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A Randomized Trial of Intravenous Fluid Supplementation Along With Phototherapy in Reducting Bilirubin in Neonates ≥ 35 Weeks With Significant Jaundice.

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Abstract
Objective: *To study the effect of Intravenous fluid supplementation along with Phototherapy in reducting bilirubin in neonates ≥ 35 weeks with significant jaundice.*
Design: *Randomized trial*
Setting& Participants: *Neonates of ≥ 35 weeks gestation with serum bilirubin ≥18 mg/dl and less than 25 mg/dl admitted to the Neonatology Division, Department of Pediatrics, Coimbatore Medical College Hospital, Coimbatore, tertiary care hospital in Tamilnadu.*
Methodology: *Eligible neonates were randomly allocated using Computer-generated randomization sequence by the principle investigator to 2 different groups A, B. Group A received phototherapy alone and group B received Phototherapy intravenous fluid supplementation . The percentage fall in serum bilirubin after 24 hours of phototherapy was evaluated.*
Results: *Percentage fall in bilirubin at 48 hours were 31, 57 in two groups A, B respectively. Though statistically not significant, exchange transfusions were less in fluid supplementation group. The use of intravenous fluid did not lead to any significant increase in the occurrence of side effects*
Conclusion: *The rate of fall in serum bilirubin was high when intravenous fluid is supplemented along with phototherapy in treating significant jaundice. Intravenous fluid supplementation is more effective and may be safe in neonates with significant jaundice.*
Keywords: *Fluid supplementation, Phototherapy, Neonate, Hyperbilirubinemia.*

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I. Introduction

During the first week after birth, more than 60% of apparently healthy full- term and 80 % of preterm newborns develop hyperbilirubinemia and the outcome is usually benign. However, approximately 5%–11% of infants will develop severe hyperbilirubinemia, defined as having total serum bilirubin (TSB) above the 95th percentile for age in hours, that requires treatment with phototherapy (1, 2, 3). Without appropriate intervention, a progressive increase to TSB values greater than 25 or 30 mg/dl (above the 99th percentile for age) places otherwise healthy neonates at risk of Bilirubin encephalopathy, it is not only the level of serum bilirubin but also various other factors like gestational age, metabolic status, infection and exposure to drugs influence the occurrence of bilirubin encephalopathy AAP define optimal phototherapy as blue light in the emission spectrum of 450 to 490 nm delivered at a light irradiance of >30 $\mu W/cm^2/nm$ to the largest possible body surface area. Newer phototherapy devices like light-emitting diodes (LEDs), as the diodes generate only a small amount of heat, it is now possible to increase the light irradiance, thereby increasing the efficacy of phototherapy devices. Studies in neonatal jaundice were done up to an irradiance of 55 $\mu W/cm^2/nm$**.** Phototherapy proves to be an effective treatment for infants with significant hyperbilirubinemia with exchange transfusions as its alternative.Photoisomers formed as a result of phototherapy are less lipophilic and can be readily excreted through bile and urine.For the effective action of phototherapy neonates hydration status is important as these photoisomsres are predominantly excreted in urine and feces.

Owing to the lack of evidence in the literature regarding the increased efficacy of phototherapy devices with intravenous fluid supplementation in neonates with significant hyperbilirubinemia, the present study was designed.

II. Methodology

Study Design:
Randomized trial

Study Centers: Neonatology Division, Department of Pediatrics, Coimbatore Medical College Hospital, Coimbatore, Tamilnadu ,India

Duration of the Study:

November 2015 to March 2016

III. Outcome Of The Study

Primary Outcome:

To evaluate the percentage fall in serum bilirubin in two groups of neonates receiving phototherapy and phototherapy with intravenous fluid supplementation after 24 hours of phototherapy.

Secondary outcomes:

1) To assess the differences in need for exchange transfusion
2) To study the effect on temperature, weight, stooling pattern,clinic status

Materials & Methods:

Subjects:

Neonates of ≥ 35 weeks gestation with serum bilirubin ≥18 mg/dl and less than 25 mg/dl admitted to the Neonatology Division, Department of Pediatrics, Coimbatore Medical College Hospital, Coimbatore, tertiary care hospital in Tamilnadu.

