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### Intravenous fluid supplementation as treatment modality in severe nonhemolytic neonatal hyperbilirubinemia

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#### Abstract

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**Introduction:** Neonatal jaundice is a common problem and researchers have always tried to find treatment modalities which can prevent exchange transfusion in neonates with significant jaundice. Fluid supplementation has been tried in significant neonatal jaundice nearing exchange levels in different doses and durations. The present study was undertaken to assess the efficacy of i.v. fluid supplementation (0.33 DNS) in non hemolytic significant neonatal jaundice.

**Methods:** This study was performed in Department of Paediatrics, Bebe Nanki Mother and Child Care Centre, Govt. Medical College, Amritsar, Punjab for a period of 15 months. Seventy two healthy term neonates with indirect non hemolytic hyperbilirubinemia were assigned randomly to receive either only breastfeed (group B ; n=36) or i.v. fluids for 8 hrs in addition to breastfeed (group A ; n=36). The rate of decrease of total serum bilirubin(TSB), total duration of phototherapy and need of exchange transfusion were compared.

**Results:** The fall in TSB in initial 8 hrs was  $3.27 \pm 1.18$  mg/dl in group A versus  $2.16 \pm 0.90$  mg/dl in group B ( $p=0.001$ ). The duration of phototherapy or hospital stay was also shorter in group A i.e.  $44.25 \pm 3.29$  hrs versus  $53.11 \pm 5.96$  hrs in group B ( $p=0.001$ ). Only 1 neonate required exchange transfusion from group B while none from group A required exchange transfusion ( $p=0.314$ ).

**Conclusion:** I.v. fluid supplementation in severe non hemolytic hyperbilirubinemia significantly decreases TSB, total duration of phototherapy or hospital stay with no impact on need for exchange transfusion.

**Keywords:** Neonatal hyperbilirubinemia, Fluid supplementation, Exchange transfusion, Phototherapy

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## Introduction

Unconjugated hyperbilirubinemia is a common neonatal problem. It occurs in 60% of term and 80% of preterm neonates.<sup>1</sup> Most neonates develop hyperbilirubinemia during the first week of their life.<sup>2,3</sup> Unconjugated bilirubin is potentially toxic to the central nervous system and can cause serious permanent side effects called kernicterus, in which brain stem nuclei and basal ganglia are damaged, resulting in athetoid type cerebral palsy.<sup>4</sup> In extreme jaundice, rapid reduction of total serum bilirubin (TSB) level is of utmost importance. Two commonly used modes of therapy are phototherapy and exchange transfusion. Phototherapy has some side effects such as diarrhea, skin rash, dehydration, overheating, mother-baby bonding disruption and feeding disruption. Exchange transfusion complications include infections, embolism, anemia, apnea, hypocalcemia and transfusion reactions.<sup>4</sup> These serious potential risks with exchange transfusion have encouraged researchers to find alternate ways of treatment like fluid supplementation to reduce TSB levels as dehydration is commonly associated with severe neonatal jaundice and to avoid exchange transfusion as far as possible. Few studies have shown that administration of extra i.v. fluids can decrease TSB levels more rapidly and it decreases the need for exchange transfusion. Extra fluid administration can decrease enterohepatic circulation, dilute the serum bilirubin and increase renal excretion of bilirubin. However other studies have revealed no relationship between extra i.v. fluid supplementation and TSB decrement. A randomized controlled trial conducted in PGIMER Chandigarh (2005) on 74 term neonates by Mehta S et al concluded that calculated amounts (70 ml/kg + 1/2 of 8 hr maintenance fluids) of N/5 D5% over 8 hrs can significantly reduce the TSB levels in term neonates with non hemolytic jaundice causing reduction in phototherapy hrs and exchange transfusion rates.<sup>5</sup> A double blind, randomized, controlled trial performed at PGIMER Chandigarh (2012) by Balasubramanian K et al compared isotonic 0.9% NS D5% versus hypotonic N/5 D5% fluids (70 ml/kg + 1/2 of 8 hr maintenance fluids) over 8 hrs for neonatal jaundice in 84 term neonates.<sup>6</sup>

