ROLE OF INTRAVENOUS HUMAN ALBUMIN IN MANAGEMENT OF NEONATAL HYPERBILIRUBINEMIA

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ABSTRACT

Background

Bilirubin is a known toxin to the newborn nervous system. Hyperbilirubinemia is treated by phototherapy and exchange blood transfusion; the intravenous infusion of human albumin can reduce the post-exchange serum bilirubin level and shorten duration of phototherpy and hence admission to hospital.

Objectives

To determine the role of intravenous administration of human albumin prior to exchange transfusion in term neonates with neonatal hyperbilirubinemia for reduction of serum bilirubin.

Patients and Methods

In this Study, fifty out-born term neonates with gestational age of >37 weeks and birth weight of >2500 grams, but otherwise healthy with high serum bilirubin required blood exchange immediately or after intensive phototherapy failure; were admitted to the neonatal unit of Raparin Pediatric Teaching Hospital in Erbil. The intervention group (n=25) received intravenous human albumin 20% (1 g/kg) one hour before exchange while the control group (n=25) underwent a blood exchange without intravenous human albumin.

Results

The mean total serum bilirubin (TSB) level in the albumin treated group was significantly lower than that in the control group at 6, 12 and 24 hours post-exchange (P<0.001). Mean duration of phototherapy was significantly reduced in the albumin treated group, compared to that in the control group (22.7±2.4 *vs*. 36±8.2 hours) respectively, (P<0.001). None of the neonates in the albumin treated group needed second exchange transfusion and no complications were observed.

Conclusion

Infusion of 20% albumin (1 g/kg) one hour prior to blood exchange transfusion can significantly reduce the post-exchange TSB, duration of phototherapy and the total duration of hospital admission.

Keywords: *Intravenous Albumin*, *Neonatal Hyperbilirubinemia*.

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INTRODUCTION

Jaundice is a yellow discoloration of the skin, sclera, and mucous membranes, clinically appeared jaundice in children occurs when serum concentration of bilirubin reaches 2-3 mg/dL, the neonate might not appear icteric until the bilirubin level is > 5 mg/dL [1].Indirect (unconjugated) hyperbilirubinemia: indicates that > 85% is unconjugated [2].

Bilirubin is bound to albumin as the dianion with a primary binding site that has a capacity of binding one molecule of bilirubin. A molar ratio of 1.0 indicates that approximately 8.3 mg bilirubin is bound to each 1 g albumin [3]. From a therapeutic viewpoint, albumin infusion may be advantageous, because an increased reserve of albumin may be protective against bilirubin toxicity by providing more binding sites, thereby reducing the levels of unbound bilirubin [4]. Intensive phototherapy for severe hyperbilirubinemia may cause photo-oxidation of albumin, resulting in a reduction of its binding affinity for bilirubin [5]. Accordingly, albumin infusion therapy might be effective on unbound-bilirubin values in term neonates with intensive phototherapy [6] Infusion of 20% albumin (1 g/kg) one hour prior to blood exchange can significantly reduce the post exchange total serum bilirubin and duration of phototherapy [7].

PATIENTS AND METHODS

This interventional study was performed in a period of six months from first of May 2011 to the end of October 2011 in the neonatal care unit of Raparin Pediatric Teaching Hospital in Erbil City-Kurdistan region, it was conducted on 50 out born neonates with jaundice admitted to the Neonatal Unit (gestational age more than 37 weeks) with a birth weight >2500 grams, with unconjugated hyperbilirubinemia and who required blood exchange immediately or after intensive phototherapy failure, they were otherwise healthy.

"Healthy" was defined as an active neonate on oral feed with normal neurological findings and physiological vital parameters, who satisfied the eligibility criteria were enrolled in the study and were randomized for receiving albumin or not [7].

The inclusion criteria were jaundiced neonates at any age indicated for exchange transfusion. We excluded those with suggested or probable cases of neonatal sepsis from the study and known cases of positive family history of G6PD deficiency without another explanation and those with direct hyperbilirubinemia (conjugated bilirubin >1 mg/dL when TSB was less than 5 mg/dL or > 20% of TSB [8].

A written consent was taken from the families of each child enrolled in this study for both cases and the control group. Information was collected from the mother of the participants or the caretaker via a face-to-face interview and included postnatal age, gender, age of the mother and occupation, residency, feeding type, poor feeding and lethargy, onset of jaundice, family history of blood diseases, of siblings with jaundice or phototherapy treatment or exchange transfusion and kernicterus.

The weight was measured by precision Seca weight scale (Beurer, max.20 kg). Participants were weighed in light clothing as far as possible. The scales were calibrated before use. The results were plotted on the CDC growth charts.

