Original Paper

Role of Intravenous Extra Fluid Therapy in Icteric Term Neonates Receiving Intensive Phototherapy

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Abstract

Background: Jaundice is a common neonatal problem. This may be due to the limited ability of a neonate to metabolize indirect bilirubin, which predisposes to the risk of encephalopathy and long-term sequelae if not managed promptly. Sufficient hydration and good urine output improve the efficacy of intensive phototherapy

The aim of this study: was to evaluate the role of intravenous extra fluid supplementation in accelerating the reduction of serum bilirubin levels in neonates and to find out whether intravenous fluid supplementation decrease the total duration of phototherapy and the need for exchange transfusion

Methods: This is a prospective clinical trial study that was conducted at phototherapy ward at Karbala teaching hospital for children, Iraq from January 2017 to December 2017. Fifty-two term neonates with non-hemolytic hyperbilirubinemia [total serum bilirubin ≥18 mg/dl (308 µmol /L) and <25 mg/dl (428 µmol /L)] were randomly divided into 2 equal groups; (non-supplemented group) received breast milk and or formula, and (supplemented group) given intravenous fluid besides breast milk or formula. Both groups exposed to intensive phototherapy. The rate of bilirubin decrement, duration of phototherapy, and rate of exchange transfusion were compared

Results: Rate of bilirubin decrement at 4 hours, 8 hours, 24 hours of study were significantly higher in supplemented group as compared to non-supplemented group (p- value ≤0.001). Duration of phototherapy required in non-supplemented and supplemented groups was 56.54 vs. 41.54 hours respectively (p-value =0.0001). No statistically significant effect of intravenous extra fluid supplementation on exchange transfusion rate between these two groups.

Conclusions: Intravenous extra fluid supplementation in non-hemolytic jaundiced term neonates can accelerate decrement of serum bilirubin levels and decreases the duration of phototherapy

Keywords: Fluid supplementation, Hyperbilirubinemia, Exchange transfusion, Neonate.

Introduction

In early neonatal period, hyperbilirubinemia is the most common complaint that requires medical attention and hospitals admission and readmissions. (1) The most dangerous alarm for healthy term newborns with jaundice is the neurotoxicity. Therefore, aggressive and early management is obligatory. Acute bilirubin encephalopathy is the acute complication of neonatal jaundice, causing irreversible bilirubin-induced neurologic dysfunction seen in the first postnatal weeks. (2)

Chronic bilirubin encephalopathy or kernicterus is the chronic plus permanent clinical consequence of bilirubin toxicity. (3-7) A public health goal for the contemporary society has been stated as: "one case of kernicterus is one too many; we can prevent them all". (8)

Phototherapy is a benign method which has continued the standard management in neonatal unconjugated jaundice. By delivering phototherapy, bilirubin is

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converted to less toxic and water-soluble photoproducts which are called photo-isomers. [9] In spite of the widespread use of conventional and intensive phototherapy, the search is continuing to discover other means of treatments for reducing the neonatal jaundice. [10]

During phototherapy, the resultant variety of less toxic photoproducts (photo-isomers) responsible for the drop-in serum bilirubin levels is excreted in bile and urine, thus maintaining adequate hydration and good urine output should improve the efficacy of phototherapy. [11, 12] Infants also experience greater water loss because insensible trans-epidermal and stool water losses. [9, 12] furthermore, severe jaundice develops in some newborns because of dehydration. [11]

While intravenous (IV) fluid is postulated to reduce concentration of bilirubin directly by lowering of hemoconcentration, increasing enteral feeding volume is proposed to decrease serum bilirubin with reduced enterohepatic circulation by an increased gut peristalsis. [4]

Although not necessary for all affected newborns, intravenous fluid supplementation added to oral feedings may be beneficial in dehydrated patients or neonates with bilirubin levels nearing those requiring exchange transfusions. [13, 12, 14]

The AAP recommend to give IV fluids for infants receiving intensive phototherapy; if oral intake in question. [17]. When severe jaundice appears in breastfed newborns the recommendation of AAP includes supplementing breast-feeding with formula in an attempt to increase the caloric intake and decrease the enterohepatic circulation. [15]

