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Incidence,Course,Outcome And Prediction of Significant Hyperbilirubinemia in Newborn

Gautam Medhi[1],Sunil Soni[2],Himadri Das[3] .
From the department of Pediatrics,Gauhati Medical College and Hospital, Guwahati ,Assam ,India.

Abstract: *Jaundice is a clinical condition that is often present is pediatric practice and constitutes one of the major issues within the neonatal period. Although most newborn with jaundice are otherwise healthy, they need to be monitored because bilirubin is potentially toxic to central nervous system .A prospective cohort study was conducted in Neonatal intensive care unit of Gauhati medical college and hospital over 1 year period from 1st June 2012 to 31st May 2013. Hence, the present study is designed with the objective to study the hospital incidence of significant- hyperbillirubinemia, its causes, course & outcome and to determine the value of an early (6th hr.) serum billirubinmeasurment in predicting development of significant- hyperbillirubinemia late during the first week of life. Out of 500 eligible infants, 50 cases were lost during study period and 450 cases completed the study for the incidence, course & prediction of significant hyperbilirubinemia and 50 newborns with hyperbilirubinemia cases were followed up for outcome .50 cases with significant hyperbilirubinemia in the present study group of 450 newborns represented a hospital incidence of 11.11%.There were no significant differences between the cases who did and who did not develop significant hyperbilirubinemia with respect to various risk factors except cephalohematoma (p value<0.05) .The present study shows ABO Incompatibility in 14 cases (28%) , Rh Incompatibility-4 cases (8%), ABO & Rh Incompatibility-3 case (6%), G6PD Deficiency-5 cases (10%), Cephalohematoma- 2 cases (4%) ,sepsis associated with 3 cases (6 %),Unknown cases- 19 (38%) for development of significant hyperbilirubinemia .At 6th hr of life, mean TSB level was 6.79 ± 1.02(range 2-9) mg/dl and Peak serum bilirubin of the 50 babies with significant hyperbilirubinemia , at 94.4 ± 24.5 hr of age, was 19.3 ± 1.9 mg/dlOut of 50 newborn with significant hyperbilirubinemia 37 were treated with phototherapy ,1 with exchange transfusion.12 neonates were below phototheraylevel.Of 50 cases eligible for the study for outcome of significant hyperbilirubinemia , 30 ≥ (60%) were followed up . 20 cases lost to follow-upAlmost all the infants were normal during physical, visual, and auditory evaluation & free of neurological sequelae on follow up .Brainstem auditory evoked responses (BAER) was also normal .Out of 450 newborns, 172 (38.22%) who had a bilirubin level of ≥ 6 mg/dl in the first 24 hours of life, 45 cases (26.16%) developed significant hyperbilirubinemia, whereas 5 cases (1.8 %) of the 278 newborns (61.77%) whose bilirubin level was <6 mg/dl on the first day of life developed significant hyperbilirubinemia.Bilirubin level of 6 mg/dl at 6th hr. of life had the high sensitivity (90 %), specificity (68.25 %), low positive predictive value (26.16 %) and high (98.20 %) negative predictive value and likehood ratio 2.83.At the mean serum bilirubin level of 6 mg/dl at 6th hr. of life, the sensitivity and negative predictive value were very high in predicting development of significant-hyperbillirubinemia late during the first week of life and the subsequent need of a phototherapy treatment.*

Keywords : *hyperbilirubinemia,cephalohematoma,phototheray,Brainstem auditory evoked responses (BAER)*

I. Introduction

Jaundice is a clinical condition that is often present in pediatric practice and constitutes one of the major issues within the neonatal period. It can be both physiological and pathological processes in newborns. Although most newborn with jaundice are otherwise healthy, they need to be monitored because bilirubin is potentially toxic to central nervous system. The American Academy of Pediatrics (AAP) in 2004 recommended that new born discharged within 48 hrs should have follow up visit often 2-3 days to detect significant jaundice. Neonatal Hyperbilirubinemia is extremely common because almost every newborn develop an unconjugated serum bilirubin level of more than 30 umol/L (1.8mg/dl) during the first week of life. Jaundice is observed during the first week of life in approximately 60% of term infant and 80% of preterm infant. Hence, the present study was designed with the objective to study the hospital incidence of significant- hyperbillirubinemia, its causes, course & outcome and to determine the value of an early (6th hr.) serum billirubinmeasurment in predicting development of significant- hyperbillirubinemia late during the first week of life.

