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Effect of intravenous fluid supplementation on exchange transfusion rate in neonatal unconjugated hyperbilirubinemia.

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Abstract

Background: Severe hyperbilirubinemia has the potential to cause permanent neurological sequelae and long-term morbidity. Fluid supplementation along with intensive phototherapy has been shown to expedite decline in serum bilirubin in non-hemolytic unconjugated hyperbilirubinemia.
Objective: Objective of this prospective cohort study was to evaluate the effect of fluid supplementation in addition to intensive phototherapy in neonates with all cause (haemolytic and non-haemolytic) unconjugated hyperbilirubinemia.
Methods: Neonates born at gestation greater than 35 weeks awaiting exchange transfusion were enrolled and administered fluid supplementation (50 ml/Kg of 5% dextrose N/5 solution along with half of the maintenance fluid) for 8 hours, in continuation with intensive phototherapy. Primary outcome was the need for exchange transfusion and secondary outcomes were rate of decline of serum bilirubin.
Results: Exchange transfusion procedure could be averted in 76% (61/80) of enrolled neonates. Baseline total serum bilirubin cut off of 27.5 mg/dl was the only factor that predicted exchange transfusion with 89.47% sensitivity and 88.52% specificity and a negative predictive value of 96.4%.
Conclusion: In neonates born at greater than 35 weeks gestation with unconjugated hyperbilirubinemia awaiting exchange transfusion, the delay in procedure due to logistic reasons in resource limited settings, can be utilized with fluid supplementation along with phototherapy to curtail the need for exchange transfusion.

Keywords: Neonates, Unconjugated hyperbilirubinemia, Jaundice, Exchange transfusion, Fluid supplementation, Phototherapy.

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Introduction

Approximately 60% healthy term neonates develop jaundice and nearly 5%-11% have hyperbilirubinemia severe enough to require exchange transfusion [1]. Severe hyperbilirubinemia puts these otherwise healthy neonates at risk for chronic bilirubin encephalopathy [2]. Rapid reduction of Total Serum Bilirubin (TSB) level, by exchange transfusion, is of utmost importance to prevent bilirubin encephalopathy. While awaiting exchange transfusion, intensive phototherapy is the main treatment modality. However, in resource-limited settings, it takes lots of time to arrange for exchange transfusion and the procedure is fraught with life threatening complications [3]. Studies have shown that fluid supplementation along with phototherapy lead to faster decline in serum bilirubin as compared to phototherapy alone in non-hemolytic unconjugated hyperbilirubinemia. This strategy can be applied in non-hemolytic unconjugated hyperbilirubinemia while waiting for the exchange transfusion. However, the studies till now have excluded hemolytic cases, though hemolysis is the most important cause for hyperbilirubinemia needing exchange transfusion. Hence, this cohort study was planned to evaluate whether fluid supplementation along with phototherapy had an impact on the rate of exchange transfusion in neonates with gestation more than 35 weeks with all-cause unconjugated hyperbilirubinemia [4].

What is known

- Neonatal hyperbilirubinemia especially due to haemolytic causes often requires exchange transfusion to prevent acute bilirubin encephalopathy.
- Exchange transfusion is an invasive procedure and has logistic challenges in resource limited settings.
- While waiting for exchange transfusion, intensive phototherapy is the main modality of management.

What is new

Fluid supplementation in addition to intensive phototherapy, can avert the need for exchange transfusion in 75% of neonates more than 35 weeks of gestation, who are awaiting the procedure due to logistic reasons.

