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To study the effect of fluid supplementation in neonatal unconjugated hyperbilirubinemia in reducing the rate of exchange transfusions

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Abstract

Background: Aims of study was to evaluate the effect of intravenous fluid supplementation on exchange transfusion rates in neonatal unconjugated hyperbilirubinemia in neonates (>35 weeks).

Methods: This study was conducted in the Department of Paediatrics, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi. As per inclusion and exclusion criteria, sample size was achieved and 80 neonates were recruited. All babies received supplemental intravenous fluids (50 ml/kg N/5 with 5% Dextrose + half of the maintenance fluid) infusion over 8 hours along with intensive phototherapy and breastfeeding on demand.

Results: In exchange transfusion done neonates mean gestation value is 37.79 ± 0.94 and non-exchange neonates is 38.22 ± 1.34. The difference is statistically not significant (p-value = 0.2). In exchange transfusion done neonates mean duration of phototherapy is 25.79 ± 5.54 and in not exchange neonates is 16.39 ± 4.32. The difference is statistically significant (p-value = 0.0001). Non exchange group neonates are required less duration of phototherapy.

Conclusion: In more than 35 weeks' gestation neonates with all cause unconjugated hyperbilirubinemia in exchange transfusion zone, time delay in arranging for the latter in resource limited settings can be cashed upon with fluid supplementation along with phototherapy to cut down the need for exchange transfusion

Keywords: Bilirubin, neonates, unconjugated.

Introduction

Neonatal hyperbilirubinemia refers to the yellow discoloration of skin and sclera of newborn babies and results from the deposition of bilirubin. Jaundice is seen first in the face, and then usually follows cephalocaudal progression to chest, abdomen and limbs. However, visual assessment of the bilirubin level can lead to wrong estimation of measuring total serum bilirubin.[1]It occurs in 60% of term and 80% of preterm neonates.[2]Most neonates develop hyperbilirubinemia during the first week of their life.[3,4] Unconjugated hyperbilirubinemia cause serious central nervous system toxicity, also known as kernicterus, primarily involvement brain stem nuclei and basal ganglia resulting in athetoid type cerebral palsy athetoid type cerebral palsy.[5] 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.[6]

Combination of oral feeding and extra i.v. fluid therapy may result in -

1. Decrease in enterohepatic circulation, so a lower rate of bilirubin reabsorption from the bowel.
2. Serum bilirubin dilution
3. Increased blood circulation to the kidneys and rise in urine output, and subsequently improve excretion of water soluble photo isomers in urine.[7]

4. On the other hand, it is suggested that high TSB levels can cause sleepiness in newborns. Hence, insufficient oral feeding in such sleepy cases can, along with increased insensible water loss during phototherapy predispose to the worsening of hyperbilirubinemia in newborns not receiving extra fluids. Breastfeeding may be affected due to sleepiness of babies with severe hyperbilirubinemia.

Some neonates with high bilirubin levels are mildly dehydrated and may need supplemental fluid to correct their dehydration. Furthermore, the photoproducts responsible for the decline in serum bilirubin are excreted in urine and bile. Hence, maintenance of adequate hydration and good urine output help to improve the efficacy of phototherapy.[8]A common reason that hospitalized children receive parenteral fluids is to treat isotonic dehydration. Although isotonic saline is recommended for acute volume expansion, hypotonic fluids with 0.45% sodium chloride are currently recommended for the remainder of the deficit therapy.[9]In our study, we evaluated the average time taken from phototherapy to exchange transfusion in neonates. Also, it is important to know the groups of neonates in whom phototherapy is unlikely to work, so that an can be performed. Considering the above points in mind, we planned and conducted the study on the efficacy of fluid supplementation, which is relatively simple and universally available, as a measure to reduce bilirubin levels.

Materials and method

Study design: prospective cohort study

Study venue: Department of Paediatrics, VMMC & Safdarjung Hospital, New Delhi

Study Period: 18 months

Study population: Neonates >35 weeks with unconjugated hyperbilirubinemia TSB levels in exchange range as per AAP charts, while awaiting for exchange transfusion, who will meet the inclusion criteria.

