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ORIGINAL ARTICLE

Role of IV Fluid Supplementation on Rate of Fall in Serum Bilirubin Levels in Icteric Term Neonates Receiving Phototherapy

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ABSTRACT

Background and Objectives: Hyperbilirubinemia or jaundice is a common condition found in neonates. If early intervention is not initiated in case of gradually increasing hyperbilirubinemia it may progress to develop a dreadful condition called kernicterus. Subclinical dehydration resulting from evaporative losses and inadequate breast milk intake may contribute to a higher incidence and increased severity of neonatal jaundice, thereby prolonging the required duration of phototherapy. Supplementation of neonates with additional intravenous fluids to dilute the blood, along with increased feeding to promote bilirubin excretion through bowel movements, has been a common practice. This study evaluated whether fluid supplementation offers any added advantage when combined with phototherapy in the management of severe neonatal hyperbilirubinemia. **Methodology:** In this interventional study, healthy term neonates (37–41 weeks of gestation) with severe hyperbilirubinemia requiring phototherapy were randomly assigned to two groups using the odd–even number method. A total of 42 term neonates with hyperbilirubinemia were enrolled. The intervention group received intravenous fluids for a total of 24 hours in addition to breastfeeding, while the control group was provided only breastfeeding along with intensive phototherapy. Serum bilirubin levels were assessed at baseline and at 4, 8, 12, 24, 36, and 48 hours after initiating phototherapy, and the rate of decline in serum bilirubin levels was calculated. **Results:** Baseline variables such as gender, age at the time of hospital visit and getting admitted, weight taken at birth, weight measured at the time of getting admitted to the hospital, mode of delivery, oxytocin use, incidence of breast feeding and serum bilirubin at the time of inclusion in study, were comparable in both groups. Variation in TSB levels at 4^{th} hour, 8^{th} hour, 12^{th} hour and 24^{th} hour of study were greater in study group. Although the drop in TSB level at 36^{th} and 48^{th} hour between two groups and PCV between the groups following intervention was not significant. **Conclusion:** It can be said that the drop in bilirubin levels and duration of phototherapy in study group was lesser than the control group after receiving additional IVF supplementation.

Keywords: Fluid supplementation, Hyperbilirubinemia, Total serum bilirubin

INTRODUCTION

In the early neonatal period, hyperbilirubinemia is the most common complaint that requires medical attention and hospital admissions. Approximately 85% of all the term newborns and most preterm infants develops clinical jaundice. Also, 6.1% of well term newborns have a peak TB level >12.9 mg/dl. A TB level >15 m g/dl is found in 3% of normal term infants [1]. Acute bilirubin encephalopathy is the acute complication of hyperbilirubinemia which causes irreversible bilirubin-induced neurologic dysfunction commonly noted during early neonatal period [2]. Chronic bilirubin toxicity to the central nervous system can result in kernicterus, a

dangerous condition that damages the brain stem nuclei and basal ganglia and causes cerebral palsy. Therefore, aggressive and early management is obligatory.

Phototherapy is a safe way which has remained the standard treatment in neonatal hyperbilirubinemia. During phototherapy, bilirubin is converted to less toxic and water soluble photoproducts which are called photo-isomers [3]. Because both bile and urine are the source of excretion of these less harmful photoproducts (photo-isomers) that are important for decreasing the bilirubin, maintaining sufficient hydration and an optimum urine excretion can assist phototherapy work more effectively [3]. Children in their first year of life usually undergo greater water loss because of insensible trans-epidermal water losses through the feces. Furthermost, severe jaundice develops in some newborns because of dehydration.

Increased enteral feeding is suggested to decrease bilirubin by reduced enterohepatic circulation through increasing gut peristalsis, while IV fluids are reported to lower bilirubin concentration by lowering hemoconcentration in a direct way [1]. When a patient has significant hyperbilirubinemia and cannot wait for a prolonged period of time without receiving exchange transfusions, the effectiveness of oral meals may not be reliable or rapid enough. The lack of available literature and the significant hospital-to-hospital differences in neonatal jaundice treatment also shows the necessity for this investigation. Therefore, the objective of the current research is to evaluate the utility of intravenous fluids supplementation on rate of drop of serum bilirubin in jaundiced healthy term infants on phototherapy and the total period of phototherapy requirement.

MATERIAL AND METHODS

This study was an interventional design conducted in the Neonatal Intensive Care Unit (NICU) of AJIMS, Mangaluru. The study population consisted of all term neonates admitted to this NICU with a diagnosis of hyperbilirubinemia.