Materials and Methods

This was a cohort study conducted over a period of 18 months at a tertiary care government medical college after taking ethical clearance (IEC/VMMC/SJH/Thesis/October/2018-07) from Institutional ethics committee. All referred neonates with gestation more than 35 weeks, admitted to out born neonatal unit with hyperbilirubinemia in exchange range as per the American Academy of Pediatrics (AAP) guidelines for exchange transfusion were recruited for the study [5]. Neonates with major congenital malformations, those already receiving intravenous fluids due to some other reasons, having features of bilirubin induced neurological damage or obvious signs of clinical dehydration and those who were severely sick needing intubation or in shock were excluded from the study. All babies while awaiting exchange transfusion were subjected to intensive LED (Light Emitting Diode) phototherapy (Make: Bird Meditech) along with fluid supplementation with 5% N/5 @ 50 ml/kg over 8 hours infusion in addition to half of the maintenance fluids (given as oral/breast feeds or intravenous infusion if not tolerating enteral feeds) [6]. Demographic, history and examination data was recorded on predesigned proforma. Baseline serum bilirubin was measured using Beckman coulter by Di-Azo principle and repeated every 4 hours till exchange was arranged or baby went out of exchange range. Intensive phototherapy was continued, and fluid supplementation was stopped after 8 hours, even if logistics for exchange transfusion was still not arranged. While undergoing fluid supplementation, once logistics were arranged, exchange was performed immediately without delay if previously available serum bilirubin was in that range. Once total serum bilirubin decreased two-digit levels below phototherapy range, it was omitted. Rebound serum bilirubin was done after 12 hours of omission of phototherapy. Once baby was out of phototherapy range, the baby was considered to have completed the study [7].

Primary outcome was the requirement of exchange transfusion after interventions. Secondary outcomes were percentage fall of serum bilirubin at four and eight hours of admission and total duration of phototherapy [8]. Data were compared for neonates who averted versus those who underwent exchange transfusion despite fluid supplementation and phototherapy to find predictors of failure of the latter. A comparative analysis was also performed for hemolytic versus non-hemolytic causes of hyperbilirubinemia [9].

Sample size

Considering 14.05% of babies undergoing exchange transfusion despite fluid supplementation plus phototherapy, margin of error as 8%, level of significance as 5%, sample size came out to be 80 neonates [8]. Using formula: $N \geq (p\ (1\ -p))/(ME/z\alpha)\ 2$ where $Z\alpha$ is value of Z at two-sided alpha error of 5%, ME is margin of error and p is proportion of non-responders [10].

Results

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non-parametric test was used. Quantitative variables were compared using Independent t test/Mann-Whitney Test between the two groups [11]. Qualitative variables were compared using Chi-Square test. Receiver operating characteristic curve was used to find out cut off point of serum bilirubin for predicting exchange transfusion. A p value of <0.05 was considered statistically significant. The data was analyzed using Statistical Package for Social Sciences (SPSS) version 21.0 [12]. We enrolled 80 neonates who fulfilled the inclusion criteria (Figure 1).

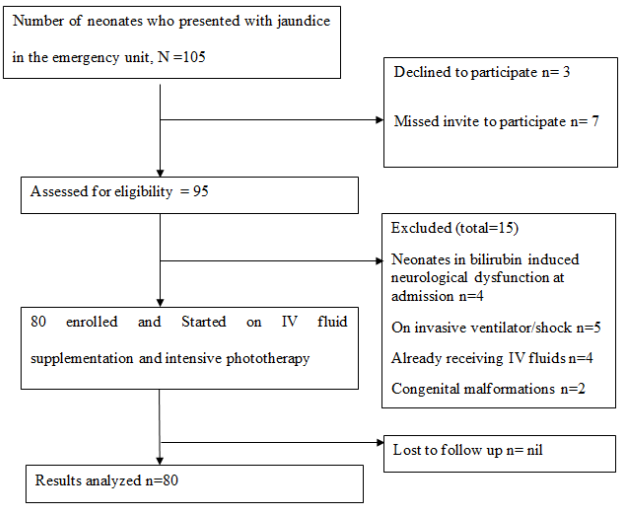

Figure 1. *Study flowchart.*

40% (32/80) neonates had blood group incompatibility; of which 25% (20/80) had ABO incompatibility and Rh incompatibility was detected in 15% (12/80). Baseline characteristics of the study cohort are given in Table 1. We found that 76.25% (61/80) babies averted the need for exchange transfusion with intravenous fluid supplementation combined with intensive phototherapy.

