

## Original Research Article

# Fluid supplementation in term neonates with severe hyperbilirubinemia: a randomized controlled trial study

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### ABSTRACT

**Background:** Severe neonatal jaundice can cause fatality and serious permanent effect, called kernicterus, in which the brain stem nuclei and basal ganglia are damaged. We are encouraged to work on efficacy of fluid supplementation in addition to photo therapy as a measure to reduce bilirubin level more efficiently.

**Methods:** A randomized control trial study was conducted in Department of Paediatric Medicine, Neonatal Unit, R.G. Kar Medical College & Hospital, Kolkata, from April 2011 to March 2012. A total 100 term neonates presenting with severe non-hemolytic hyperbilirubinemia (>18 mg/dl to <25 mg/dl) were enrolled as study population. The study subjects were divided into two equal groups, study group and control group by randomization. The study group was given IV fluid supplementation in addition to photo therapy. Total serum bilirubin (TSB) level assessed periodically and results compared with control group.

**Results:** The study results reveal a statistically significant association between the percent fall in TSB at 12 ( $\text{Chi}^2=7.18, p=0.000$ ) and 24 hours ( $\text{Chi}^2=10.69, p=0.000$ ) in the intervention arm compared to the control group.

**Conclusions:** Fluid supplementation along with double surface phototherapy in term neonates presenting with severe hyperbilirubinemia decreases the rate of exchange transfusion and duration of phototherapy.

**Keywords:** Fluid supplementation, Neonatal hyper bilirubinemia, Phototherapy

### INTRODUCTION

Jaundice is present in most newborns and usually benign, it is imperative to carefully monitor newborns to identify those at developing bilirubin-induced neurologic dysfunction. Severe neonatal jaundice can cause fatality and serious permanent effect, called kernicterus, in which the brain stem nuclei and basal ganglia are damaged. In severe neonatal jaundice, conventional therapy includes progressive reduction in the serum bilirubin level using phototherapy and exchange transfusions.<sup>1</sup> Phototherapy has some side effects such as diarrhoea, skin rash, dehydration, overheating, impaired mother-baby bonding and feeding disruption.<sup>2,3</sup> On the other hand, complications of exchange transfusion includes infection,

embolism, anaemia, apnoea, hypocalcaemia, and transfusion reactions.<sup>4-6</sup> Besides, exchange transfusion and phototherapy are not available everywhere. Considering these potential drawbacks of phototherapy and exchange transfusion, we are encouraged to work on efficacy of fluid supplementation as a measure to reduce bilirubin level which is relatively simple and universally available. Although few reports of efficacy of this measure are already available, literature is still scanty on this subject.<sup>7-10</sup> Hence we planned a randomized control trial on fluid supplementation in term neonates with severe non-hemolytic hyperbilirubinemia. The objectives of the study were to evaluate the effectiveness of fluid supplementation in reducing the bilirubin level,

decreasing the rate of exchange transfusion and reduce duration of phototherapy.

## METHODS

The study was conducted in Department of Paediatric Medicine, Neonatal Unit, R.G. Kar Medical College and Hospital Kolkata, between April 2011 to March 2012. A total 100 term neonates with severe non-hemolytic hyperbilirubinemia (>18 mg/dl to <25 mg/dl) were enrolled as study population.

### Inclusion criteria

- i. Body weight  $\geq 2.5$  kg
- ii. Total serum bilirubin  $\geq 18$  mg/dl to  $\leq 25$  mg/dl
- iii. Non-haemolytic type of jaundice
- iv. Total conjugated type of bilirubin <15% of total serum bilirubin.

