Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

The effects of the serum albumin levels at the time of admission on the duration of hospitalization in indirect hyperbilirubinemia

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ARTICLE INFO

Keywords:
Hyperbilirubinemia
Serum albumin
Serum bilirubin
Newborn

Received: Dec 09, 2022
Accepted: Feb 24, 2023
Available Online: 24.03.2023

DOI:
10.5455/annalsmedres.2022.12.366

Abstract

Aim: Indirect hyperbilirubinemia (IHB) is the most common cause of neonatal intensive care unit admissions. Low serum albumin levels are considered to be a risk factor for the development of IHB. We aimed to examine the effect of serum albumin levels during hospitalization on hospital stay in newborns requiring hospitalization due to IHB.

Materials and Methods: This retrospective study included 316 newborns. The serum albumin, total bilirubin and bilirubin/albumin ratio were measured at admission for all newborns. The patients were divided into two groups according to the length of hospital stay.

Results: Patients hospitalized for longer than 2 days due to IHB were classified as extended hospitalization (Group 1) and hospitalization shorter than 2 days (Group 2). It was observed that 59 (22.9%) of the patients required hospitalization for more than 2 days due to IHB. The serum albumin levels measured at admission were significantly lower in group 1 (2.92±0.99 gr/dl) and group 2 (3.68±0.35 gr/dl) respectively (p=0.034). The serum albumin level cut off value $\leq$ 3.55 gr/dl was a good predictive value with a sensitivity of 67.8% and specificity of 76%.

Conclusion: The serum albumin level measured at hospitalization can give information about the length of hospital stay. Thus, informing the family about the length of stay at the time of admission to the hospital can reduce the family's anxiety.

Introduction

Indirect hyperbilirubinemia (IHB) is the most common cause of neonatal intensive care unit (NICU) admissions. The treatment approach for jaundice in newborn babies is based on the American Academy of Pediatrics (AAP) charts determined according to serum total bilirubin levels for the term and preterm babies. These charts depend on the presence of risk factors (low birth week, sepsis, and hemolytic disease) and the absence of risk factors [1]. Previous studies have shown that; free bilirubin levels have a more important role than serum total bilirubin levels in the development of bilirubin encephalopathy [2]. Serum total bilirubin levels can be easily determined biochemically. However, it is not possible to detect free plasma bilirubin by routine methods. Therefore, free plasma bilirubin can be predicted by the Bilirubin/Albumin (B/A) ratio.

Albumin aids in hepatic transport and excretion of bilirubin. Due to this feature of albumin, low albumin levels in newborn babies have been associated with the development of IHB in the following days. Low serum albumin levels are considered to be a risk factor for the development of IHB, as it will cause a decrease in bilirubin excretion [3]. Therefore, the duration of hospitalization and the need for treatment of the newborn will increase. In our study, we aimed to examine whether serum albumin level is helpful in predicting length of stay in hospital for IHB. When we reviewed the literature, we saw no such study before.

Materials and Methods

A total of 523 newborn were hospitalized at Dr. Sami Ulus Maternity and Children Research and Training Hospital with the diagnosis of IHB between January 2016 and January 2020 was included in this retrospective study. Infants with severe jaundice requiring intensive phototherapy or exchange transfusion and infants with gestational age >34 weeks were included in the study.

We analyzed a sub-cohort of 316 infants after excluding missing albumin data (109 cases), insufficient outcome documentation (37 cases), or comorbid disease unrelated

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to jaundice (61 cases). This study was ethically approved by the Dr. Sami Ulus Obstetrics, Child Health and Diseases Training and Research Hospital Ethical Committee (No: E-21/02-92). Management of indirect hyperbilirubinemia was assessed as the need for phototherapy or exchange transfusion according to the neonatal hyperbilirubinemia management guidelines of the AAP. Serum bilirubin, albumin values and blood samples for complete blood count are taken from all patients hospitalized with IHB, in accordance with the protocol of our hospital. The samples were measured for serum albumin level using bromocresol green method with an automated clinical chemistry analyzer (Roche/Hitachi 912), serum bilirubin (total and direct) level by Colorimetric method, hemoglobin concentration using cell counter T 660. In our study, the primary output was higher indirect bilirubin levels in patients with lower albumin levels. Our endpoint is that the need for treatment is longer in IHB cases with lower albumin levels. In this context, all cases were divided into two groups according to the length of hospital stay.

