



Effects of TSB Levels above 5mg/dl on Primitive Reflex Responses and Righting Reactions in Preterm Newborns

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Abstract

Objective: to identify the mean total serum bilirubin (TSB) level in preterm newborns with abnormal primitive reflex responses at corrected age (CA) of one month; to determine whether there is an association between TSB levels and abnormal primitive reflex responses and righting reactions; and to investigate the influence of phototherapy on primitive reflexes.

Design: we conducted a prospective cohort study with 10-week follow-up.

Settings: intermediate care and rooming-in units at a teaching hospital, and maternity clinic in Petrópolis, Rio de Janeiro, Brazil.

Patients: sample of 343 infants with gestational age below 36 weeks, five-minute Apgar score of ≥ 7 , and no history of intraventricular hemorrhage detected using transfontanelle ultrasound performed up to corrected gestational age (CGA) of 40 weeks.

Main outcome measures: assessment of primitive reflexes and righting reactions at CGA of 35 weeks; physical examination using the Dubowitz examination ("The Neurological Assessment of the Preterm and Full-term Newborn Infant"); retest of primitive reflexes and righting reactions at CA of one month on infants weighing ≥ 2500 g on the day of the test.

Results: mean birth weight and TSB were 1814 ± 465 g and 8.3 ± 2.7 mg/dL ($5.6 - 23.8$ mg/dL), respectively, in the abnormal response group, compared to 2152 ± 525 g and 6.2 ± 3.8 mg/dL ($1.8 - 18$ mg/dL), respectively, in the normal response group. Phototherapy was used on 67.9% of the infants in the abnormal response group, compared to 24.1% in the normal response group. The findings reveal that infants who underwent phototherapy with TSB > 8.3 mg/dL showed the following abnormal primitive reflex responses and righting reactions: palmar grasp, plantar support, sucking, Babkin, Moro, neck righting, and labyrinthine righting, as well as asymmetrical tonic neck reflex and tonic labyrinthine reflex, both of which are pathological reflexes.

Conclusion: infants with TSB $> 8.3 \pm 2.7$ mg/dL showed abnormal primitive reflexes and righting reactions, despite undergoing phototherapy.

Keywords: Primitive Reflex; Hyperbilirubinemia; Kernicterus; Bilirubin Encephalopathy

Introduction

Neonatal hyperbilirubinemia causes bilirubin encephalopathy, otherwise known as kernicterus [1,2]. The regions of the brain most commonly affected are the basal ganglia, hippocampus, geniculate bodies, and cranial nerve nuclei [3]. This condition is cause for serious concern among neonatologists and health care teams treating infants because the damage caused by bilirubin

neurotoxicity directly interferes with the acquisition and development of motor control and muscle tone [4,5]. Bilirubin-induced neuromotor dysfunction in infants can be identified by a combined physical examination and assessment of primitive reflexes and righting reactions [6]. Neuroimaging is of limited use; however, it can help rule out other diagnoses [7].

There is still a lack of consensus on the ideal total serum bilirubin (TSB) level for initiating phototherapy. This is especially the case in preterm newborns given the diversity in all aspects of this age group and immaturity of their systems. System maturity is directly correlated with gestational age (GA), birth weight, and the various risks newborns are exposed to. In many premature infants, especially newborns with a GA of less than 34 weeks [8], it is not possible to determine the etiology of kernicterus, hampering timely preventive interventions [9-11].

Previously referred to as kernicterus, chronic bilirubin encephalopathy (CBE) is used to describe the chronic and irreversible post-icteric sequelae of extreme hyperbilirubinemia [12]. The prevention of kernicterus in premature infants is still a difficult problem to solve. After reviewing the relevant literature, [13] concluded that there is no evidence-based consensus on the management of hyperbilirubinemia in preterm newborns.

The lack of consensus has been explained by the variability and spectrum of bilirubin encephalopathy and uncertainty about the risks and benefits of interventions to reduce TSB levels. However, delay in initiating phototherapy can leave infants, especially extremely low birth weight preterm newborns ($\leq 1000\text{g}$), more exposed to CBE [14]. Neonatal hyperbilirubinemia is perhaps the most common disease in hospital nurseries, especially among premature infants. In Brazil and other countries, the management of TSB levels varies across services and sometimes even among professionals working within the same maternity unit [15].

The objectives of this study were to: 1) identify the mean TSB level in preterm newborns with abnormal primitive reflex responses and righting reactions; 2) determine whether there is a relationship between TSB levels and abnormal primitive reflex responses and righting reactions; 3) investigate the influence of phototherapy on primitive reflexes and righting reactions; and 4) identify a possible TSB threshold for protection against kernicterus in preterm newborns.