### Exclusion criteria

- i. Body weight  $\leq 2.5$  kg,
- ii. Newborn with feature of acute bilirubin encephalopathy,
- iii. Evidence of haemolysis
- iv. Obvious features of dehydration
- v. Major congenital malformation
- vi. Baby already receiving IV fluid for any reason
- vii. Features suggestive of septicemia

The study subjects were divided into two equal groups, study group and control group by randomization. The study group was given IV fluid supplementation with 1/5 normal saline in 5% dextrose for a period of 24 hours. The volume of supplementation included a presumed deficit of 50 ml/kg (equivalent to mild dehydration), half of daily maintenance fluid for 24 hours in accordance to standard norms and extra 20 ml/kg per day as a photo therapy allowance. In addition, they continued breast feeding. After 24 hours the subjects of study group were offered 30 ml/kg/day of extra oral feed (expressed breast

milk) until discontinuation of therapy. The control group was continued on breast feeding *ad lib* as, before the randomization procedure. All the infants got photo therapy by standard method.<sup>1</sup> Photo therapy was discontinued when the bilirubin level will be <15 mg/dl.

Hydration status, serum bilirubin, serum Na<sup>+</sup>, urea, creatinine was assessed at admission. Hydration status was strictly monitored to avoid over hydration also. Exchange transfusion was done at a level of bilirubin of  $\geq 20$  mg/dl. The number of exchange transfusion, duration of photo therapy, percentage drop in serum bilirubin at 12 hours and 24 hours were determined in both the study and control group. The outcome was compared statistically to find effectiveness of fluid supplementation.

## RESULTS

A total of 100 term neonates with severe non-hemolytic hyperbilirubinemia were selected for the study and randomized into control and fluid supplementation study group equally.

Term neonates presenting with severe non-hemolytic hyperbilirubinemia (>18 mg/dl to <25 mg/dl) was enrolled as study population. Newborn with acute bilirubin encephalopathy, evidence of haemolysis, obvious features of dehydration (sunken fontanelle, reduce skin turgor, dry mucosa, tachycardia, delayed capillary refill, excessive weight loss corroborated with serum Na<sup>+</sup>, serum urea and urea - creatinine ratio' major congenital malformation and infants already receiving iv fluid for any reason were excluded. Haemolysis was diagnosed by direct Coomb's test, peripheral blood smear, reticulocyte count (>6%). Comparison of baseline demographic features at admission of neonates including age, weight, sex, CRP, DCT and G6PD of the fluid supplementation and control groups are presented in Table 1. G6PD showed significant value when compared both the groups. Comparison of baseline laboratory variables between the two groups are tabulated in Table 2 which reveals that serum urea value of both the groups are significantly different.

**Table 1: Comparison of baseline demographic features between the two groups.**

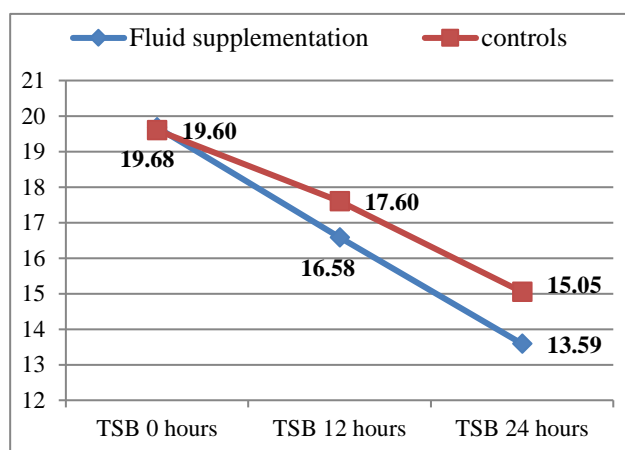
Variable (at admission)	Groups	Fluid supplementation	Control	Test# value	df	p-value
Age		81.56 $\pm$ 17.28	79.28 $\pm$ 13.10	0.79	110	0.431
Weight		2.82 $\pm$ 0.30	2.80 $\pm$ 0.25	0.38	110	0.701
Sex	Male	30 (%)	34 (%)	0.14	-	0.891
	Female	24 (%)	24 (%)			
CRP	Positive	3 (%)	1 (%)	0.58	-	0.560
	Negative	51(%)	57 (%)			
DCT	Positive	3 (%)	2 (%)	0.11	-	0.914
	Negative	51 (%)	56 (%)			
G6PD	Negative	31(%)	36 (%)	5.8	-	0.000*
	Not done	23(%)	22 (%)			