The sample size was determined to be 42 neonates, a calculation based on a previous study. This number was estimated to be sufficient to detect a difference of 2.85 mg/dl in bilirubin levels at 48 hours between groups, assuming a 95% confidence interval, 90% power, and a pooled standard deviation of 2.9. Regarding participant allocation, the neonates were first divided into two primary groups based on the cause of their jaundice: Haemolytic and Non-haemolytic. Each of these groups was then further subdivided using the odd and even number method for randomization. Within both the Haemolytic and Non-haemolytic groups, every odd-numbered participant was assigned to the study group, while every even-numbered participant was assigned to the control group.

Before the study began, ethical approval was obtained from the Institutional Ethics Committee (IEC).

Inclusion criteria

- All healthy infants born at 37 weeks – 42 weeks of gestation and weighing more than 2.5kgs with neonatal hyperbilirubinemia requiring phototherapy or exchange transfusion.

Exclusion criteria

- Babies with obvious clinical signs of dehydration at enrolment (sunken AF, CFT >3 sec, weight loss of >12% of body weight, loss of skin turgor).
- If exchange transfusion is performed after admission.
- Neonates with features of acute bilirubin encephalopathy.
- Major congenital malformations.
- Neonates with confirmed congenital haemolytic anaemia or G6PD deficiency.
- Haematocrit >65%.
- Neonates already receiving IV fluids.
- Neonates with sepsis.
- Neonates having direct hyperbilirubinemia (DB >15% of TSB)
- Neonates having Hypoxic Ischemic Encephalopathy.
- In outborn neonate requiring formula milk if mother is not admitted.

Parental consent

Before randomization all the rules and regulation of ICMR guidelines for academic clinical trials were followed, informed written consent was obtained by either parent of the neonates to be enrolled in the study. In all the newborns, relevant information were collected in a predesigned proforma.

Randomization

All term healthy newborns with hyperbilirubinemia requiring phototherapy and fulfilling the inclusion criteria were included in the study. The need for phototherapy was based on the Norwegian guidelines or if TSB >15 mg/dl. After enrolment, relevant investigations were sent, and they were classified into Hemolytic or Non- Hemolytic groups. Hemolysis was diagnosed by presence of ABO/Rh incompatibility with DCT- positive or Peripheral smear suggestive of hemolysis or Reticulocyte count >6%. Each of the groups were further subdivided into study group and control group randomly by odd and even numbering. Every odd number in both haemolytic and non-hemolytic groups belonged to the study group and every even number in both haemolytic and non-hemolytic group

belonged to control group. Sequentially Numbered, Opaque, Sealed Envelope technique was used in the study to ensure allocation concealment. The study group received IV fluids for 24 hrs in addition to breast feeds and the control group received only breast feeds. The volume of fluids given was 25% of their maintenance fluids and an additional 20ml/kg/day as phototherapy allowance. The daily maintenance fluids required was calculated as: for Day 1- 60ml/kg/day, Day 2- 80ml/kg/day, Day 3- 100ml/kg/day, Day 4- 120ml/kg/day, Day 5- 140ml/kg/day, Day 6 and onwards- 150ml/kg/day. After 24 hours of IV fluid supplementation, the fluids were stopped, and the babies were continued on demand breast feeding.

Phototherapy: All the infants receive double surface phototherapy in the same type cradles. Babies were fully exposed except for their eyes and nappy areas. The phototherapy light panel were placed at a distance of 25cm above the neonatal cradle. Phototherapy was discontinued when 2 total serum bilirubin values obtained 12 hrs apart were below phototherapy requirement level. Rebound bilirubin levels was checked after 12 hours of stopping phototherapy.

Fluid protocol

IV fluid type: for Day 1 and Day 2- 10% dextrose

Day 3 onwards- N/5 saline in 5% dextrose (isolyte-p)44

IV fluid supplementation was given for a period of 24 hours. Volume of supplementation included 25% of daily maintenance requirement for 24 hours, in accordance with standard norms, and an extra 20 ml/kg/day as phototherapy allowance.

Laboratory tests

Just before commencement of phototherapy, specimens of blood were obtained from infants for the following investigations.

Serum bilirubin levels (total serum bilirubin and direct bilirubin levels), PCV, haemoglobin, platelet count, reticulocyte count, blood group, direct coombs test, peripheral smear, DCT. Mother's blood group was taken from the records available.