Prior to the exchange or starting phototherapy, complete blood count, blood group and Rh typing of neonates and mothers, direct Coombs test, reticulocyte count, serum albumin and serum bilirubin levels (total and direct) were performed and all information regarding demographic data were recorded. To meet the inclusion criteria, all the neonates involved in the study were tested for C-reactive protein, it was negative in all cases. The Direct Coombs test also was negative in all the involved jaundiced neonates.

Twenty five neonates in the intervention group received intravenous 20% human albumin (human albumin 20% BAXTER), with a dose of 1g/kg, one hour before exchange while the control group only underwent a blood exchange. Blood exchange transfusions were done for the intervention group immediately or after intensive phototherapy failure defined as, the inability to produce a decline of 1 to 2 mg/dL within 4 hours after the initiation of phototherapy [9]. Those neonates received intensive phototherapy using 8 special blue tube lamps (ARDO. Anelux) positioned within 15 to 20 cm of the patient's body. TSB was measured every 6 hours for both groups during the first 24 hours following the exchange using the Autoanalyzer biochemistry (bt35i) at 6 and 12 hours (serum sample), and by Apel bilirubinometer (BR501) at 24 hours (capillary sample). Follow up during hospitalization and after the discharge day for 36-

48 hours for the cases and the control done by measuring the TSB by using the bilirubinometer. Data were entered into Statistical Package for Social science (SPSS) program for Windows version 18. Quantitative variables were summarized by finding mean ± SD. T-Test was used to test the difference in the mean between cases and control and p value less than 0.05 was regarded significant [10, 11].

RESULTS

Baseline demographic characteristics before treatment in both groups are presented in (table 1); there were no statistically significant differences in gestational age, postnatal age, onset of jaundice, mother age, birth weight, mode of delivery, maternal occupation, and history of a sibling with neonatal jaundice or phototherapy treatment or kernicterus between the two groups.

The type of feeding between both cases and control showed no significant difference between the two groups (p value=0.71), exclusive breast feeding was the dominant setting in (72%) in both groups, (table 2).

Blood groups of the mothers and babies were incompatible in 8 cases (32%) of the albumin treated group, and in 10 cases (40%) in the control group, there was no significant difference between the two groups (p value=0.57).

Baseline investigations done for both the albumin treated and non-treated groups and there was no significant difference between the two groups, (table 3).

Table 1. Demographic Characteristics of cases and control.

Parameters	Albumin group mean ± SD	Control group mean ± SD	P value
Gestational age (wk)	38.6±0.3	39.2±0.43	0.53
Age in hours	131.72±30.8	125.44±36.3	0.51
Onset of jaundice (h)	62.48±17	54.24±14.3	0.07
Mother age (y)	25.56 ± 5	26.16±5.5	0.69
Birth weight (g)	3148±0.3	3208±0.32	0.5
Mode of delivery (C/S)	11±0.5	12± 0.44	0.22
Mother (housewife)	20±0.41	23±0.28	0.23
Poor feeding and lethargy	10±0.5	6±0.44	0.23
Sibling with jaundice	4±0.37	10±0.5	0.61
Sibling with phototherapy treatment	5±0.4	±0.467	0.52
Sibling with kernicterus	1±0.2	±0.21	0.32

Table 2. Distribution of feeding type between cases and control.

Type of feeding	Frequency		Percent	P value
	Treated group (n=25)	Control group (n=25)		
Exclusively breast fed	18	18	72%	
Formula fed	2	4	12%	
Mixed feeding	5	3	16%	
Total	50		100%	0.71

Table 3. Baseline investigations for the cases and control.

Investigation	Results		The Reference Value [13]	Total Number	P value
	Control group (mean ± SD)	Albumin treated group (mean ±SD)			
Hb(g/dl)	17 ± 1.1	17.5 ± 1.2	15-24	50	0.17
PCV (%)	52.8 ± 7	51 ± 6	44-70	50	0.5
Reticulocyte count (%)	2.4 ± 0.73	2.1 ± 0.9	1 day=0.4-6.0 7 days=<0.1-1.3 1-4wk=1.0-1.2	50	0.8
PLT(10^3/uL)	308 ± 81	268 ± 89	84-478	50	0.4
MCV(fL)	93.7±	101.8±	99-115	50	0.17
WBC(10^3/uL)	8.9 ± 3	9.9 ± 3.2	9.1-34	50	0.3
Direct bilirubin level mg/Dl	1.7 ± 0.6	1.9 ± 0.5	< 2	50	0.09

Baseline albumin level and its level after 6-12 hours after exchange were compared and there was no significant difference between the mean in the two groups (3.7±0.33 and 3.8±0.25 g/dL, respectively) before (3.7±0.3 *vs* 3.7±0.32 g/dL, respectively) and after, (p value=0.14, p value= 0.87) respectively, (table 4).