Data are mean  $\pm$  SD or n (%) when appropriate. # chi<sup>2</sup> or Z value depending on the statistical test used. \*statistically significant

**Table 2: Comparison of baseline laboratory variables between the two groups.**

Variable (at admission)	Fluid supplementation	Control	t-test	Df	p-value
Hb	17.85 ± 2.47	17.63±2.23	0.5	110	0.621
Reticulocyte count	1.94±0.52	2.16±1.03	1.41	110	0.161
Serum sodium	136.26±3.23	136.94±2.41	1.27	110	0.207
Serum urea	28.83±10.63	32.47±7.54	2.10	110	0.037*
Serum creatinine	0.71±0.16	0.67±0.18	1.24	110	0.217

\*statistically significant



**Figure 1: Decrease in mean serum bilirubin (mg/dl) in the first 24 hours of phototherapy in case and fluid supplementation groups.**

The decrease in mean TSB from baseline to 24 hours (0, 12 and 24 hours) of both the groups were evaluated and presented in Figure 1. TSB levels were decreased in both the groups, but in fluid supplementation group the decreasing percentage is higher and significant. TSB levels are similar in both the groups at baseline and the fluid supplementation study group showed a significantly higher percentage at 24 hours than the control group.

$$\text{Percent fall in TSB} = \frac{\text{TSB at baseline} - \text{bilirubin at specified time}}{\text{TSB at baseline}}$$

Numbers are different at 24 hours because children with kernicterus and infection have been removed from phototherapy for exchange transfusion. There is a statistically significant association between the percent fall in TSB at 12 (Chi<sup>2</sup>= 7.18, p=0.000) and 24 hours (Chi<sup>2</sup>=10.69, p=0.000) in the intervention arm compared to the control group.

**Table 3: Comparison of percent fall in TSB in the two groups.**

Variable	Fluid supplementation			Control			T test	DF	P-value
	Numbers	TSB (mg/dl)	Percent fall in TSB (mg/dl)	Numbers	TSB (mg/dl)	Percent fall in TSB (mg/dl)			
At baseline	54	19.68±1.21	-	58	19.60±1.38	-	-	-	-
12 hours	54	16.58±1.33	15.77± 3.91	58	17.60± 1.55	10.22±4.25	7.18	110	0.000*
24 hours	50	13.59±1.04	30.81± 4.36	50	15.05±1.31	22.67±3.16	10.69	98	0.000*

\*statistically significant

**Table 4: Outcome of newborns with hyperbilirubinaemia following phototherapy.**

Outcome	Supplemental hydration (n=54)		Control (n=58)		Chi <sup>2</sup>	p-value
	N	%	N	%		
Recovery	50	92.6	50	86.2	0.79	0.431
Exchange transfusion	3	5.6	7	12.1	0.88	.380
Infection	1	1.8	1	1.7		

The outcome of newborns with hyperbilirubinaemia following phototherapy is presented in Table 4. 92.6% of neonates were recovered in fluid supplementation group

which is higher than that in control group. Only 5.6% neonates of the study group underwent exchange transfusion when that value is 12.1% in control group.

Out of total in each group 1 patient showed infection after phototherapy.

## DISCUSSION

In order to minimize possible bias due to different types of phototherapy machines, we used only one type of phototherapy machine adjusted to 25 cm above the infants' cots. The irradiance of the phototherapy lights was monitored weekly to maintain at 25-35  $\mu\text{W}/\text{cm}^2$  per nm. By confining our patients to well, term infants only and by stratifying the patients according to type of therapy, one group only exclusive breast feeding and another group breast feeding plus maintenance iv fluid, a number of potential confounding factors are eliminated. The rates of decrease of serum bilirubin during intensive phototherapy in healthy term infants provided with either breast feeding alone or both breast feeding and intravenous fluid are comparable.