Methods

Participants

The sample was selected from a cohort of infants from a study investigating primitive reflexes and righting reactions in preterm newborns (N = 450). Inclusion criteria: infants of both sexes with GA below 36 weeks irrespective of birth weight and five-minute Apgar score of ≥ 7 . Exclusion criteria: infants admitted to the neonatal intensive care unit; infants with malformations or intraventricular hemorrhage detected using transfontanelle ultrasound performed up to corrected gestational age (CGA) of 40 weeks; presence of any

type of syndrome or convulsions and use of anticonvulsant drugs; hemodynamic instability or use of oxygen therapy on the day of the examination. The retest was conducted in a maternity clinic during the period June 2008-June 2016.

There were 23 losses (infants with abnormal primitive reflex responses and righting reactions discharged from the rooming-in unit without testing for TSB levels and referred to the follow-up clinic).

Intervention

We assessed the following primitive reflexes and righting reactions in infants with a CGA of 35 weeks in the maternity hospital: palmar and plantar grasp, plantar support, stepping, Moro, Galant, sucking, rooting, Babkin, neck righting, and labyrinthine righting. We collected the following information from the newborn's medical records: TSB level, birth weight, gestational age, and use of phototherapy (yes or no). The physical examination was performed using the Dubowitz examination (1991): "The Neurological Assessment of the Preterm and Full-term Newborn Infant" [16]. The retest of primitive reflexes and righting reactions was conducted at corrected age of one month (± 3 days) on infants weighing $\geq 2500\text{g}$. Both examinations were performed blindly by the same examiner. The first examination was conducted without prior consultation of the infant's medical records.

Outcome assessment

Abnormal primitive reflex responses and righting reactions were found to be abnormal in the initial test in some infants with TSB $\geq 5.6\text{mg/dL}$, who also showed abnormal reflex responses and head-lag in the retest.

According to the Dubowitz examination, abnormal is defined as the absence of or abnormalities in normal reflex response and righting reaction patterns and low muscle tone, determined by the presence of asymmetrical tonic neck reflex (ATNR) and head-lag.

The reflex was considered to be abnormal for the analysis of the quality of primitive reflex response and righting reaction patterns and we assessed the association between quality and TSB level.

Statistical analysis

The following descriptive statistics were used: means and medians, standard deviation, and coefficients of variation. The data were entered into an electronic spreadsheet (Excel 2007) and the statistical analysis was performed using SPSS version 18. The infants were divided into two groups: normal response and abnormal response. These groups were compared using the t-test for nu-

merical variables and Pearson’s chi-squared test for the categorical variables. A ROC analysis was performed to illustrate the primitive reflexes and righting reactions. Cut-off values were determined for TSB level and use of phototherapy to identify the association between these variables and reflex response status (normal or abnormal). A significance level of $p < 0.05$ was adopted.

Ethical approval

The study protocol was approved by the Pediatrics Institute research ethics committee at the Federal University of Rio de Janeiro

in June 2008. The parents or legal guardians of the infants agreed to participate in the study and signed an informed consent form.

Results

The final sample was therefore made up of 343 infants. Of these, 123 (35.9%) underwent their first examination in the intermediate intensive care unit, 49 (14.3%) in the nursery (area for weight gain, suction, and/or administration of medication), and 171 (49.8%) in the rooming-in unit (where mothers and infants stay together in the same room after delivery). Figure 1 shows the flow chart of the study. Of these 144 (42%) showed abnormal responses.

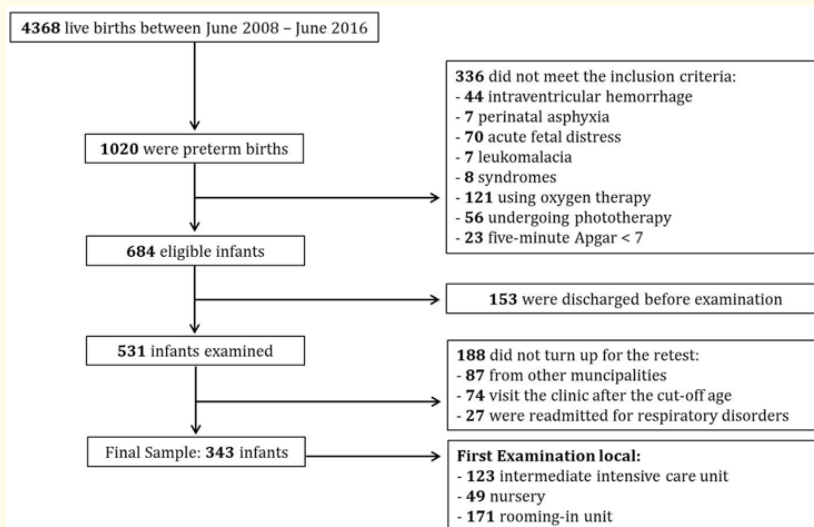


Figure a: Flow chart of the study.

