

SUPPLEMENTAL INTRAVENOUS FLUIDS AS A TREATMENT MODALITY FOR SEVERE NON- HEMOLYTIC NEONATAL HYPERBILIRUBINEMIA

By

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ABSTRACT

Background: Phototherapy is a standard treatment for neonatal hyperbilirubinemia. During phototherapy, since photoproducts that cause the decrease in serum bilirubin are eliminated in bile and urine, so adequate hydration should enhance the effectiveness of phototherapy.

Aim of work: To evaluate the role of intravenous (IV) fluid supplementation in decreasing total serum bilirubin (TSB) levels and duration of phototherapy in severe non-hemolytic neonatal hyperbilirubinemia.

Patient and Methods: This prospective study was carried out on 48 full-term neonates with indirect non-hemolytic hyperbilirubinemia in the neonatal intensive care unit (NICU), at Menoufia University Hospitals. Included neonates were assigned randomly to receive either intravenous fluid during the first 8 hours of phototherapy in addition to breast milk (Group 1, n=24) or exclusive breast milk (Group 2, n=24). TSB was documented at presentation and then at 12, 24, 48, 72, 96, 120, and 144 hours after admission. Both groups' rates of TSB reduction and the duration of phototherapy were compared.

Result: There was a significant difference in mean TSB (19.62 in group 1 versus 18.98 in group 2). Following IV fluid supplementation, TSB levels showed significant reduction at 12, 24-, 48-, 72- and 96-time hours ($p < 0.001$) in group 1 (supplemented IV fluid group) compared to exclusive breast milk (Group 2). Moreover, supplemented IV fluid group had a significantly shorter duration of phototherapy and NICU stay.

Conclusion: Additional IV fluid supplementation during the initial 8 hours with phototherapy in neonatal hyperbilirubinemia may considerably shorten the overall phototherapy time and TSB level in severe non-hemolytic newborn hyperbilirubinemia.

Keywords: Hyperbilirubinemia, Intravenous Fluid, NICU, Phototherapy, Non-Hemolytic.

INTRODUCTION

Jaundice is an extremely prevalent clinical condition in the neonatal intensive care unit (NICU). Approximately 60% of healthy newborns develop clinical jaundice within the first week of life. Significantly, elevated bilirubin levels may cause bilirubin encephalopathy, followed by kernicterus, which can cause severe permanent neuro-developmental disabilities (Coelho & Apetato, 2016). Bilirubin typically peaks between 3 and 5 days of age, but it may continue to rise through factors that limit bilirubin clearance, such as poor feeding, infection, or prematurity (Elhaj YM and Hamad, 2020).

The prevalence of hyperbilirubinemia has been found to vary seasonally, rising during the summer. The incidence and severity of jaundice in neonates can rise because of subclinical dehydration caused by evaporative losses and inadequate breastfeeding. At presentation, three-fourths of newborns with severe hyperbilirubinemia have subclinical dehydration (Hansen et al., 2020). In severe neonatal jaundice, phototherapy and exchange transfusions may be required to gradually lower the serum bilirubin levels. Phototherapy can cause adverse

reactions including diarrhea, skin rashes, dehydration, hyperthermia, interrupted feedings, and a reduction in mother-baby bonding. The resulting photoproducts from phototherapy are eliminated in both urine and bile decreasing serum bilirubin levels (Jain et al., 2017).

Fluid supplementation may be beneficial in the treatment of severe hyperbilirubinemia. A higher rate of bilirubin reabsorption from the intestine may follow a reduction in enterohepatic circulation brought on by fluid supplementation. Further, it seems that additional fluid treatment may reduce serum bilirubin, increase renal blood flow and urine production, and eventually enhance the elimination of water-soluble photo isomers in urine (Kaur et al., 2018). Jaundiced neonates may get sleepy from high serum bilirubin levels. Thus, insufficient oral feeding plus increased insensible water loss during phototherapy could delay the decrease in serum bilirubin in neonates who do not get additional fluid (Lai et al., 2017).