Monitoring

The serum bilirubin level was measured at the initiation of phototherapy and at 4th, 8th, 12th, 24th, 36th and 48th hours after starting phototherapy. PCV was checked at the start of the study and then at 24th and 48th hour of the study. If phototherapy was stopped because of bilirubin levels falling below phototherapy range, then the rebound bilirubin levels were checked 12 hours after stopping phototherapy. The drop in total serum bilirubin was calculated by using the formula; Drop of TSB= TSB at specific time – TSB at inclusion. The clinical signs suggestive of kernicterus (poor sucking reflex, abnormal muscle tone, high pitched cry) were checked every 12th hourly till serum bilirubin level comes below phototherapy range. Clinical assessment of hydration every 12th hourly was done. Feeding details, fluid intake, urine, stool frequency, daily body weight were also noted down.

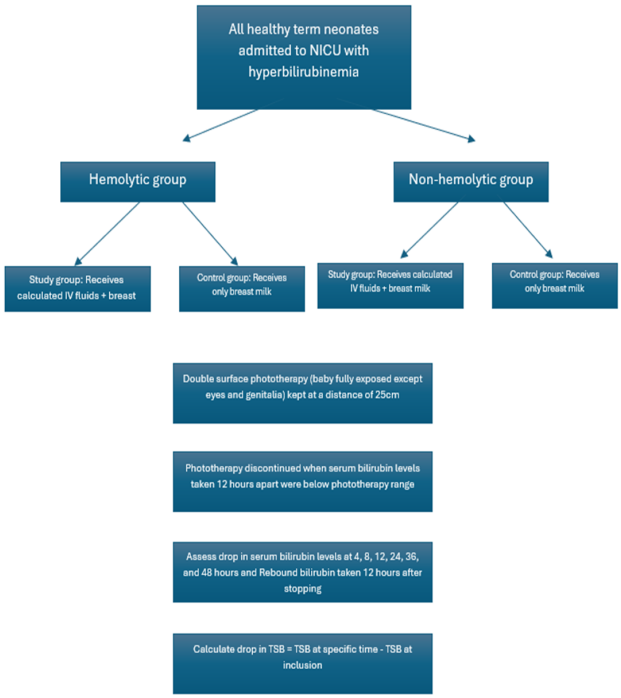

Fig. 1: Methodology flowchart

RESULTS

The study involved 42 term neonates with jaundice, divided equally into two groups: one receiving intravenous fluid (IVF) supplementation along with standard phototherapy (study group) and the other receiving only phototherapy (control group). Both groups included haemolytic and non-haemolytic cases, with 18 participants (42.9%) each in non-haemolytic study and control groups, and 3 (7.1%) each in haemolytic groups. Gender distribution was comparable: 52.4% female and 47.6% male.

Table 1: Maternal factors that may contribute to neonatal hyperbilirubinemia

Natal history	Study group	Control group	Total	P value
Rupture of membrane				
Spontaneous	7 (33.3%)	12 (57.1%)	19 (45.2%)	
Artificial rupture of membrane	7 (33.3%)	6 (28.6%)	13 (31.0%)	0.239
Not applicable	7 (33.3%)	3 (14.3%)	10 (23.8%)	
Oxytocin given				
Yes	1 (4.7%)	1 (4.7%)	2 (4.8%)	1
No	20 (95.3%)	20 (95.3%)	40 (95.2%)	
Mode of delivery				
Normal delivery	10 (47.6%)	14 (66.7%)	24 (57.1%)	0.35
Caesarean section	11 (53.4%)	7 (33.3%)	18 (42.9%)	
Type of Caesarean section				
Emergency	10 (47.6%)	9 (42.8%)	7 (45.2%)	0.474
Elective	11 (52.3%)	12 (57.1%)	11 (54.7%)	

Maternal risk factors such as rupture of membranes, oxytocin use, and mode of delivery were similar across groups as represented in Table. 1. No significant differences were found in APGAR scores at 1, 5, and 10 minutes. Most neonates (92.9%) had normal birth weight, with low birth weight in 7.1%, and 2.4% each classified as SGA and LGA.