Data analysis

The sample size calculation was based on the sensitivity of serum blood albumin to predict the occurrence of indirect hyperbilirubinemia. A priori power analysis was used to determine the required number of patients for the study. According to our preliminary data, serum albumin levels were 2.92±0.99 gr/dl in patients extended hospitalization period and 3.68±0.35 gr/dl in patients with short hospitalization period.

When the power was taken as 95.0% with an effect size of 0.65 and alpha level of 0.05%, the required numbers were calculated to be 52 cases and 52 control subjects to reject the null hypothesis for a control subject (G * Power 3.1.9.4). Statistical analyzes were performed using the statistical package for the Social Sciences (SPSS), version 21 (IBM SPSS Statistics for Windows,Version 21.0 Armonk, NY: IBM Corp.). Kolmogorov–Smirnov test was preferred to determine the normality of distribution. Since the data did not follow a normal distribution, comparison between groups was performed using Mann–Whitney test for quantitative variables. The chi-square test was used for categorical variables. Categorical variables were expressed as percentages, and continuous variables have been denoted as mean (± standard deviation) or median, as appropriate. Paired-Samples t-test was performed for repeated measurements. Pearson's test was used for correlation analyses. Receiver operating characteristics (ROC) curve analysis was performed to describe the predicted extended hospitalization. P value less than 0.05 was considered statistically significant.

Results

A total of 316 newborns were included in the study. Of the patients, 171 (54.1%) were male, 145 (45.9%) were female.

In addition, patients hospitalized for longer than 2 days due to IHB were classified as extended hospitalization (Group 1) and hospitalization shorter than 2 days (Group 2). It was observed that 59 (22.9%) of the patients required hospitalization for more than 2 days due to IHB.

Table 1. Clinical characteristics of all patients by study group.

Characteristics	Group 1(extended hospitalization) (n:59)	Group 2 (short hospitalization) (n:257)	p value
Gestational age,weeks	38±1.6	37.4±1.7	0.04
Admission day	4.1±4	5.1±3	0.038
Birthweight,grams	3154.5± 479.8	3147.4±505.4	0.92
Gender (Male)	36 (61%)	135 (52%)	0.23
Mode of delivery (Ceserean)	24 (40.6%)	136 (52.9%)	0.91
Apgar at 1 min	9(5-9)	9(5-9)	0.26
Apgar at 5 min	9 (7-10)	10 (6-10)	0.29
IVIG	3 (5%)	1 (0.38%)	0.004
Exchange transfusion	4 (6.7%)	0	0.00
Hospital stay, day	5.5±3.8	1.5±0.5	0.00
Risk factor			0.004
ABO incompability	29 (49.1%)	89 (34.6%)	
Rh incompability	4 (6.7%)	17 (6.6%)	
Subgroup incompability	3(5%)	3 (1.1%)	
Cephal/surrenal hematoma	2 (3.3%)	6 (2.2%)	
G6PD/ Pyruvate kinase deficiency	0	2 (0.8%)	
Hypothyroidism	1 (1.6%)	1 (0.38%)	
Sepsis	6 (10.1%)	3 (1.1%)	
Dehydration	2 (3.3%)	7 (2.7%)	
None	7 (11.8%)	120 (46.6 %)	
Polycythemia	3 (5%)	3 (1.1%)	
Rh+ABO incompability	2 (3.3%)	6 (2.2%)	

G6PD: glucose-6-phosphate dehydrogenase, IVIG: intravenous immunoglobulin.

