RESEARCH PAPER

Pre-exchange Albumin Administration in Neonates with Hyperbilirubinemia: *A Randomized Controlled Trial*

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Objective: To evaluate the efficacy of pre-exchange transfusion albumin priming in neonates with non-hemolytic hyperbilirubinemia.

Design: Single center, randomized controlled trial.

Setting: Level III Neonatal unit.

Participants: Fifty healthy term and late preterm neonates with non-hemolytic hyperbilirubinemia requiring exchange transfusion.

Interventions: 5 mL/kg of either 20% human albumin (*n*=23) or 0.9% saline (*n*=27) infusion one hour prior to exchange transfusion.

Main outcome measure: Post-exchange transfusion phototherapy duration.

Results: The post-exchange transfusion phototherapy duration was not different between albumin and saline groups [Median (IQR): 29 (24-48) h *vs*. 33 (24-43) h; *P*=0.76]. The total amount of bilirubin removed during exchange transfusion was also similar [Median (IQR): 34 (28-46) mg *vs*. 33 (27-38) mg; *P*=0.46]. Serial changes in total serum bilirubin following exchange transfusion and need for repeat exchange transfusion were comparable between the groups.

Conclusions: In healthy late preterm and term neonates with non-hemolytic hyperbilirubinemia, priming with 1 g/kg of 20% albumin prior to exchange transfusion is not superior to equi-volume 0.9% saline in reducing post- exchange transfusion phototherapy duration or amount of bilirubin mass removed.

Key words: *Exchange transfusion, Jaundice, Neonate, Phototherapy.* **(CTRI/2012/03/002530)**

Exchange transfusion (ET) is indicated in neonatal hyperbilirubinemia when other standard therapeutic modalities like phototherapy (PT) have failed and the risk of acute bilirubin encephalopathy is high [1]. The efficacy of ET depends on many factors such as initial total serum bilirubin (TSB), presence of hemolysis, volume, speed, route and method of ET, size of aliquots, and albumin concentration in infant's plasma and donor blood [2]. Albumin within intravascular space decreases the level of unbound bilirubin in plasma; to maintain equilibrium between intravascular and extravascular compartments, unbound tissue bilirubin moves into plasma, and may be removed during ET. By increasing albumin concentration in plasma, efficacy of ET may improve. Studies evaluating the efficacy of albumin for ET in terms of bilirubin removal and its clinical consequences have shown variable results [3-11]. We conducted this trial to evaluate the efficacy of pre-ET albumin priming in healthy term and late preterm neonates with significant non-hemolytic hyperbilirubinemia.

Methods

This randomized controlled trial was conducted in a tertiary care neonatal unit in Northern India between November 2011 and January 2013. Healthy (on oral feeds, neurologically normal and physiologically normal vital parameters) term and late preterm neonates who were to undergo ET for unconjugated hyperbilirubinemia as per the decision of the treating team were considered eligible for enrolment. Infants who were small for gestational age (SGA) or had evidence of acute bilirubin encephalopathy [12], hemolysis [13], congestive cardiac failure, hydrops, hematocrit <21% or major congenital malformations, were excluded. Enrolled infants were randomized into two groups based on a web-generated random number sequence [14]. Allocation was concealed in opaque, sealed envelopes which were kept with a person not involved in any other aspect of the study. Separate personnel, in a separate room away from patient care area, prepared the study drug. Blinding was ensured by using special black colored, completely opaque syringes (Original PerfusorSpritze – OPS 50 mL leur lock, B. Braun Germany) and brown colored opaque extension intravenous tubing (Lectrogaurd, Vygon, France) for loading and administration of study drugs. Neonates randomized to the albumin-primed group

received an infusion of 20% human albumin (Human Albumin 20%, Biotest Pharma, Germany) in a dose of 1 g/kg (5 mL/kg) over one hour prior to ET. Those randomized to control arm received 0.9% saline at 5 mL/kg over one hour prior to ET. Investigators, members of treating team and laboratory technicians remained masked to the intervention. After enrollment, blood samples were collected for determining TSB and serum albumin just prior to the start of the drug infusion. Study participants were closely monitored for adverse effects such as signs of fluid overload and anaphylactic reactions. All neonates received phototherapy as soon as hyperbilirubinemia was diagnosed and continued to receive phototherapy while study drug was being administered.