The American Academy of Pediatrics (AAP) recommends that for intensive phototherapy to be effective, it should reduce the serum bilirubin levels by 1-2 mg/dl (17-34  $\mu\text{mol}/\text{l}$ ) within 4h of treatment (or at a rate of 4.3-8.5  $\mu\text{mol}/\text{l h}$ ).<sup>11</sup> in this study, the rate of decrease in serum bilirubin in patients during the first 12 hr after admission is between 0.173 mg/dl (2.945  $\mu\text{mol}/\text{l}$ ) and 0.335 mg/dl (5.695  $\mu\text{mol}/\text{l}$ ) per hr and decrease of bilirubin in 24 hour of admission are 6.05 mg/dl/day in fluid supplementation group and in control group is only 4.39 mg/dl/day. This rate of decrease in serum bilirubin (greater than that recommended by the AAP) could be due to the use of more effective phototherapy lights. Studies have shown evidence of increased fluid loss due to insensible water loss via the skin and stool in infants during phototherapy.<sup>12,13</sup> Thus, during the present study, an additional 20% of maintenance fluid is added to the daily fluid intake of the infants based on a recommendation provided by De Carvalho et al and additional fluid volume is given if there are signs of dehydration.<sup>14</sup>

This study chose to focus on infants with TSB 18 to 25 mg/dl (306 to 425 mmol/L) because of the high rate of exchange transfusion and frequent need for phototherapy. In accordance with the American Academy of Pediatrics (AAP) guidelines for managing hyperbilirubinemia in newborns >35 weeks gestation, exchange transfusion is usually given at TSB >25 mg/dl (427 mmol/L)<sup>2</sup> however, the cut off followed in many Asian units, including ours, is >20 mg/dl (342 mmol/L). This is based on a 9.8% risk of kernicterus with TSB 20 to 25 mg/dL (342 to 427 mmol/L).<sup>15</sup> Exchange transfusion carries a mortality rate of 0.1% to 3.2% and complication rate of 6.3% apart from the risks associated with massive blood transfusion.<sup>16</sup> Phototherapy units, although simple, are also expensive and difficult to maintain. If providing fluid supplementation obviates the need for exchange transfusion and decreases the need for phototherapy without undue risks, then it will be cost effective.

In a randomized controlled trial from the department of Pediatrics, Post Graduate Institution of Medical Education and Research, Chandigarh, India showed that fluid supplementation in the first 12 hours of diagnosis in severe non hemolytic jaundice (serum bilirubin >18 mg / dl to <25 mg/ dl) number of exchange transfusion was lower in extra fluid group than in the control group i.e. 16% vs 54% (p= 0.001; relative risk =0.30; 95% confidence interval = 0.14 to 0.66).<sup>7</sup> The duration of photo therapy was also shorter in extra fluid group 52 $\pm$ 18 hours vs 73 $\pm$ 31 hours (p= 0.004). Which is very similar to this study. A similar study by Boo et al showed effectiveness of fluid supplementation is reducing serum bilirubin level.<sup>9</sup>

Our study provides the fluid deficit along with half of the maintenance requirements by the IV rather than oral route, because the effectiveness of oral rehydration may not be sufficiently reliable and fast in the setting of critical hyperbilirubinemia. One of the mechanisms by which fluid supplementation could have helped is expansion of intravascular volume, leading to slight dilutional lowering of TSB. The more important effect would be enhanced biliary and bowel function.<sup>17,18</sup> Oral supplementation of feeds that accompanied and followed the initial IV supplementation possibly helped decrease enterohepatic circulation and reabsorption of bilirubin from the gut.<sup>19</sup>

## CONCLUSION

The following conclusions can be drawn considering the foregoing results, their analysis and discussion. Fluid supplementation along with double surface phototherapy in term neonates presenting with severe hyperbilirubinemia decrease the rate of exchange transfusion and duration of phototherapy. Fluid supplementation along with phototherapy increases the rate of bilirubin reduction per hour.