The mean birth weight, 5-minute APGAR score, gender was similar among the groups (Table 1) (p>0.05).

In Table 2, laboratory results of all patients were compared. There were no significant differences among the groups for serum levels of total bilirubin, direct bilirubin levels at admission and B/A ratios. The serum albumin levels measured at admission was significantly lower in group 1 (2.92±0.99 gr/dl) (p=0.034).

The optimum cut off value for serum albumin level as shown by the ROC curve for neonates with extended hospitalization was ≤ 3.55 gr/dl with a sensitivity of 67.8% and specificity of 76%.

All patients received phototherapy. Intravenous immunoglobulin (IVIG) was given to 3 (5%) of the extended-hospitalized patients and only 1 (0.38%) of the short hospitalized patients (p=0.004). Exchange transfusion requirement was observed only in 4 patients in group 1.

Table 2. Laboratory properties of all cases according to groups.

Characteristics	Group 1 (extended hospitalization) (n:59)	Group 2 (short hospitalization) (n:257)	p value
Admission total bilirubin, mg/dl	18.09±7.09	17.87±3.37	0.81
Admission direct bilirubin, mg/dl	0.77± 0.75	0.67± 0.15	0.31
Admission albumin, g/dl	2.92±0.99	3.68±0.35	0.03
Admission total protein, g/dl	5.35± 0.52	5.35±0.53	0.93
Admission B/A ratio, mg/g	5.56±4.52	4.86±0.99	0.24
Total bilirubin at 24.hour,mg/dl	11.98±3	11.75±2.5	0.62
Direct bilirubin at 24.hour,mg/dl	0.73±0.6	0.72±0.19	0.94
Total bilirubin at discharge,mg/dl	10.31± 2.82	10.58± 2.2	0.48
Direct bilirubin at discharge,mg/dl	0.64± .21	0.68± 0.17	0.14
Admission hemoglobin,g/dl	16.68± 2.69	17.01±2.17	0.39
Admission platelet, $x10^3/\mu l$	289741± 92073	312721± 97144	0.1
Admission MPV,fL	9.03±1.29	9.06±1.23	0.84
Crp, mg/L	4.51±2.2	1.2±1	0.003

B/A ratio: Bilirubin/albumin ratio, MPV:Mean platelet volume, Crp:C-reactive protein.

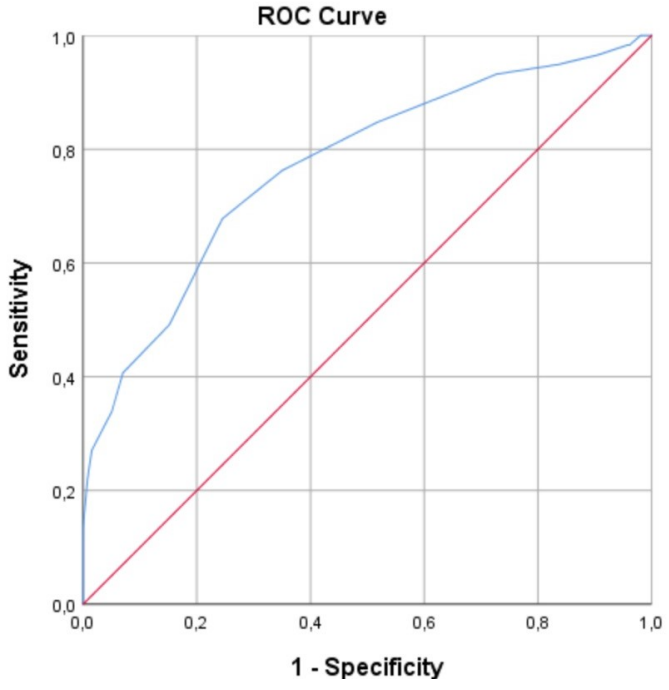

Figure 1. ROC curve analysis for serum albumin level.