Few studies have shown that increasing IV fluid administration may decrease TSB levels more rapidly and lessen the need for exchange transfusions. Increased renal excretion of bilirubin,

diluted serum bilirubin, and decreased enterohepatic circulation may all result from the more fluid supply (Kaur et al., 2018; Lai et al., 2017). However, several studies have shown no association between the provision of more IV fluid and a reduction in TSB (Morshed et al., 2017).

This study aimed to evaluate the role of IV fluid supplementation in decreasing TSB levels in severe non-hemolytic neonatal hyperbilirubinemia and to observe its effect on the duration of phototherapy.

Ethical consideration:

1. Approval by the local ethical committee was obtained before the study.
2. Written informed consent was obtained from patients or their legal guardians.
3. The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.
4. All the data of the patients and results of the study are confidential and the patients have the right to keep them.
5. The authors received no financial support for the

research, authorship and /or publication of the article.

Sample size:

(Kaur et al., 2018) do a similar study, at a power of 80% and a confidence level of 95%. The sample size was calculated and found to be 30 subjects. And this will be increased to 34 subjects to avoid the dropout of the patients. 17 subject in each group with a ratio of (1:1).

Inclusion criteria:

All neonates admitted to the NICU with indirect exaggerated physiological hyperbilirubinemia were included provided they full fill the following criteria:

- Full term healthy birth.
- Gestational period more than 37 wks.
- Breastfeeding or formula feedings.
- Aged 2 to 10 days.
- On breastfeeding and or formula feeding.
- Total serum bilirubin level of more than 18 mg/dl.
- Initial serum C-reactive protein is negative.

Exclusion criteria:

- Neonates with pathological jaundice.
- Neonates with sepsis.

- Neonates with major congenital anomalies.
- Neonates with inborn errors of metabolism.
- Newborn with dehydration.
- Traumatic delivery.

Study design:

All neonates were subjected to the following:

1. Complete history taking with stress on (antenatal, natal, and post-natal history),
2. General examination including vital signs, body weight, hydration status, and local systemic examination (heart, chest, and abdomen).
3. Laboratory study:

All studied neonates were subjected to the following investigation:

1. Serum bilirubin (Total and direct):

- i. Method: Using automated (Cobas C111) (Roche)
- ii. Timing: at admission, 24, 48, 72 hrs of admission, at discharge

2. Complete blood count: using automated cell counter (cell dyne).

3. C reactive protein: using laxative serology test.

4. Reticulocyte count: By Brilliant cresyl blue stain (supravital staining).

5. Rh and blood grouping for mother and babies.

6. Coombs test (DIRECT).

Methods:

In our study, we collect 48 patients randomly divided into two groups:

Group 1: 24 neonates on breastfeeding on demand or formula feeding (20 ml of milk every 3 during admission) with extra IV fluid supplementation of normal saline /D5 (3:1) over period of 8 hrs in the first day of admission through peripheral vein.

Group 2: 24 neonates receiving breast milk or formula only in the same schedule as group 1, Both groups received the same type of LED continuous triple phototherapy. The eyes were protected from the light by eye shield to avoid retinal damage. To expose the most skin to light, the posture was regularly changed. Neonates were only ever brought out to be fed or change wet diapers and were always kept under phototherapy. Follow-up of TSB was done at time points 12, 24, 48, 72, 96, 120, and 144 hours of admission with a comparison between both groups regarding

TSB level and duration of phototherapy.

Statistical Analysis:

The analysis was carried out using SPSS version 22 and R version 4.1 (IBM, United States). Continuous variables were

presented in terms of mean and standard deviation. Fisher's Exact tests and chi-square tests were used to compare the proportion of patients in each therapy group. A p-value <0.05 was considered significant.

RESULTS

All results will be demonstrated in the following tables and figures:

Table (1): Shows the demographic characteristics of the two groups

Variables	Group1 (N= 24)	Group 2 (N= 24)	P-value*
Weight at admission /Grams			0.609
Mean (±SD)	3037 ± 384.9	3096 ± 404.2	
Gestational age			0.474
Mean (±SD)	38.50 ± 0.9325	38.33 ± 0.6370	
Age at admission(days)			0.327
Mean (±SD)	6.000 ± 1.615	6.458 ± 1.587	
Sex			0.561
Female	12 (50.0%)	9 (37.5%)	
Male	12 (50.0%)	15 (62.5%)	

This table shows insignificant differences regarding demographic characteristics between both groups.