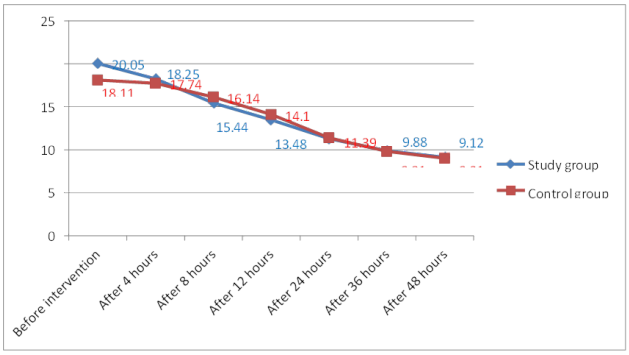

Fig. 2: Comparison of mean total Bilirubin following intervention

At baseline, the mean total bilirubin level was higher in the study group (20.05±3.42 mg/dl) than in the control group (18.11±2.73 mg/dl; p=0.05). Over time, bilirubin levels declined in both groups, with a more significant drop in the study group at 4, 8, and 24 hours (p<0.05). Specifically, bilirubin reductions at 4, 8, 12, and 24 hours were greater in the IVF group: 1.79, 4.73, 6.59, and 8.77 mg/dl compared to 0.37, 2.87, 6.71, and 6.71 mg/dl in controls. After 24 hours, the rate of decline was similar. Whereas the reduction was not much in the later phase during next 36 hours and 48 hours. The findings are depicted in Fig. 2.

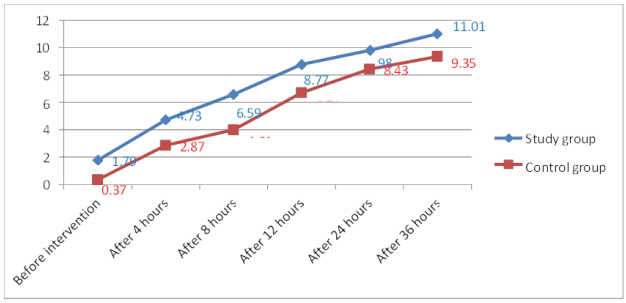

Fig. 3: Comparison of drop in total Bilirubin following intervention

Fig. 3 compared the drop in Total bilirubin after intervention. Percentage reductions in bilirubin were consistently greater in the study group at early time points: 9.6%, 23.3%, 32.5%, and 42.8% vs. 1.9%, 10.9%, 21.4%, and 36.1% in the control group. At 36 and 48 hours, reductions were comparable.

No rebound rise in bilirubin occurred after stopping phototherapy; final levels were 8.67±1.03 mg/dl (study) and 8.60±1.11 mg/dl (control). Notably, phototherapy duration was significantly shorter in the IVF group by 5.2 hours (p<0.0001).

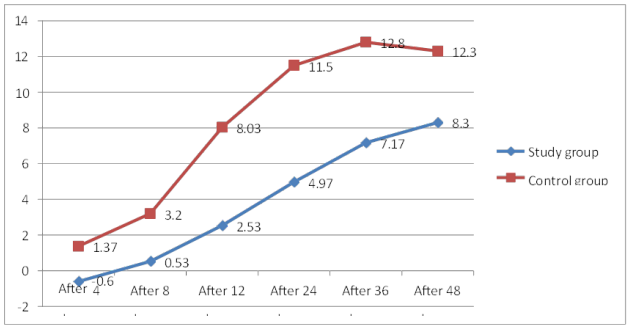

Fig. 4: Comparing Bilirubin drop post intervention between the haemolytic groups

In non-haemolytic neonates, bilirubin decline remained significant up to 48 hours with no rebound. Among haemolytic cases (n=3/group), differences were not statistically significant; a slight increase in bilirubin post-4 hours in two IVF cases was noted but considered inconclusive due to the small sample size. The findings have been illustrated in the Fig. 4.

DISCUSSION

Neonatal hyperbilirubinemia is a common condition, primarily due to the immature hepatic function of infants, which limits their ability to adequately process bilirubin, a byproduct of red blood cell breakdown. Phototherapy remains the standard treatment, while exchange transfusion is recommended if bilirubin levels remain markedly elevated despite phototherapy. Various adjunctive treatments have been explored, including the administration of additional intravenous fluids to dilute the blood and increased feeding to promote bilirubin excretion via bowel movements. In this study, data from 42 neonates with hyperbilirubinemia were analyzed to assess whether fluid supplementation offers any additional benefit alongside phototherapy.

The rate of decline in total serum bilirubin (TSB) at 4, 8, 12, and 24 hours was significantly greater in the fluid supplementation group compared to the control group. However, no significant difference in bilirubin reduction was observed between the groups at 36 and 48 hours of phototherapy. Additionally, our study found that the duration of phototherapy required was significantly shorter in the intervention group than in the control group.

The expansion of intravascular volume, which results in a dilutional decrease of TSB, is one of the hypothesized ways by which fluid supplementation could have been beneficial. Improved intestinal, biliary, and renal functions would be the most significant benefit. This is because the bilirubin photoproducts produced during phototherapy are excreted in the urine and faeces. Breastfeeding at will during and after the initial IV fluid supplementation may have benefited by reducing the enterohepatic circulation and preventing bilirubin absorption from the stomach. We did not give any formula feeds to both the groups because we did not want to interrupt the mother child bonding. It has been suggested of late that breast-fed infants can autoregulate and increase milk intake and decrease the insensible water loss as well while receiving phototherapy; however, it may not always be true. This would suggest that we cannot satisfactorily rely on the infants' own autoregulatory mechanisms to augment the intake of breast milk in the presence of severe hyperbilirubinemia.

