Effect of intravenous fluid supplementation in healthy term neonates with non-hemolytic hyperbilirubinemia: A randomized controlled trial

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ABSTRACT

Objective: The objective of this study was to evaluate the effect of intravenous fluid supplementation in healthy term neonates with non-hemolytic hyperbilirubinemia receiving phototherapy. **Study Design:** Randomized controlled trial conducted in a tertiary level neonatal care unit of a teaching institute in North Karnataka. **Methods:** A total of 60 healthy term neonates with non-hemolytic hyperbilirubinemia (total serum bilirubin [TSB] >15 mg/dL [256 µmol/L]–<25 mg/dL [428 µmol/L]) were randomized to two groups. Group I (case group, n=30) received 1/3rd the maintenance intravenous fluid in addition to breastfeeding and phototherapy. Group II (control group, n=30) received only breastfeeding and phototherapy. The duration of phototherapy and rate of fall of bilirubin was compared. **Results:** Both the groups were comparable with respect to mean birth weight, gestational age, gender, mode of delivery, age at admission, admission weight, percentage of weight loss at admission, and TSB at inclusion. There was a significant difference in the duration of phototherapy between the two groups (mean [standard deviation (SD)] Group I, 39.6 [7.8] h and Group II, 45.2 [10.22] h, $p<0.05$). Percentage of fall in bilirubin was not significant at 4, 12, 48, and 60 h but was significant at 24 and 36 h. **Conclusion:** Intravenous fluid supplementation in healthy breastfed term neonates with non-hemolytic hyperbilirubinemia significantly reduces the duration of phototherapy.

Key words: *Bilirubin, Breastfed, Duration, Phototherapy*

Phototherapy is a standard treatment for neonatal jaundice. Its relative freedom from complications together with its non-invasive nature, ease of usage, and convenience has resulted in widespread acceptance in virtually all neonatal units [1]. The increase in the amount of body water loss through insensible transepidermal loss due to phototherapy along with stool water loss is commonly seen in newborn suffering from jaundice [2]. Some infants with high bilirubin level are mildly dehydrated and may need supplemental fluid to correct their dehydration. Furthermore, the photoproducts responsible for the decline in serum bilirubin are excreted in urine and bile. Hence, maintaining adequate hydration and good urine output help to improve the efficacy of phototherapy [3]. Studies done on fluid supplementation on term neonates have shown variable results [2,4,5]. Hence, this randomized control trial was conducted to evaluate whether parenteral fluid supplementation helps in reducing the duration of phototherapy in healthy term neonates with non-hemolytic hyperbilirubinemia.

MATERIALS AND METHODS

This study was conducted in a tertiary level neonatal care unit of a teaching institute in North Karnataka over a period of 12 months from December 2012 to November 2013. Healthy term neonates (≥37 weeks) weighing ≥2.5 kg at birth presenting with jaundice and total serum bilirubin (TSB) ≥15 mg/dL (256 µmol/L) from 2nd to 14th day of life were included. Written informed consent was obtained from either parent of the neonate. Ethical clearance was obtained from the institutional ethical committee.

Neonates with bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, and high-pitched cry) [6], TSB >25 mg/dL (428 µmol/L), conjugated bilirubin >20% of the TSB, evidence of hemolysis, signs of dehydration (weight loss >10% of birth weight, reduced skin turgor, dry mucosa, fever, and tachycardia), jaundice persisting beyond 14 days of life, sick neonates, major congenital anomalies, born to gestational diabetic mother, cephalhematoma, and neonates on intravenous fluid for any reason were excluded (Box I). Hemolysis was diagnosed if direct Coombs test was positive, peripheral blood smear showed features of hemolysis and increased reticulocyte count [7].

During the study period, 92 term neonates were admitted for jaundice, 28 neonates were excluded, and 4 parents refused to give consent (Fig. 1). Hence, 60 neonates were randomized to one of the two groups (case group n=30, control group n=30). Neonates of both the groups received exclusive breastfeeding.

Neonates were allotted using computer-generated random number, and the corresponding serial numbered was opened by an opaque, identical envelope containing group allocation to either of the

Box I: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Healthy term neonates (≥37 weeks) ≥2.5 kg at birth Presenting with jaundice from 2nd to 14th day of life Total serum bilirubin (TSB) ≥15 mg/dL (256 µmol/L)	Signs of bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, and high-pitched cry)[6] TSB>25 mg/dL (428 µmol/L) Conjugated bilirubin>20% of the TSB Evidence of hemolysis Signs of dehydration (weight loss>10% of birth weight, reduced skin turgor, dry mucosa, fever, and tachycardia) Jaundice persisting beyond 14 days of life Sick neonates Major congenital anomalies Born to gestational diabetic mother Cephalhematoma Neonates on intravenous fluid for any other reason