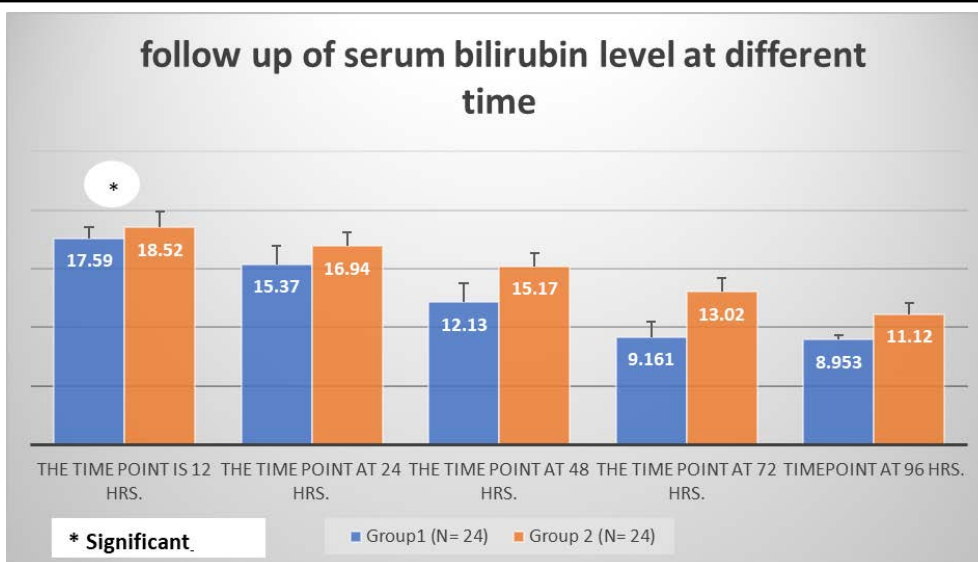


Figure (1): Serum bilirubin level at different time points

This figure shows significant differences regarding serum bilirubin level between both groups.

Table (2): Comparison of laboratory findings

Variables	Group1 (N= 24)	Group 2 (N= 24)	P-value*
Total serum bilirubin level at admission			
Mean (±SD)	19.62 ± 0.9096	18.98 ± 0.9469	0.0222*
Hematocrit			
Mean (±SD)	43.36 ± 3.926	41.48 ± 7.358	0.277
Hemoglobin			
Mean (±SD)	15.34 ± 1.405	15.04 ± 1.552	0.477
Reticulocytes			
Mean (±SD)	2.058 ± 0.7048	2.508 ± 0.9171	0.0636

This table shows significant differences regarding serum bilirubin at admission but insignificant differences regarding Reticulocytes, Hemoglobin and Hematocrit in both groups.

Table (3): Total bilirubin level at different time points stratified by treatment

Time point	Group1 (N= 24)	Group 2 (N= 24)	P-value*
The time point is 12 hrs.			
Mean (±SD)	17.59 ± 0.9492	18.52 ± 1.334	0.00777*
The time point at 24 hrs.			
Mean (±SD)	15.37 ± 1.597	16.94 ± 1.164	<0.001*
The time point at 48 hrs.			
Mean (±SD)	12.13 ± 1.661	15.17 ± 1.129	<0.001*
The time point at 72 hrs.			
Mean (±SD)	9.161 ± 1.300	13.02 ± 1.136	<0.001*
Timepoint at 96 hrs.			
Mean (±SD)	8.953 ± 0.3630	11.12 ± 0.9367	<0.001*

* P-value <0.05 = significant

This table shows significant differences regarding serum bilirubin at time 12 hrs. and high

significance at time 24, 48, 72, 96 hrs.