Inclusion Criteria:

Neonates ≥ 35 weeks gestation presenting with significant hyperbilirubinemia (total serum bilirubin ≥ 18 mg / dl and less than 25mg / dl)

Exclusion Criteria:

1.Unstable neonates (respiratory distress requiring oxygen / ventilator support, cardiovascular instability requiring ionotropes) and babies with clinical evidence of severe dehydration
2. Major lethal congenital malformations
3. Conjugated hyperbilirubinemia (direct bilirubin > 20%)
4. Neonates with evidence of acute bilirubin encephalopathy
5. Neonates requiring immediate exchange transfusion

Procedure/Intervention:

Eligible neonates satisfying the inclusion criteria were randomly allocated by the principle investigator to 2 different groups A, B after obtaining consent from any one parent. Neonates received phototherapy alone or fluid supplementation with phototherapy as per the randomization sequence allocation . Brilliance LED phototherapy devices (Phoenix Medical Systems, India) optimized to deliver the required irradiance at a peak wave length of 451 nm was used. A fixed distance of 30 cm from the phototherapy device to the baby was maintained throughout the study period. All the babies received bidirectional phototherapy from these devices.

American Academy of Pediatrics (AAP) guidelines (6) on phototherapy and blood exchange transfusion for neonates more than 35weeks was followed for decision regarding management of jaundice. Neonates were allowed to breast feed at libitum. Fluid supplementation (80ml/kg) of 0.3% GNS over 8 hours was given in babies allocated to group B. Management of other co morbid conditions was as per unit policy. The primary and secondary outcomes were studied in all two groups.

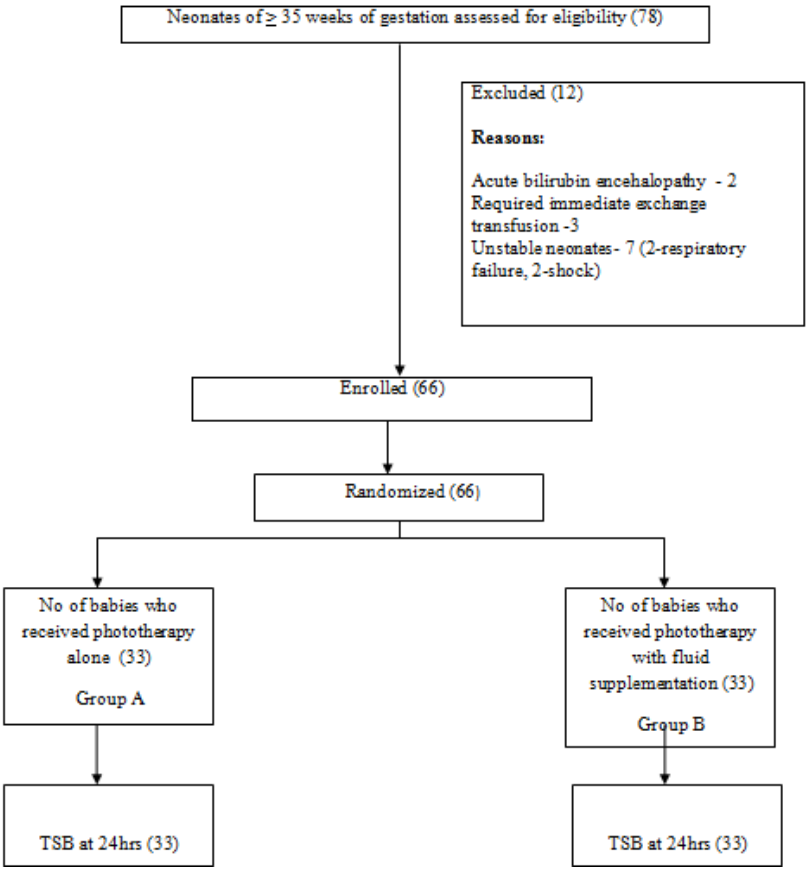
Data collection and Monitoring:

Neonatal baseline characteristics like birth weight, gender, gestational age, postnatal age and co morbid conditions like sepsis, cephalhematoma , subgaleal hemorrhage were recorded. Data collection on maternal characteristics included age, gravity, mode of delivery, oxytocin use, pregnancy induced hypertension and gestational diabetes mellitus. At the time of recruitment apart from serum bilirubin ,blood grouping , Rh typing, direct coombs test, serum sodium, hemoglobin, hematocrit , peripheral smear and reticulocyte count were performed.All the babies were subjected to bilirubin measurements at 6, 24 hours after initiating phototherapy. Neonates under the study underwent daily monitoring for body weight, hydration status, fluid intake, stool frequency and clinical signs of bilirubin encephalopathy. The infants were closely monitored for side effects like fluid overload, rashes, hyperthermia etc.

IV. Statistical Analysis

The data was analyzed using SPSS 17.0 for Windows. The baseline clinical characteristics and outcome variables were compared with the ANOVA for parametric and Kruskal-Wallis test for non-parametric comparisons of continuous variables, and chi square test for categorical variables.

Study Flow



V. Observations And Results

The data is presented as numbers (percentage) for categorical variables. Continuous variables are represented as mean (SD) for normal distribution and median (IQR) when the distribution was skewed.