Table 1 presents the study variables by group. The findings show that the normal response group had higher mean birth weight, older GA, and lower TSB level. The latter was statistically significant.

Variable	Primitive reflexes (n = 343)		p-value
	Normal response group (n = 199)	Abnormal response group (n = 144)	
Birth weight (g)	2152 ± 525	1814 ± 465	NS
GA* (weeks/days)	34.1 ± 1.6	33.6 ± 2.2	NS
TSB** (mg/dL)	6.2 ± 3.8	8.3 ± 2.7	< 0.0001

Table 1: Study variables by group (data presented as means and standard deviations).

*GA: Gestational Age; **TSB: Total Serum Bilirubin; NS: Not Significant

A large proportion of the sample (41.9%) showed abnormal responses for all of the following reflexes and righting reactions: palmar grasp, plantar support, sucking, Babkin, Moro, neck reflex, labyrinthine righting, as well as the asymmetrical tonic neck reflex and tonic labyrinthine reflex, both of which are pathological reflexes (Table 2).

Primitive reflexes and righting reactions	N	%	95% CI
Normal	199	58.1	52.7 - 63.1
Abnormal	144	41.9	36.8 - 47.2
Total	343	100.0	

Table 2: Status of primitive reflexes and righting reactions.

Table 3 shows the status of primitive reflexes according to use of phototherapy in the retest. There was no statistically significant difference between presence of normal and abnormal reflexes in the group that underwent phototherapy ($p = 0.86$). In contrast, a statistically significant difference was found in the group that had not undergone phototherapy ($p < 0.001$).

Variable		Primitive reflexes (n = 343)		p-value
		Normal response group (n = 199)	Abnormal response group (n = 144)	
Phototherapy	No	154 (75.9%)	45 (32.1%)	< 0.0001
	Yes	45 (24.1%)	99 (67.9%)	= 0.86

Table 3: Status of primitive responses according to use of phototherapy in the retest.

The ROC curve in figure 1A below shows the sensitivity and specificity indices for use of phototherapy. Figure 1B shows the optimal TSB cutoff value for protection against kernicterus, revealing that 100% of the preterm newborns with $TSB \geq 5.3\text{mg/dL}$ had abnormal responses.

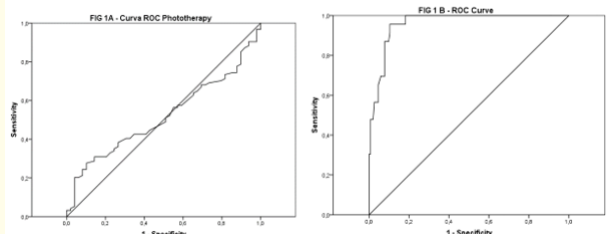


Figure 1: A: ROC curve showing that there was no statistically significant difference in presence of normal responses between infants who had undergone phototherapy and those who had not. B: ROC curve showing the optimal TSB cutoff value for protection against kernicterus.

Table 4 shows that the group with the largest proportion of infants with abnormal reflex responses and reactions was the TSB between 6.1 and 14mg/dL group (82 or 70.1% of cases), followed by the TSB between 14.1 and 25mg/dL group (31 or 26.5% of cases) and TSB $\leq 6\text{mg/dL}$ group (4 or 3.4% of cases).

Figure 2A shows that infants with normal reflex responses and reactions had lower mean TSB levels. Figure 2B demonstrates that 67.9% (n = 99) of the infants who had undergone phototherapy showed abnormal reflex responses and reactions and presented higher TSB levels.

	Primitive reflex		Total
	Normal	Abnormal	
0 - 6 mg/Dl	137 (67.5%)	4 (3.4%)	141 (44.1%)
6.1 - 14 mg/Dl	59 (29.1%)	82 (70.1%)	141 (44.1%)
14.1 - 25 mg/Dl	7 (3.4%)	31 (26.5%)	38 (11.9%)
	203 (100.0%)	117 (100.0%)	320 (100.0%)

Table 4: Distribution of primitive reflex responses and righting reactions and categorized TSB levels. Pearson's chi-squared test: $P < 0.0001$.

