Brief Report

Pre-exchange 5% Albumin Infusion in Low Birth Weight Neonates with Intensive Phototherapy Failure—A Randomized Controlled Trial

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Summary

Objective: To evaluate the role of 5% albumin infusion before exchange transfusion in reducing post-exchange unconjugated serum bilirubin (UCB) levels in low birth weight (LBW) neonates with intensive phototherapy failure.

Methods: In a placebo-controlled Randomized Controlled Trial, 42 healthy LBW (birth weight between 1000 and 2499 g and gestational age ≥ 32 weeks) neonates were randomly allocated into intervention and control groups. Post-exchange UCB at 6 and 12 h were compared in the two groups along with the duration of post-exchange phototherapy, repeat-exchange requirement, adverse effects of albumin and hospital stay.

Results: The intervention group (n = 21) with mean birth weight 1619 ± 324 g, gestational age 34.5 ± 1.65 weeks, peak UCB 19 ± 3.85 mg dl⁻¹, was demographically comparable with the control group (n = 21) (1660 ± 320 g, 34 ± 1.6 weeks, 19.4 ± 3.59 mg dl⁻¹, respectively). Significant reduction in the post-exchange UCB (10.55 ± 1.53 mg dl⁻¹ at 6 h; 5.86 ± 1.21 mg dl⁻¹ at 12 h in albumin group; 15.26 ± 1.78 mg dl⁻¹ at 6 h; 11.69 ± 1.52 mg dl⁻¹ at 12 h in control group) and phototherapy duration (23.8 ± 3.2 h vs. 40.3 ± 7.2 h) was observed in the intervention group (p < 0.0001). Repeat exchange requirement was reduced by 86% (RR = 0.14; 95%CI: 0.19–1.06). Mean duration of hospital stay was significantly lower (10.1 ± 5.8 days vs. 12.4 ± 6.6 days) (p = 0.021). No albumin transfusion-related complications were observed.

Key words: 5% albumin, exchange transfusion, low birth weight, intensive phototherapy, hyperbilirubinemia.

Introduction

Neonatal hyperbilirubinemia is one of the commonest abnormal findings in the early neonatal period. The prevalence of neonatal jaundice has been documented to be ~50–60% in term and 80% in preterm neonates [1]. With increased survival of preterm infants, there has been a resurgence of hyperbilirubinemia as a very common secondary complication, which are especially difficult to manage with standard phototherapy due to the increased risk of bilirubin encephalopathy at lower serum bilirubin levels [2]. Exchange transfusion is then indicated in these situations when other therapeutic modalities have failed [3].

Albumin infusion has long been used as an adjunct to phototherapy or prior to exchange transfusion to

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improve the outcome in the management of neonatal hyperbilirubinemia. Significant reduction in post-exchange bilirubin in term neonates following priming with 20% albumin has been shown by Shahian et al. [4]. Studies by Hosono et al. [5], Tomoaki et al. [6] and Wood et al. [7] have similarly shown favourable results. On the contrary, Chan and Schiff have reported no significant difference in the efficiency of bilirubin removal following albumin loading prior to exchange transfusion [8]. While most of these studies have been carried out in term healthy neonates using 20% albumin, little is known about the efficacy of this intervention in preterm low birth weight (LBW) neonates. A Cochrane Database review on albumin infusion in preterm neonates in 2007 also revealed dearth of sufficient evidence to assess whether albumin infusion is associated with significant side effects [9].

During exchange transfusion, 5% albumin has been successfully used by Kitchen et al. [10] as partial substitution for the whole blood. During partial exchange transfusion in the management of neonatal polycythaemia [11], 5% albumin has also been used without documented side effects.

Taking these facts into consideration, we carried out this study to evaluate the role of 5% albumin infusion prior to exchange transfusion in reducing the unconjugated serum bilirubin levels in LBW neonates suffering from neonatal hyperbilirubinemia with intensive phototherapy failure.

Methods
Design
We performed a placebo-controlled randomized controlled trial in the Neonatal Intensive Care Unit of the study institution between July 2008 and September 2009. Ethical clearance was obtained from the Institutional Ethics Committee and all procedures were in accordance with the ethical standards of the committee and with the Helsinki’s declaration in 1975 as revised in 1983. Written informed consent was obtained from the parents of the neonates meeting our inclusion criteria during the study period.

Subjects
Neonates with a birth weight between 1000 and 2499 g requiring exchange transfusion due to intensive phototherapy failure were enrolled for our study. We excluded neonates with a gestational age <32 weeks, documented haemolytic disease of the newborn, severe birth asphyxia (hypoxic ischaemic encephalopathy Grades II and III), Glucose-6-Phosphate Dehydrogenase (G-6PD) deficiency and direct hyperbilirubinemia (>1.5 mg/dl% and 20% of total serum bilirubin).

