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Research Article

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Predisposing Factors for Progression of Hyperbilirubinemia from Low Risk to High Risk in Healthy Full Term Neonates

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ABSTRACT

Introduction: The great burden of neonatal hyperbilirubinemia is exemplified by the fact that globally about 60% of the term and the 80% of preterm babies develop jaundice. Concerns regarding an apparent increase in kernicterus had put forward non invasive new approaches in its prevention and diagnosis in worldwide mainly focusing on body weight loss and feeding pattern in newborns. **Objectives**: To correlate post natal weight loss with serum bilirubin level during first 72 hours in term newborns and to determine the association of other factors. **Method**: This prospective observational study included 350 full term neonates who were assessed for clinical jaundice, body weight loss and feeding pattern for the first 72 hours of life. Daily TcB and TSB was done on Day 3. **Results**: Among the 350 term neonates they were categorized into risk zone based on TSB level in which 217 (62%) were in low, 127 (36%) were in intermediate and 7 (2%) were in high risk zone. The study revealed a significant ($p < 0.001$) difference in mean body weight loss (%) values between these risk groups and can be used as a predictor for significant jaundice (area under roc curve 0.83).The feeding pattern, Kramer's scale, TcB, urine and stool frequency were also significant ($p < 0.05$) in these groups. **Conclusion**: Body weight loss percentage can predict neonatal hyperbilirubinemia in the initial 72 hours of life. Other factors were feeding pattern, urine and stool frequency.

Key Words: *Neonatal hyperbilirubinemia, Body weight loss, TcB and Kramer's scale*

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INTRODUCTION

Neonatal hyperbilirubinemia is a common clinical problem encountered during the neonatal period, especially in the first week of life. When the total serum bilirubin (TSB) rises above the 95th percentile for age (high-risk zone) during the first week of life, it will be considered as hyperbilirubinemia. Neonatal physiologic jaundice results from simultaneous occurrence of the following two phenomena: [1]

a) Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates [2].
b) Hepatic excretory capacity is low both because of low concentrations of the binding protein, ligandin in the hepatocytes and because of low activity of glucuronyltransferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation).

Even though breast feeding is known to have advantages there is evidence that due to improper feeding method breastfeeding is associated with increased, severe and /or early neonatal hyperbilrubinemia [3-5]. Inadequate fluid and / or caloric intake causing decreased hepatic excretion and increased absorption of bilirubin (enterohepatic circulation) have been suggested as mechanism [6-8]. Weight loss of greater than 7% from birth weight indicates possible feeding problems. A large scale population study has shown that increased weight loss percentage instead of breastfeeding per se is important in neonatal hyperbilirubinemia pathogenesis.

Neonatal symptoms of hyperbilirubinemia include low urine output, weight loss and hypernatremia. A growing body of evidence indicates that increased bodyweight loss and / or less breastfeeding are the significant factors for neonatal hyperbilrubinemia [7]. The present study mainly focuses on to correlate the body weight loss at 2nd and 3rd days of age along with other risk factors for prediction of subsequent neonatal hyperbilirubinemia.

AIMS

To determine predisposing factors for progression of neonatal hyperbilirubinemia in term neonates

OBJECTIVES

Primary

1. To determine correlation of postnatal weight loss with serum bilirubin level during first 72 hours in term newborn infants

Secondary

2. To determine association of the feeding pattern with neonatal hyperbilirubinemia.
3. To determine association of urine and stool frequency with neonatal hyperbilirubinemia.

MATERIAL AND METHODS

Study Centre: Done in a Government urban tertiary care hospital.

