RESEARCH PAPER

Effect of Albumin Administration Prior to Exchange Transfusion in Term Neonates with Hyperbilirubinemia – *A Randomized Controlled Trial*

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Objective: To determine the role of intravenous administration of human albumin prior to blood exchange in term neonates for reduction of total serum bilirubin (TSB).

Design: Randomized controlled trial.

Setting: Neonatal Unit of Nemazee Hospital, affiliated with Shiraz University of Medical Sciences, southern Iran.

Patients: Fifty out-born term neonates with gestation age >37 weeks, birth weight >2500 g, otherwise healthy with TSB ≥25 mg/dL requiring blood exchange due to intensive phototherapy failure.

Intervention: 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.

Outcome Measures: TSB level at 6 and 12 hours post-exchange, total duration of phototherapy, need for a second exchange transfusion and adverse effects.

Results: The mean TSB level in albumin-treated group was significantly lower than that in the control group at 6 and 12 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 (8.6±2.4 *vs.* 25±8.2 hours) ($P<0.001$). None of the neonates in albumin-treated group needed exchange transfusion again and no side effects were observed.

Conclusion: 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.

Key words: *Albumin, Exchange transfusion, Hyperbilirubinemia, Management, Neonate.*

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Rapid reduction in serum unbound bilirubin may be theoretically effective for the prevention of bilirubin encephalopathy. Bilirubin is bound to albumin as the dianion with a primary binding site that has a capacity of binding of one molecule of bilirubin. A molar ratio of 1.0 indicates that approximately 8.3 mg bilirubin is bound to each 1 g albumin(1). 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(2). Intensive phototherapy for severe hyperbilirubinemia may cause photo-oxidation of albumin, resulting in a decrease or disappearance of its binding affinity for bilirubin(3). Accordingly, albumin infusion therapy might be effective on unbound-bilirubin values in term neonates with intensive phototherapy(4). Exchange transfusion is indicated for severe jaundice when other therapeutic modalities have failed(5). The present study aims at investigating the effect of intravenous administration of human albumin prior to exchange transfusion on reduction of total serum bilirubin levels (TSB).

Accompanying Editorial: Pages 231-232.

METHODS

This randomized controlled study was conducted between February and July 2006 on 50 outborn neonates with jaundice admitted to the Neonatal Unit of Nemazee Hospital, affiliated with Shiraz University of Medical Sciences, southern Iran. Term neonates (gestational age more than 37 weeks) with birthweight >2500 g with TSB ≥25 mg/dL, requiring blood exchange due to intensive phototherapy failure and otherwise healthy, entered our study. "Healthy" was defined as an active neonate on oral feed with normal neurological findings and physiological vital parameters. We excluded neonates with hemolytic diseases (Rh or ABO incompatibility and a positive Coombs' test), infectious diseases (congenital or acquired), G6PD deficiency and direct hyperbilirubinemia (conjugated bilirubin >1.5 mg/dL and 10% of TSB). These parameters were checked prior to randomization.

Assuming the least expected difference to be 6 mg/dL between intervention and control groups and the standard deviation of 1.5, a two sided alpha of 0.05 and power of 0.9 ($\beta = 0.1$) with equal allocation, the estimated sample size would be 42 (21 neonates in each group). To avoid loss to follow up, we enroled 25 neonates in each group. Enroled neonates were randomized into intervention and control groups based on simple randomization. The random numbers were computer generated and slips bearing the allocated group were placed in serially numbered, opaque, sealed envelopes. The primary outcome was the TSB level at 6 and 12 hours post exchange. Secondary outcomes were the total duration of phototherapy, need for a second exchange transfusion and adverse effects (respiratory distress, edema, etc).

All neonates received intensive phototherapy using 8 special blue tube lamps (Philips TL 20 W/52) positioned within 15 to 20 cm of the patient's body. Irradiance was checked by a photoradiometer to maintained approximately 20 μw/nm/cm^2 at all times. Blood exchange transfusions were done for the above-mentioned neonates due to 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(6). Prior to the exchange, complete blood count, blood group typing of neonates and mothers, direct Coombs test, reticulocyte count, albumin and serum bilirubin levels (total and direct) were performed and all information regarding demographic data were recorded. Twenty five neonates in intervention group received intravenous 20% human albumin (Biotest, Germany) within one hour, with a dose of 1g/kg, one hour before exchange, while the control group only underwent a blood exchange. TSB was measured every 6 hours for both groups during the first 24 hours following the exchange using a Unistat® bilirubinometer (Reichert-Germany). All the infants were examined 2 days after discharge in outpatient clinic for further evaluation of their jaundice and any side effects of the drug.

***Statistical analysis*:** The data obtained were analyzed using SPSS software version 11.5 for Windows. Numerical variables were compared between the two groups by using the independent student's test. The Chi-square test was used to compare sex and route of delivery between the two groups. *P* values of less than 0.05 were considered as statistically significant.

Informed consent was obtained from the parents and the study protocol was approved by the University Ethical Committee.