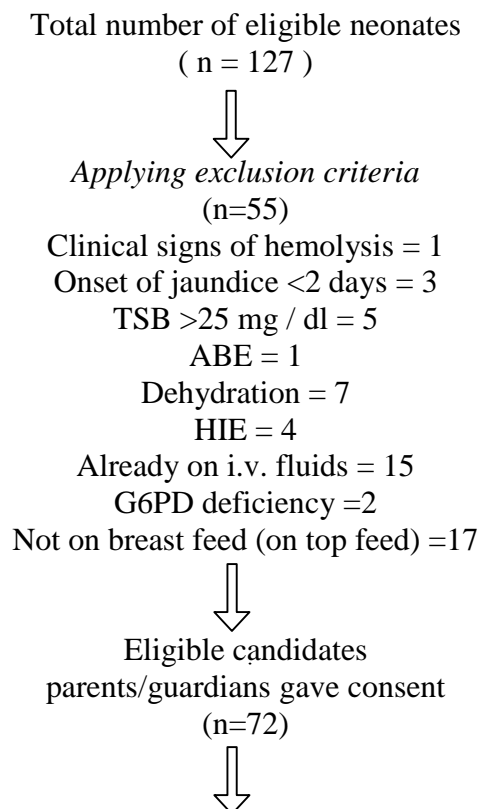
Results suggest that both groups had similar decrease in TSB levels, phototherapy duration and exchange transfusion rates. Hyponatremia and hypernatremia were observed respectively in isotonic and hypotonic fluid group.<sup>6</sup> Hence, it appears that an ideal fluid might be somewhere between N.S. and N/5. Based on the study by Aperia et al, a term healthy neonate of 3 kg could excrete a maximum of 12 mEq of sodium over 8 hrs in urine.<sup>7,8</sup> An ideal fluid for supplementation in such neonates could be N/3 D5% which would give a sodium load of 4 mEq/kg over 8 hrs (12 mEq for a 3 kg neonate).<sup>7,8</sup> A randomized controlled study carried out by Boo NY et al in NICU of Hospital University Kebangsaan, Malaysia (2002) including 54 term neonates concluded that i.v. fluids for 4 hrs along with oral feed in first 4 hrs of phototherapy have no added advantage over simple oral feed in decreasing TSB levels.<sup>9</sup> Another study done in Al-Zahra hospital, Isfahan, Iran by Iranpour et al (2004) on 60 neonates concluded that 25% maintenance fluids over 24 hrs (N/2 D5%) along with breast feed have no added advantage over oral feed in decreasing TSB levels.<sup>10</sup> A randomized controlled trial by Goyal P et al (2017) on 150 neonates with severe hyperbilirubinemia concluded that i.v. fluids (50 mL/kg) had no effect on duration of phototherapy or need of exchange transfusion but decline in TSB was significantly greater in i.v. fluid group as compared to 2 other groups, supplemental oral rehydration solution (ORS) and only phototherapy group in first few hrs.<sup>11</sup> Keeping in view the conflicting results of these studies, we conducted this prospective study to determine the role of supplementation of i.v. fluids (N/3 D5%) in reducing TSB levels in term neonates with non hemolytic severe hyperbilirubinemia taking breastfeed and receiving phototherapy.

## Materials and Methods

This randomized controlled study was performed in Department of Paediatrics, Bebe Nanki Mother and Child Care Centre, Govt. Medical College, Amritsar, Punjab from May 2016 to July 2017 for a period of 15 months. The aim of this study was to evaluate the role of i.v. fluid supplementation in decreasing TSB levels in severe neonatal hyperbilirubinemia and to observe decrease in

