ASSOCIATION BETWEEN TOTAL SERUM BILIRUBIN LEVEL AND MANIFESTATIONS OF KERNICTERUS

S. Behjati-Ardakani[1], A. Nikkhah[1], M. R. Ashrafi[2] and M. Sedaghat[3]

1) Department of Neonatology, Children's Hospital Medical Center, School of Medicine, Medical Sciences/University of Tehran, Tehran, Iran
2) Department of Pediatric Neurology, Children's Hospital Medical Center, School of Medicine, Medical Sciences/University of Tehran, Tehran, Iran
3) Department of Social Medicine, Children's Hospital Medical Center, School of Medicine, Medical Sciences/University of Tehran, Tehran, Iran

Abstract- Kernicterus (bilirubin induced encephalopathy) is an uncommon disorder with tragic consequences, especially when it affects healthy term and near-term neonates. Appointment of cut off value of total serum bilirubin level that have a safe margin for early prompt treatment, as a result, prevention of kernicterus. In our study, all of icteric neonates that admitted in our center in 1 year were enrolled. From 305 neonates, 25 cases have kernicterus manifestations. These 25 neonates have not any conditions that mimic kernicterus manifestations (such as birth trauma, intra cranial hemorrhage, asphyxia). We divided neonates to 2major groups: neonates < or = 7 days and > 8 days-old. Also these cases were divided to high-risk and low-risk neonates. In this study, 220 neonates (72.1%) were ≤ 7days and 85 neonates (27.9%) were > 8 days-old. Also 109 neonates (35.7%) were or with risk factors and 196 neonates (64.3%) were or without risk factors. Risk factors were prematurity, acidosis, hemolysis, duration of hyperbilirubinemia, sepsis and respiratory distress. Cutoff value of bilirubin level for neonates ≤ 7 days was 25.15 mg/dl and for neonates > 8 days was 22.25 mg/dl that no statistically significant difference was found. Cut off value of bilirubin level for high-risk neonates was 22.35 mg/dl and for low-risk neonates was 27.95 mg/dl that statistically significant difference was found. The lower limit of bilirubin in neonates with kernicterus was 16.5 mg/dl and the upper limit was 44 mg/dl. The high-risk neonates need prompt treatment of hyperbilirubinemia at lower levels of total bilirubin compared with low-risk neonates.

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Key words: Serum bilirubin, kernicterus manifestation, neonate, bilirubin encephalopathy

INTRODUCTION

Kernicterus, or bilirubin encephalopathy, is a neurologic syndrome resulting from the deposition of unconjugated bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial. Its onset is usually in the 1st week of life. In healthy term infants, kernicterus has developed when bilirubin levels exceed 30 mg/dl, although the range is wide (21-50 mg/dl) (1-5). The early manifestations of kernicterus may be subtle and indistinguishable from some systemic illnesses (sepsis, hypoglycemia...) lethargy, poor feeding and loss of the Moro reflex are common initial signs. Other manifestations: opisthotonus, high-pitched cry, hypo or hypertonic. As previous studies, kernicterus will develop in one third of infants with bilirubin levels excess of 25-30

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*** Corresponding Author:**
S. Behjati-Ardakani, Department of Neonatology, Children's Medical Center, School of Medicine, Medical Sciences/University of Tehran, Tehran, Iran
Tel: +98 912 3278210, Fax: +98 21 88501067
E-mail: behjatis@sina.tums.ac.ir

mg/dl. Kernicterus is not a disease of the past. Pathologically, the surface of the brain is usually pale yellow. The exact incidence of kernicterus is unknown (5). Our purpose in this study was determination of cut off value of serum total bilirubin level in low-risk and high-risk icteric neonates that have a safe margin for prevention of kernicterus. The null hypothesis was that in high-risk neonates prompt treatment of hyperbilirubinemia should be done at low-levels compared with low-risk neonates.

MATERIALS AND METHODS

All of neonates in the study were icteric and were admitted in our hospital for treatment of hyperbilirubinemia in duration of 1 yr (2003-2004). There were no exclusion criteria in this study.

In our study, 305 neonates (age: 1-28 days) was evaluated. History taking and physical examination was performed. Also complete blood count (CBC), peripheral blood smear (PBS), retic count, direct Coombs' test, total and direct bilirubin level,G6PD, electrolytes, blood sugar, arterial blood gas, thyroid function test, cerebrospinal fluid (CSF) analysis, CSF culture, blood culture, urine culture, brain sonography and ABR (auditory evoked brainstem response) was performed for all of these neonates. A questionnaire was designed and completed. Each neonate that had even one sign of acute kernicterus (high pitch cry, opisthotonus, limited upward gaze, reverse Moro reflex,…) with hyperbilirubinemia and negative cultures in association with some degree of hearing loss (abnormal ABR) and normal blood sugar and arterial blood gas and especially normal brain sonography, was diagnosed as kernicterus. So, 25 cases from 305 cases (8.1%) had kernicterus. All of these neonates divided to two groups based on neonatal age: ≤ 7 day-old and > 8 day-old. Also based on risk factors, these neonates divided to two groups: low-risk and high-risk with or without risk factors.