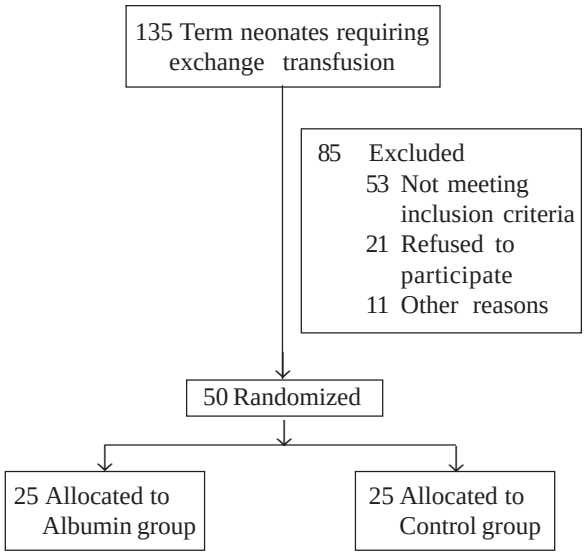

FIG. 1. *Study flow chart.*

RESULTS

Of 135 term neonates with TSB >25 mg/dL that received intensive phototherapy and required exchange transfusion, 50 infants who satisfied the eligibility criteria were enrolled in the study and were randomized (***Fig.*1**). Baseline demographic characteristics were comparable between the two groups (***Table* I**).

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 and 12 hours post exchange. Baseline albumin level and its level at 24 hours after exchange were compared and there was no significant difference between the mean of serum albumin levels in the two groups. No neonate in albumin-treated group required phototherapy after 12 hours, but 8 (32%), 13 (52%), and 4 neonates (16%) in the control group received phototherapy till 18, 24 and 36 hours post-exchange, respectively. The difference between the duration of phototherapy in albumin-treated group and the control group was statistically significant (P<0.001) ***(Table* II**).

On serial examination during hospitalization and two days after discharge in the outpatient clinic, no rise was observed in the TSB levels and no side effects were evident. None of the neonates in 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.

TABLE I DEMOGRAPHIC CHARACTERISTICS AND LABORATORY DATA OF PATIENTS AT ADMISSION

Parameters	Albumin group *mean* ± SD	Control group *mean* ± SD	*P value*
Gestation (wk)	39.3±1.2	39.5±1.5	0.6
Birthweight (g)	3239±585	3264±428	0.86
Cesarean section	7	8	0.75
Apgar at 1 min	8.6±1.2	8.8±1.3	0.57
Age (d)	7±1.1	8±1.0	0.001
Albumin (g/dL)	3.4±0.4	3.5±0.6	0.49
pH	7.40±0.04	7.41±0.05	0.43
TSB (mg/dL)	30±3.64	29±3.65	0.34
Direct bilirubin (mg/dL)	0.5±0.30	0.4±0.35	0.28
Sex (female) (%)	12 (48)	13 (52)	0.777

TABLE II OUTCOME IN THE TWO GROUPS

Variables	Albumin-treated group(n=25)	Control group (n=25)	*P value*
TSB levels after 6 h (mg/dL)	14.4 ± 1.7	21.7±3.2	<0.001
TSB levels after 12 h (mg/dL)	8 ± 1.5	16.1±2.1	<0.001
Albumin level at 24 h (g/dL)	3.5±0.5	3.4±0.3	0.39
Duration of phototherapy(h)	8.6±2.4	25±8.2	<0.001

**TSB: total serum bilirubin.*

DISCUSSION

Our results suggest that administration of albumin 20% (1 g/kg) to neonates one hour prior to the exchange transfusion increases the efficiency of bilirubin removal by shifting more tissue-bound bilirubin into the circulation and significantly reduces the post-exchange TSB level and the duration of phototherapy.

There have been insufficient studies to determine the effect of albumin infusion on TSB level along with a double volume blood exchange but there are some studies about albumin administration combined with phototherapy in the treatment of hyperbilirubinemia. Hosono, *et al*.(7) showed that albumin priming may be effective for an immediate reduction in serum unbound bilirubin values.

Albumin infusion prior to exchange transfusion decreases the unbound bilirubin in the intravascular space and due to equilibration between plasma bilirubin and extravascular space, more bilirubin would shift from tissue to plasma. Tsao and Yu(8) have reported that there was a marked increase in total intravascular bilirubin as well as plasma volume after priming with albumin. Therefore, more bilirubin would be removed through exchange transfusion leading to a decrease in total body bilirubin concentration. So, the rebound of plasma bilirubin in post-exchange would increase less in albumin-treated

WHAT IS ALREADY KNOWN?

- Treatment with albumin prior to exchange transfusion is not routinely recommended.

WHAT THIS STUDY ADDS?

- Albumin infusion prior to exchange transfusion in term neonates can effectively decrease the total serum bilirubin without any side effects.

group. The present study was not able to determine the unbound bilirubin level and its changes during the albumin infusion, because the measurement of free bilirubin level was not possible in the studied center. We selected otherwise healthy term neonates to reduce the risk of alterations in blood brain barrier permeability because theoretically, the transient increase in TSB concentration after albumin administration may increase the risk of kernicterus if the barrier is disrupted with some predisposing factors in sick neonates(6).

We also demonstrated that there was a significant difference in the reduction of TSB levels in albumin-treated group compared to the control group at 6 and 12 hours post-exchange ($P<0.001$). Also, the duration of phototherapy and the risk of second exchange transfusion were reduced in the former. There was no significant difference between the baseline albumin level and its level at 24 hours post-exchange in albumin-treated group and the same result was reported by Hosono, *et al.*(7). The unchanged albumin level may be due to the generated plasma oncotic pressure induced by albumin infusion that draws fluid out of the extravascular into vascular space and the dilution effect of the expanded plasma volume.

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