In our study, the total serum bilirubin levels at the beginning of phototherapy when compared between the two groups was higher in study group. However, no significant difference in absolute serum bilirubin levels was observed between the groups at 4, 8, 12, 24, 36, and 48 hours after initiation of phototherapy. In contrast, analysis of the rate of decline in bilirubin revealed that the study group demonstrated a significantly greater reduction at 4, 8, 12, and 24 hours. Beyond 24 hours, the difference in the rate of bilirubin decline between the two groups was not statistically significant.

In a study by Mehta *et al.,* [5] it was noted that rate of drop in TSB at 4, 8, and 24 hours of study was significantly greater in the study group. Another study done by Patel *et al.,* 46 showed that when IV fluids were supplemented the rate of drop in bilirubin levels till 12 hours of phototherapy was statistically significant. A study by Iranpour *et al.,* [6] showed that there was no statistical significance in serum bilirubin values at the time of inclusion and within 84 hours after phototherapy. study by Al-Masri [7] also failed to show any association between extra fluid during phototherapy and decline in serum bilirubin levels. In our study even though serially monitored bilirubin values after initiation of phototherapy was similar in study and control group, the rate of fall in bilirubin was significantly higher in the fluid supplementation group. This observation may be due to higher values of serum bilirubin in the study group at inclusion. This shows the beneficial role of additional fluid supplementation in neonatal hyperbilirubinemia.

Rebound bilirubin levels were checked after 12 hours of stopping phototherapy and the values were not different between the two groups and both the groups did not require further phototherapy. Studies regarding the effect of fluid on rebound hyperbilirubinemia was not available in the literature.

In our study it was noted that there was significant reduction in the duration of phototherapy in the study group as compared to the control group. Study done by Mehta *et al.,* [5] showed that the mean duration of phototherapy had reduced by 22 hours in study group when compared to the control group. In another study by Patel *et al.,* [8] it was also found that fluid supplementation would reduce the total duration of phototherapy requirement significantly. But in studies done by Goyal P *et al.,* [9] and Demirsoy *et al.,* [10] it was concluded that IV fluid supplementation had no effect on duration of phototherapy. This difference could be because of the variation in route, amount of fluid supplemented and selection of babies with higher percentage of dehydration at inclusion.

When the study population was sub grouped into non-haemolytic and haemolytic cases, it was noted that the non-haemolytic group followed the same trend as the total study population. However, in the haemolytic group after IV fluid supplementation there was no significant

difference in drop in bilirubin levels between the study and the control group. No studies were found that studied the effect of IV fluid on haemolytic cause of hyperbilirubinemia. In our study since the number of cases in the haemolytic group was small, it was difficult to interpret the validity of our observations. Also, various other factors like the type of incompatibility, sensitization of the mother and also the degree of haemolysis could have affected the results. A larger study or performing the evidence synthesis using systematic review and meta analysis would be beneficial for the scientific community.

The limitations were that we did not have oral fluid supplementation limb in our study. As suggested by some studies, in infants with severe hyperbilirubinemia, it may be necessary to supplement extra fluids by oral route alone in the form of EBM or a recognized equivalent. We advise further research to determine whether additional fluid can reduce TSB in premature neonates who are jaundiced during phototherapy. Small sample size was also a limitation of our study. In subgroup analysis we could get only very few neonates to be included in the haemolytic group.

CONCLUSION

The findings of this study indicate that the study group experienced a significantly greater reduction in serial total serum bilirubin levels during the first 24 hours compared to the control group. However, beyond 24 hours of intervention, the rate of bilirubin decline was comparable between the two groups. Additionally, the total duration of phototherapy required was significantly shorter in the study group. Thus, the routine use of IVF supplementation should be considered cautiously and primarily for selected cases, pending further research.

Recommendations

Thus, from the above study we can recommend that more studies are required on role of IV fluid supplementation in haemolytic jaundice. The multicentre studies are required to validate the results of our study. This intervention can be performed in a study of larger sample size so as to have more inclusivity and larger representation. Also, evidence synthesis can be done by using a larger systematic review and meta-analysis of the topic.

DISCLOSURE

Funding

None.

Conflict of Interest

None.

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