Based on previous similar studies, assuming the least expected difference in post-exchange serum bilirubin levels between the intervention and control group to be 7 mg/dl% with a standard deviation of 2, a two-sided α of 0.05 and a power of 0.99 (β = 0.01) with equal allocation, the estimated sample size would be 10 (five in each group) [4]. Expecting more subtle differences in the mean and to avoid loss to various reasons including procedure-related complications, we enrolled 42 neonates during the study period. Enrolled neonates were randomized into intervention (n = 21) and control (n = 21) groups. Randomization was done using statistical software and slips containing the allocated group were placed in serially numbered sealed envelopes.

The primary outcome measures were post-exchange UCB levels at 6 and 12 h and the total duration of post-exchange phototherapy in the two groups. We also evaluated the need for repeat exchange transfusion, any adverse effects of albumin infusion and the duration of hospital stay.

Procedure
All neonates were subjected to intensive phototherapy based on their total serum bilirubin levels as per the standard guidelines for the management of hyperbilirubinemia in LBW neonates [12]. Intensive phototherapy was given using eight special blue lamps (Philips TL 20 W/52) positioned within 20 cm of the neonates body [4]. Irradiance of the phototherapy unit at the level of the skin of abdomen of the neonate was monitored once daily using standard flux meter (Ginevri, Rome, Italy) sensitive to wavelengths of 425–475 nm. The tubes were replaced during the study period when the irradiance fell below 15 μW cm⁻² nm⁻¹ [13]. Intensive phototherapy failure was defined as the inability to produce a decline of 1–2 mg dl⁻¹ within 4 h after the initiation of phototherapy [12].

Prior to exchange transfusion, we performed a single blood culture using BACTEC blood culture system and septic screen including total leucocyte count, absolute neutrophil count, immature to total neutrophil ratio, micro ESR and C-reactive protein. The haemoglobin percentage, reticulocyte counts, Direct Coombs Test, ABO and Rhesus (Rh) blood group if the mother is of O blood group or is Rh negative, G-6PD level, serum albumin and serum bilirubin levels were also evaluated. Total serum bilirubin(TSB) and its unconjugated fraction were measured in the biochemistry laboratory using modified Jendrassik and Grof’s method (Lifechem™) [14]. Sepsis was defined as a positive blood culture or two or more abnormal sepsis screen parameters [15]. Severe birth asphyxia was ruled out using the Sarnat staging system [16].

The neonates in the intervention group received infusion of 5% albumin solution (AlbuRel™) over 2 h in a dose of 1 kg⁻¹, 2 h prior to exchange transfusion. Five percent albumin is a sterile solution.
of pooled human protein separated from plasma by cold-alcohol fractionation process and stabilized with 0.004 M sodium caprylate and 0.004 M acetyl tryptophan. It has a sodium content of 130–160 meq l\(^{-1}\) and a potassium content of 2 meq l\(^{-1}\) [17]. The neonates in the control group received maintenance intravenous fluid at 20 ml kg\(^{-1}\) over the same duration of 2 h. Double volume exchange transfusion was then performed in both the groups using fresh blood, obtained within 72 h of collection. Following the procedure, all neonates were subsequently put on phototherapy. Serum total and unconjugated bilirubin levels were measured every 6 h in the both the groups in the first 24 h. Phototherapy was discontinued when TSB level was 2 mg dl\(^{-1}\) below the recommendation for phototherapy requirement for that age [13]. The total duration of intravenous fluids, mean age of starting enteral feeds and time required to achieve full enteral feeds were recorded in both groups. The total duration of post-exchange phototherapy, duration of hospital stay and need for repeat exchange transfusion were recorded.

The neonates were clinically evaluated for evidence of patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC) and pulmonary oedema by two senior paediatricians separately. Inter-observer variations in assessment of severity of birth asphyxia and albumin infusion related complications were assessed using \(k\)-statistics. Excellent inter-observer agreement was noted for all the parameters evaluated (\(k\) ratios being 0.78 for modified Sarnat staging and 0.83 for evaluation of albumin infusion related complications).

**Statistical Analysis**

Data was analysed using SPSS version 17.0 statistical software. Unpaired Student \(t\)-test was applied for analysis of all quantitative data sets. Fischer’s exact test was used to compare sex, mode of delivery and need for a repeat exchange between the two groups. A \(p\)-value of <0.05 was considered statistically significant.