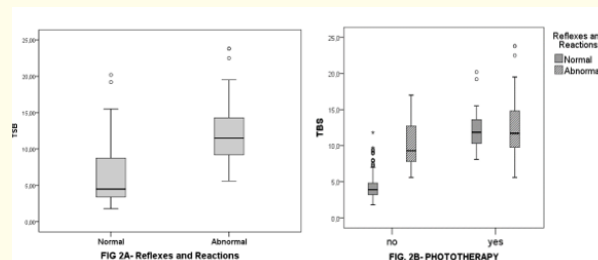


Figure 2: A: Status of primitive reflexes and righting reactions according to TSB levels. B: Status of primitive reflexes and righting reactions according to TSB levels and whether infants received phototherapy or not.

Discussion

What is already known on this topic is the neonatal hyperbilirubinemia can cause chronic bilirubin encephalopathy (CBE), mostly in preterm newborns. The best way of preventing kernicterus is knowing TSB levels and using preventive phototherapy. This study shows that a protective factor against CBE in premature infants with gestational age below 36 weeks is maintaining TSB levels $\leq 5\text{mg/dL}$.

Almost all term and late preterm infants (gestational age ≥ 35 weeks) develop TSB levels of $>1\text{ mg/dL}$, which is the upper limit for normal for adults. Neonates with severe hyperbilirubinemia (defined as $TSB >25\text{ mg/dL}$) are at risk of developing bilirubin-induced neurologic dysfunction (BIND), which occurs when bilirubin crosses the blood-brain barrier and binds to brain tissue, causing neurotoxicity. Vulnerable infants are at risk of developing BIND at lower TSB values [12]. In the present study, 41.9% (144) of the infants with $TSB < 25\text{mg/Dl}$ showed signs of BIND.

Okumura, *et al.* [17] conducted a study with 8 preterm infants with athetoid cerebral palsy and GA of ≤ 34 weeks. Six of the 8 in-

fants had a GA of ≤ 26 weeks and birth weight was $<1000\text{g}$ in 5 infants. Total bilirubin levels were measured frequently in the majority of infants; peak values of $>15\text{ mg/dL}$ were observed in 3 infants. None of the infants showed neurologic symptoms characteristic of classical acute bilirubin encephalopathy during the neonatal period. Dystonic posture and abnormal muscle tone were first recognized within 6 months' corrected age in all patients. The ages, birth weights and TSB levels are similar to those in the present study.

Our findings show that a large proportion of the infants who underwent phototherapy (67.9%) showed abnormal reflex responses and reactions in the retest, suggesting that phototherapy may not have been performed in a timely manner, thus not preventing the neurotoxic effects of bilirubin and resulting in the staining of the basal ganglia.

The mean TSB level in the abnormal response group ($n = 144$ or 41.9% of the sample) was $8.3 \pm 2.7\text{ mg/dL}$. This rate is considered low risk by other authors such as GOVAERT, *et al.* [18], who suggest that phototherapy should be started at 5mg/dL at birth, 6.5mg/dL at 24 hours, 8mg/dL at 48 hours, 9.5mg/dL at 72 hours, and 11mg/dL at 96 hours. The American Academy of Pediatrics [19] states that the best way of preventing kernicterus is to measure TSB levels and use preventive phototherapy. MAISELS [20] recommends that phototherapy should be initiated at 5 to 8 mg/dL in preterm newborns. It is therefore important to rethink neonatal care facility protocols for monitoring TSB levels, especially during the first 5 days of life, to ensure timely intervention to prevent kernicterus.

In 2012 Maisels, Watchko, Bhutani, and Stevenson [13] presented *consensus-based recommendations* for the better management of hyperbilirubinemia in preterm infants aged < 35 weeks (Table 5). Briefly, they recommend phototherapy for TSB levels between 5-14 mg/dL and exchange transfusion for TSB levels between 11-19 mg/dL.

Our findings underline the importance of reviewing when to implement phototherapy, as proposed by the American Academy of Pediatrics [19]. It is important to highlight that certain clinical conditions significantly increase the risk of hyperbilirubinemia in preterm newborns. Our study did not include infants undergoing oxygen therapy and who had perinatal asphyxia or a five-minute Apgar score of ≥ 7 because these factors can influence the integrity of the central nervous system (CNS), affecting reflex responses and reactions. Patients admitted to the neonatal intensive care unit are more likely to be exposed to risk factors for penetration of bilirubin into the CNS.

