of the first day of life in predicting the development of substantial hyperbilirubinemia

Percentile track as risk demarcator		**Outcome: Subsequent Significant hyperbilirubinemia**		**Predictive characteristics**			
Percentile Track as risk demarcator	Number of Newborns (Total 150)	Present (Total 11)	Absent (Total 139)	PPV	NPV	Sensitivity	Specificity
Above 95th percentile	15	7	8	46	97	63	94
Below 95th percentile	135	4	131				
Above 75th percentile	30	10	20	33	99	90	85
Below 75th percentile	120	1	119				
Above 40th percentile	50	11	39	22	100	100	72
Below 40th percentile	100	0	100				

Table (6) shows a total of 11(7.3) newborns who developed significant hyperbilirubinemia and needed phototherapy. 46.7 %, 20% and 5% needed phototherapy in high risk zones, high intermediate risk and low-intermediate risk respectively and no one of the babies in the low-risk zone given phototherapy.

Table (6): Determining the subsequent need of phototherapy treatment

Risk zone	**Number of Newborns**	**Number of newborns needed phototherapy (%)**
Low risk zone	100	0
Low intermediate risk zone	20	1(5%)
High intermediate risk zone	15	3(20%)
High risk zone	15	7 (46.7%)
Total	150	11(7.3%)

Figure (1) shows that 10%, 10%, 13.3% and 66.7%% of newborns were corresponding to high risk, high intermediate risk, low intermediate risk, and low-risk zones respectively.

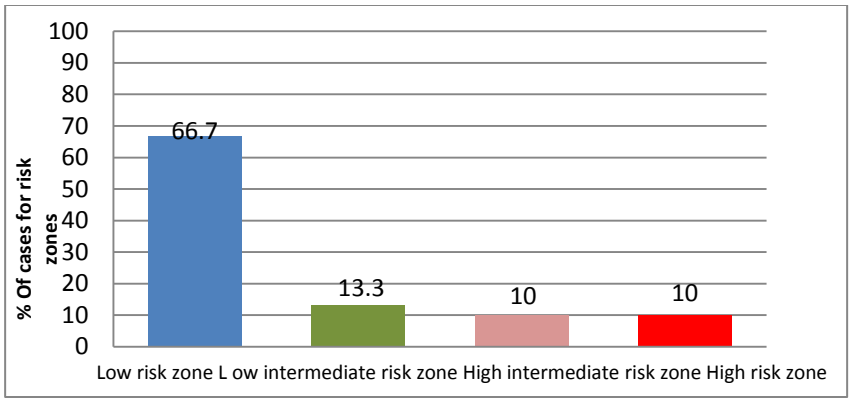

Figure (1): Risk stratification of studied babies founded on daily TSB level

Figure (2) shows risk zones of term babies grounded on their days-specific TSB levels. The high-risk zone is nominated by the 95th percentile track. The intermediate-risk zone is segmented into upper- and lower-risk zones by the 75th percentile path. The low-risk zone has been demarcated by the 40th percentile track.

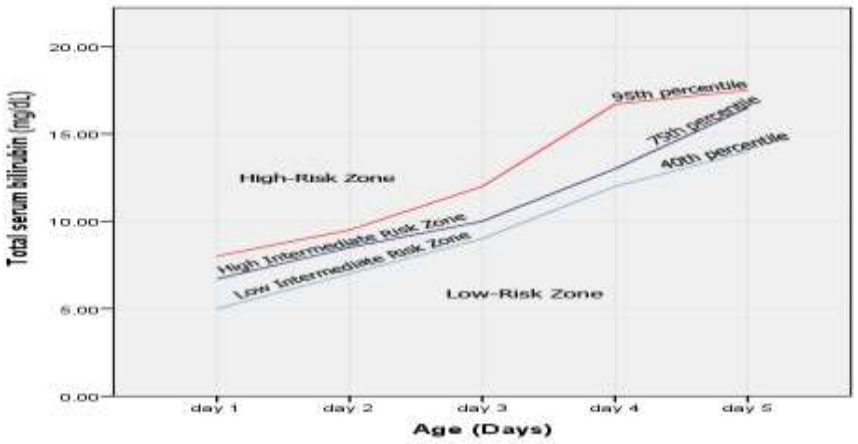

Figure (2): Risk zones of mature babies according to the percentile paths founded on their days-specific TSB levels

Discussion

The necessity for an early estimate of hyperbilirubinemia has become progressively significant for recognizing those newborns at risk of neonatal jaundice as the severe neurologic morbidities instigated by bilirubin toxicity [5].

In this article, we evaluated the ability of first day bilirubin level to be a means for showing the risk of succeeding neonatal hyperbilirubinemia. The frequency of substantial hyperbilirubinemia has been described to be 7.3%. In 5 articles from 5 different states exploring the foretelling value of first-day TSB measurement on foreseeing the later development of substantial hyperbilirubinemia, the occurrence of substantial hyperbilirubinemia has been described to be between 4.4% - 23.3% [11-15].

There was a substantial association between the male gender and the

development of substantial hyperbilirubinemia (P<0.05) Table (1) and Table (2).This is consistent with the other studies [16,17].There is no clear mechanism explains that the healthy male can susceptible to the development of significant hyperbilirubinemia; such an effect need in the future analysis of a more comprehensive data set.