Discussion

Indirect hyperbilirubinemia is still the first in neonatal intensive care admissions, and despite advanced methods and treatments, it is still up to date in today's neonatal emergency management practice. Families are in anxiety during their hospitalization and the first question asked at the time of hospitalization is the time of discharge. Therefore, it is necessary to find new markers to predict the length of stay in the intensive care unit and to reduce the anxiety of the family at the time of hospitalization.

It is emphasized that male gender is a risk factor for IHB compared to female gender. In studies conducted in our country, it has been observed that the male/female ratio is between 1.2 and 1.5 [4,5]. The male-female ratio of 1.17 in our study group was found to be consistent with our country's data.

Today, newborn babies are hospitalized in neonatal intensive care units by evaluating their total serum bilirubin levels according to the risk factors in the AAP charts. Likewise, their treatments are shaped according to AAP charts [1]. Serum albumin value as well as serum total bilirubin value at the time of hospitalization in IHB can guide us about the severity of the picture. Albumin has an important role in the transport of bilirubin to the liver and its excretion from the body. A low serum albumin level decreases bilirubin clearance and thus increases marked hyperbilirubinemia [6]. In addition to serum albumin levels in newborn babies, the bilirubin binding capacity of albumin also plays an important role in the development and course of IHB. [7]. In the previous studies, it was seen that cord albumin was used as a marker to predict neonatal jaundice. Neonates that did not develop IHB had significantly higher cord serum albumin levels than those who did [8]. In our study, the admission serum albumin levels of newborn babies who had to be hospitalized for more than two days due to IHB were found to be significantly lower than the group that was hospitalized for less than 2 days. This showed us that in addition to serum total bilirubin levels, serum albumin values can be used to predict the duration of hospitalization of infants during hospitalization due to IHB. When the literature was examined, no other study was found that investigated the effect of serum albumin on the length of stay in hospitalizations due to IHB.

A cord serum albumin level below 2.8 g/dl has been defined as a risk factor for the development of severe IHB in many studies [9,10]. Low serum albumin, especially below 2.5 g/dl, has been associated with more neurotoxicity in newborns [11]. However, in our study, although serum albumin levels were found to be lower in newborns who needed extended hospitalization compared to the control group, they were found to be above 2.8 g/dl. Therefore, in our study group, more acute bilirubin encephalopathy was not observed in the group with low serum albumin levels. A cut-off of 3.55 g/dl serum albumin value by ROC curve analysis showed that it had a good predictive value for extended hospitalization with 67.8% sensitivity and 76% specificity (Figure 1).

The B/A ratio reflecting free bilirubin is more useful than serum total bilirubin levels in predicting the development of acute bilirubin encephalopathy [2]. In our

study, although the B/A ratio was found to be numerically higher in the extended hospitalization group, no statistically significant difference was found between the two groups (p=0.24).

Free bilirubin easily crosses the blood-brain barrier and causes acute bilirubin encephalopathy. In our study, only 3 (0.94%) of the patients hospitalized with the diagnosis of IHB had moderate bilirubin encephalopathy findings, and no severe bilirubin encephalopathy was found. In conclusion, IHB is an important cause of morbidity and mortality in the neonatal period and constitutes the majority of neonatal intensive care admissions. We wanted to draw attention to the fact that the serum albumin value can be used in addition to the total serum bilirubin value, which can predict the length of stay in the intensive care unit, in order to reduce the anxiety of the families in terms of the length of stay in the intensive care unit.

Due to the lack of studies on serum albumin value and its effects on IHB length of stay, this study opens a window for further studies in this area and larger-scale studies involving preterm newborns are needed.

Conclusion

The serum albumin level measured at hospitalization can give us information about the length of hospital stay. Thus, informing the family about the length of stay can reduce the family's anxiety.

Ethical approval

This study was ethically approved by the Dr. Sami Ulus Obstetrics, Child Health and Diseases Training and Research Hospital Ethical Committee (No: E-21/02-92).

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