Seasonal variations in the incidence of hyperbilirubinemia have been observed, with an increase in the summer months. [16,17] Phototherapy causes the increase of skin evaporation in open regions; moreover, one of the causes of jaundice is the insufficiency of mother's milk. Thus, fluid therapy is purposed as a beneficiary intervention in jaundice. [18] There is a strong association between the frequency of breast feeding and a decreased incidence of significant elevated bilirubin levels. [19]

Shortage of literature and the considerable hospital to hospital variations in the treatment of neonatal jaundice and provision (or not) of fluid supplementation are also warrants this study. [20]

Aims of the study

The aims of this study were to evaluate the role of extra IV fluid supplementation in reducing serum bilirubin levels and to evaluate the probable effect, if any, of extra IV fluid in decreasing the duration of phototherapy and the rate of exchange transfusion in term neonates with non-hemolytic hyperbilirubinemia who were treated by intensive phototherapy.

Methods

This is a prospective clinical trial study that was performed at phototherapy ward at Karbala teaching hospital for children, Iraq from January 2017 to December 2017.We involved in this study fifty-two non-hemolytic jaundiced term newborns (37-41weeks gestation) with total serum bilirubin (TSB) ≥ 18 mg/dl [307.8 μmol /l] and less than 25 mg/ dl [428 μmol /l] who were received intensive phototherapy.

The exclusion criteria:

- Jaundice in first 48hours(hrs.) of life;
- Exchange transfusion if it was performed shortly after admission;
- Neonates with features of acute bilirubin encephalopathy;
- A venous hematocrit >65%;
- Neonates with signs of hemolysis (anemia, dark color urine, organomegaly, history of ABO or Rh incompatibility, Family history of hemolytic disease, positive coomb's test, G6PD deficiency);
- Neonates with obvious features of dehydration (sunken fontanelle, a decrease in skin turgor, dry mucosa,

capillary refill time more than 3 seconds, excessive weight loss>12% from birth weight);[21]
- Infants already receiving oral or intravenous fluids for any cause;
- Neonates with signs of infection, sepsis or inborn errors of metabolism: vomiting, lethargy, tachypnea, reduced feeding, hepatosplenomegaly, temperature instability, excessive weight loss, and apnea;
- Direct hyperbilirubinemia > 20% of the TSB levels;
- Prolonged jaundice persisting longer than 2 weeks of age;
- Antibiotics taken;
- Critically-ill newborns;
- Any congenital malformation; and
- Hypoxic ischemic encephalopathy.

Laboratory investigations:
- TSB was measured by (APEL Bilirubin Meter, BR-501, japan), and determination of direct bilirubin was made by the colorimetric method.
- Complete blood cell count was done by (automated hematology analyzer, sysmex).
- Blood smear, reticulocyte count.
- Maternal and baby blood group and Rh factor.
- Direct coomb's test.
- Glucose-6-phosphate dehydrogenase enzyme levels by (spectrum-G6PDH kits for determination of G6PDH activity in red blood cell, Egypt). G6PDH activity= 4.6-18.7 U/g Hb at 30-37°C. [22]

Fluid supplementation: Infants in the study group was given a full of their maintenance fluid requirement. The daily maintenance requirement measured 90 ml/ kg /day on day three, 100 ml/kg/day on day four and 120-150 ml/kg/day on day five and thereafter. The supplementary fluid was given for 24 hours as continuous intravenous dextrose 4 % and sodium chloride 0.18% (4% and 1/5th normal saline, isotonic solution). [23]

Intensive phototherapy: Both groups received the same form of phototherapy, including intensive phototherapy equipment developed by Médipréma, country of origin is France. The therapy chamber is a horizontal cylinder containing 16 blue tube lights, 20w/52 Philips fluorescent tubes (lamp wattage 20w, color code 52, emission peak at 450 nm, Germany). [24]

Monitoring: TSB levels and hematocrit were measured at admission, 4 hours after admission, 8 hours after admission, and 24 hours after admission. The newborns were treated naked except for eye and diaper area.