duration of phototherapy and need for exchange transfusion. This study included 72 term, 2 to 10 days old newborns admitted with indirect non-hemolytic jaundice with TSB 18 and <25 mg/dl who had no other problem(s) such as congenital abnormalities, sepsis and dehydration symptoms. These were randomly placed into 2 groups A and B. Permuted-block randomization was done. Informed consent was obtained from parents/guardians. The first TSB level was taken at admission at the start of the study period and then at 8 hrs and later as per unit protocol. Clinical signs of bilirubin encephalopathy were monitored every 4 hrs and hydration status at the start of study, at the end of i.v. infusion(8 hrs) and every 24 hrs thereafter. Serum Na levels were measured at 8 hrs and at 24 hrs. Other blood tests including mother and neonate blood group and Rh factor, complete blood count and peripheral blood smears for hemolysis were also simultaneously taken. Blood samples including TSB and measures such as discontinuation of phototherapy, exchange transfusion and discharge were done according to unit protocol. In group A, neonates were fed with breast milk and extra i.v. fluids

(N/3 D5% 70 ml/kg+ ½ of 8 hrs maintenance fluids) were administered through a peripheral vein for a period of 8 hrs while group B neonates were fed only with breast milk. Both groups received same type of LED phototherapy(Phoenix Medical system, India) optimized to deliver required irradiance at a peak wave length of 451 nm. The primary outcome considered was decrease in TSB levels after fluid supplementation and secondary outcomes were decrease in phototherapy hrs and need for exchange transfusion. We excluded neonates with any of following: jaundice on first day of life, any manifestations of kernicterus, any form of hemolysis, dehydration, major congenital malformation, taken antibiotics, already received i.v. fluids for any reason, direct bilirubin above 15% of the TSB, exchange transfusion if it was performed soon after admission. This study was approved by Ethics and Thesis Committee, Government Medical College, Amritsar. Data was analyzed using t test, Chi-square, fisher-exact test and z score. A p-value <0.05 was considered significant. Analysis was done using statistical software SPSS version 23.0.



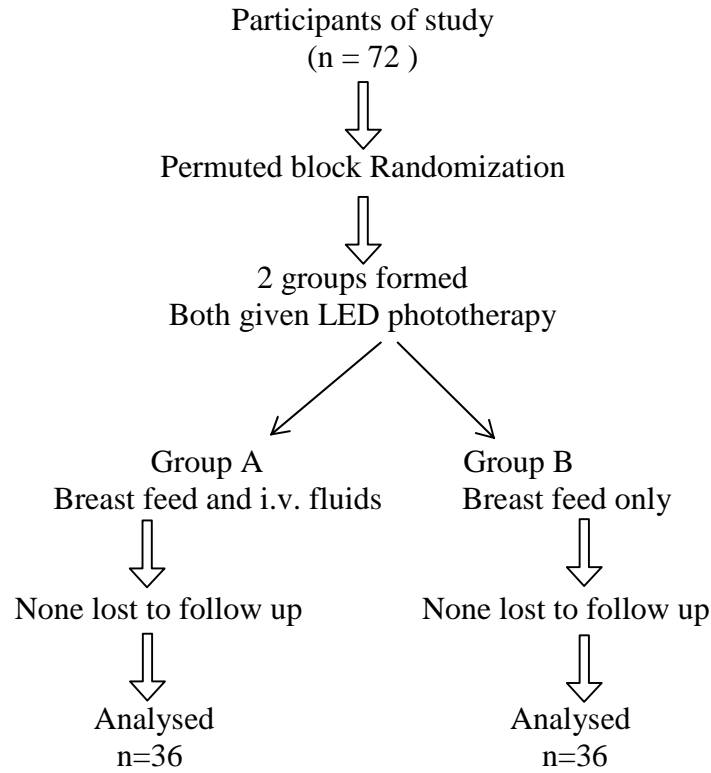


Fig 1 Flow of patients in study

**Results**

Table 1 Comparison of baseline characteristics of patients in 2 groups

Patient characteristics	Group A	Group B	p value
Male/female(in %)	55.56/44.44	63.89/36.11	0.471
Mean weight(in kgs)	2.64±0.44	2.68±0.43	0.715
Mean gestation (in weeks)	38.69±1.34	38.64±1.22	0.856
Mean age (in days)	5±1.70	4.75±1.74	0.541
Inborn/outborn (in %)	50/50	58.33/41.67	0.478
Vaginal delivery/LSCS (in %)	52.78/47.22	55.56/44.44	0.81
Mean TSB at admission(mg/dl)	20.78±2.29	19.57±1.60	0.06

Table 1 shows that the baseline characteristics of neonates in group A and group B were similar.