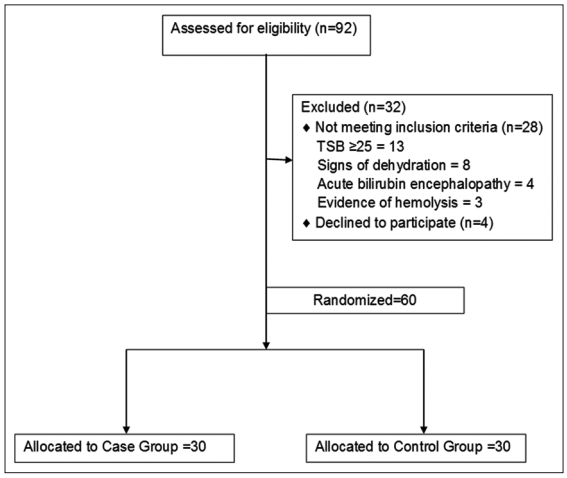

Figure 1: Patients flow diagram

two groups. Group I (case group) received supplemental intravenous fluid along with phototherapy and breastfeeding. Group II (control group) received only phototherapy and breastfeeding.

Phototherapy was provided by special blue light phototherapy unit (Phoenix Blue CFL-tubes PL-L-18W/52/4P Chennai, Tamil Nadu). Neonates were fully exposed except for their eyes and nappy areas. Phototherapy unit was placed at a distance of 25 cm over the neonate. Phototherapy was discontinued after TSB value obtained below 15 mg/dL (256 µmol/L) by 2 mg/dL (34.1 µmol/L). Neonates in case group received 1/3rd the daily maintenance fluid (80 mL/kg on day 2, 100 mL/kg on day 3, 120 mL/kg on day 4, 140 mL/kg on day 5, and 160 mL/kg on or after day 6) of 1/5th normal saline with 5% dextrose by peripheral vein till they received phototherapy. All the neonates received exclusive breastfeeding on demand. Investigations were sent for serum bilirubin (total and direct), hemoglobin, and for evidence of hemolysis (reticulocyte count, direct Coombs test, and peripheral smear for hemolysis). Maternal blood group was obtained from mother's records.

Neonates were periodically monitored for hydration, adequacy of feeding, signs of acute bilirubin encephalopathy, urine, and stool frequency. Daily weight was recorded. Serum bilirubin (total and direct) was repeated at 4th and 12th h and every 12 hourly by EM360 fully automated autoanalyzer using diazo method. Primary outcome measures were the duration of phototherapy and percentage of fall of TSB.

RESULTS

There was no significant difference with respect to birth weight, gender, weight at admission, mode of delivery, and age at admission between the two groups (Table 1). Mean (standard deviation [SD]) percentage of weight loss (case vs. control group was 5.09% [2.78] vs. 4.84% [2.2]) was not significant. Laboratory parameters (hemoglobin, reticulocyte count, and TSB at inclusion) were similar in both the groups (Table 1). Hence, factors affecting bilirubin was similar in both the groups.

There was a significant difference in the duration of phototherapy (case group 39 [7.8] h vs. control group 45.2 [10.22] h, p=0.0248). The average duration of phototherapy was shorter by 6 h in the fluid supplemented group. The percentage of fall in bilirubin at 4, 12, 48, and 60 h was not significant, but it was significant at 24 and 36 h (Table 2).

All the babies in both the groups responded to phototherapy, none of them needed exchange transfusion or developed signs of bilirubin encephalopathy. None of the neonates developed complications related to phototherapy and intravenous cannula (thrombophlebitis or evidence of sepsis).

DISCUSSION

Our study showed that intravenous fluid supplementation significantly reduced the duration of phototherapy in healthy term exclusively breastfed neonates presenting with non-hemolytic hyperbilirubinemia though the percentage of fall in bilirubin was not significant at all times.

The quantity of fluid supplemented differs between different studies. In one of the study, Iranpour R supplemented their study participants with 25% of the maintenance showed no benefit [2], while a study by Mehta *et al.* showed benefit with supplementation of 50% of daily maintenance [4]. Hence, our study was conducted to evaluate whether fluid supplementation of 1/3rd the maintenance has any benefit. We chose to give fluid by intravenous route as we believe that oral supplementation might interfere with breastfeeding, and the effectiveness of oral rehydration may not be sufficiently reliable and fast [4].