Table 1. *Baseline characteristics of the study cohort.*

Parameters	Total n=80
Gender female	48 (60)
Mode of Delivery	66 (82.5)
Vaginal	

Gestation (in weeks)	38 (37.3-38.8)
Birth weight (grams)	2700 (2550-2900)
Age of presentation (hours of life)	108 (73-128.5)
Range	16-330
Percentage weight loss at admission	1.79 (0-3.6)
Range	0-8
Baseline serum sodium (meq/L)	140.7 ± 5.9
Baseline serum bilirubin (mg/dl)	26.4 ± 4.5
Mean Hb (mg/dl)	15.1 ± 1

On analysing the predictors of failure of the intervention, baseline characteristics were similar in neonates who finally underwent exchange transfusion (exchange group) versus those who did not (non-exchange group) (Table 2).

Table 2. *Primary and secondary outcomes (N=80).*

Outcomes	**Exchange Transfusion group (N=19)**	**Non-Exchange group (N=61)**	**p value**
Primary outcome$	19/80 (23.7%)	61/80 (76.2%)	< 0.001
Secondary outcomes			
Serum bilirubin at 4 hours mg/dl#	29.5 ± 4.3	21.7 ± 3.2	< 0.001
Percentage fall in serum bilirubin at 4 hours from baseline*	55 (52.7-7)	70(55-90)	0.075
Serum bilirubin at 8 hours mg/dl#	26.4 ± 5	18.2 ± 3.3	< 0.001
Percentage fall in serum bilirubin from baseline*	57.5(51.9-71.9)	78.8 (67.6-91.2)	0.201
Duration of phototherapy (hours)*	26 (22-28)	16 (12-20)	< 0.001

We found significant difference between serum bilirubin at baseline, at 4 hours and at 8 hours of fluid supplementation and phototherapy between the two groups. However, there was no difference in rate of decline of serum bilirubin between exchange and non-exchange groups (Table 3).

Table 3. *Comparison of characteristics between exchange transfusion and non-exchange groups.*

Parameter	**Exchange group(n=19)**	**Non-exchange group (n=61)**	**p value**
Gender female$	8 (42.11)	40 (65.57)	0.068
Mode of DeliveryVaginal	17 (89.5)	49 (80.3)	0.5
Gestation (in weeks)	37.9 (37.2-38.1)	38.1 (37.28-38.8)	0.2
Birth weight (grams)	2700 (2600-2900)	2700 (2550-2990)	0.646
Age of presentation (hours of life) range	97 (76-128.5)	108 (73-127)	0.95
	39-180	16-330	
Percentage weight loss at admissionRange	1.85 (0-4.2)	1.79 (0-3.3)	0.426
	0-8	0-6.98	
Baseline Serum sodium (meq/L)	139.1 ± 5.9	141.16 ± 5.7	0.192
Baseline serum bilirubin (mg/dl)	31.9 ± 4.2	24.8 ± 2.9	<0.001
Mean Hemoglobin mg/dl	14.3 ± 0.5	14.2 ± 0.6	0.41
Hemolytic cause of jaundice	7 (36.8)	23 (37.7)	0.94

Using ROC curve, we found a baseline total serum bilirubin of 27.5 mg/dl predicts the requirement of exchange transfusion with 89.47% sensitivity and 88.52% specificity and a negative predictive value of 96.4%. Area under the ROC curve (AUC) was 0.91, standard error 0.0533 with 95% CI: 0.825 to 0.962 (Figure 2).

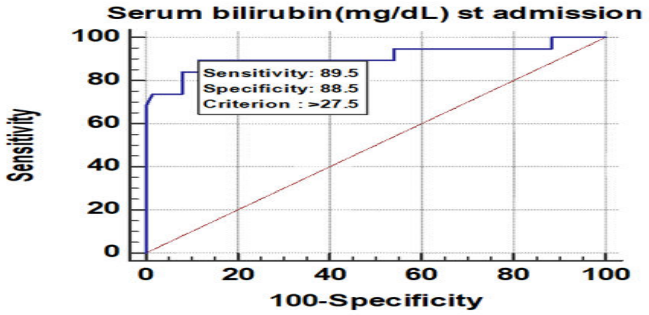

Figure 2. *Receiver operator characteristic curve depicting cut off serum bilirubin at admission for predicting exchange transfusion.*

We also compared demographic and outcome variables for hemolytic versus non-haemolytic causes; except for the mean haemoglobin level at presentation, none of the factors were found to be statistically significantly different in the two groups (Table 4).