Table (4): time of discontenting of phototherapy and patients discharge in both studied groups

Time Point		Group 1 (N=24)	Group 2 (N=24)	Overall (N=48)	P-value*
Timepoint at 96 hrs.	Discharged	20 (83.3%)	0 (0%)	20 (41.7%)	0.00000002657*
	Remain	4 (16.7%)	24 (100%)	28 (58.3%)	
Timepoint at 120 hrs.	Discharged	24 (100%)	2 (8.3%)	26 (54.2%)	0.000000001177*
	Remain	0 (0%)	22 (91.7%)	22 (45.8%)	
Timepoint at 144hrs.	Discharged	24 (100%)	21 (87.5%)	45 (93.8%)	0.234
	Remain	0 (0%)	3 (12.5%)	3 (6.3%)	

This table shows significant differences regarding serum bilirubin at time 12 hrs. and high significance regarding

discontinuous of phototherapy and patients discharge remaining at time 96,120 and 144.

DISCUSSION

Unconjugated hyperbilirubinemia is a common newborn issue. 60% of term and 80% of preterm neonates may

experience it. Unconjugated bilirubin has the potential to be harmful to the central nervous system and can lead to kernicterus, resulting in long-term disability. So, in severe hyperbilirubinemia

rapid reduction of total serum bilirubin level is of utmost importance (**Bedi et al., 2018**). The most often used strategy to lower serum bilirubin is phototherapy (**Bhola et al., 2015**). Many neonates with hyperbilirubinemia who are admitted to the hospital also have some degree of dehydration, primarily because of difficulties with breastfeeding. Affected infants often display symptoms like lethargy, fever, and severe jaundice. By increasing insensible water loss, phototherapy may worsen these newborns' fluid deficits even more, especially in the preterm population (**Manning et al., 2007**).

In our study, in newborns with severe non-hemolytic hyperbilirubinemia receiving phototherapy, we investigated the effectiveness of IV fluid supplementation against non-supplementation in TSB reduction.

Some studies previously investigated the role of intravenous fluid supplementation in the treatment of severe neonatal hyperbilirubinemia. The duration of the intervention varied from two to three hours, 24 hours, up to three or four days. Despite the American Academy of Pediatrics (AAP), the literature review revealed no conclusive evidence that excessive fluid delivery

impacts the blood bilirubin concentration, a modest relative dehydration may have a role in lowering the response to phototherapy (**IRAN et al., 2004**).

Additional fluid therapy lowers serum bilirubin levels by enhancing the elimination of water-soluble photo isomers in urine by increasing blood flow to the kidneys. More insensible water loss during phototherapy combined with further insufficient oral feeding in sleepy babies due to significant hyperbilirubinemia can render newborns at risk for worsening hyperbilirubinemia if they don't receive supplementary fluids (**Kaur et al., 2018**).

Because the first eight hours of phototherapy are the most crucial because there is a high risk of exchange transfusion if phototherapy is unable to reduce TSB, and because breastfeeding rates were comparable between the two groups throughout the study, we decided to only supplement fluids during this time.

Follow-up of TSB at different time points revealed a significant reduction of TSB in group 1 than in group 2 at 12 hours ($p=0.007$) with highly significant differences at other times (24, 48, 72, and 96) hours ($p<0.001$). According to **Iranpour, 2004, Al-Masri, 2012, and Easa, 2013**, At 12 hours,

children who received IV fluid supplementation had somewhat lower serum bilirubin levels than those who did not (MD -10.21 mol/L, 95% CI -18.45 to -1.97; participants = 204; I2 = 0%) (**IRAN et al., 2004**; 13. **Al-Masri, 2012**; **Easa, 2013**).

Moreover, according to **Iranpour, 2004**, **Mehta, 2005**, **Al-Masri, 2012**, and **Easa, 2013**, babies who received IV fluid supplementation had a slightly reduced serum bilirubin at 24 hours compared to babies who did not (MD -6.06 mol/L, 95% CI -11.12 to -1.00; participants = 252; I2 = 11%) (**IRAN et al., 2004**; **Al-Masri, 2012**; **Easa, 2013**; **Mehta et al., 2005**).

Goyal, 2018 has demonstrated that adding 50 ml/kg of intravenous fluid in the initial few hours of treatment, accelerates the reduction of TSB. Throughout the intervention, the serum bilirubin levels in the IVF group decreased by 15.5%, those in the oral rehydration solution group (ORS) by 9.1%, and those in the control group by 8.0% ($p < 0.001$). Comparing the IVF group to the ORS and control groups, there was a noticeably larger percentage drop in TSB (**Goyal et al., 2018**).