Following double blood volume exchange, TSB was measured every 6 hours, The mean TSB in albumin-treated group was statistically lower than that in the control group at 6, 12 and 24 hours post exchange, (table 5).

One neonate only (4%) in the albumin-treated group required phototherapy after 24 hours till 36 hours, but 4 (16%), 13 (52%), and 1 neonate (4%) in the control group received phototherapy till 36 , 48 and 72 hours post-exchange, respectively.

One neonate in the albumin-treated group needed exchange transfusion again but four neonates in the control group underwent a second exchange due to the relapse of severe hyperbilirubinemia,

all of these five neonates in the both groups were blood group compatible with their mothers.

Mean duration of phototherapy in hours from the onset of phototherapy till the fall of bilirubin to levels <12 mg/dL [9-11] was shorter for the albumin treated group compared to the non treated group, and the p value was very highly significant (< 0.001), (table 6).

Mean duration of hours of stay in the hospital was significantly different between the albumin treated group and the non treated one (p value= 0.02), (table7).

Table 4. Albumin concentrations before and after treatment in both the cases and control.

Variables	Albumin-treated Group (n=25)	Control group (n=25)	P value
Albumin level before any treatment(g/dL)	3.7±0.33	3.8±0.25	0.14
Albumin level after 6-12 h of admission(g/dL)	3.71±0.3	3.73±0.32	0.87

Table 5. Total Serum Bilirubin Levels in the cases and control groups.

Variables	Albumin-treated group (n=25)	Control group(n=25)	P value
TSB on admission (mg/dL)	23.4±2.5	24.5±3.1	0.18
TSB level after 6 h(mg/dL)	15.5**±2.1**	19.5±2.2	<0.001
TSB level after 12 h(mg/dL)	11.9**±1.6**	17.2**±2.6**	<0.001
TSB level at 24 h (mg/dL)	9.9**±1.8**	13**±2.1**	<0.001
TSB level at discharge	9.9**±1.0**	9.3**±1.0**	0.13

Table 6. Mean Duration of phototherapy.

Variable	Albumin-treated group (n=25)	Control group (n=25)	P value
Duration of phototherapy (h)	22.7±4.9	36±10	< 0.001

Table 7. Mean Duration of hours of stay in the hospital.

Variable	Albumin-treated group (n=25)	Control group (n=25)	P value
Duration of stay in hospital (h)	29±0.3	38±1.6	0.02

DISCUSSION

Although the mechanism responsible for bilirubin encephalopathy remains controversial, serum unbound bilirubin may play an important role in bilirubin encephalopathy [12].

Our study showed that albumin priming may be effective for an immediate reduction in serum unbound bilirubin values which agrees with what Shahian M, Moslehi MA. and Hosono, *et al*. showed [7, 13].

We demonstrated that there was a significant difference in the reduction of TSB levels in albumin-treated group compared to the control group at 6, 12 and 24 hours post-exchange (P<0.001), this agrees with Shahian M, Moslehi MA [7] findings with one difference at the 24 hour bilirubin level which was significantly lower in our study and disagreed with their results.

Further, the duration of phototherapy and the risk of a second exchange transfusion were reduced in the albumin treated group. The difference between the duration of phototherapy in albumin-treated group and the control group was statistically significant (P<0.001) which agrees with Shahian M, Moslehi MA [7].

Furthermore, the mean duration of hours of stay in the hospital was significantly shorter in the albumin treated group than the non treated one (p value= 0.02).

There was no significant difference between the baseline albumin level and its level at nearly 8 hours post exchange in albumin-treated group; A similar result was reported by Shahian M, Moslehi MA and Hosono, *et al*. [7, 13].

The amount of bilirubin removed per kilogram of birth weight was not found to be related to the etiology of the hyperbilirubinemia, the infant's age, or to the body weight at the time of the exchange. As reported by Shahian M, Moslehi MA and Odell [7, 14], also it was not related to gestational age, onset of jaundice, mother age, mode of delivery, maternal occupation, and history of a sibling with neonatal jaundice or phototherapy treatment or kernicterus in our study.

In conclusion; Albumin priming is effective for an immediate reduction in serum unbound bilirubin values, and in decreasing its levels in the next 24 hours by providing extra albumin sites when used prior to exchange transfusion by one hour, also it decreases the duration of phototherapy and the length of stay in hospital. So we recommend administering 1g/kg of human albumin by intravenous route to all cases undergoing exchange transfusion before the procedure by one hour.

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