A RANDOMIZED CONTROLLED TRIAL OF FLUID SUPPLEMENTATION IN TERM NEONATES WITH SEVERE HYPERBILIRUBINEMIA

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Objective To evaluate the effectiveness of fluid supplementation in decreasing the rate of exchange transfusion and the duration of phototherapy in term neonates with severe nonhemolytic hyperbilirubinemia.

Study design This was a randomized controlled trial conducted in a tertiary care referral unit in northern India. Seventy-four term neonates with severe nonhemolytic hyperbilirubinemia (total serum bilirubin > 18 mg/dL [308 μmol/L] to < 25 mg/dL [427 μmol/L]). The subjects were randomized to an "extra fluids" group (intravenous fluid supplementation for 8 hours and oral supplementation for the duration of phototherapy; n = 37) or a control group (n = 37).

Results At inclusion, 54 infants (73%) had high serum osmolality, including 28 (75%) in the extra fluids group and 26 (70%) in the control group. The proportion of infants who underwent exchange transfusion was lower in the extra fluids group than in the control group: 6 (16%) versus 20 (54%)(P = .001; relative risk = 0.30; 95% confidence interval = 0.14 to 0.66). The duration of phototherapy was also shorter in the extra fluids group: 52 ± 18 hours versus 73 ± 31 hours (P = .004).

Conclusion Fluid supplementation in term neonates presenting with severe hyperbilirubinemia decreased the rate of exchange transfusion and duration of phototherapy. *(J Pediatr 2005;147:781-5)*

Seasonal variations in the incidence of hyperbilirubinemia have been observed, with an increase in the summer months.[1,2] Subclinical dehydration due to evaporative losses and poor intake of breast milk can lead to an increased incidence and severity of jaundice in newborns. Fluid supplementation may play a role in treating extreme hyperbilirubinemia while arrangements are being made for exchange transfusion. However, very little information is available on the effects of providing extra fluids to infants presenting with severe jaundice.[3] This randomized controlled trial was conducted to determine whether fluid supplementation given to term neonates presenting with severe hyperbilirubinemia can decrease the need for exchange transfusion and phototherapy.

METHODS

This study was carried out in a tertiary care referral neonatal unit in northern India over a 10-month period (September 2003 to June 2004). Term (≥37 weeks gestation) neonates presenting with severe nonhemolytic hyperbilirubinemia (total serum bilirubin [TSB] >18 mg/dL [308 μmol/L]) were eligible for enrollment. Infants with TSB > 25 mg/dL (427 μmol/L), acute bilirubin encephalopathy (kernicterus), evidence of hemolysis, obvious signs of dehydration (ie, sunken fontanel, reduced skin turgor, dry mucosa, tachycardia, delayed capillary refill, excessive weight loss), or major congenital malformations, as well as infants already receiving intravenous (IV) fluids for any reason, were excluded. Hemolysis was diagnosed if direct Coombs test was positive, peripheral blood smear demonstrated evidence of hemolysis, or reticulocyte count was > 6%.[4]

A bedside physician assessed hydration status independently based on the parameters mentioned earlier. At the time of evaluation, samples were obtained for tests of serum and urine osmolality, serum sodium, base deficit, and urine specific gravity.

Assignment to the various groups was based on stratified block randomization with variable block size. We used serially numbered opaque brown envelopes that were opened

AAP	American Academy of Pediatrics	IV	Intravenous
ANOVA	Analysis of variance	TSB	Total serum bilirubin

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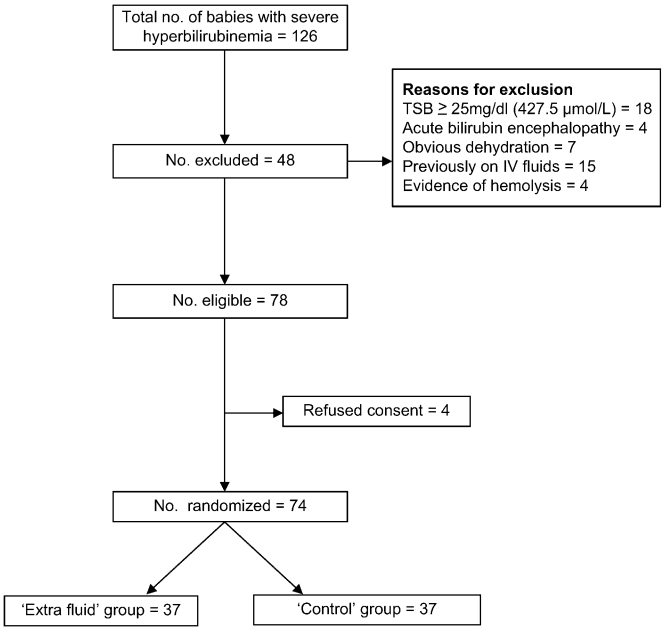

Figure. Flow of patients in the study.

after enrollment. The strata were TSB ≥ 18 mg/dL (308 μmol/L) to < 20 mg/dL (342 μmol/L) and TSB ≥ 20 mg/dL (342 μmol/L) to < 25 mg/dL (427 μmol/L) at enrollment.