These data was entered to computer with SPSS statistical program. For appointing of judgment (cut off value), we used ROC analysis method. Confidence interval was 95%.

RESULTS

Results showed that 72.1% of neonates were ≤ 7 days and 27.9% were >8 days. Also, 35.7% of these neonates were high-risk and 64.3% were low-risk.

For neonates ≤ 7 day-old, Area under curve was 0.949 and cutoff value of bilirubin level with 88% specificity and 87.5% sensitivity was 25.15 mg/dl. For neonates > 8 day-old, Area under curve was 0.863 and cut off value of bilirubin level with 72% specificity and 89% sensitivity was 22.25 mg/dl. No statistically significant difference was found (P > 0.05).

For high-risk neonates, Area under curve was 0.900 and cut off value of bilirubin level with 76% specificity and 94.5% sensitivity was 22.35 mg/dl. For low-risk neonates, Area under curve was 0.981 and cut off value of bilirubin level with 93% specificity and 100% sensitivity was 27.95 mg/dl. There is statistically significant difference (P < 0.001).

DISCUSSION

In previous studies about association of kernicterus manifestations and total serum bilirubin level, no clear-cut level of bilirubin existed above which encephalopathy is assured and below which neurologic safety exists, but, birth weight, gestational age, chronologic age, infant's systemic condition, fluid and nutritional status, acid-base status and the presence or absence of known pathology are all important. Acute bilirubin toxicity appears to occur in the first few days of life of the term infant. Preterm infants may be at risk of toxicity for slightly longer than a few days. If injury has occurred, the first phase of kernicterus appears within the first week of life (1). The clinical features of the first phase of kernicterus are: Decreased alertness, hypotonia and poor feeding (1).

In our study, we show that, there is no statistically significant difference between cutoff value of neonates ≤ 7 days and neonates > 8 days. Even a neonate > 8 days may need to treatment at lower levels of total serum bilirubin than a neonate ≤ 7 days.

Table 1. Total serum bilirubin, age, sex, duration of hyperbilirubinemia and risk factors in 25 studied neonates

No.	TSB (mg/dl)*	Age (day)	Sex	Duration of hyperbilirubinemia (day)†	Risk Factor‡
1	28	3	F	2	High (H)
2	33	10	M	6	High (P)
3	28	5	F	3	High (H)
4	23.3	5	F	3	Low (P)
5	**16.5**	9	M	7	Low
6	22.4	8	M	6	Low
7	34	5	M	2	Low
8	38	9	F	6	Low
9	25.3	5	M	3	High (P)
10	35.9	4	M	3	High (H)
11	29	8	F	4	High (P + R)
12	35	12	M	9	Low
13	35	4	F	3	High (H)
14	29	6	M	3	Low
15	36	6	M	3	High (P)
16	31.9	9	M	6	Low
17	38	5	M	3	High (H)
18	42.9	6	F	3	High (P + R)
19	22.7	6	F	4	Low
20	28	12	M	8	Low
21	37.5	11	F	8	High (H)
22	34.6	6	M	3	High (H)
23	**44**	3	M	1	High (HY+A)
24	43.8	6	F	4	High (P)
25	39	6	F	3	High (H)

Abbreviations: TBS, total serum bilirubin; F, female; M, male; H, hemolysis; P, prematurity; A, acidosis; R, respiratory distress; HY, hypoglycemia.
*The mean duration of hyperbilirubinemia was 4 days.
†The mean of TSB was 32 mg/dl.
‡60% of neonates were high-risk.

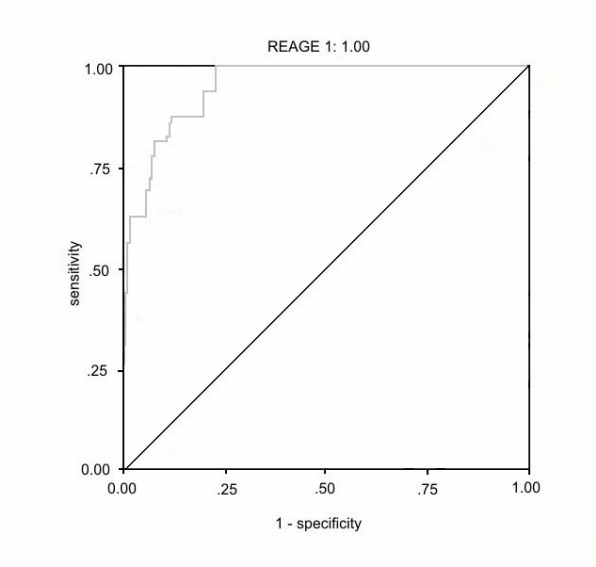

Fig. 1. Area under curve and cut off value based on age (≤ 7 days).