Table 2 : Primary and Secondary outcomes

Outcome	Group A	Group B	p-value
Decline of TSB over initial 8 hrs(mg/dl)	3.27±1.18	2.16±0.90	0.001
Mean phototherapy duration(in hrs)	44.25±3.29	53.11±5.96	0.001
Mean exchange rate(in %)	0	2.77	0.314

Table 2 shows that the decline of TSB was significantly more and mean phototherapy duration was significantly less in group A as compared to group B while mean exchange

transfusion rate was less in group A in comparison to group B but the decrease was not statistically significant.

Fig 2: Line diagram presenting mean decline of TSB over initial 8 hrs

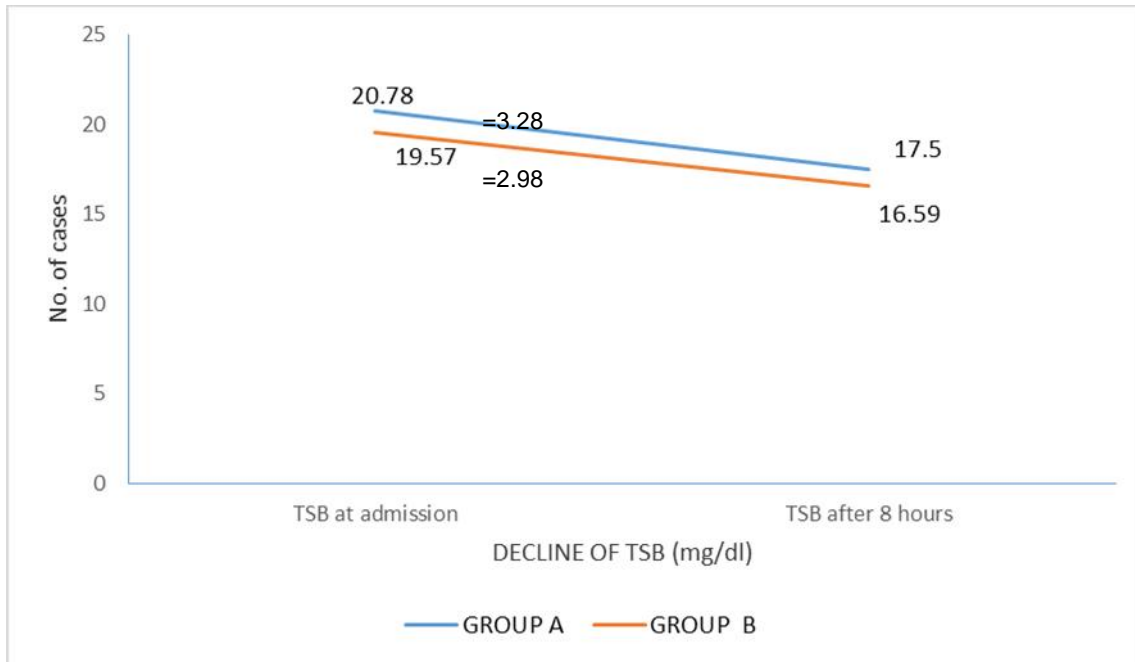


Table 3: Serum sodium levels in group A

Normal S.Na <sup>+</sup>	135-145 mEq/L
Mean S.Na <sup>+</sup> after 8 hrs	140.32 mEq/L
Mean S.Na <sup>+</sup> after 24 hrs (done in 15 cases only)	139.5 mEq/L

Table 3 shows that the mean serum sodium level was normal after 8 hrs and after 24 hrs (done only if value abnormal at 8 hrs) of fluid supplementation. After 8 hrs of fluid therapy 6(16.66%) babies had mild hyponatremia, 24(66.66%) had normal serum sodium and 6(16.66%) had mild hypernatremia.