Table 4. *Comparison of characteristics between hemolytic and non-hemolytic cause of hyperbilirubinemia.*

Parameter	Hemolytic cause of hyperbilirubinemi aN=30	Non-hemolytic cause of hyperbilirubinemi a N=50	p value
Gender female	19 (63)	27 (54)	0.414
Mode of delivery vaginal	24 (80)	42 (84)	0.649
Gestation in weeks	37.9 ± 1.2	37.6 ± 1.3	0.347
Birth weight grams	2773.3 ± 279	2683.1 ± 425	0.18
Age of presentation (hours of life)	101 ± 66.7	113.1 ± 38.4	0.45
Percentage weight loss at admission	25.9 ± 4.1	26.6 ± 4.6	0.906
Serum bilirubin @ admission (mg/dl)	25.9	26.6	0.381
Serum bilirubin @ 4 hours (mg/dl)	23 ± 4.3	23.9 ± 6	0.589
Serum bilirubin @ 8 hours(mg/dl)	19.9 ± 4.8	20.3 ± 5.3	0.788
Mean hemoglobin (mg/dl)	14.1 ± 0.7	15.8 ± 0.6	<0.001
Need for exchange transfusion	7 (23.3)	12 (24)	0.947, OR=0.037 95% CI (-1.029-1.103)

On multivariate analysis, only serum bilirubin level of more than 25 mg% at admission was found to be statistically significantly associated with the need for exchange transfusion (Table 5).

Table 5. *Multivariate analysis for factors affecting the need for exchange transfusion.*

S. no	Parameter	Adjusted odds ratio	95% CI	p value
1	Age	1.85	0.25 to 13.65	0.54
2	Gender	0.57	0.17 to 1.89	0.36
3	Hemolytic cause of hyperbilirubinemia	1.45	0.41 to 5.12	0.55
4	Birth weight less than 2500 g	0.47	0.07 to 3.09	0.43
5	Gestation less than 37 weeks	0.62	0.05 to 7.32	0.71
6	Mode of delivery	1.36	0.23 to 7.80	0.72
7	Bilirubin level at admission	12.52	1.84 to 85.14	0.01

Discussion

Exchange transfusion in neonatal unconjugated hyperbilirubinemia with bilirubin level in exchange zone is a medical emergency as the procedure needs to be performed as early as possible to prevent lifelong morbidity like kernicterus. However, in Low Middle-Income Countries (LMIC) this is far from reality. To arrange blood and logistics for an exchange transfusion is itself a difficult proposition and takes a longer time. Again this facility is available mostly in the tertiary care hospitals. However, till now, many studies have shown that fluid supplementation along with phototherapy reduces the rate of need for exchange transfusion. A Cochrane review by Lai et al. found that fluid-supplemented infants were less likely to require exchange transfusion (RR 0.39, 95% CI 0.21 to 0.71; RD-0.01, 95% CI-0.04 to 0.02), but they concluded that the evidence was of low quality, downgraded one level due to inconsistency, and another level due to suspected publication bias and the estimate was affected by unexplained heterogeneity. They suggested studies to be done in population with higher baseline risk of bilirubin related neurological complications, at risk population and with hemolytic hyperbilirubinemia [13].