Sample size: 350

Considering that prevalence of neonatal hyperbilirubinemia as 50% at 5% level of significance and 10% of relative error using the formula for sample size.

n=z2 PQ/L2 P=50

Q=50

z=1.96 at 5%Level of significance

L=10% of 50=5

n=350

Study Design: Prospective study

Study period: 2 years

Inclusion Criteria:

1. All neonate with gestational age ≥35 weeks
2. All neonates with birth weight >2.5kg

Exclusion Criteria:

1) All term newborns with risk factor for developing hyperbilirubinemia such as evidence of hemolysis (positive Coombs test), cephalhematoma, congenital infection, congenital hypothyroidism, perinatal asphyxia and sepsis.
2) All neonates with early onset (less than 48 hours of life) neonatal hyperbilirubinemia were excluded (pathological jaundice)

Methods

This prospective observational study was conducted in a Government urban tertiary care hospital. All babies who fulfilled inclusion criteria were enrolled for study as case. A written consent was taken from parents or care taker before enrollment of baby.

All cases were then clinically examined and graded according to kramer's scale and serially monitored for severity of neonatal jaundice. Cases were studied on following parameters.

1) Antenatal and post natal history
2) Clinical presentation
3) Urine & stool frequency
4) Type & frequency of feeding
5) Percentage body weight loss
6) Transcutaneous bilirubin level
7) Serum TSB monitoring on 72 hours of birth

Case definition:-

1) Hyperbilirubinemia: defined as TSB 95th percentile on the hour specific Bhutani nomogram or total serum bilirubin exceeds 5 to 7 mg/dL [15]

2) Clinical jaundice: defined as jaundice in neonates is visible in eyes and skin.

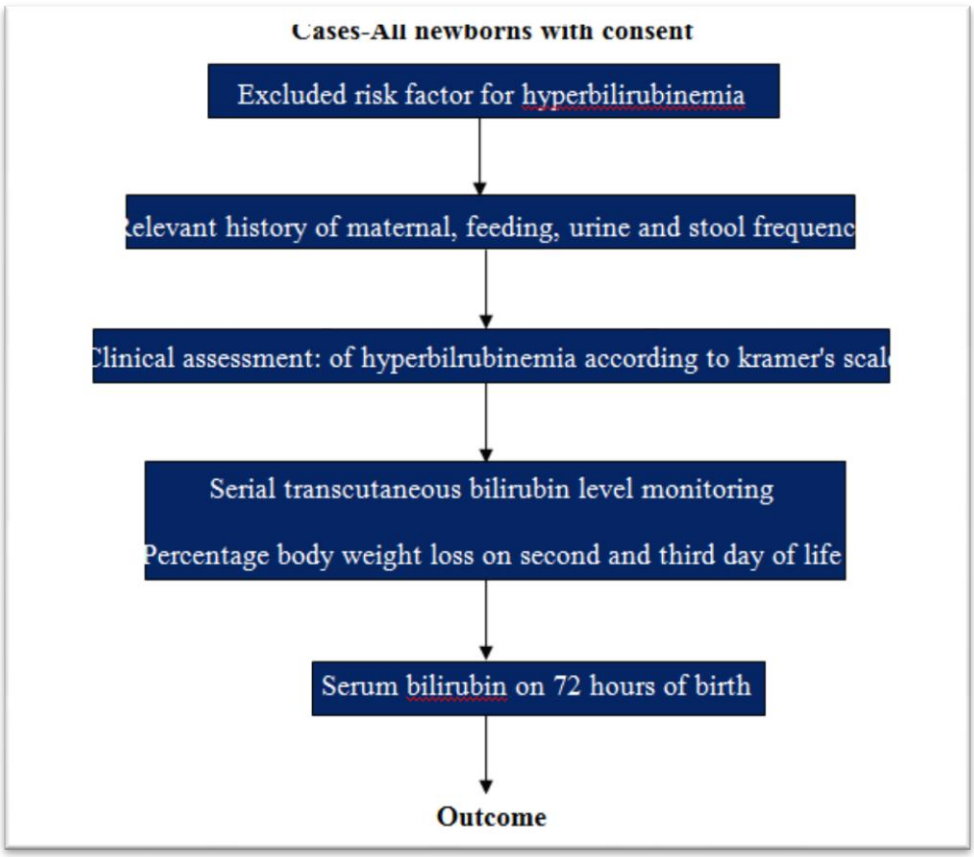
3) Risk zone of neonatal hyperbilirubinemia: American Academy of Pediatrics Nomogram for Risk category For Term neonates [16] -

a. Low risk: 11mg/dl
b. Intermediate risk: 11mg/dl to 16 mg/dl
c. High risk : >16mg/dl