Baseline neonatal characteristics

Parameters	Group A n=33	Group B n=33	P Value
Male	17(51)	20(60)	0.75
Post natal age (hrs)	116.6 ± (46.1)	112.7 ± (43.6)	0.84
Gestational Age (weeks)	38.36 ±(1.08)	38.64 ±(1.05)	0.09
Birth weight (kg)	2.79 ± (0.51)	2.75 ± (0.44)	0.5
Small for gestational age	10(30)	8(24)	0.68
Mode of delivery Normal vaginal LSCS Instrumentation	 19(57) 11(33) 3 (9)	 15(45) 16(48) 2 (6)	0.69
APGAR score <7 @ 5min	4 (12)	4 (12)	0.69

The neonatal demographic variables like gestational age, birth weight, gender, mode of delivery and APGAR that could affect serum bilirubin levels were evenly distributed and there was no statistical difference between two groups.

Risk factors of neonatal jaundice

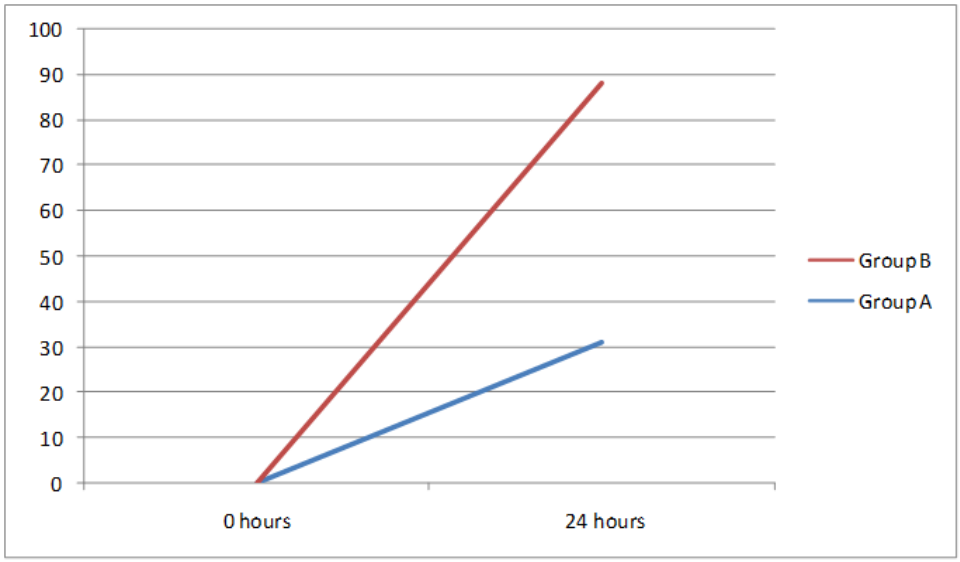
Parameters	Group A n=33	Group B n=33	P Value
Breast Feeding	23 (69)	21 (63)	0.81
Sepsis	5 (15.1)	4 (12.1)	0.75
Jaundice in previous sibling	1 (3)	2 (6)	0.81
Serum sodium	139 ± (4)	139± (3)	0.96
Hematocrit	43 ± (2)	42± (1)	0.42
Reticulocyte Count	4.1 ± (1.1)	4.2 ± (1.0)	0.49

Rh incompatibility	2 (6)	3 (9)	0.87
ABO incompatibility	10 (30)	14(42)	0.17
Cephalhematoma	2 (6)	1 (3)	0.77
Subgaleal bleed	2 (6)	1 (3)	0.58
Baseline Bilirubin	20.3 ± (1.4)	20.4 ± (1.3)	0.19

Risk factors like breast feeding, sepsis, jaundice in previous sibling, hematocrit , features of hemolysis and blood extravasation that could affect the rate of fall in bilirubin were equally distributed in between the groups .

Primary outcome:

Percentage fall of Bilirubin



Percentage fall in bilirubin at 24 hours were 31, 57 in the groups A,B respectively. There seems to be greater percentage fall in TSB in babies receiving fluid supplementation along with phototherapy.

Secondary outcome:

Change in mean bilirubin between two groups

Change in mean bilirubin at 24 hours were 6 , 3.5 in groups A, B respectively. Significant decline in mean bilirubin was noted at 24 hours when phototherapy is supplemented with intravenous fluids .

Sub group analysis between hemolytic and non hemolytic jaundice

In sub group analysis of hemolytic and non hemolytic jaundice, there was a significant increase in percentage fall of bilirubin with in fluid supplementation group at 24 hours(32,50). We didn't notice any difference in fall of bilirubin between hemolytic and non hemolytic babies within the same group.

