International Journal of Contemporary Pediatrics
Xavier R et al. Int J Contemp Pediatr. 2016 Nov;3(4):1430-1434
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291
DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20163693

Original Research Article

Reticulocytosis: the unevaluated parameter in neonatal jaundice requiring phototherapy

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Received: 27 August 2016
Accepted: 27 September 2016

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ABSTRACT

Background: Majority of the jaundiced neonates requiring phototherapy do not have an identifiable cause for the jaundice. Reticulocyte count more than 4% on day 3 of life is called reticulocytosis in neonates. So far no studies have evaluated the prevalence of reticulocytosis among jaundiced neonates requiring phototherapy. Objective of the study was to identify babies with only reticulocytosis as cause for jaundice and identify factors contributing to reticulocytosis.
Methods: An observational study was carried out over a period of one year in the neonatal unit of a tertiary care hospital on 200 jaundiced neonates requiring phototherapy for determining the incidence of jaundice with unknown etiology. This data was analysed for prevalence of reticulocytosis and its contributing factors.
Results: 67 of 200 babies with jaundice had reticulocytosis. An etiology for the reticulocytosis was found in 37 babies. 12 of the remaining 30 babies had dehydration (weight loss more than 10%) contributing to jaundice. 18 babies had no identifiable cause for the reticulocytosis. Mildly significant correlation was found with sibling history of neonatal jaundice ($p = 0.052$). No significant correlation was found with any other contributing factors.
Conclusions: Reticulocyte count should be done for any baby with jaundice requiring phototherapy. Screening for irregular antibodies and genetic studies need to be promoted along with routine tests, to identify the cause for reticulocytosis after working out the costs involved.

Keywords: Irregular antibodies, Neonatal jaundice, Phototherapy, Reticulocytosis

INTRODUCTION

60 to 80% of neonates develop jaundice in the first week of life.[1] Only 8-11% of these babies develop jaundice that is significant enough, to need further evaluation and phototherapy.[2] Identification of cause helps in early counselling regarding future incidence of haemolysis, anaemia and bilirubin cholelithiasis.[3]

Reticulocytosis has been defined as >7% at birth, >4% at day 3 of life and > 1% after 7 days of life.[4,5] As of now, to the author's knowledge, there are no studies evaluating the prevalence of or factors contributing to reticulocytosis in jaundiced neonates requiring phototherapy.

METHODS

An observational study was carried out over a period of one year in the neonatal unit of a tertiary care hospital on all jaundiced neonates who required phototherapy, for determining the incidence of jaundice with unknown etiology (idiopathic neonatal jaundice/ exaggerated physiological jaundice).[6]

From this data, all neonates >35 weeks who required phototherapy as per Bhutani's chart and in whom reticulocyte count was evaluated were included in the study. Jaundiced neonates on phototherapy in whom reticulocyte count was not evaluated were excluded from the study.

During the study period 861 neonates were born after 35 completed weeks of gestation. 344 babies required phototherapy. In 144 of these babies reticulocyte count was not evaluated for various reasons, and hence were excluded. Remaining 200 neonates were evaluated for prevalence of reticulocytosis, and for correlation with factors contributing to reticulocytosis.