4) **Significant hyperbilirubinemia:** High risk group who needed intervention to decrease serum bilirubin by phototherapy or exchange transfusion

Tools:-

a) Electronic weighing machine
b) Transcutaneous bilirubinometer
c) Hour specific Bhutani normogram & AAP Risk zone Normogram



RESULTS

Table1: Demographic profile of study population.

Demographic profile		**Count**	**%**
Address	Rural	174	49.71
	Urban	176	50.29
Sex	Female	169	48.29
	Male	181	51.71
Gestational age	38to39 weeks	226	64.57
	39to40 weeks	102	29.14
	>40Weeks	22	6.29
Risk Zone	Low risk	217	62
	Intermediate risk	127	36
	High risk	7	2

Table 1 illustrates the descriptive data of population. 350 term neonates were enrolled. Among the 350 term neonates 181(51.71%) were males and 169 (48.29%) were females. According to gestational age majority were between 38 to 39 weeks and least were from more than 40 weeks. They were categorized into risk zone based on TSB level in which 217 (62%) were low risk, 127 (36%) were intermediate risk and 7 (2%) were in high risk zone. Here 343 (98%) neonates had non significant hyperbilirubinemia and 7 (2%) neonates had significant hyperbilirubinemia.

Table 2: Correlation of body weight loss percentage at 48 hours with neonatal hyperbilirubinemia

Risk Zone	No of Cases	Mean Weight loss in %	Std. Deviation	95% Confidence Interval for Mean		ANOVA	
				Lower Bound	Upper Bound	F Sign	Sig
Low	216	3.6475	2.18436	3.3545	3.9404	8.312	.000
Intermediate	127	3.8414	2.35987	3.4270	4.2558		
High	7	7.2000	3.41565	4.0411	10.3589		
Total	350	3.7889	2.32322	3.5446	4.0331		

As per table 2 the mean of the body weight loss percentage in low risk zone was 3.6%, intermediate risk zone was 3.8% and high risk zone was 7.2%. High risk zone had more weight loss compared to other two groups whereas difference between low risk and intermediate risk was less on Day 2.Since correlation coefficient = 0.221, p value = 0.0000297 there was significant correlation between day 2 body weight loss percentage and TSB.

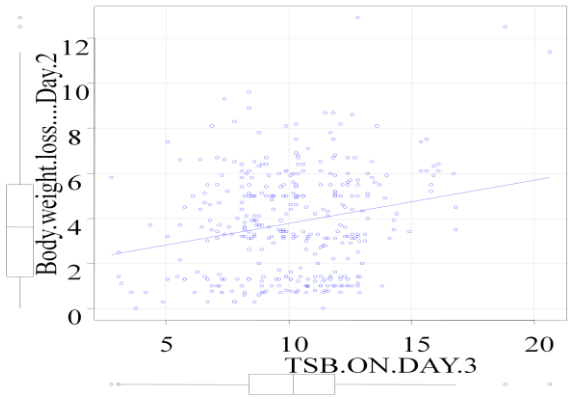


Figure 1: Correlation of TSB and Day 2 body weight loss percentage

Since correlation coefficient = 0.221, p value = 0.0000297 there was a significant correlation between day 2 body weight loss percentage and TSB

Table 3: Correlation of Day 3 body weight loss percentage with risk zone of neonatal hyperbilirubinemia

	Number of cases	Mean weight loss in %	Std.Deviation	95% Confidence Interval for Mean		ANOVA	
				Lower Bound	Upper Bound	F Sign	Sig
Low	216	6.3373	3.39818	5.8815	6.7930	10.577	0.000
Intermediate	127	6.9213	3.62226	6.2852	7.5573		
High	7	12.4000	5.13193	7.6538	17.1462		
Total	350	6.6704	3.61299	6.2906	7.0503		

On applying ANOVA test there was a significant difference in mean body weight loss (%) values of Day 2 and 3 between low, intermediate and high risk groups. Low risk groups had lower mean values whereas high risk group had higher mean values. When we did multiple comparisons there was no difference between low and intermediate risk groups, but there was significant difference between low and high, high and intermediate groups.