ET was followed immediately after the end of albumin/saline infusion. In the first aliquot of blood drawn from the infant, TSB, serum albumin and G6PD were measured. A double volume ET (160 mL/Kg) was done in all cases. The donor blood used for ET was collected not before five days of ET. During the process of ET, the blood drawn out (waste blood) was collected in a graduated conical glass flask. The flask was pre-heparinized by the addition of 2500 units of heparin before the start of the procedure. To further prevent clotting, a thin glass rod was kept inserted in the flask to intermittently stir the collected blood. The total volume of waste blood was measured and its hematocrit and TSB was determined. All infants were started on phototherapy and TSB was monitored immediately after the completion of the ET, and at 2, 6, 12, and 24 hours following ET. Double surface, standard–length Fluorescent Tube light (STL, 20W/52, Phillips India) system was used to provide phototherapy in both the groups. Before starting phototherapy, the irradiance was checked by a photoradiometer (Fluoro-lite 451®, Minolta/Air Shields, USA). An irradiance of at least 15 $\mu W/nm/cm^2$ was maintained at all times and lamps were replaced whenever necessary. The babies were placed as close as possible to light source. All attempts were made to ensure that maximum surface area of baby was exposed to the light source. Phototherapy was discontinued when 2 TSB values at least 4 hours apart were 2 mg/dL or more below the phototherapy threshold for that postnatal age [15]. American Academy of Pediatrics charts adapted as per the unit protocol were followed for phototherapy and ET thresholds in neonates ≥35 weeks gestation; for neonates <35 weeks, birthweight-based guidelines were used [15]. Infants in both the groups received intravenous fluid supplements at presentation, as per unit policy [16,17]. Written informed consent from one of the parents was obtained before enrolment. Institutional ethics committee approved the protocol.

Primary outcome was post-exchange duration of phototherapy. Total mass of bilirubin removed, need for repeat ET, change in TSB level immediately post-ET, and serial change in TSB levels at 2, 6, 12, 24 hrs post-ET were secondary outcomes. The post-exchange duration of phototherapy was calculated from the time of finishing ET to stopping phototherapy following ET. The total mass of bilirubin removed during ET (mg) was calculated by standard formula [8]. TSB was measured by direct spectrophotometry (Twin Beam Micro-bilimeter, Ginevri, Italy). Bromocresol purple (BCP) dye binding method [18] was utilized for measuring albumin in serum with Dimension clinical chemistry system [Siemens Dimension R_x L Max, Siemens Healthcare diagnostics. Atlanta, USA; CV=1.7%]. G6PD screen was done by Fluorescent spot test.

Sample size and statistical analysis: To detect a 25% decrease in post-ET phototherapy duration in albumin-priming group in comparison to non-priming group, with a two-tailed α of 0.05 and power of 80%, 21 infants per group were required to be enrolled. To account for attrition, it was decided to enroll a total of 50 infants**.** Data entry and analysis was done using statistical software packages IBM-SPSS v.20 (SPSS Inc. Chicago, IL, USA) and Microsoft Excel. Mann Whitney U test was applied for primary outcome, change in TSB level post-ET as compared to pre ET levels and total mass of bilirubin removed. Unpaired sample Student t test was applied for mass of bilirubin removed/kg body weight (birth weight). Serial changes in TSB level post-ET were compared using Repeated Measures ANOVA (analysis of variance). An Intention to Treat (ITT) analysis was done and a *P* value of <0.05 was considered significant.

RESULTS

Of the total 50 infants enrolled, ET was done in all, except one in albumin group, in whom TSB decreased below the exchange cut-off level following albumin infusion (***Fig.*1**). The baseline demographic characteristics and factors that could affect post-ET TSB levels were similar in both groups (***Table* I** and **II**).