In a study done by Mehta *et al.* [4], benefit of fluid supplementation in term neonates presenting with severe

hyperbilirubinemia in the form of decreased rate of exchange transfusion and duration of phototherapy was seen. However, the case group in this study received intravenous fluid for first 8 h followed by oral supplementation with expressed breast milk or formula feeds. This study also showed the non-reliability of infants with own autoregulatory mechanisms to increase oral intake in the presence of severe hyperbilirubinemia. In a study, Saedi *et al.* [8] showed that additional parenteral fluid therapy in term neonates with non-hemolytic hyperbilirubinemia accelerates the reduction in serum bilirubin in first 24 h of admission. However, case group received full maintenance intravenous fluid along with breastfeeding. Boo and Lee [5] in a randomized controlled trial on severely jaundiced healthy term infants receiving intensive phototherapy showed no benefit of oral or intravenous fluid supplementation. However, the quantity of fluid given to both the groups (enteral and intravenous group) was similar, only the route of administration was different (oral vs. intravenous) and was only studied for first 4 h of phototherapy. A study by Goyal *et al.* [9] found no significant difference in the duration of phototherapy or exchange transfusion between the non-supplemented and fluid supplemented (by both intravenous and oral route) neonates receiving phototherapy for severe hyperbilirubinemia.

Table 1: Demographic and laboratory parameters of the neonates*#

Parameter	Case group n=30	Control group n=30
Male n (%)	19 (63)	16 (53)
Birth weight in kg	3.02 (0.32)	3.07 (0.34)
Admission weight (kg)	2.87 (0.31)	2.92 (0.33)
Weight loss (%)	5.09 (2.78)	4.84 (2.2)
Mode of delivery n (%)		
Vaginal	11 (36.6)	11 (36.6)
Cesarean	14 (46.6)	17 (56.6)
Instrumental	5 (16.6)	2 (6.6)
Age at admission (days)	5.17 (2.07)	5.07 (1.78)
Hemoglobin (g/dL)	15.83 (1.4)	15.61 (1.39)
Reticulocyte count (%)	1.61 (0.39)	1.43 (0.76)
TSB (mg/dL) at inclusion	17.35 (1.45)	16.11 (0.04)

***Results expressed as mean (SD), #all P>0.05 between both groups. SD: Standard deviation, TSB: Total serum bilirubin**

None of the neonates of either of the groups developed features of bilirubin encephalopathy or needed an exchange transfusion. Cochrane review showed no benefit of intravenous fluid supplementation on complications related to excessive bilirubin (bilirubin encephalopathy, kernicterus, or cerebral palsy) in healthy term neonates as a risk of developing these complications was very low [10]. The American Academy of Pediatrics [3] states that there is no evidence of excessive fluid administration affecting the serum bilirubin concentration and does not recommend routine intravenous fluid, or other supplementation of the term and near-term infants receive phototherapy unless there is evidence of dehydration. However, mild dehydration may not have significant clinical signs [11]. The significance of our finding might be due to an expansion of intravascular volume leading to a slight dilutional lowering of the bilirubin, but the more important effect would be enhanced biliary and bowel function [4]. Cochrane review of the previous studies showed that additional fluid supplementation in healthy term neonates with unconjugated hyperbilirubinemia shortened the average duration of phototherapy by 10.7 h; however, its clinical significance was unclear [9].

The major limitation of our study was the lack of laboratory parameters to determine dehydration. However, neonates of both the groups had no clinical signs of dehydration, weight loss on admission was not significant, and the possibility of subclinical dehydration will be equally distributed between both the groups. Furthermore, complete blinding was not possible in our study. We could not rule out the glucose-6-phosphate dehydrogenase deficiency in our subjects due to non-availability of the investigation at our institution.

CONCLUSION

Parenteral fluid supplementation along with exclusive breastfeeding does not affect the final outcomes but helps to reduce the duration of phototherapy which will reduce the duration of hospital stay and facilitate early discharge in such neonates. Further studies comparing fluid supplementation by oral or intravenous routes with no additional fluids involving a large sample size are required to find the beneficial effect if any.

Table 2: Percentage of fall in TSB and duration of phototherapy

Time (h)	Case group		Control group		p value
	n	% of fall in TSB	n	% of fall in TSB	
4	30	1.42 (0.75)	30	1.22 (1.42)	0.506
12	30	6 (3.26)	30	4.63 (5.84)	0.266
24	30	11.06 (5.16)	30	6.85 (6.28)	0.006*
36	29	17.32 (6.86)	29	11.36 (7.54)	0.002*
48	8	23.89 (9.11)	16	19.02 (9.55)	0.06*
60	2	26.47 (8.14)	8	21.87 (9.44)	0.30
Total duration of phototherapy (h)		39.6 (7.8)		45.2 (10.22)	0.0248*

Results expressed as mean (SD). *Significant P<0.05. TSB: Total serum bilirubin, SD: Standard deviation

$$\% \text{ of fall in TSB} = \frac{\text{TSB (at inclusion - at specified time)}}{\text{TSB at inclusion}} \times 100$$

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