**Results**

During the study period, 183 LBW neonates received intensive phototherapy and required exchange transfusion. Among them 42 neonates who satisfied the eligibility criteria were enrolled and randomized (Fig. 1). All baseline demographic variables including data on additional interventions were found to be comparable between the groups \((p > 0.05)\) (Table 1).

Following exchange transfusion, the unconjugated bilirubin levels in the albumin-treated group \((10.55 \pm 1.53 \text{ mg} \text{ dl}^{-1} \text{ at } 6 \text{ h}; 5.86 \pm 1.21 \text{ mg} \text{ dl}^{-1} \text{ at } 12 \text{ h})\) were found to be significantly lower than their respective levels in the control group \((15.26 \pm 1.78 \text{ mg} \text{ dl}^{-1} \text{ at } 6 \text{ h}; 11.69 \pm 1.52 \text{ mg} \text{ dl}^{-1} \text{ at } 12 \text{ h})\) both at 6 as well as at 12 h post-exchange \((p < 0.0001)\). The mean difference in serum UCB concentrations between the albumin-treated group and the control group were found to be \(-4.705\) (95% CI: \(-3.666\) to \(-5.743\)) at 6 h and \(-5.830\) (95% CI: \(-7.125\) to \(-4.535\)) at 12 h post-exchange. The total duration of post-exchange phototherapy was also significantly reduced in the intervention group \((p < 0.0001)\). Seven out of the control group neonates required a repeat exchange transfusion compared with only one in the intervention group \([p = 0.045; \text{Relative Risk (RR) = 0.14; 95\% CI: 0.02–1.06}]\). There was a 18.5% reduction in the mean hospital stay in the intervention group \((12.4 \pm 6.6\text{ days})\) compared with the control group \((10.1 \pm 5.8\text{ days})\) which was statistically significant \((p = 0.021)\) (Table 2).

No adverse effects of albumin infusion were noted in any of the neonates in the intervention group.

**TABLE 1**

Demographic characteristics and additional intervention profile of enrolled neonates

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Intervention group ((n = 21))</th>
<th>Control group ((n = 21))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>34.5 ± 1.65</td>
<td>34 ± 1.6</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1619 ± 324</td>
<td>1660 ± 320</td>
</tr>
<tr>
<td>Serum UCB (mg dl(^{-1}))</td>
<td>19 ± 3.85</td>
<td>19.4 ± 3.59</td>
</tr>
<tr>
<td>Age at exchange (days)</td>
<td>6.23 ± 1.6</td>
<td>6.67 ± 1.43</td>
</tr>
<tr>
<td>Sex (male) (%)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Serum albumin (g dl(^{-1}))</td>
<td>2.69 ± 0.43</td>
<td>2.68 ± 0.44</td>
</tr>
<tr>
<td><strong>Additional interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV fluids (days)</td>
<td>4.2 ± 1.9</td>
<td>3.8 ± 1.8</td>
</tr>
<tr>
<td>Enteral feeds start (days)</td>
<td>2 ± 0.8</td>
<td>2.3 ± 1.2</td>
</tr>
<tr>
<td>Full enteral feeds (days)</td>
<td>4.8 ± 2.3</td>
<td>4.2 ± 1.6</td>
</tr>
</tbody>
</table>

UCB, Unconjugated bilirubin.
transfusion (RR = 0.14). Most importantly, this intervention reduced the duration of hospital stay of the albumin-treated neonates by 18.5% which is of prime importance in this overburdened health care system of the developing countries.

Jaundice in preterm LBW neonates is one of the commonest causes of prolongation of hospital stay in the neonatal units. Data obtained from the Medical Records department of our institution revealed that hyperbilirubinemia accounted for an average 38.2% (32.3–44.2%) of LBW neonates admitted to the neonatal unit from June 2008 to June 2009. A retrospective analysis of the effectiveness of exchange transfusion in LBW neonates over the same period revealed that a significantly more number of repeat exchange transfusions were required in the LBW neonates when compared to their normal birth weight counterparts \((p = 0.028); \text{Odds Ratio} = 1.43, 95\% \text{CI: 1.04–1.97})\). There was also a significantly prolonged duration of post-exchange phototherapy in the LBW neonates during this period \((p = 0.0023)\). These statistics emphasized the need to evaluate newer means to improve the outcome of exchange transfusion in LBW neonates.