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## REFERENCES

1. Piazza AJ, Stoll BJ. Jaundice and Hyperbilirubinemia in the Newborn. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson text book of Pediatrics: 18<sup>th</sup> Ed. New Delhi; Saunders Elsevier; 2007:755-766.
2. American Academy of Pediatrics Subcommittee on hyperbilirubinemia. Clinical practice guideline: management of hyperbilirubinemia in newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297-316.
3. Dhaded SM, Kumar P, Narang A. Safe bilirubin level for term infants With non hemolytic jaundice. Indian Pediatr. 1996;33:1059-60.

4. Newman TB, Xiong B, Gonzales VM, Escobar GJ. Prediction and prevention of extreme neonatal hyperbilirubinemia in a mature health maintenance Organization. *Arch Pediatr Adolesc Med*. 2004;154:1140-7.
5. Jackson JC. Adverse events associated with exchange transfusion in healthy and ill newborn. *Pediatrics*. 1997;99:e7.
6. Hansen TWR. Acute management of extreme neonatal jaundice: The Potential benefits of intensified phototherapy and interruption of enterohepatic bilirubin circulation. *Acta Paediatr*. 1997;86:843-6.
7. Mehta S, Kumar P, Narang A. A randomized controlled trial of fluid supplementation in term neonates with severe hyperbilirubinemia. *J Pediatr*. 2005;147:781-5.
8. Saeidi R, Heydanan F, Fakehi V. Role of intravenous extra fluid therapy in icteric neonates receiving photo therapy, Saudi Med J. 2009;30(9):1176-9.
9. Boo NY, Lee HT. Randomized controlled trial of oral versus intravenous fluid supplementation on serum bilirubin level during phototherapy of term infants with severe hyperbilirubinaemia. *J Paediatr Child Health*. 2002;38:151-5.
10. Iranpour RR, Nohekhan R, Haghshenas I. Effect of intravenous fluid supplementation on serum bilirubin level in jaundiced healthy neonates during conventional phototherapy. *J Res Med Sci*. 2004;4:186-90.
11. American Academy of Paediatrics Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia Practice Parameter: Management of hyperbilirubinaemia in the healthy term infants. *Paediatr*. 1994;94(4):558-65.
12. Oh W, Karecki H. Phototherapy and insensible water loss in newborn infants. *Am J Dis Child*. 1972;124:230-2.
13. Wu PY, Moosa A. Effect of phototherapy on nitrogen and electrolyte levels and water balance in jaundiced preterm infants. *Pediatrics*. 1978;61:193-8.
14. De Carvalho M, Hall M, Harvey D. Effect of water supplementation on physiological jaundice in breast-fed babies. *Arch Dis Child*. 1981;56:568-9.
15. Newman TB, Xiong B, Gonzales VM, Escobar GJ. Prediction and prevention of extreme neonatal hyperbilirubinemia in a mature health maintenance organization. *Arch Pediatr Adolesc Med*. 2004;154:1140-7.
16. Jackson JC. Adverse events associated with exchange transfusion in healthy and ill newborn. *Pediatrics*. 1997;99:e7.
17. Ennever JF, Costarino AT, Polin RA, Speck WT. Rapid clearance of a structural isomer of bilirubin during phototherapy. *J Clin Invest*. 1987;79:1674-8.
18. McDonagh AF. Light effects on transport and excretion of bilirubin in newborns. *Ann NY Acad Sci*. 1985;453:65-72.
19. Nicoll A, Ginsburg R, Tripp JH. Supplementary feeding and jaundice in newborns. *Acta Paediatr Scand*. 1982;71:759-61.

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