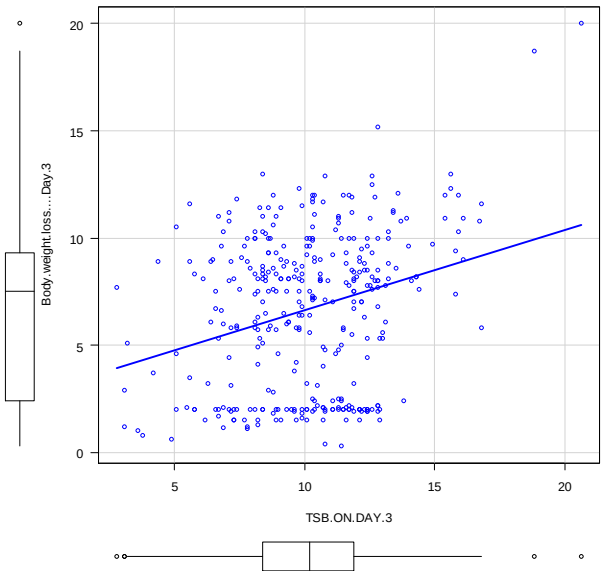


Figure 2: Correlation of TSB and Day 3 weight loss percentage

Since correlation coefficient = 0.277, p value = 0.000000134 there was a significant correlation between day 3 body weight loss percentage and TSB

Table 4: Correlation of significant hyperbilirubinimeia in terms of body weight loss and risk zone group

			Neonatal Hyperbilirubinemia		Total
			Significant	Non Significant	
Body weight loss (%) Day 3	Significant	Count	2	6	8
		% within Body weight loss (%) Day 3	25.0%	75.0%	100.0%
		% within Risk Zone	28.6%	1.7%	2.3%
	Non significant	Count	5	337	342
		% within Body weight loss (%) Day 3	1.5%	98.5%	100.0%
		% within Risk Zone	71.4%	98.3%	97.7%
Total		Count	7	343	350
		% within Body weight loss (%) Day 3	2.0%	98.0%	100.0%
		% within Risk Zone	100.0%	100.0%	100.0%

In table 4 body weight loss of $\geq$ 12.4% was taken as a cut off for significant and non significant hyperbilirubinemia as high risk group on day 3 had body weight loss $\geq$ 12.4% . About 25% of significant group (high risk group) and 75% of non significant group (low and intermediate group) followed this criteria. A ROC curve was plotted based on this observation.

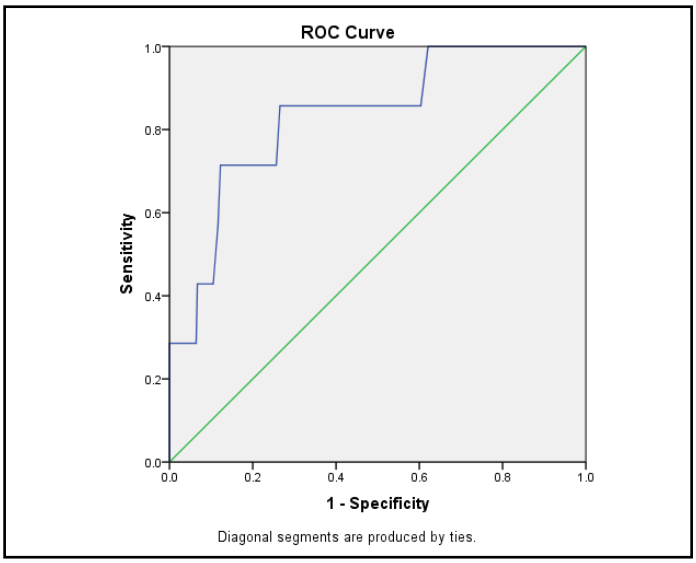


Figure 3: ROC curve on Day 3 body weight loss percentage to predict significant neonatal bilirubinimia