In this study, there was a substantial relationship between the newborns whose mother was given oxytocin for induction of labor and development of substantial neonatal jaundice (p<.05) Table (2). This is consistent with the other studies [15,18,19].This could be clarified by the mechanism of jaundice with oxytocin induction of labor. Oxytocin persuades hyponatremia and hypo-osmolality in the mom by virtue of its anti-diuretic and saluretic properties. These biochemical variations are intensified by the distillation of electrolyte-free dextrose fluid used as a van for giving oxytocin. Transplacentally spread hypo-osmolality in the fetal blood, leads to boosted osmotic brittleness of the red blood cells. The distended and hyper brittle erythrocytes are effortlessly stuck by the spleen ending in net higher bilirubin creation [20].

A substantial relationship was noted between the existence of siblings with hyperbilirubinemia and the development of substantial hyperbilirubinemia (P<0.05) Table (2).This is in agreement with the earlier studies [21-23].Positive family history can serve as a marker for shared genetic susceptibility [24].Gene polymorphisms in the hepatic uridine diphosphate glucuronosyl-transferase isoenzyme 1A1 (UGT1A1) and the solute transporter organic anion carrier 1B1(SLCO1B1), alone or in the mixture, impact the occurrence of neonatal jaundice [1].

Regarding high intermediate risk zone, (3/15 or 20%) of babies in the high intermediate risk zone moved upwards to high risk zone, while (5/15 or 33.3%) stayed in a similar area and (4/15 or 26.7%) progressed down to low intermediate risk zone and (3/15 or 20%) moved down to low risk zone. On the other hand, low-intermediate risk zone (8/20 or 40%) remained in same zone, while (9/20 or 45%)moved down wards to low risk zone and (2/20 or 10%)and (1/20 or 5%)moved upwards to high intermediate risk zone and high risk zone respectively. 66.7% of the babies (100/150) was in the low-risk zone (<40th percentile) and there was no computable risk for substantial jaundice. The proportion of newborns in risk zones was nearly to that described in texts by Tiberi *et al* [11] and Pathak *et al* [25].

Kireeti and Srividya [26] found that 94.8%) did not develop substantial hyperbilirubinemia and 5.2% had substantial hyperbilirubinemia. 33.33% (15/45) of babies in the intermediate risk zone remained in low risk zone. 17.77% (8/45) neonates in the intermediate risk zone went up to low-intermediate risk zone. 26.66% (12/45) babies in the intermediate risk zone went up to high-intermediate risk zone. 22.22% (10/45) newborns in the intermediate risk zone went into high risk zone. All the 3 newborns belonging to high risk zone remained in high risk zone.

In this study, the TSB of 5 mg/dL on day one of life had a sensitivity of 100% and

specificity of 72%, the positive predictive value of 22% and negative predictive value of 100% in predicting the risk of developing significant jaundice. A 100% negative predictive value in this study proposes that detection of TSB in the first day of life can help recognize those babies who are not likely to need further assessment and interference. Compared to previous studies on the predictive values of various TSB levels in the first day of life in foreseeing the development of substantial hyperbilirubinemia [11-15], our series shows some similarities and differences . These variances may be related to different inclusion standards, as they comprised all live births, while we encompassed a definite group of live birth. In adding to tribal and environmental disparities in diverse inhabitants, different design of the study and laboratory variability in the measurement of bilirubin. Sriram and Paramahamsa [27] found that 1st 24hours bilirubin level of >4.9mg/dl /dL had a sensitivity of 88.89%., specificity of 71.68%, the negative predictive value of 97.6%. % and positive predictive value of 32.9% in predicting significant neonatal hyperbilirubinemia. Mittana and Arimilli [28], found that with the 1st 24 hours bilirubin level of 5.45 mg/dl disclosed that it has a sensitivity of 87.9 %., specificity of 82%, the negative predictive value of 97.16%% ,and positive predictive value of 49.15%, in predicting neonatal hyperbilirubinemia. When the facts were evaluated for the consequent risk of evolving hyperbilirubinemia, a total of 11(7.3) neonates established substantial hyperbilirubinemia and needed phototherapy. 5% of (1/20) , 20 (3/15%) and 46.7 (7/15%) needed phototherapy in low intermediate risk, high intermediate risk and high risk zones respectively and no one of the babies in the low-risk zone given phototherapy. Our study line with that of Kishore Kumar *et al*.,[29] , who found that 4%, 26%, and 77%needed phototherapy in low-intermediate risk, high- intermediate risk and high risk zones respectively and none of the babies in the low-risk zone given phototherapy. In the Bhutani series 2%,13%,40 needed phototherapy in low intermediate risk, high intermediate risk and high-risk zones respectively and no one of the babies in the low-risk zone given phototherapy [11].

At the mean serum TSB level of ≥5 mg/dL in the first day of life, the sensitivity(100%) and negative predictive value(100%) were very high in foreseeing the ensuing necessity of phototherapy.This result was in agreement with other studies [11, 30].

No baby in the study group requisite an exchange transfusion or settled a TSB level >25 mg/dL. No one had acute signs of bilirubin encephalopathy. All have had normal development at about 1 year of age during follow up.

Limitations of the study were, only full term healthy neonates were taken for the study and a large number trial that include both mature and premature newborns and large multicentric studies need to be done on Yemen babies before the conclusions can be generalized and to establish more sensitive and more predictive rules.

Conclusions

A TSB detection and the use of precarious bilirubin value of 5 mg/dl in the first day of life will forecast early all well term babies

who will have substantial hyperbilirubinemia and will define all those infants who will necessitate a phototherapy later during the first few days of life.

Recommendations

So the treating clinicians will take care of the problem to make decision about the mode of therapy and whether to discharge the baby home safely.

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Ethical clearance: This study was granted ethical approval from the Ethical Committee of the Collage of Medicine at Diyala medical University

Conflict of interest: The authors of this article have no conflict of interest of any type.

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