In this cohort study, we found that exchange transfusion could be averted in 76.25% (61/80) of the enrolled neonates, by intravenous fluid supplementation (5% N/5 @ 50 ml/kg over 8 hours) along with intensive phototherapy, while waiting for the blood to be arranged for exchange transfusion [14]. Significantly lower exchange transfusion rates (as compared to ours 23.7%), were also found in intravenous fluid supplementation group versus control group in a randomized trial by Mehta et al (16% *vs.* 54%), and even lower by Bandopadhyay et al (5.6% *vs.* 12%). [9,10] All these studies had excluded neonates with hyperbilirubinemia of greater than 25 mg/dL, those requiring immediate exchange transfusion and hyperbilirubinemia of hemolytic causes unlike ours, as we included all neonates with unconjugated hyperbilirubinemia with serum bilirubin in exchange range irrespective of bilirubin level and cause. This inclusion makes our study more generalizable for the treatment of hyperbilirubinemia. Also, the primary outcome in these studies were the rate of fall of serum bilirubin level in first 24 hours, not the decline in rate of exchange transfusion and were not powered to ascertain the decrease in the rate of exchange transfusion rates. Similar to our study, Sasikaran et al included similar cohort of neonates with all cause hyperbilirubinemia and reported lower rate of exchange transfusion (3% versus 12.1%, respectively with intervention and without intervention). They found no difference in outcomes between hemolytic and non-hemolytic hyperbilirubinemia, like in our study. In another study by Essa et al, there was reduction in rates of exchange transfusion with additional fluid therapy. The reason may be that they used a lower volume for supplementation [15].

Coming to rate of fall of serum bilirubin, we found significant rate of fall at 4 hours and at 8 hours of fluid supplementation then those who received only phototherapy which was similar to the Cochrane review by Lai et al, who concluded that in term, healthy new-born infants who received IV fluid supplementation while undergoing phototherapy had modestly lower serum bilirubin at four and eight hours after the commencement of intervention compared to infants who did not [16]. Further analysis of neonates who failed the fluid supplementation and phototherapy, showed no significant difference in total duration of phototherapy in babies who failed intravenous fluid plus phototherapy and required exchange transfusion. Various studies have diverse conclusions, with few finding no difference with fluid therapy [17]. While others embarked decreased duration of phototherapy in fluid supplementation group as compared to no fluid supplementation. [18]. This could be because of the variation in route, amount of fluid supplementation and selection of patients with percentage of dehydrated babies or those with weight loss more than 10%. The study reports, only one mortality after 28 days of admission due to severe sepsis during hospital stay, unrelated to the procedure and the rest all neonates were discharged home. Literature shows that exchange transfusion carries a mortality rate of 0.1% to 3.2% and complication rate of 6.3%, besides the risks associated with massive blood transfusion.

We found that babies who finally required exchange transfusion despite fluid supplementation had a higher baseline total serum bilirubin. On logistic regression, none of the factors except total serum bilirubin of more than 25 mg% at admission was found to be statistically significantly associated with need for exchange transfusion. A bilirubin cut off above 27.5 mg% predicted the need for exchange transfusion with high sensitivity, specificity, and negative predictive value in the

present study. One randomized controlled trial by Balasubramanian et al found that administration of hypotonic fluid (0.2% NS) to prevent exchange transfusion in term neonates was associated with a higher incidence of hyponatremia while isotonic (0.9% NS) fluid was associated with hypernatremia at the end of 8 hours [19]. There were no apparent adverse effects of fluid therapy noted for fluid overload and sodium imbalance in our study.

We did not include neonates with gestation less than 35 weeks where morbidity due to hyperbilirubinemia is high and threshold for brain damage is lower, due to the reason that safety of intravenous fluid supplementation has not been studied yet in the context of hyperbilirubinemia in this group. The current study is applicable to neonates above 35 weeks and is generalizable, especially in resource limited settings as blood for exchange transfusion takes a long time to arrange is fraught with life threatening complications and delay causes risk of permanent brain damage. In this study, the observed time needed for arrangement of blood for exchange transfusion to be 9.47 ± 1.93 hours (mean ± SD). The study population comprised of out born neonates without mother/maternal blood group/maternal blood sample being available and referred to us in emergency. After this study, we took quality measures to decrease the time needed for arranging exchange transfusion in out born neonates.

The current study included all cause exchange range hyperbilirubinemia cases and has more generalizability to units which are tertiary care referral centers for out born neonates. However, the mean hemoglobin of the neonates in this study was 15.1 ± 0.6 mg/dl and lowest was 12.9 mg/dl, therefore, thus it is difficult to comment on fluid supplementation in neonates with severe anemia due to hemolysis [20].

Conclusion

In neonates born at greater than 35 weeks gestation, and presenting with unconjugated hyperbilirubinemia in exchange transfusion range, the delay in procedure due to logistic reasons in resource limited settings, can be utilized with fluid supplementation along with intensive phototherapy to curtail the need for exchange transfusion. Also before referring the patient for exchange transfusion to a higher center, fluid therapy could be started from the referring point.