## Discussion

Based on our findings, additional i.v. fluid (N/3 D5% 70 ml/kg+ ½ of 8 hrs maintenance fluids) administration during initial 8 hrs can significantly decrease TSB levels. Previously, different studies have used different fluids (0.9 N.S., N/5 D5%, N/3 D5%, D10% etc.) for variable duration of time. Bandyopadhyay A et al<sup>12</sup> and other studies showed similar results

though they used different fluids for variable duration of time.<sup>5,6,11,13,14,15,16,17</sup> Torkaman M et al<sup>18</sup> (2006) and few other studies showed no significant difference in the mean rate of TSB level decline with i.v. fluid supplementation.<sup>9,10,19</sup> This may be due to the fact that none of these studies used N/3 D5% and i.v. fluid therapy was for lesser duration. Additional fluid therapy causes dilution of serum bilirubin, increase blood flow to kidneys which improves excretion of water soluble photo isomers in urine. Further inadequate oral feeding in sleepy neonates due to significant hyperbilirubinemia along with increased insensible water loss during phototherapy can predispose to the worsening of hyperbilirubinemia in newborns not receiving extra fluids.

Our analysis showed that group A required lesser duration of phototherapy, hence lesser hospital stay. Mean duration of phototherapy in group A was  $44.25 \pm 3.29$  hrs while that in group B was  $53.11 \pm 5.96$  hrs ( $p=0.01$ ).

A study by Sasikumar B R et al and Patel M concluded that i.v. fluids can significantly decrease the phototherapy duration.<sup>15,16</sup> Similar results are reported in many studies in literature though they used different fluids for variable duration of time.<sup>5,6,12,13,14</sup> Goyal P et al and Demirsoy et al concluded that i.v. fluids supplementation had no effect on duration of phototherapy.<sup>11,20</sup> It may be because of less volume of i.v. fluids used in these studies. Gender and mode of delivery had no impact on decline of TSB levels and phototherapy duration in group A in our study.

Our analysis showed that as only 1 neonate required exchange transfusion in group B while none in group A required exchange transfusion ( $p$ -value 0.34), hence there was no statistically significant difference in two groups. Similar results were found in few other studies.<sup>11,14,16</sup> Mehta S et al (2005) concluded that 70 ml/kg + 1/2 of 8 hr maintenance fluids of N/5 D5% over 8 hrs can significantly reduce the exchange transfusion rates.<sup>5</sup> Similar results were found in many other studies.<sup>6,12,15</sup> In our study, initial TSB levels were below exchange transfusion range in all cases. So, with phototherapy, TSB levels fell because we had excluded all conditions which could aggravate hyperbilirubinemia like Rh / ABO or other minor blood group incompatibility, cephalhematoma, sepsis, dehydration etc. Hence the need of exchange transfusion came out to be minimal.

There was no significant hypo/hyponatremia associated with use of N/3 D5% (70 ml/kg + 1/2 of 8 hrs maintenance) over initial 8 hrs in group A. We followed the suggestion of a study by Balasubramanian K et al (2012) which concluded that use of isotonic 0.9% NS D5% was associated with hypernatremia while use of hypotonic N/5 D5% was associated with hyponatremia and recommended the use of N/3

D5% to prevent hypo or hypernatremia keeping in view the neonatal kidney physiology.

Therefore our study shows that i.v. fluid supplementation in term neonates already receiving phototherapy and breastfeed ad lib causes more fall in TSB levels in initial 8 hrs resulting in decrease in need of phototherapy duration / hospital stay but has no effect on rate of exchange transfusion.

## Conclusion

Additional i.v. fluid administration during initial 8 hrs can significantly decrease TSB levels and total phototherapy duration in severe non hemolytic neonatal hyperbilirubinemia. There is no impact on rate of exchange transfusion with fluid supplementation. No significant hypo/hypernatremia was associated with use of N/3 D5%. The mode of delivery or gender has no effect on fall of TSB or reduction in phototherapy hrs in babies receiving i.v. fluids.

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