Sample Size: 80

The study of Shiv Sajan Saini, et al observed that 14.05% of patients were non-responders. Taking this value as reference, the minimum required sample size

with 8% margin of error and 5% level of significance is 73 patients. To reduce margin of error, total sample size taken is 80.

Formula used is:

$N \geq (p(1-p))/(ME/z_\alpha)^2$

Where Z_α is value of Z at two-sided alpha error of 5%, ME is margin of error and p is proportion of non-responders.

Calculations

$n>=((.1405*(1-.1405))/(.08/1.96)^2=72.49=73$(approx.)

Inclusion criteria: All neonates >35 weeks of gestation with total serum bilirubin in exchange range as per AAP chart while waiting for exchange transfusion procedure were included in the study.

Exclusion criteria

Neonates with obvious clinical signs of dehydration or acute bilirubin encephalopathy.

Neonates with previously diagnosed cardiac, renal and other major congenital malformations.

Neonates already receiving IV fluids for any reason or had already undergone exchange transfusion were excluded from the study.

Statistical Analysis

Categorical variables will be presented in number and percentage (%) and continuous variables will be presented as mean ± SD and median. Normality of data will be tested by Kolmogorov-Smirnov test. If the normality is rejected, then non parametric test will be used.

Statistical tests will be applied as follows:

1. Quantitative variables will be compared using unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables will be compared using Chi-Square test /Fisher's exact test.

A p value of <0.05 will be considered statistically significant.

The data will be entered in MS EXCEL spreadsheet and analysis will be done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

This study was conducted in the Department of Pediatrics, Vardhman Mahavir medical college & Safdarjung hospital New Delhi from November 2018 to April 2019. As per the criteria of inclusion and exclusion mentioned in the plan of thesis, a sample size of 80 patients was selected. All of these received supplemental intravenous. fluids (N/5 saline D5% @) 50ml/kg along with intensive phototherapy and breastfeed on demand for initial 8 hours and were analyzed for the primary outcome which was rate of exchange transfusion. We found 76.25% (61) babies averted the need for exchange transfusion with intravenous fluid supplementation.

Table 1: Comparison of baseline characteristics

Baseline characteristics	Exchange transfusion done (n=19)	Exchange transfusion not done (n=61)	Total (n=80)	P value	Test performed
Gender					
Female	8 (42.11%)	40 (65.57%)	48 (60%)	0.068	Chi square test,3.325
Male	11 (57.89%)	21 (34.43%)	32 (40%)		
Mode of delivery					
Normal vaginal	17 (89.47%)	49 (80.33%)	66 (82.50%)	0.5	Fisher

delivery					Exact test
LSCS	2 (10.53%)	12 (19.67%)	14 (17.50%)		
Gestation in weeks					
Mean ± Stdev	37.79 ± 0.94	38.22 ± 1.34	38.12 ± 1.27	0.2	t test;1.291
Median (IQR)	37.86(37.214-38.143)	38.14(37.286-38.857)	38(37.286-38.857)		
Range	35.43-39.86	35.57-41.29	35.43-41.29		
Birth weight(gm)					
Mean ± Stdev	2773.16 ± 298.48	2699.43 ± 400.02	2716.94 ± 377.93	0.646	Mann Whitney test;539
Median (IQR)	2700(2600-2900)	2700(2550-2900)	2700(2550-2900)		
Range	2370-3500	1220-3800	1220-3800		
Serum bilirubin(mg/dL)					
Mean ± Stdev	31.94 ± 4.16	24.68 ± 2.92	26.4 ± 4.48	<.0001	Mann Whitney test;104.5
Median (IQR)	32.6(29.25-35.55)	25(23.6-26.2)	25.85(24-28.2)		
Range	22.1-37.8	15.6-30	15.6-37.8		
Serum electrolyte sodium(mEq/L)					
Mean ± Stdev	139.11 ± 5.95	141.16 ± 5.79	140.68 ± 5.86	0.192	Mann Whitney test;464.5
Median (IQR)	140(136-143)	142(138-145)	142(136-145)		
Range	127-148	129-150	127-150		
Serum electrolyte potassium(mEq/L)					
Mean ± Stdev	4.34 ± 0.84	4.42 ± 0.64	4.4 ± 0.69	0.461	Mann Whitney test;514.5
Median (IQR)	4.1(3.85-4.9)	4.3(3.9-5)	4.3(3.9-5.025)		
Range	2.9-6.2	2.9-5.6	2.9-6.2		
Age in hours					
Mean ± Stdev	105.95 ± 38.28	109.05 ± 62.9	108.31 ± 57.8	0.95	Mann Whitney test;574
Median (IQR)	97(76-128.5)	108(73-127)	108(73-128.5)		
Range	39-180	16-330	16-330		
Percent weight loss					
Mean ± Stdev	2.74 ± 2.75	1.94 ± 1.8	2.13 ± 2.07	0.426	Mann Whitney test;510.5
Median (IQR)	1.85(0-4.167)	1.79(0-3.448)	1.82(0-3.571)		
Range	0-8	0-6.98	0-8		