II. Materials And Methods

It was a prospective cohort study conducted in Neonatal intensive care unitof Gauhati medical college and hospital over 1 year period from 1st June 2012 to 31st May 2013.Neonates with gestational age between 37 to 42 weeks (240–294 days) based on first day of the mother's last menstrual period and confirmed when necessary by the New Ballard Score and birth weight ≥ 2.5 kg were included for the study.Newborn with low

Apgar score ,Congenital anomalies were excluded from study.Significant Hyperbilirubinemia was defined as the placement of any of the first weeks total serum bilirubin level reaching into the high-risk zone (95th percentile track).Newborns with total serum bilirubin levels of >12 mg/dL on day 2, >15 mg/dl on day 3, and >17 mg/dL on days 4, 5, and 7 for birth weights ≥2500 kg defined as significant hyperbilirubinemia.500 newborn cases were studied for the incidence, course & prediction of significant hyperbilirubinemia and 50 newborn cases with hyperbilirubinemia were followed up for outcome during 1 yr. of study period.Theinformations were collected in all eligible subjects at enrolment with the help of predesignedproforma.Total serum bilirubin measurements were initially made at the (early) 6th hour of life and repeated daily at 24 hr. interval for the next 4 days, and a last measurement was performed on the 7th day.To find out the cause; Hb level, ABO & Rh grouping ,Direct Coombs test, Glucose-6-phosphate dehydrogenase activity, Peripheral blood smear and Reticulocyte count were performed routinely in all cases at entry into the study.Bilirubin values were plotted on previously established nomograms and Gaussian Distribution Curve with 95^{th} ,75^{th},40^{th} percentile tracks were obtained from the serum total bilirubin level measured at the specific hours.

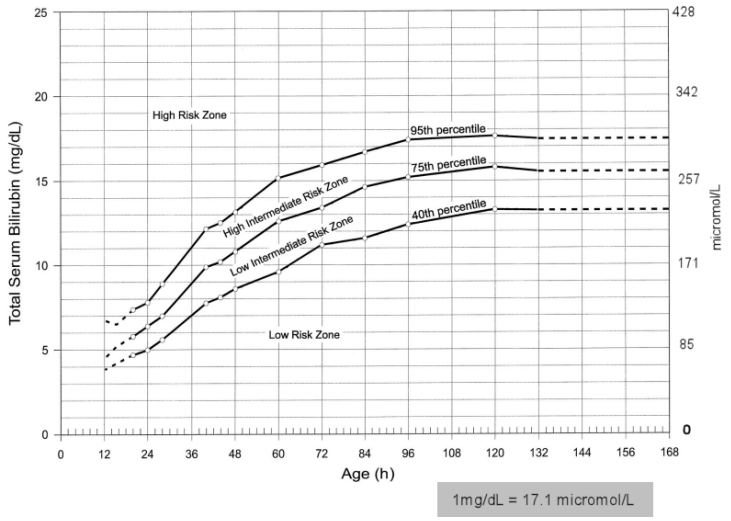


Fig.Normogram for risk designation of term and near termwell neonates based on their hour spefic serum bilirubin levels (Bhutani et al [1])

On the age-specific nomogram, the zone >95th percentile was labeled as high risk, and that <40th percentile was labeled as low risk. Serum total bilirubin values between the 40th and 75th, 75th and 95th percentiles were designated as being in the low-intermediate, and high-intermediate risk zones, respectively.
The predictive ability of the 6th-hour serum total bilirubin value in determining the development of significant hyperbilirubinemia in the term group was assessed on the basis of the placement of any of the first week's serum bilirubin measurements in the >95th percentile of the study population.