The clinical well-being, feeding details, hydration condition, urine output and color of urine, and neurological condition of neonates were clinically assessed. Breast-fed or bottle-fed infants were continuing feeding every 2-3 hours. [21] Serum urea and electrolytes were not measured because the neonates were well hydrated. The decision to stop phototherapy or to treat with ET was based on the clinical practice guidelines given by AAP for the treatment of Neonatal hyperbilirubinemia. Phototherapy was discontinued when TSB values were ≤12 mg/dl (205 μmol /l). [17] Rebound of hyperbilirubinemia was clinically assessed twelve hours after cessation of phototherapy. If the serum bilirubin level did not increase again or if it continued to decrease and the newborn remained well, he/she was discharged. No one of the newborns in either group developed features of bilirubin encephalopathy, any consequent episodes of dehydration or over-hydration, thrombophlebitis, or evidence of local or systemic infection.

Outcome measures: The initial outcome was rate of bilirubin decrement at 4hours, 8hours, and 24 hours of the study. Final outcomes were duration of phototherapy and the rate of exchange transfusion.

Result

A total of 52 non-hemolytic jaundiced term neonates with TSB ≥ 18 mg/dl and < 25 mg/ dl were randomly divided to 2

groups; control group (non-supplemented group) received breast milk and or formula, and study group (supplemented group) received IV Fluid in addition to breast milk or formula.

Table (1) shows the basic demographic data of control group in which no additional intravenous fluid added to the feeding, and the study group which supplemented with intravenous fluid. There were 18 males and 8 females (p-value =0.82, chi-square test) in non-supplemented group; 12 males and 14 females in supplemented group. The mean age of patients in non-supplemented group was 125.85 hours, and 123.75 hours in supplemented group (p-value =0.94, t test). The mean weight on admission was 3.35 ± 0.32kg in control group, and 3.37 ± 0.4 kg in study group (p-value =0.70, t test). The mean gestation age was 37.6 ± 0.4 weeks for non-supplemented group and 37.6 ± 0.69 weeks for supplemented group (p-value =0.26, t test). There was no significant difference between these two groups regarding use or not use oxytocin during delivery (p-value = 0.65, p-value = 0.72 respectively).

Table (2) shows the following results: There were no statistically significant differences in the mean of hematocrit and TSB levels at the time of admission between the two groups. The TSB levels on admission in non-supplemented and supplemented group were ranged from 18 to 22 mg/dl and 18.5 to 23 mg/dl, respectively. The mean TSB levels in the two groups of neonates during intensive phototherapy were significantly different after 4hours, 8hours, and 24hours respectively.

Table 1. Demographic data of neonates in non-supplemented and supplemented groups. Data are mean ± SD

Data		Non-supplemented group (n=26)	Supplemented group (n=26)	P value *
Age at admission (hrs.)		125.85 ± 59.9	123.75 ± 65.12	0.940
Gestation age (wks.)		37.6 ± 0.4	37.6 ± 0.69	0.264
Weight (kg)		3.35 ± 0.32	3.37± 0.4	0.700
sex	Male	18	12	0.821
	Female	8	14	
Types of feeding	Breast milk	16	17	0.862
	Bottle	6	5	0.763
	Mixed	4	4	1
Type of delivery	VD	18	20	0.746
	C/S	8	6	0.597
oxytocin Use	Yes	9	11	0.655
	No	17	15	0.724

*All p values >0.05 between the two groups.

Table 2. The laboratory data in non-supplemented and supplemented groups

Data	**Groups**	**N**	**Mean ± SD**	**95% CI***	**P value****
Hematocrit (%)	Non-supplemented	26	50.85 ± 5.74	48.54-53.15	0.630
	supplemented	26	51.62 ± 5.75	49.29-53.49	
TSB at admission (mg/dl)	Non-supplemented	26	19.65 ± 1.01	19.23-20.06	0.078
	supplemented	26	20.83 ± 1.45	20.24-21.48	
TSB after 4 hrs.	Non-supplemented	26	19.24 ± 1.79	18.51-19.96	**0.001**
	supplemented	26	17.77 ± 1.59	17.13-18.42	
TSB after 8 hrs.	Non-supplemented	26	16.69 ± 1.01	16.28-17.10	**0.0001**
	supplemented	26	15.13 ± 1.43	14.55-15.7	
TSB after 24 hrs.	Non-supplemented	26	13.61 ± 0.68	13.33-13.89	**0.0001**
	supplemented	26	11.70 ± 1.18	11.22-12.18	

*95% CI (CI, confidence intervals). **P value ≤ 0.05 is significant (t -test).