Table 1 shows comparison of baseline characteristics gender, gestation in weeks, birth weight, weight loss, age in hours, mode of delivery, baseline serum bilirubin, baseline serum electrolytes (sodium, potassium). All these parameters were similar in exchange transfusion group and non-exchange group. Fall of serum bilirubin in exchange transfusion group and non-exchange group was significant (p value<0.0001).Mean serum bilirubin 31.94 ± 4.16, 24.68 ± 2.92 in exchange done group or not done group and Median (IQR) is 32.6(29.25-35.55), 25(23.6-26.2) in both exchange and not exchange group. Mean gestation is 37.79 ± 0.94, Median(IQR) 37.86(37.214-38.143) in exchange transfusion done babies and Mean is 38.22 ± 1.34, Median(IQR) 38.14(37.286) in non-exchange. Serum electrolyte sodium (mEq/L) in exchange done Mean is 139.11 ± 5.95, Median is 140(136-143) and exchange transfusion not done Mean 141.16 ± 5.79, Median is 142(138-145). Similarly serum potassium Mean ± Stdev 4.34 ± 0.84, Median (IQR) 4.1(3.85-4.9) in exchange done and 4.42 ± 0.64, 4.3(3.9-5) in exchange not done. No fluid electrolytes disturbance seen in both exchange and not done exchange.

Age in hours Mean ± Stdev105.95 ± 38.28, Median (IQR) 97(76-128.5 in exchange group and 109.05 ± 62.9,108(73-127) in non-exchange group. P value is 0.95 which is not significant.

Table 2: Comparison of outcome measures

Characteristics	Exchange transfusion done (n=19)	Exchange transfusion not done (n=61)	Total	P value	Test performed
Duration of phototherapy(hours)					
Mean ± Stdev	25.79 ± 5.54	16.39 ± 4.32	18.62 ± 6.11	<.0001	Mann Whitney test;110.5
Median (IQR)	26(22-28)	16(12-20)	18(12-22)		
Range	15-36	8-26	8-36		
Serum bilirubin at 4 hours(mg/dL)					
Mean ± Stdev	29.48 ± 4.36	21.74 ± 3.23	23.58 ± 4.82	<.0001	Mann Whitney test;95.5
Median (IQR)	30(27.6-33.4)	22.3(20.5-23.5)	22.75(21.425-25.45)		
Range	19.5-35.7	10.3-27.5	10.3-35.7		
Serum bilirubin at 8 hours(mg/dL)					
Mean ± Stdev	26.41 ± 5.02	18.23 ± 3.34	20.17 ± 5.15	<.0001	Mann Whitney test;141.5
Median (IQR)	27.5(23.55-30.6)	18.6(17.5-20)	19.1(17.6-22.175)		
Range	17-32.7	7.2-24.5	7.2-32.7		
Percentage change in S.BIL(@4hrs) (mg/dL)					
Mean ± Stdev	61.32 ± 22.58	73.57 ± 26.76	70.66 ± 26.22	0.075	t test;1.803