It is likely that neurotoxicity in healthy premature infants is associated with a range of TSB levels rather than a specific critical

level. In practice, jaundice-related complications are rare due to the liberal use of phototherapy. However, risks still exist and various recent studies have shown that even low and moderate TSB levels can lead to bilirubin-induced brain damage in sick preterm newborns [21]. Sick preterm newborns may develop kernicterus at lower TSB levels than healthy newborns [22].

In neonates, the TSB thresholds adopted by health facilities vary substantially from region to region because of differences in racial composition, prevalence of genetic factors that affect bilirubin production and metabolism, and breastfeeding practices. Risk assessments are based on TSB rather than unconjugated bilirubin levels alone because elevated TSB levels in the first week of life are mostly due to increased bilirubin production, resulting primarily in unconjugated bilirubin and rarely associated with cholestasis, which presents primarily with elevated conjugated bilirubin [23].

However, despite clinical trials and studies investigating hyperbilirubinemia in preterm infants, etiology remains unknown in the majority of cases of kernicterus [20,24,25]. In practice, the main concern when hyperbilirubinemia is diagnosed is not the etiology, but rather the timely initiation of prophylactic phototherapy to lower TSB levels while trying to discover the precise etiology, bearing in mind that hyperbilirubinemia can lead to kernicterus.

Our findings do not show any significant difference in the status of primitive reflexes (normal and abnormal) between infants who received phototherapy and those who did not, with both jaundiced and non-jaundiced babies showing abnormal primitive reflex responses. This may be because phototherapy was not performed in a timely manner, resulting in staining of the basal ganglia in infants who are more sensitive to lower TSB levels.

Greater attention should be paid to monitoring TSB from birth to ensure timely phototherapy and to preventing discharge on the third day of life without measuring TSB. Early discharge of premature infants is a major concern [26-29].

In a case report by Odutolu, *et al.* [30], a child with 36 + 6-week gestation infant on day 3 and 4 showed a rise in TSB levels above the phototherapy threshold but below the exchange threshold with less than 10% conjugated fraction. At no point during treatment did the TSB level exceed the NICE [31] recommended exchange transfusion threshold. The neonate was started on double phototherapy; however, 5 hours into phototherapy treatment on day 4 the infant was noted to have abnormal movements with opisthotonus and intermittent dystonic movements in the upper limbs. The results of this study suggest that phototherapy was initiated late

in relation to bilirubin toxicity in the CNS. It is worth remembering that SB concentration in preterm newborns on day 4 can reach between 10 and 12mg/dL [32].

It is suggested that a threshold of SB \leq 5mg/dL is maintained to protect against kernicterus in preterm infants born with a CGA of up to 35 weeks and 6 days, remembering that “kernicterus is only preventable, but hyperbilirubinemia is preventable and treatable” [1].

Study limitations include the large percentage of infants who did not turn up for the retest at the cut-off age, the fact that TSB was not measured in some preterm newborns with global motor patterns that are similar to those in infants with kernicterus, and the high early hospital discharge rate (less than 4 days of life).

Conclusion

Based on the clinical evidence provided by the present study, it is suggested that a threshold of TSB \leq 5mg/dL is maintained to protect against kernicterus in preterm newborns born with a GA of less than 36 weeks, considering that the lower the birth weight and GA, the higher the exposure to bilirubin neurotoxicity. It is therefore important to review the concept of prevention, given that it is difficult to define a reference threshold for this group due to the diverse range of adverse events in premature infants.

Abnormal primitive reflexes and righting reactions were observed in preterm newborns with TSB levels as low as 5.4mg/dL. The following reflexes showed abnormal responses: palmar grasp, plantar support, sucking, Babkin, Moro, neck reflex, labyrinthine righting, as well as asymmetrical tonic neck reflex, and tonic labyrinthine reflex, which are abnormal reflexes.

Our findings do not show any significant difference in the state of primitive reflexes (normal and abnormal) between infants who received phototherapy and those who did not, our hypothesis is that, perhaps phototherapy is starting late and in more sensitive neonates, it may have already occurred the neurotoxicity. A TSB concentration of 5mg/dL is suggested as a safe level to prevent neurotoxicity.

Recommendations

In light of the results of this study, it is important to reflect upon the importance of physical examination, focusing on the assessment of primitive reflexes and righting reactions and observation of response quality. The premature infants in our sample showed changed reflexes and actions when assessed at a CGA of 35 weeks; however, the motor patterns were weak due to the GA at assessment, when flexor tone is still immature, which may confuse the

examiner because of the subtle difference in response pattern. On retesting at corrected age of one month, abnormal primitive reflex responses and righting actions persisted in 41.9% of the infants.

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Conflict of Interest

Declare if any financial interest or any conflict of interest exists.

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