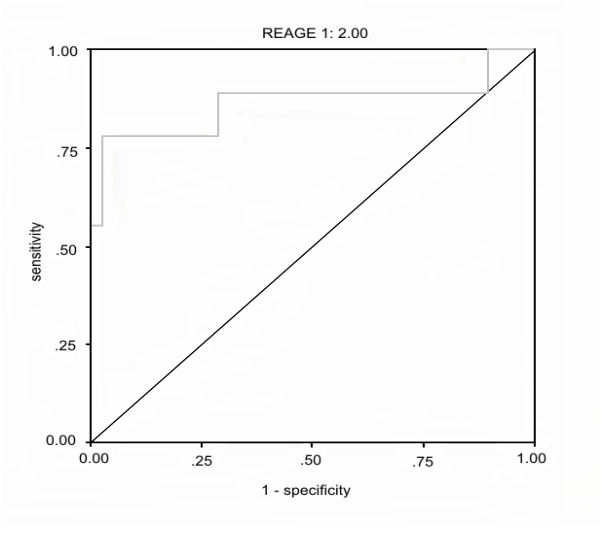

Fig. 2. Area under curve and cut off value based on age (> 8 days).

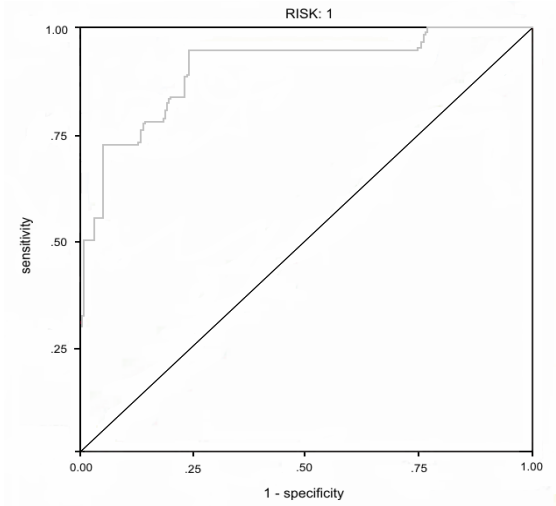

Fig. 3. Area under curve and cut off value based on risk factor (high-risk).

We explain this unreasonable result based on difference between time of beginning of hyperbilirubinemia and treatment onset in hospital. In fact, duration of hyperbilirubinemia at > 8 day-old neonates was more than neonates ≤ 7 day-old neonates, so duration of hyperbilirubinemia can be a risk factor for kernicterus. For example, in our study, a 9 day-old neonate that duration of his hyperbilirubinemia was 7 days, had kernicterus with total serum bilirubin of 16.5 mg/dl and without any risk factor, but, a 5 day-old neonate that duration of his hyperbilirubinemia was 2 days, did not have any sign of kernicterus with total serum bilirubin of 33.5 mg/dl.

Based on clinical experience, as well as chemical and in vitro data, acidosis (especially respiratory acidosis) is thought to augment bilirubin toxicity (2).

Many guidelines for the management of hyperbilirubinemia in infants include suggestions for lowering the intervention levels in septic/ infected infants (3).

In our study, we divided the icteric neonates to high-risk and low-risk neonates. Risk factors: prematurity, hypoglycemia, sepsis, acidosis, hemolysis and respiratory distress. We show that, there is statistically significant difference between cutoff values of high-risk and low-risk neonates. So, we must begin prompt treatment of hyperbilirubinemia in high-risk neonates compared with low-risk neonates. It is interesting that, none of the neonates with kernicterus was septic. Also, duration of hyperbilirubinemia is an important risk factor for kernicterus. Our recommendations: recognize the clinical significance of jaundice within the first 24 hr after birth (6), early recognition of risk factors and prevention of kernicterus by prompt treatment of them. Treatment of severe hyperbilirubinemia aggressively with intensive phototherapy or exchange transfusion for hazardous bilirubin levels (6) and educate parents for early coming to hospital and appropriate investigation of their neonatal jaundice as soon as possible (7).

Conflict of interests

The authors declare that they have no competing interests.

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