Forty-seven (94%) infants received intravenous fluid supplementation prior to intervention as per unit protocol. Volume, rate and type of the supplemental fluid received were similar in both groups. Duration of post-ET phototherapy was similar in the two groups (***Fig.* 2, *Table* III**). Total mass of bilirubin removed, bilirubin removed per kg body weight (birth weight), need for repeat ET and fall in TSB immediate post-ET were all

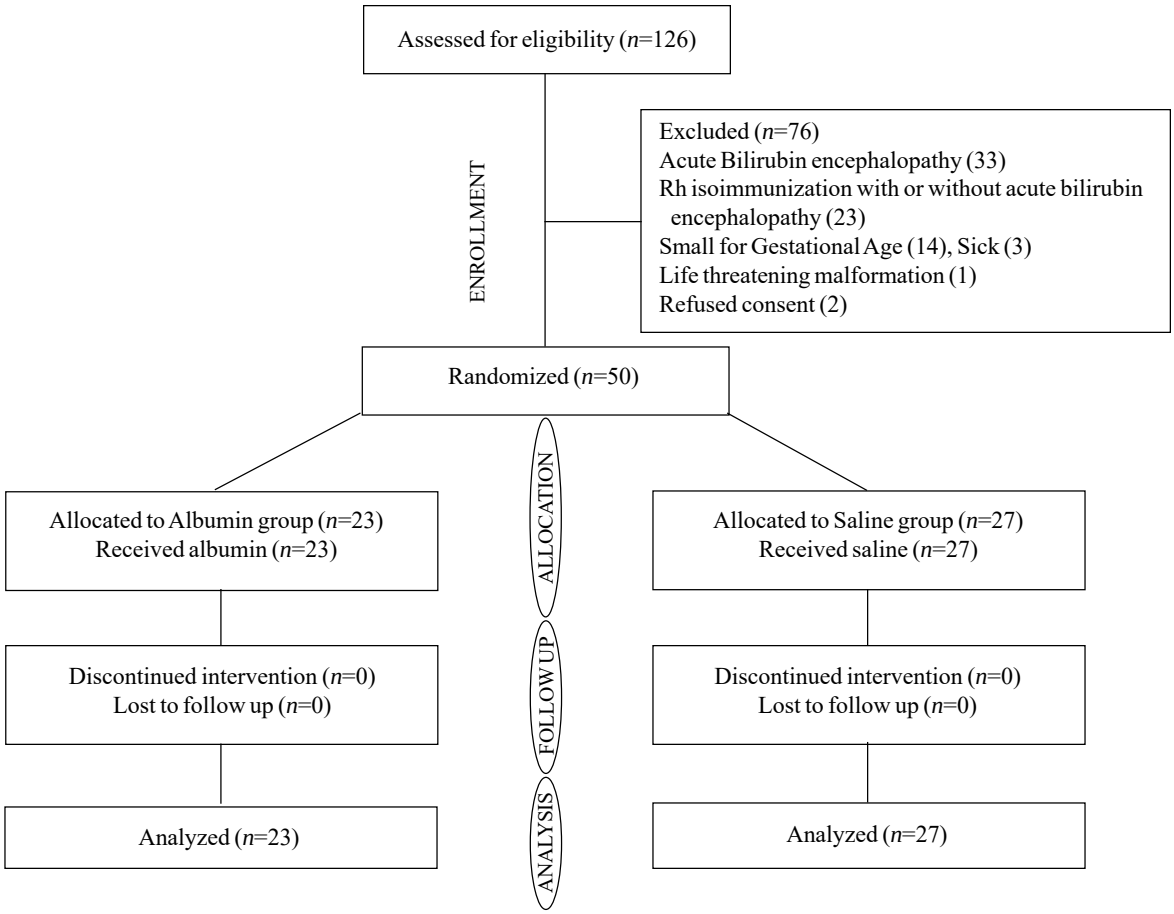

FIG.1 *CONSORT diagram of flow of patients in the trial.*

similar in both groups (***Table* III**). Serial change in TSB levels post-ET at different time intervals was not statistically different between both the groups (***Fig.* 3**). G6PD was found to be deficient in five donor blood samples (2 in albumin group and 3 in saline group). A subgroup analysis of these cases did not show any difference in primary outcome between study groups.