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Competing Interests

The authors declare that they do not have any conflict of interest or competing interest.

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References

1. Kleigman RM, Stanton BF, St Geme JW, et al. Jaundice and hyperbilirubinemia in newborn nelson textbook of pediatrics 19th Ed philadelphia saunders. 2012;603-607.
2. Bhutani VK, Johnson LH, Keren R, et al. Diagnosis and management of hyperbilirubinemia in the term neonate: For a safer first week. Pediatr Clin North Am. 2004;51:843-61.
3. Dennery PA, Seidman DS, Stevenson DK, et al. Neonatal hyperbilirubinemia. N Engl J Med. 2001;344:58-90.
4. Ip S, Chung M, Kulig J, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics. 2004;114:130-53.
5. Boo NY, Lee HT. Randomized controlled trial of oral versus intravenous fluid supplementation on serum bilirubin level during phototherapy of term infants with severe hyperbilirubinemia. J Paediatr Child Health. 2002;38:151-5.
6. Kaur R, Singh N, Singh P, et al. Intravenous fluid supplementation as treatment modality in non-hemolytic neonatal hyperbilirubinemia. Int J Curr Res Med Sci. 2018;4:46-52.
7. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35or more weeks of gestation. Pediatrics. 2004;114:297-316.
8. Saini SS, Kumar P, Balasubramanium K, et al. Fluid Supple mentation in Hyperbilirubinemia. Indian J Pediatr. 2011;78:1096-9.
9. Mehta S, Kumar P, Narang A, et al. A randomized controlled trial of fluid supplementation in term neonates with severe hyperbilirubinemia. J Pediatr. 2005;147:781-5.
10. Bandyopadhyay A, Maiti R. Fluid supplementation in term neonates with severe hyperbilirubinemia: a randomized controlled trial study. Int J Contemp Pediatr. 2017;4:853-7.
11. Sasikumar BR, Senthilkumar P, Sathyan VK, et al. A Randomized trial of intravenous fluid supplementation along with phototherapy in reducing bilirubin in neonates > 35 weeks with significant jaundice. IOS-JDMS. 2017;16:40-5.
12. Lai NM, Ahmad Kamar A, Choo YM, et al. Fluid supplementation for neonatal unconjugated hyperbilirubinaemia. Cochrane Database Syst Rev. 2015;9:CD011891.
13. Easa ZO. Effect of intravenous fluid supplementation on serum bilirubin level during conventional phototherapy of term infants with severe hyperbilirubinemia. Al-Qadisiah Medical J. 2013;9:36-45.
14. Boo NY, Lee HT. Randomized controlled trial of oral versus intravenous fluid supplementation on serum bilirubin level during phototherapy of term infants with severe hyperbilirubinaemia. J Paediatr Child Health. 2002;38:151-5.
15. Torkaman M, Afsharpeyman SH, Amirsalary S, et al. The effect of fluid supplementation on serum bilirubin level during phototerapy in term infants. Tehran Uni Med J. 2006;64:85-9.

16. Goyal P, Mehta A, Kaur J, et al. Fluid supplementation in management of neonatal hyperbilirubinemia: A randomized controlled trial. J Matern Fetal Neonatal Med. 2018;31:2678-84.
17. Saeidi R, Heydarian F, Fakehi V, et al. Role of intravenous extra fluid therapy in icteric neonates receiving phototherapy. Saudi Med J. 2009;30:1176-9.
18. Patel M, Munshi S, Mehariya KM, et al. Effect of fluid supplementation in neonatal hyperbilirubinemia. IJSR. 2014;3:2524-6.
19. Jackson JC. Adverse events associated with exchange transfusion in healthy and ill newborn. Pediatrics. 1997;99:e7.
Balasubramanian K, Kumar P, Saini SS, et al. Isotonic vers us hypotonic fluid supplementation in term neonates with severe hyperbilirubinemia-a double-blind, randomized, controlled trial. ActaPaediatr. 2012;101.

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