Significant difference in the first day serum bilirubin values of infants who subsequently did and those who did not develop significant hyperbilirubinemia were demonstrated.The critical 6^{th} hr of life TSB levels with different sensitivity and specificity values were determined with the receiver operating characteristic (ROC) curve analysis. On the basis of the percentile tracks with various sensitivity, specificity, negative and positive predictive values were calculated. Statistical data were analyzed with the descriptive analysis and the independent sample *t* and χ^2 tests.Babies were treated according to need by phototherapy and exchange transfusion. Serum bilirubin levels were monitored from time to time. Post phototherapy TSB values were excluded from the nomogram. Early & frequent breast feeding was encouraged during study period.The infants with hyperbilirubinemia were followed up for physical, visual, auditory evaluation and other neurological sequelae.Informed written consent was obtained from all parents of the newborns in the study. The ethical committee of institution approved the study.

III. Results And Observations

Out of 500 eligible infants, 50 cases were lost during study period and 450 cases completed the study for the incidence, course & prediction of significant hyperbilirubinemia and 50 newborn cases were followed up for outcome during 1 yr. of study period. The mean age at presentation was 39.52±1.2 gestational weeks,Mean weight was 2.852 ± 354 gm, 56.66% were male and 43.44 were female, 68.88% Vaginally delivered and 31.11% by C/S, 91.11% Exclusively breast fed and 8.89 % were mixed fed,12.22% had H/O jaundice in sibling,33.33 % had H/O maternal oxytocin infusion, Cephalhematoma in 0.66%, Sepsis in

4.8%,Hypothyroidism in 0.88%, ABO incompatibility in 23.33%,Rh incompatibility in 6%,G6PD deficiency in 18.88% cases.
Out of 450 newborns in the study, 50 (11.11 %) cases developed significant hyperbilirubinemiaand 400 (88.88 %) did not developed significant hyperbilirubinemia .

Causes associated with significant hyperbilirubinemia:

Causes	Cases(Total=50)	%
Unknown	19	38%
ABO Incompatibility	14	28%
G6PD Deficiency	5	10%
Rh Incompatibility	4	8%
ABO & Rh Incompatibility	3	6%
Sepsis	3	6%
Cephalohematoma	2	4%

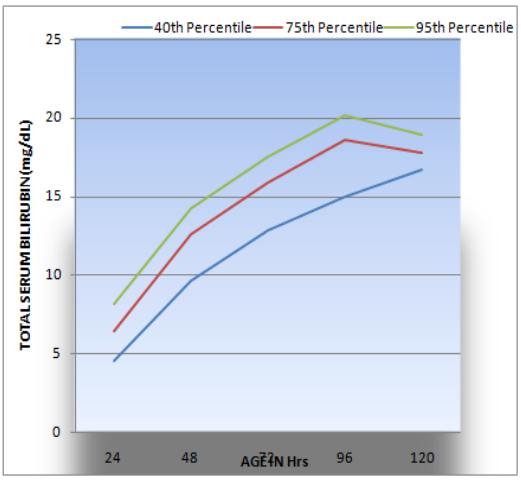
Newborns who developed significant hyperbilirubinemia had serum bilirubin range between 5.77-7.81 mg/dl on day-1, between 11.24-14.48 mg/dl on day-2, between 15.76-18.04 mg/dl on day-3, between 16.88-20.6 mg/dl on day-4, between 15.97-18.45mg/dl on day-5.
Difference is statistically significant in both group**.**

Treatment of neonates with significant hyperbilirubinemia:

Treatment	No. of Cases	%
Phototherapy	37	74%
Exchange transfusion	1	2%
No treatment	12	24%

All 50cases did not turn out for follow up.Only 30 could be followed up. 30 cases showed normal feeding pattern,crying,tone,hearing and vision.BAER was normal in all cases.No infant had history of seizure during follow up period.

Gaussian distribution curve:



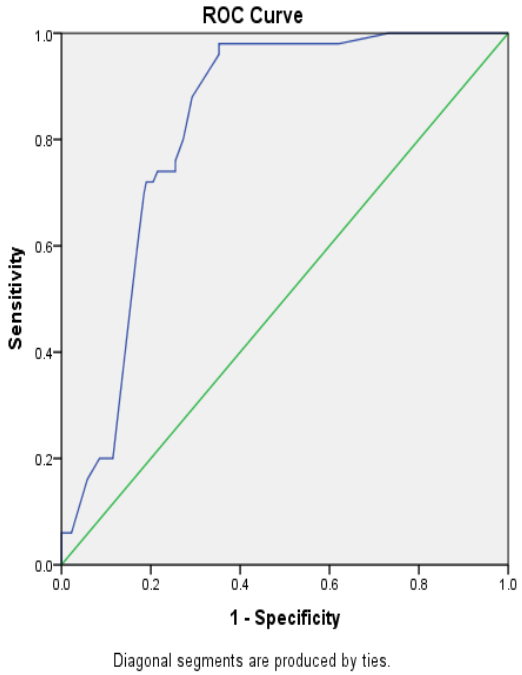
Observation: shows that Risk zones of newborns according to the percentile tracks based on the hour-specific serum bilirubin values. HRZ, high-risk zone designated > 95th percentile track; HIRZ, high-intermediate risk zone between the 95th and 75th percentile tracks; LIRZ, low-intermediate-risk zone between the 75 th and 40th percentile tracks;, low risk zone < 40^{th} percentile tracks.

Table: Predictive ability of pre discharge total serum bilirubin for subsequent significant hyperbilirubinemia:

Pre-discharge Serum Total Bilirubin		Outcome			Test Performance		
Risk Zone	**Percentile**	**Total**	**SHB**	**NSHB**	**P:A ratio**	**Probability**	**LR+**
High-risk	>95th	24	8	16	1:2	1/3	4.00
Upper-intermediate	75th-94th	88	18	70	1:4	1/5	1.87
Lower-intermediate	40th-74th	158	15	143	1:9	1/10	0.84
Low-risk	<40th	188	9	179	1:20	1/21	0.40
		450	50	400	1:8	1/9	

Observation: shows thatamong 450 cases ,24 (5.3%) neonates pre-discharge STB was more than 95th percentile of age-specific distribution.Of these 8 neonates developed subsequent significant hyperbilirubinemia:

Receiver operating characteristic (ROC):



Observation:shows ROC analysis, a mean serum bilirubin level of 6 mg/dL in the first 24 hours of life (6^{th}hr) was determined to have the highest sensitivity (90%) to predict the newborns who would develop significant. The area under the ROC curve is 0.8.

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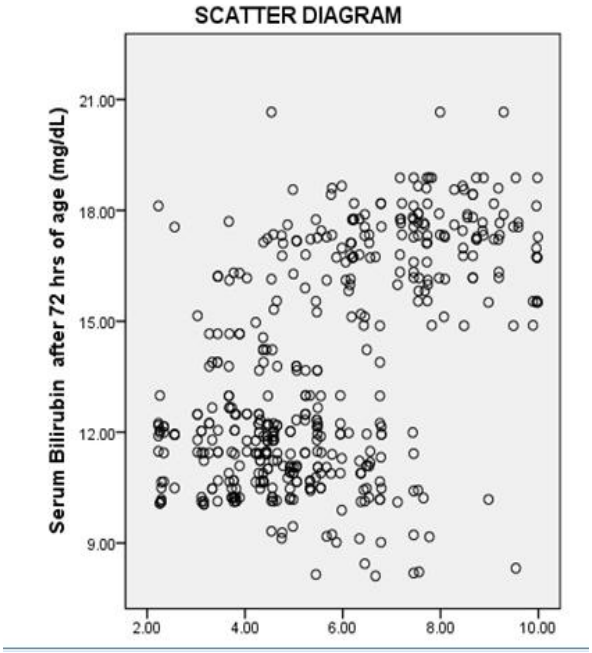
Scatter Diagram:



Observation: shows schematic representation of the relationship between the first day critical bilirubin level of 6 mg/dL and the development of significant hyperbilirubinemia.

Demographic characteristics who had TSB <6 mg/dl &>6 mg/dl in first 24 hrs. of life:

Characteristic	TSB>6mg/dl	TSB<6mg/dl	P-value
Total cases	172(38.22)	278(61.77%)	
Weight	2.672±0.076kg	2.891±1.1kg	>0.05
POG	38.99 ± 0.8 weeks	39.89±0.7weeks	>0.05
Gendar Male Female	 105 (41.17 %) 67 (34.45%)	 150 (58.82%) 128 (65.64%)	 >0.05
MOD Vaginal C/S	 126 (40.64%) 46 (32.85%)	 184 (59.35%) 94(67.14%)	>0.05
Maternal Oxytocin used	47(31.33%)	103 (68.66%)	<0.05
H/O Sibling Jaundice	11(20%)	44 (80%)	<0.05
Maternal Illness	7(11.66%)	53 (88.33%)	
Feeding EBF Formula Mixed	 161(39.26%) 2(40%) 9 (25.71%)	 249(60.73%) 3(60%) 26(74.28%)	 >0.05
Cephalhematoma	2(66.66%)	1 (33.34%)	>0.05
Sepsis	5(22.72%)	17 (77.27%)	>0.05
Hypothyroidism.	--	4 (100 %)	>0.05
ABO incompatibility	70(66.66%)	35 (33.33%)	>0.05
Rh incompatibility	14(51.85%)	13 (48.14%)	>0.05
Both	3(75%)	1 (25%)	
G6PD	40 (47 %)	45 (52.94%)	>0.05

Observation:shows thatthere are no significant differences between the cases who had TSB <6 mg/dl &>6 mg/dl in first 24 hrs. of lifewith respect to the risk factors except the cases with H/O maternal oxytocin infusion and jaundice in sibling.

Table Sensitivity,Specificity,Predictive value of serum bilirubin of 6 mg/dl within<24 hr of age in determining the development of significant hyperbilirubinemia

TSB <24 Hr age	SHB	NSHB	Sensitivity	Specificity	PPV	NPV
> 6 mg/dl (172case)	45(26.16%)	127	90%	68.25%	26.16%	8.2%
<6 mg/dl (278cases)	5 (1.8 %)	273				

Observation:- Table shows thatout of450 cases,172newborns who had a bilirubin level of ≥ 6 mg/dl in the first 24 hours of life, 45 (26.16%) developed significant hyperbilirubinemia, whereas only 5 (1.8 %) of the 273 newborns whose bilirubin level was <6 mg/dl on the first day of life developed significant hyperbilirubinemia. Bilirubin level of 6 mg/dl on the first day had the high sensitivity (90 %), specificity (68.25 %), low positive predictive value (26.16 %) and high (98.20 %) negative predictive value.

IV. Discussion

50 cases with significant hyperbilirubinemia in the present study group of 450 newborns represented an incidence of 11.11%.Bhutani et al[1], 1999 found 4.4% incidence of significant hyperbilirubinemia.Seidman et al[2], 1999 found 5.1 % incidence of significant hyperbilirubinemia.Awasthietal[3], 1998 found 12.4 % incidence of significant hyperbilirubinemia.F. Alpayet al[4], 2000 found 12.05 % incidence of significant hyperbilirubinemia.
In this present study sepsis was associated with 6% cases of significant hyperbilirubinemia which is almost same as in other available literature.
Singhalet al[5,]1992 found 5.7% of cases of significant hyperbilirubinemia associated with sepsis.

In the present study ABO incompatibility was associated with 28 % cases of significant hyperbilirubinemia. Singhal et al[5], 1992 found 14.3 % of cases of significant hyperbilirubinemia associated with ABO incompatibility.

In the present study Rh incompatibility was associated with 8 % cases of significant hyperbilirubinemia.Singhalet al[5], 1992 found 8.1 % of cases of significant hyperbilirubinemia associated with Rh incompatibility.

In the present study G6PD Deficiency was associated with 10 % cases of significant Hyperbilirubinemia.Singhalet al[5], 1992 found 5.1 % of cases of significant hyperbilirubinemia associated with G6PD Deficiency.

In this present study Cephalohematoma was associated with 4 % cases of significant hyperbilirubinemia.Singhalet al[5], 1992 found 2.95 % of cases of significant hyperbilirubinemia associated with Cephalohematoma.Narang et al, 2001 found 6.3 % of cases of significant hyperbilirubinemia associated withCephalohematoma Of 50 cases eligible for the study for outcome of significant hyperbilirubinemia, 30 (60%) were followed up .20 cases were lost to follow-up. In the present study almost all the infants were normal during physical, visual, and auditory evaluation & free of neurological sequelae on follow up. Brainstem auditory evoked responses (BAER) was also normal.Soorani et al[6], 2001 found minor neurological dysfunction in 14/20 hyperbilirubinemia infants. Baradaranfar et al[7], 2011 found 26 (74.3%) with normal hearing; 4 (11.4%) with mild to moderate hearing loss and 5 (14.3%) with severe to profound hearing loss among 35 infants with hyperbilirubinemia during 1 yr follow up. Bjerre et al[8], 2008 found that out of 113 infant with hyperbilirubinemia, 43 infants had symptoms of early-phase acute bilirubin encephalopathy; 1 infant had advanced-phase symptoms during 1 year follow up.