DISCUSSION

In this randomized controlled trial of pre-ET priming with 1 g/kg of 20% albumin in term and late preterm infants with non-hemolytic hyperbilirubinemia, we did not observe a significant reduction in the post-ET phototherapy duration or an increase in bilirubin removal following ET. The need for a second ET was not different between the groups.

Two important limitations in the current study are intravenous fluids supplementation in majority of the study subjects before intervention, and possibly lesser albumin dose for priming as the study neonates had relatively lower albumin levels at baseline. Intravenous fluid supplementation has been hypothesized to cause a faster drop in TSB levels due to the effects on volume expansion and glomerular filtration rate; infants in both the groups received IV fluids as part of the unit protocol based on previous published studies [16,17]. The effect of IV fluid supplementation on bilirubin albumin binding and movement of bilirubin across the capillaries, if any, is not known. Earlier studies with a beneficial effect of albumin priming had a higher baseline serum albumin level (3-3.5 g/dL), and a post-priming albumin level of >5g/dL [4,5,7,8]. A higher serum albumin level may provide more binding sites for bilirubin and might facilitate the diffusion of bilirubin into intravascular space better, but safety and efficacy of high doses need to be demonstrated in our population.

Few studies showed increased bilirubin removal following priming with 1g/kg of albumin 1-4 hours prior to ET as compared to simple ET [3-6], whereas others could not demonstrate a similar effect [7-10]. Shahian and Moslehi [4] demonstrated a significant reduction in mean TSB levels at 6 and 12 hours after ET as well as

TABLE I BASELINE DEMOGRAPHIC AND LABORATORY CHARACTERISTICS

Characteristics	*Albumin group (n=23)*	*Saline group (n=27)*
Gestational age (wk)	38.2 (1.5)	37.7 (1.7)
Gestational age 34 – 36 wk	3 (13)**	5 (19)**
≥ 37 wk	20 (87)	22 (81)
Birth weight (g)	2952 (382)	2926 (626)
Breastfeeding	22 (96)**	19 (70)**
Age of onset of jaundice (h)	88.2 (36.4)	83.2 (39.6)
Age at admission (h)	119.7 (59.3)	107.1 (42.1)
TSB at admission (mg/dL)	25.5 (3.6)	26.1 (4.4)
Pre–ET PT duration (h)	19 (12, 27)*	20 (12, 26)*
TSB prior to ET (mg/dL)	25.6 (3.6)	24.8 (3.9)
G6PD deficient	9 (39)**	8 (30)**
Serum albumin (g/dL)	2.8 (0.4)	2.8 (0.5)
Bilirubin: Albumin ratio[#]	9.1 (1.9)	9.0 (1.5)
Baseline hematocrit (%)	46 (7.9)	50 (6.5)

*TSB: total serum bilirubin, ET: exchange transfusion, G6PD: glucose 6 phosphate dehydrogenase, PT: phototherapy. All values in mean (SD) except *Median (IQR), **number (%); [#]in mg: g per dL.*

TABLE II EFFECT OF PRE-EXCHANGE TRANSFUSION FLUID INFUSION ON SERUM BILIRUBIN AND ALBUMIN LEVELS

Characteristics	*Albumin group (N=23)*	*Saline group (N=27)*	*P*
Postinfusion TSB (mg/dL)	24.2(4.8)	22.5 (3.9)	0.16
Change in TSB (mg/dL).	-1.4(-3.3, 0.7)[#]	-2.3 (1.2, 3.4)[#]	0.36
Post- infusion serum albumin (g/dL)	3.4 (0.6)	2.7 (0.4)	<0.001
End of drug infusion to ET interval (min)	40 (20, 60)*	30 (15, 60)*	0.32
Post – ET hematocrit (%)	49 (4)	48 (4)	0.57

*ET: blood exchange transfusion, TSB: total serum bilirubin. Values in Mean (SD), *Median (IQR) or* [#]mean difference (95% CI)

duration of phototherapy in the albumin priming group in comparison to the control group. The mechanism underlying the benefit was not reported in their study as well as by a similar study in low birth weight infants [3], as the amount of bilirubin removed was not measured in both the studies. Apart from its bilirubin binding properties, albumin infusion also causes volume expansion [7], which could independently lead to a reduction in the bilirubin levels after administration. To prove the hypothesis that albumin priming would increase the bilirubin removal through its bilirubin-binding properties, the confounding effect of the volume expansion property of albumin infusion has to be counter-balanced by using a mother fluid. Most previous studies did not use any comparator fluid in control group, or used fluid with a much lower sodium content [3].