With the cut off value 12.4 of body weight loss (%) Day 3, for predicting the risk of neonatal hyperbilirubinemia, area under curve is 0.833.Hence the body weight loss (%) Day 3 was a good predictor for risk of neonatal hyperbilirubinemia.

Table 5: Correlation of breast feeding frequency, stool frequency and urine frequency with neonatal hyperbilirubinemia

		RISK ZONE			TOTAL
		H	I	L	
Breast feeding frequency	≤6	6	108	129	124
	≥7	1	19	201	221
Stool Frequency	<5	7	1	2	10
	5-10	0	125	8	133
	≥10	0	1	206	207
Urine frequency	≤6	7	115	2	124
	>6	0	12	214	226
Total		7	127	216	350

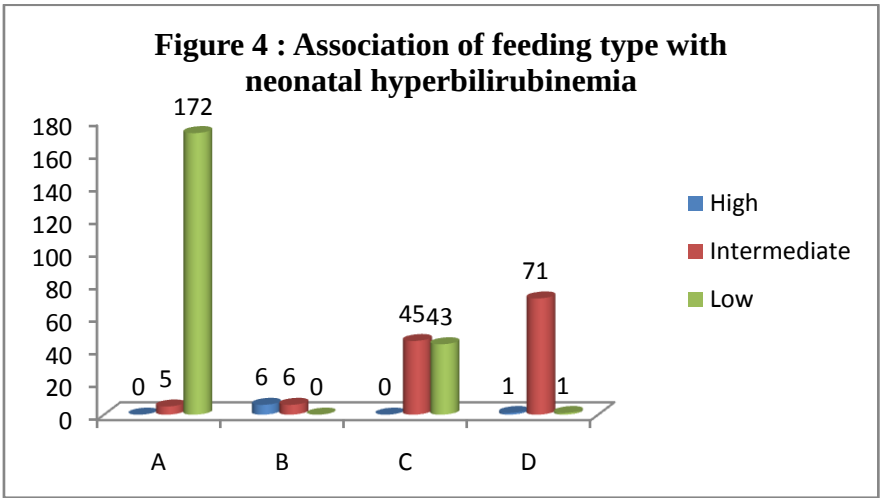
According to table 5 high risk group had average breast feeding frequency≤ 6 times, stool frequency < 5 times and urine frequency ≤6 times. Comparing to low risk group who had average breast feeding frequency ≥ 7 times, stool frequency ≥ 10 times and urine frequency >6 times. A This was a significant correlation with p value < 0.05.

Table 6: Association of feeding type with neonatal hyperbilirubinemia

Feeding type	Risk zone			Total	p value
	H	I	L		
A	0	5	172	177	<0.05
B	6	6	0	12	
C	0	45	43	88	
D	1	71	1	73	
Total	7	127	216	350	

A – Breast feed
B – Top feed
C – Predominantly breast feed
D – Predominantly top feed

Among the study population out of 7 high risk zone newborns 6 newborns (85.7%) were topfed. In low risk zone of 216 newborns 172 (79.6%) were breastfed. This association was significant as p value was <0.05.Top fed increased the risk zone of neonatal hyperbilirubinemia.