Median (IQR)	55(52.5-75)	70(55-90)	66.25(52.5-88.125)		
Range	27.5-110	12.5-137.5	12.5-137.5		
Percentage change in S.BIL(@8hrs) (mg/dL)					
Mean ± Stdev	69.08 ± 36.96	80.66 ± 17.19	77.91 ± 23.67	0.2	t test;1.322
Median (IQR)	57.5(51.875-71.875)	78.75(67.5-91.25)	75(62.5-89.062)		
Range	31.25-195	50-122.5	31.25-195		

In exchange group, mean (±SD) duration of phototherapy was 25.79 ± 5.54 hours in exchange group and 16.39 ± 4.32 in non-exchange group (p value <.0001).

There was significant fall in serum bilirubin at 4 hours and 8 hours as depicted in table 26 in exchange group versus non-exchange group (p<0.001). Mean ± Stdev29.48 ± 4.36, Median (IQR)30(27.6-33.4) in exchange group and Mean ± Stdev21.74 ± 3.23, Median (IQR)22.3(20.5-23.5) in non-exchange group.

Percentage fall in serum bilirubin between admission to 4hours and 8 hours post fluid therapy between exchange and non-exchange group was not significant (p value 0.075 and 0.2 respectively).

Discussion

This study was conducted in the Department of Paediatrics, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi. As per inclusion and exclusion criteria mentioned in the plan, sample size was achieved and 80 neonates were recruited. All babies received supplemental intravenous fluids (50 ml/kg N/5 with 5% Dextrose + half of the maintenance fluid) infusion over 8 hours along with intensive phototherapy and breastfeeding on demand. We analysed the data in all babies with regards to primary outcome exchange transfusion and secondary outcomes total duration of phototherapy, rate of decline of serum bilirubin and side effects of fluid supplementation. Literature available for fluid supplementation shows studies have been done in non-hemolytic hyperbilirubinemia and excluded the hemolytic ones due to fear of anemia and fluid overload but keeping in mind that this subset of babies are at maximum risk of going into exchange transfusion, we included all causes incorporating hemolytic ones also in our study and that is the strength of our study.

Our cohort study revealed that 76.23% (61/80) of the enrolled neonates, with unconjugated hyperbilirubinemia in exchange range, successfully averted exchange transfusion with fluid supplementation along with phototherapy. Our rate is comparable to that reported by other studies where intravenous fluid supplementation group had similar rates of exchange transfusion (14%-16%).[10]are available from other authors like Mehta S et al (2005) using 70 ml/kg + 1/2 of 8 hour maintenance fluids of N/5 saline D5% over 8 hours.[11]

Our primary outcome was rate of exchange transfusion and secondary outcome was percentage fall in serum bilirubin at 4 and 8 hours. Most of the studies had very small numbers of babies ending up with exchange transfusion (1-10) and so they used decline in serum bilirubin values as the primary outcome.[12]Inour study, when we compared neonates ending up in exchange

transfusion (exchange group) with those averting exchange (non-exchange group), we found that the percentage of fall of total serum bilirubin over 4 and 8 hours similar in both groups.Cochrane systematic review by Lai et al concluded that term healthy newborn 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. Possible mechanisms for decline in serum bilirubin could be due to decreased enterohepatic circulation, so a lower rate of bilirubin reabsorption from the bowel, dilution of serum bilirubin by fluids, increased blood circulation to the kidneys and rise in urine output, and subsequently improve excretion of water soluble photo isomers in urine.[7]

Conclusion

In more than 35 weeks' gestation neonates with all cause unconjugated hyperbilirubinemia in exchange transfusion zone, time delay in arranging for the latter in resource limited settings can be cashed upon with fluid supplementation along with phototherapy to cut down the need for exchange transfusion.

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