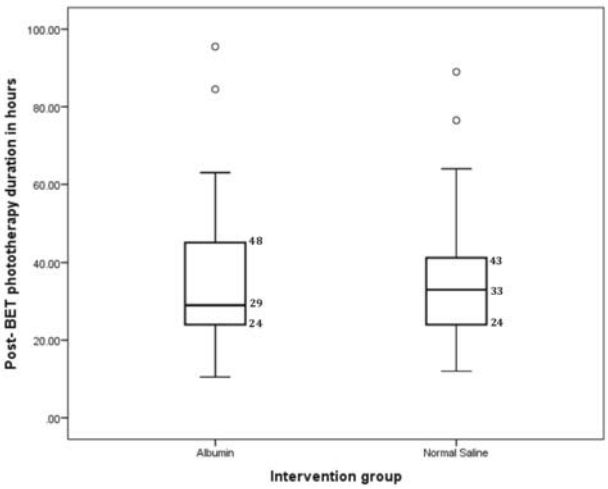

FIG. 2 *Box and Whisker plot of post exchange transfusion phototherapy duration.*

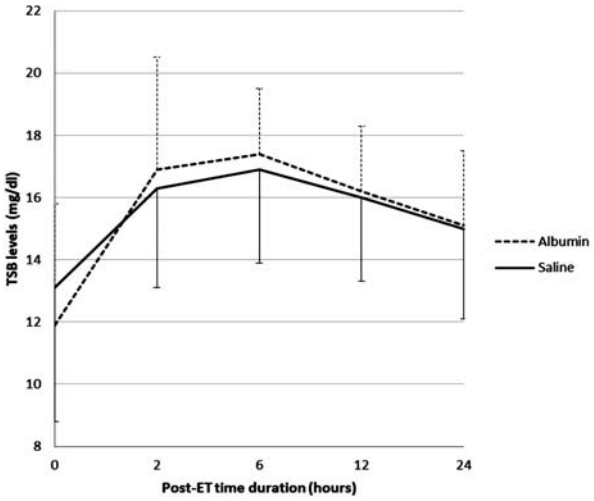

FIG. 3 *Serial changes in total serum bilirubin level following exchange transfusion.*

We conclude that priming with 1 g/kg of 20% human albumin in comparison to equi-volume 0.9% saline does not result in an increase in efficacy of exchange transfusion in healthy term and late preterm infants with significant non-hemolytic hyperbilirubinemia. Future studies should evaluate larger doses of albumin, and the effect of this intervention in hyperbilirubinemia associated with hemolysis.

WHAT IS ALREADY KNOWN?

- Albumin binds to intravascular bilirubin and helps draw bilirubin from extra- to intra-vascular space.,

WHAT THIS STUDY ADDS?

- Albumin priming before exchange transfusion does not increase its efficacy in comparison to priming with equal volume of 0.9% saline.

TABLE III COMPARISON OF OUTCOME BETWEEN INTERVENTION AND CONTROL GROUPS

Characteristics	*Albumin group; n=23*	*Saline group; n=27*	*P*
Duration of post-ET phototheraphy (h)	29 (24, 48)*	33 (24, 43)*	0.76
Total mass of bilirubin removed during ET (mg)	34 (28-46)*	33 (27-38)*	0.46
Bilirubin removed/kg birth weight (mg/kg)	12.5 (3.6)	12.1 (3.4)	0.69
TSB at the end of ET (mg/dL)	11.9 (3.9)	13.1 (4.3)	0.31
Maximum TSB post- ET (mg/dL)	18.5 (2.8)	17.9 (2.9)	0.50
Hours post- ET maximum TSB	6 (2-12)*	6 (2-12)*	0.50
Need for second ET	2 (9)#	2 (7.5)#	1.00

*ET:exchange transfusion, TSB: total serum bilirubin. All values are represented as mean (SD) except *Median (IQR)and # number (%).*

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