Tank, 2018 similarly agreed with us, reporting that the study group's TSB decline was

significantly larger than the control group's at 4 hours, 8 hours, 24 hours, 36 hours, and 48 hours. Although there was no significant variance in the TSB level drop between the two groups at 60 hours (**Tank et al., 2018**). Moreover, a meta-analysis by **Gu, 2021** indicated that intravenous fluid supplementation can significantly reduce the TSB at 8, 12, 24, and 36 h as well as the frequency of exchange transfusion for neonatal hyperbilirubinemia but has no noticeable impact on the duration of phototherapy (**Gu et al., 2021**).

Despite this, multiple trials have documented the addition of intravenous fluids for severe hyperbilirubinemia. **Al-Masri, 2012** trial reported that intravenous fluid administered for the first 24 h of phototherapy, had no significant differences in terms of the mean rate of decrease in TSB levels, or the proportion of neonates requiring exchange transfusion 13. Moreover, **Balasubramanian, 2012** documented that the rate of fall in STB at 4, 8, 12, and 24 hours was similar between the two groups and was unaffected by the fluid type ($p > 0.05$) (**Balasubramanian et al., 2012**).

Previous studies reported conflicting results about the effect of IV fluid supplementation on the

duration of phototherapy. Our results revealed a decrease in the duration of phototherapy in group 1 as only 4 out of 24 patients in group 1 remained on phototherapy at 96 hours in contrast, all 24 patients in group 2 were still on phototherapy ($p=0.000$). Similarly, **Sajjid, 2013**, reported that intravenous fluids supplementation was useful in significantly reducing the need for blood exchange transfusion ($p = 0.001$). Also, the fluid supplementation group's overall phototherapy duration was considerably shorter ($p = 0.013$) (**Sajjid, 2013**). In addition, **Mehta, 2005** and **Romero, 2018** reported significant improvement in time to recovery in newborns with neonatal jaundice supplemented with intravenous fluid during phototherapy ($P < .001$) (**Mehta et al., 2005; Romero et al., 2018**).

In the same context, **Patel, 2014** and **Sasikumar, 2017** concluded that IV fluids can significantly decrease the phototherapy duration and similar results were reported in many studies though they used different fluids for a variable duration of time (**Sasikumar, 2017; Patel et al., 2014**). It's interesting to note that **Lai, 2017** discovered that newborns who got IV fluid supplementation had a

considerably lower need for exchange transfusions than infants who weren't supplemented. No patients in our study needed exchange transfusions, which can be attributed to the fact that all of the patients' initial TSB levels were below the range for exchange transfusions and that we excluded all conditions that could exacerbate hyperbilirubinemia, such as Rh/ABO or other minor blood group incompatibilities, cephalhematoma, sepsis, dehydration, etc. Thus, there was little need for exchange transfusion (**Lai et al., 2017**).

On the other hand, other studies reported no significant differences in the mean rate of STB decrease or in the proportion of neonates requiring exchange transfusion despite giving IV fluid supplementation (**Goyal et al., 2018; Demirsoy et al., 2011**). Because of the noninvasive nature of the IV route, complications like infections and thrombophlebitis can be associated with intravenous cannulation. However, no complications were reported in our study.

Therefore, our study found that IV fluid supplementation for 8 hours with breastfeeding in term neonates already receiving phototherapy causes more fall in TSB levels leading to shorter

duration of phototherapy and hospital stay.

CONCLUSIONS

Additional IV fluid supplementation during the initial 8 hours with phototherapy in neonatal hyperbilirubinemia may considerably shorten the overall phototherapy time and TSB level in severe non-hemolytic newborn hyperbilirubinemia. Future research is recommended to focus on higher-risk populations such as preterm neonates or neonates with hemolytic hyperbilirubinemia (which causes a rapid rise in bilirubin).

Recommendation

1. We recommend the administration of extra i.v. fluids normal saline /D5 (3:1) over period of 8 hrs. of the first day of admission through peripheral vein.
2. Further studies about the role of extra i.v. fluids on physiological hyperbilirubinemia are needed using a larger sample size.

LIMITATIONS

A small sample size may lead to bias in the level of TSB at admission as it was higher in group 1 compared to group 2.

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