Figure (1) shows the following: Rate of decrement of bilirubin was a statistically significant in study group as compared to control group at 4 hours, 8 hours, and 24 hours of study (p-value < 0.001, t test).
Figure (2) shows there was significant difference in the duration of phototherapy required in both groups. Patients with supplemented intravenous fluid stay less than other group 41.54 hours vs. 56.54 hours (p-value =0.0001, t-test).
Table (3) shows there was no significant effect of IV fluid therapy in the rate of exchange transfusion between these two groups.

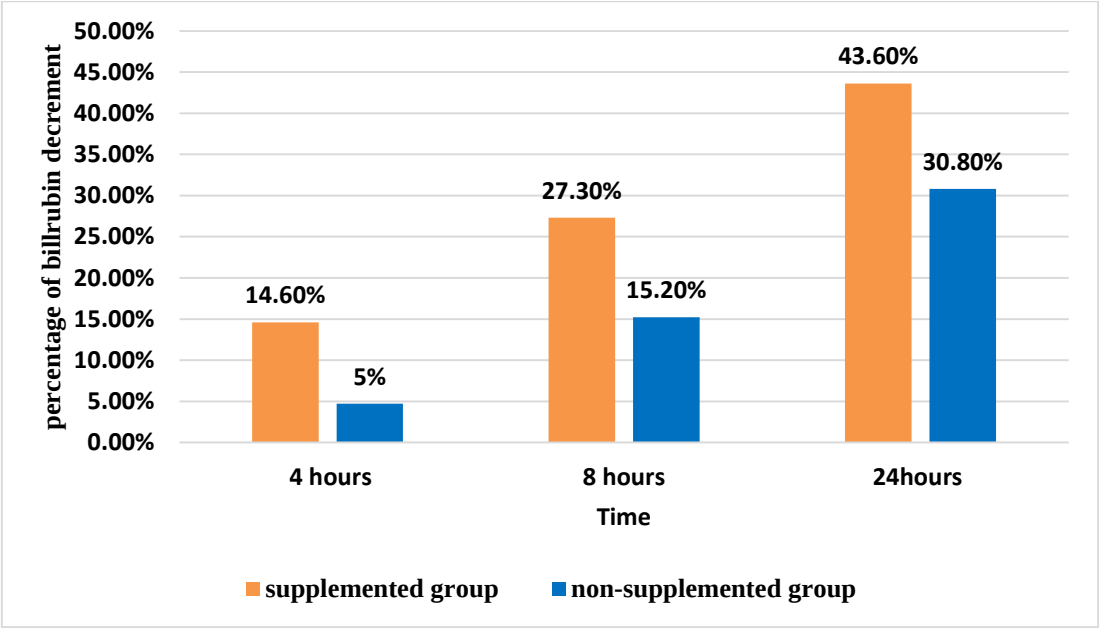

Figure 1. Percentage of bilirubin decrement at different times after admission

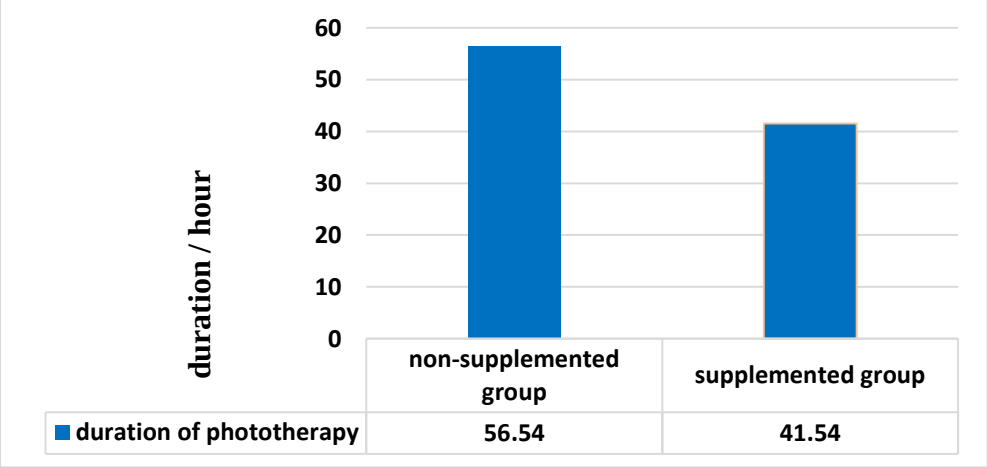

Figure 2. Duration of phototherapy in non-supplemented and supplemented groups

Table 3. Comparison between rate of exchange transfusion in non-supplemented and supplemented groups