STATISTICAL TOOL

Chi square test was done to find the association of different risk zone of hyperbilirubinemia with various categorical variables such asmaternal age, sex, parity, mode of delivery, gestational age, feeding pattern, day 1 urine & stool frequency and krammer's scale day 3.ANOVA test was done to find the mean difference of TcB, TSB, body weight and body weight loss percentage between low risk, intermediate risk and high risk groups of hyperbilirubinemia. Repeated measures ANOVA test was done to find the difference in mean values of day 1, 2 and 3 of TcB and body weight values. Paired t test was done to find mean difference in Body weight loss (%) day 2 and day 3. TSB was correlated with day 2 and day 3 body weight loss percentage using Pearson correlation test. SPSS version 20 and eZR software were used and p value <0.05 was considered significant.

DISCUSSION

This study emphasize that body weight loss percentage can be taken as a predictor for significant neonatal hyperbilirubinemia in term neonate without any risk factors like cephalhemtoma, delayed or absent cry, ABO incompatibility, sepsis etc.

Among 350 term neonates, 7 (2%) newborns had significant hyperbilirubinemia. The body weight loss percentage of these newborns on Day 2 was 6.2% and on Day 3 was 12.4%. Yang W et al [9] conducted a study on bodyweight loss in predicting neonatal hyperbilirubinemia 72 hours after birth in term newborn infants in the year 2007-2008. The results were a total of 115 (33%) neonates presented with significant hyperbilirubinemia 72 hours after birth and those infant had optimum BWL cut off percentages 4.48% on first day of life,7.6% on day 2 and 8.15% on day 3. Huang et al [10] also concluded that gestational age and the BWL influenced by dehydration and reduced calorie intake can predict the neonatal hyperbilirubinemia.

This study demonstrated that significant group had breastfeeding frequency ≤6 times whereas non significant group had breastfeeding frequency ≥7 times.The same inference was put forward by ZakerihamidiM et al [11] in his cross sectional study .But there is no association with night feed,time of initiation of breastfeeding after birth or mode of delivery with neonatal hyperbilirubinemia in this study.

This study showed that high risk group had average stool frequency of <5 times when compared to low risk group with average stool frequency ≥10 times. Thus stool frequency and urine frequency showed a negative association with neonatal bilirubinemia. But according to Buiter H D et al [12] and Sarici U S et al [13] stool frequency and urine frequency are not related to neonatal hyperbilirubinemia.

The improper feeding technique contributing to weight loss were also assessed in association with neonatal hyperbilirubinemia. This study demonstrated that out of 7 high risk zone newborns 6 newborns (85.7%) were topfed. In low risk zone group of 216 newborns 172 (79.6%) were breastfed. Thus a statistically significant association was found between feeding type and hyperbilirubinemia. The study done by Bertini G et al [17] had the same inference. But in contrast to this Salariya M et al [16] and Chen C et al [18] illustrated that breastfed neonates were more icteric compared to topfed or mixed fed. It was further supported by Lin Y et al [19] focussing on the increased incidence of neonatal jaundice following BFHI programs in the hospitals. The inadequate feeding and reduced breast milk in the initial days were the reasons justified for this result. Thus they warranted the necessity of maternal counselling.

CONCLUSION

This study concluded that:

- Day 2 and Day 3 body weight loss had positive correlation with the development of neonatal hyperbilirubinemia.
- Also Day 3 body weight loss percentage could be taken as a predictor for significant hyperbilirubinemia.
- The other risk factors associated are
  - top feed
  - reduced breast feeding
  - delayed first feed
  - reduced urine and stool frequency
  - raised TcB
  - high Kramer scale
  - gestational age of 35-37 weeks.
- Other factors like maternal age, parity, mode of labour, nightfeed, sex and birth weight had no association with significant hyperbilirubinemia.

IMPLICATION

First 72 hours body weight loss should be monitored as early predictor of hyperbilirubinemia to consider early follow up. Breast feeding, urine frequency and stool frequency should also be monitored as preventive measures.

KEY MESSEGE

WHAT IS ALREADY KNOWN?

Reduced calorie intake can cause bodyweight loss and neonatal hyperbilirubinemia.

WHAT THIS STUDY ADDS?

Establishes body weight loss cut off percentages as a predictor of significant neonatal hyperbilirubinemia.

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