Sub group analysis between 35-37 weeks and ≥ 38weeks of gestation

In sub group analysis between 35-37 weeks and ≥ 38weeks of gestation, there was a significant increasee in percentage fall of bilirubin with in fluid supplementation group at 24 hours. When comparing the fall of bilirubin in 35-37 weeks gestation(30,54) with ≥ 38 weeks gestation (31,59) babies in 2 groups there seems to be a positive correlation of bilirubin fall with fluid supplementation.

Need for exchange transfusion

No of babies who underwent exchange transfusion were 4, 1 in the groups who received phototherapy alone with phototherapy with fluid supplementation respectively. There was no significant statistical difference in need for exchange transfusion in between two groups.

Side effects

Outcome	**Group A n=33**	**Group B n=33**	**P Value**

Percentage of weight gain	2.1(-1,3.1)	2.3(-.1.1,3.1)	0.72
Skin Dryness	19(57)	16 (48)	0.58
Stool output (> 6/day)	0	1 (3)	0.60
Hyperthermia	3 (9)	2 (6)	0.69
Rashes	9 (27)	6 (18)	0.16
Fluid overload	0	0	0

Skin dryness was encountered more commonly in all the three groups. Effects such as weight change, stool output > 6/day, hyperthermia, rashes were evenly encountered between the groups.

VI. Discussion

In our study, we wanted to learn whether the phototherapy with fluid supplementation would reduce the need for exchange transfusion as conventional phototherapy units alone may have higher failure rate in these neonates who had significant jaundice due to hemolytic and non hemolytic causes Exchange transfusion carries a mortality rate of approximately 3 in 1000 procedures and significant morbidity in the form of apnea, bradycardia, cyanosis, vasospasm, thrombosis, necrotizing enterocolitis occurring in as many as 5% of exchange transfusion. Also the risks associated with the use of blood products must always be taken into consideration. In a study by Kang et al 1995(7), concluded that increasing the dose of irradiance from 9 to 35μW/cm^2/nm with the use of double phototherapy compared with single conventional phototherapy shortens the duration of hyperbilirubinemia without complications. In the study done by Vandborg et al (5) by increasing the irradiance level from 20 μW/cm^2/nm to 55 μW/cm^2/nm they found a positive linear correlation with the percentage fall of bilirubin levels in babies with insignificant hyprerbilirubinemia A linear dose-response relationship has previously been proved by Vandborg et al (5) and Mims et al (8) using unidirectional phototherapy from above with neo LED and blue fluorescent tubes respectively, although at relatively lesser light irradiances than our study.Tan et al (9,10) studied the dose response relationship using phototherapy unit containing blue and white fluorescent tubes.He reported that the saturation point was achieved at an irradiance level of 30 μw/ cm2/nm.His findings were in contrast to the findings of Vandborg et al (5) and Solana et al (4) who could not demonstrate any saturation point.

During phototherapy, infants have an increased insensible water loss. We used intense bidirectional phototherapy which may augment the excess loss of fluid. All the studies done previously were dealing with babies of insignificant jaundice where hydration may not be major factor but our inclusion were neonates with significant jaundice where hydration plays a major role in the excretion of photoisomers. The overall result showed a highly significant positive correlation between intravenous fluid supplementation and percentage fall of bilirubin at 24 hours. When fluid is supplemented with phototherapy , percentage fall of bilirubin increased from 31% to 57%. Average weight gain during phototherapy was 2.2% and it was not significantly related to fluid supplementation. The other side effects observed were loose stools, rashes, hyperthermia but they did not vary among 2 groups. It was in accordance to Vandborg et al(5) where he observed 1% weight gain during phototherapy at 24 hours and no significant difference in other side effects such as loose stools, rashes, hyperthermia among the groups. The association between percentage fall of serum bilirubin and gestational age was positive. More matures babies exhibited a higher decline in serum bilirubin levels at 24 hours in both the groups. Liver maturity might be the influencing factor.

Conclusions

1. Fluid supplementation along with phototherapy results in higher percentage fall in bilirubin at 24 hours. (31 to 57%)
2. Though statistically not significant , exchange transfusions were more in group treated with phototherapy alone
3. The use of intravenous fluid supplementation with phototherapy did not lead to any significant increase in occurrence of side effects.

Implications for practice

Fluid supplementation with phototherapy are more effective and may be safe in neonates with significant jaundice even due to hemolytic process thus reducing the need for Double volume exchange transfusion.

Implications for research

Study of preterm neonates with significant hyperbilirubinemia exposed to phototherapy and fluid supplementation has to be done to study the consequences secondary to exposure of more fluids.

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