	Non-supplemented group (n=26)	Supplemented group (n=26)	P-value
Exchange transfusion	6	1	0.0993
Non- exchange transfusion	20	25	

Discussion

We chose to provide the maintenance fluid requirements by the intravenous rather than oral route, because the effectiveness of oral rehydration may not be sufficiently reliable and fast in the setting of critical jaundice. We did not estimate the volume of formula milk, and we could not measure the volume of breast milk taken by neonates, but since there was significant difference in the rate of decreasing of TSB, it seems that breast milk and formula milk could not compensated the fluid loss during intensive phototherapy. Our findings are similar to Iranian study by (Saeidi et al 2009) in which healthy term neonates with severe non-hemolytic jaundice were received a full maintenance IV fluid during the first 24 hours after admission. It showed that rate of serum bilirubin decrease per hour was significantly more in extra fluid group during the first 24 hours of research period (p-value = 0.02). [25]

Similarly, a study from India by (Mehta et al 2005) with different rate of fluid supplementation in that study, in which extra IV fluids were given for 8 hours at a rate half of the maintenance. Further, the infants were given additional 20 ml/kg/day as a phototherapy allowance. Subsequently, the infant was continued on breast/formula feeds as before and offered 30 ml/kg/day of extra oral feeds (expressed breast milk or formula) until the discontinuation of phototherapy. This extra fluid management has resulted in the drop of serum bilirubin levels significantly. [26] The addition of extra fluid to the oral feeding may result in the decrease in enterohepatic circulation and decrease rate of bilirubin reabsorption from the bowel. The duration of phototherapy in supplemented group has been shorter than the phototherapy alone group (Figure 2). Similarly, (Mehta et al), (Ebrahimi 2003) [27] and (Tank et al 2017) [28]. Regarding exchange transfusion rates: one neonate underwent ET in supplemented group, and six neonates underwent ET in non- supplemented group. But the requirement for exchange transfusion was not statistically significant between the two groups (Table 3). These findings may be related to the low sample size. Studies by (Mehta et al), (Balasubramanian et al 2012) [29] and (Tank et al) were showed that using IV fluid therapy reduces the need for exchange transfusion.

This study is opposite to (Iran Pour et al 2004) [30] in which a 25% of maintenance fluid was taken in supplemented group showed that administration of additional IV fluid in non-hemolytic jaundice in healthy terms, breastfed newborns have no beneficial result on the rate of serum bilirubin reduction during 84 hours after conventional phototherapy units that consisted of four special blue lamps. Another randomized controlled trial study by (Boo et al 2002) [31] which compared extra oral fluids against extra oral and IV fluids showed the beneficial effect of additional fluid in reducing serum concentration of bilirubin in severely jaundiced healthy term infants during intensive phototherapy, but the finding was not statistically significant. But, there was no control group in that study to compare the drop in the bilirubin concentrations in the receiving fluid group against non-receiving group. Previous study in Karbala by (Easa 2013) [32] showed no beneficial effect of IV fluid on the rate of serum

bilirubin reduction. This difference may be in some extent due to the amount of given IV fluid, in which neonates in supplemented group received a 25% of their maintenance fluid requirement (1/5 normal saline and 5% dextrose), that is 1/4 in the present study, and to the type of phototherapy used, we used 16 special blue lamps (intensive) instead of three special blue lamps (conventional) in pervious study.

Conclusions

Intravenous extra fluid supplementation in term neonates presenting with non-hemolytic hyperbilirubinemia can significantly accelerate reduction in serum bilirubin levels per hour in the first 24 hours of admission. Extra IV fluid can reduce the duration of intensive phototherapy.

Recommendations

- It is advisable to add extra IV fluid to oral feedings in infants with bilirubin levels nearing those requiring exchange transfusions.
- Another study in which rising enteral feeding volume in one more group during hospitalization versus to IV fluid supplemented and non- supplemented groups.

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