The use of albumin in neonatal jaundice is based on the physiological fact that 1 g of albumin binds 8.3 mg of unconjugated bilirubin, which is then transported to the liver for conjugation and excretion [18]. Wood et al. have reported that intensive phototherapy for severe hyperbilirubinemia causes photo-oxidation of albumin thus resulting in decrease or disappearance of its binding affinity for bilirubin [7]. Thus if the albumin reserve is increased, more binding sites will be provided for the unconjugated bilirubin thereby reducing the levels of unbound bilirubin which ultimately reduces the risk of central nervous system toxicity [19]. It has been shown that there is marked increase in total intravascular bilirubin after priming with albumin due to equilibration between plasma bilirubin and extravascular space [20, 21]. Thus if infused prior to exchange transfusion, it would result in more efficient removal of intravascular bilirubin and a consequent reduction in total body bilirubin concentration and a lower rebound increase in post-exchange bilirubin [22].

Most of these studies have been carried out in term neonates using 20% albumin solution. Possible complications of albumin infusion in preterm LBW neonates like PDA, NEC and pulmonary oedema have been documented in literature [23, 24]. With these facts in view, 5% albumin was used in our study with a prolonged duration of infusion over 2 h to minimize the risk of any adverse events. With these precautions, no adverse effects were reported in any of the albumin-treated neonates in our study.

However, our study was limited by the fact that the unbound fraction of serum bilirubin prior to and following the intervention and the actual amount of bilirubin removed during the procedure and was not documented. Hence in spite of the positive results of our study our hypothesis could not be directly evaluated. Estimation of the unbound fraction of bilirubin was important since it has been shown by Ebbstein et al. [25] that infusion of 9% albumin in LBW neonates increases the non-binding fraction of serum albumin and the concentration of bilirubin-albumin ratio remains unchanged.

During exchange transfusion, extravascular bilirubin moves into the vascular compartment and thus the effect of the procedure on post-exchange TSB depends on both the pre-exchange extravascular and vascular bilirubin levels [26]. Significant variation exists in the vascular bilirubin–albumin relation thus confounding the relation between TSB and extravascular bilirubin levels [27]. Thus, in spite of similar pre-exchange unconjugated bilirubin levels in the two groups \((p = 0.733)\), there could be variations in the extravascular bilirubin levels which could have affected the final outcome [28].

To conclude, 5% albumin infusion prior to exchange transfusion was found to significantly reduce the post-exchange bilirubin levels and phototherapy requirement in our study. But in view of the variable results documented in world literature, use of pre-exchange albumin infusion should be accompanied by estimation of the amount of bilirubin removed and the levels of unbound bilirubin fraction pre- and post-exchange to evidently document the efficacy of this intervention in practice.

### Table 2
Comparison of post-exchange outcome variables in the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group ((n = 21))</th>
<th>Control group ((n = 21))</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCB at 6 h* (mg dl(^{-1}))</td>
<td>10.55 ± 1.53</td>
<td>15.26 ± 1.78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>UCB AT 12 h* (mg dl(^{-1}))</td>
<td>5.86 ± 1.21</td>
<td>11.69 ± 1.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of post-exchange phototherapy* (h)</td>
<td>23.8 ± 3.2</td>
<td>40.3 ± 7.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Repeat exchange** requirement</td>
<td>1</td>
<td>7</td>
<td>0.045</td>
</tr>
<tr>
<td>Hospital stay* (days)</td>
<td>10.1 ± 5.8</td>
<td>12.4 ± 6.6</td>
<td>0.021</td>
</tr>
</tbody>
</table>

UCB, Unconjugated bilirubin.

*Student’s \(t\)-test used.

**Fischer’s exact test used.

### Discussion

The results of our study showed that pre-exchange 5% albumin infusion in LBW neonates was significantly effective in reducing the post-exchange unconjugated bilirubin levels and the duration of post-exchange phototherapy. There was an 86% reduction in the requirement of repeat exchange transfusion \((RR = 0.14)\). Most importantly, this intervention reduced the duration of hospital stay of the albumin-treated neonates by 18.5% which is of prime importance in this overburdened health care system of the developing countries.

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To conclude, 5% albumin infusion prior to exchange transfusion was found to significantly reduce the post-exchange bilirubin levels and phototherapy requirement in our study. But in view of the variable results documented in world literature, use of pre-exchange albumin infusion should be accompanied by estimation of the amount of bilirubin removed and the levels of unbound bilirubin fraction pre- and post-exchange to evidently document the efficacy of this intervention in practice.
Furthermore, most of the studies in this field having been carried out in term neonates with 20% albumin solution, there is a dearth of clinical experience with the use of 5% albumin in preterm LBW neonates. Thus further randomized trials exploring the efficacy of pre-exchange 5% albumin in jaundiced LBW neonates need to be carried out to develop a consensus statement on this issue.

References