The study group (ie, the extra fluids group) was given IV fluid supplementation with N/5 saline in 5% dextrose for a period of 8 hours. The volume of supplement included a presumed deficit of 50 mL/kg (equivalent to mild dehydration); half of daily maintenance requirements for an 8-hour period, in accordance with standard norms; and an extra 20 mL/kg/day as a phototherapy allowance. In addition, the infant was allowed breast/formula feeds as given before entry into the study. At the end of the 8-hour period, hydration status was reassessed and IV fluids were discontinued. Subsequently, the infant was continued on breast/formula feeds as before and offered 30 mL/kg/day of extra oral feeds (expressed breast milk or formula) until the discontinuation of phototherapy. The control group was continued on breast/formula feeds ad lib or as given before the randomization procedure. In both the study and control groups, prefeed and postfeed test weighing was done during the first 8 hours of the study period and once every 24 hours thereafter, to estimate the volume of breast milk intake.

The following clinical and laboratory variables were monitored: (1) TSB at the start of the study period and then at 4 hours, 8 hours, and 12 hours by a dual-wavelength spectrophotometer (Ginevri, Italy); (2) clinical signs of bilirubin encephalopathy every 4 hours until TSB was consistently < 20 mg/dL (342 μmol/L); (3) hydration state at the start of the study, at the end of IV infusion (8 hours), and every 24 hours thereafter; (4) laboratory assessment of hydration (serum sodium, base deficit, and urine specific gravity) at 8 and 24 hours; and (5) feeding details, fluid intake, urine and stool frequency, and daily body weight.

All infants received special blue light phototherapy (Philips TL52, 20W; Philips, The Netherlands). The irradiance to the infant was recorded daily using a flux meter (Minolta, Germany). Phototherapy was discontinued when 2 TSB values obtained 12 hours apart were < 15 mg/dL (256 μmol/L). Exchange transfusion was done if at 4 hours into the study period, TSB increased by > 2 mg/dL (34 μmol/L) over the value at the start of the study, or if at 8 hours into the study period, TSB remained ≥ 20 mg/dL (342 μmol/L).

The primary outcome was the number of infants receiving exchange transfusion. Duration of phototherapy and percentage drop in TSB at 4, 8, and 24 hours of the study were secondary outcomes.

In the control group, 75% of the infants were expected to undergo exchange transfusion (PGIMER, personal communication). To detect a 50% difference in the need for exchange transfusion with 95% confidence ($\alpha = 0.05$) and 80% power ($\beta = 0.2$), 62 infants (31 in each group) were needed. Assuming an attrition rate of 20%, 74 infants were enrolled (37 in each group).

Proportions were compared using the χ^2 test; means, by an unpaired Student *t*-test. Analysis of variance (ANOVA) was used to compare serial changes in breast-feeding frequency, volume, fluid intake, and lab values over the study period. A post hoc analysis was planned according to serum osmolality levels to check whether fluid supplementation was useful in any particular subgroup.

Infants with obvious signs of dehydration were excluded from the study and were given fluids in accordance with their individual requirements. Written informed consent from a parent was obtained for all infants enrolled in the study. The institutional ethics committee approved the study protocol.

RESULTS

During the study period, 126 term infants with severe hyperbilirubinemia were admitted. Of these, 74 infants were randomized after exclusions based on the predefined criteria (Figure) (extra fluids group, n = 37; control group, n = 37).

The demographic variables and other factors that could affect TSB were distributed evenly between the extra fluids group and the control group (Table I). The age of onset of jaundice (3.3 ± 0.6 vs 3.1 ± 0.8 days) and the age at entry into the study (5.3 ± 1.2 vs 5.5 ± 1.4 days) were similar in the 2 groups.

On day 1 of the study, infants in the extra fluids group received 208 ± 34 mL/kg total fluids (including 71 ± 11 mL/kg of IV fluids), compared with 116 ± 32 mL/kg for the control group. The extra fluids group received 172 ± 29 mL/kg of fluids on study day 2, 165 ± 36 mL/kg on day 3, and 179 ± 30 mL/kg on day 4; the control group received 129 ± 34 mL/kg on day 2, 122 ± 31 mL/kg on day 3, and 125 ± 37 mL/kg on day 4 ($P < .05$). At the beginning of the study, mean serum osmolality was high but similar in the 2 groups (Table II). The cumulative weight loss at presentation was also similar in the 2 groups (Table I); only 1 infant (in the extra fluids group)