In this study, the bilirubin level of 6 mg/dl on the first day had the high sensitivity (90 %), specificity (68.25 %), low positive predictive value (26.16 %) and high (98.20 %) negative predictive value and likehood ratio 2.83.

Awasthi et al[3], 1998 found TSB level 3.99 mg/dl has a predictive value for development of significant hyperbilirubinemia.Seidman et al[2], 1999 found TSB level 5 mg/dl has a predictive value for development of significant hyperbilirubinemia.R. Agrawal et al[9], 2002 found TSB level 5 mg/dl has a predictive value for development of significant hyperbilirubinemia.

S. Randev et al, 2010 found TSB level 6.4 mg/dl has a predictive value for development of significant hyperbilirubinemia.The first day predictive total serum bilirubin level observed in the present study is higher than 3.99 mg/dl by Awasthi et al[3], 1998 , 5 mg/dl by Seidman et al[2], 1999, 5 mg/dl by R. Agrawal et al[9], 2002 and similar to 6 mg/dl by Alpay et al, 2000 , close to 6.4 mg/dl by S. Randev et al, 2010.

Bhutaniet al[1], 1998 have no infant who had a bilirubin level of <5 mg/dl at 20 to 28 hours of life develop significant hyperbilirubinemia (ie. ≥17 mg/dl), whereas 33% of those whose serum bilirubin level at the same hours was at least 8 mg/dl developed significant hyperbilirubinemia.

Bhutani et al[1], 1999 in another study found that out of 6.1% of neonates who had pre-discharge serum bilirubin in 95th percentile zone, 32.1% showed hyperbilirubinemia subsequently . Neonates with pre-discharge TSB levels in the low risk zone (<40th percentile) did not show hyperbilirubinemia subsequently.In present study out of 5.3 % of neonates who had pre-discharge serum bilirubin in 95th percentile zone, 33.3 % showed hyperbilirubinemia subsequently.

However, R. Agrawal et al[9], 2002 commented on this study that there was an important source of bias. Out of around 13,000 neonates, subsequent bilirubin estimation could be done in only around 25%. It is likely that infants without significant problems were not included while developing these percentile charts.

In a similar study by Seidman et al[2], (1999) 5 mg/dL was reported to have a high specificity (91.9%) and a low sensitivity (45.5%) for detecting significant hyperbilirubinemia; the positive predictive value was very low (8.9%) and the negative predictive value was very high (99.0%).

V. Conclusion

The hospital incidence of neonatal significant hyperbilirubinemia in the present study (11.11%) is comparable to other available studies in India. Few infants were in the hospital till 72-96 hr of life, if they did not have significant clinical jaundice. It is possible that some of these infants might have developed late jaundice and were missed. However this seems more of theoretical risk. The cause of normal outcome in present study is most probably due to short duration of follow up & because newborn were put under phototherapy as they developed hyperbilirubinemia of phototherapy level. Therefore it is possible that if cohort is followed up for a longer period, detection of outcome would have been better.

According to the results, a critical cutoff level of 6 mg/dL at 6th hr. of life predicted 90% of the newborns who developed jaundice with sensitivity (90 %),specificity (68.25%), low positive predictive value (26.16%) and high (98.20%) negative predictive value and likehood ratio (2.83), However, the bilirubin level of < 6 mg/dl did not completely exclude the development of significant hyperbilirubinemia; 1.8 % of the newborns with bilirubin levels of < 6 mg/dL developed jaundice.

Moreover, results of the present study are applicable only to healthy term newborns, and further studies including larger numbers of newborns should be conducted to establish more sensitive and more predictive guidelines. It is also noteworthy that it is a prospective observational study in which enrolled babies were studied during their hospital stay, thus avoiding sampling bias.

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