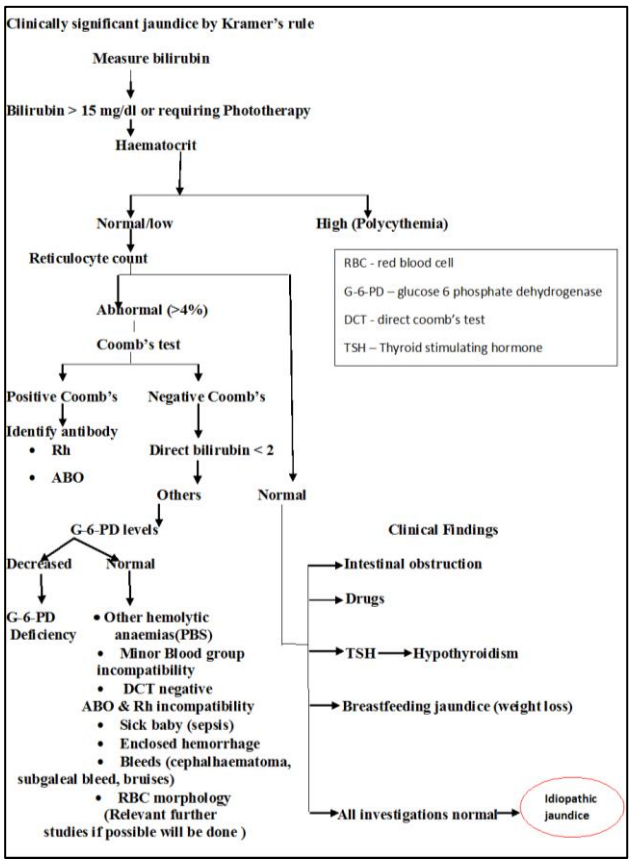

Figure 1: Determination of etiology of jaundice.

A complete history with respect to the onset of the jaundice, feeding history, risk factors present, family and sibling history of jaundice or blood transfusion, maternal illnesses, mother and baby blood group, starting of phototherapy and number of days phototherapy given were taken. A proper clinical examination was done for features of sepsis, bruises or cephallhaematomas.

200 babies were analysed for the cause of jaundice as per Figure 1. Babies in whom no cause were found was labelled as idiopathic jaundice. Babies in whom more than 10% weight loss was found without any other cause for jaundice requiring phototherapy were labelled as dehydration jaundice. The babies in whom reticulocytosis was found (reticulocyte count more than 4%) were further evaluated as per figure 1, for identifying the etiology for reticulocytosis. Babies in whom no etiology could be found for reticulocytosis; were further evaluated for significant correlation with contributing factors like baby blood group, presence of risk factors, sibling and family history of jaundice or blood transfusion, caste and community of origin.

Descriptive and inferential statistical analysis has been used in the present study.[7] Data was entered in Microsoft Excel spread sheet. Data was analysed using SPSS (statistical package for social sciences) version 20 for Windows.

Continuous variables were interpreted using mean and standard deviation. Categorical variables were interpreted using number and percentages.

Fischer exact test and ANOVA were used to test the statistical significance. $P < 0.05$ was considered as statistically significant.

RESULTS

92 were females and 108 of the 200 jaundiced babies were males. 125 babies delivered normally and 75 of 200 babies by caesarean section. 156 babies were born at term and 44 of the 200 babies were born preterm.

87 of the 200 babies had no identifiable cause for the neonatal jaundice and were hence classified as idiopathic jaundice. 39 babies had only dehydration as cause for jaundice.

67 of the remaining 74 babies had reticulocytosis on evaluation. The remaining 7 of 200 babies had identifiable causes other than reticulocytosis for jaundice (Table 1).

Table 1: Etiology of jaundice.

Cause for jaundice	No of babies	Percentage	Onset (hours)	Duration (hours)	Peak bilirubin (mg/dl)	Mean reticulocyte count (%)
Physiological jaundice	87	43.5	66.68±28.40	64.81±28.88	17.29±3.37	2.23±1.32
Only dehydration	39	19.5	72.10±19.21	65.03±26.72	18.20±4.64	2.35±1.32
Reticulocytosis	67	33.5	54.04±16.58	67.67±27.12	18.82±6.63	7.23±4.8
Causes other than reticulocytosis for jaundice	7	3.5	64.71±24.46	63.35±33.63	19.31±6.64	2.19±1.17
P value (ANOVA)			0.001	0.921	0.262	0.001

Table 2: Etiology for reticulocytosis in neonatal jaundice requiring phototherapy.

Cause for reticulocytosis (reticulocyte count >4%)	No of babies	Onset (hours)	Duration (hours)	Peak bilirubin (mg/dl)	Mean reticulocyte count (%)
ABO incompatibility	17	55.29±19.05	72.24±27.24	17.86±2.50	8.51±5.18
Rh incompatibility	13	47.00±14.54	74.77±30.86	26.78±11.54	6.87±3.65
ABO + Rh incompatibility	2	55.00±21.21	46±36.77	20.05±2.76	6.15±1.77
Sepsis	4	42.25±9.32	78.25±25.41	18.05±2.09	7.00±4.43
G6PD	0	0	0	0	0
Membrane defects	0	0	0	0	0
Hemoglobinopathies	0	0	0	0	0
Cephalhaematoma/bruises	1	56	80	17	4.4
With dehydration only	12	60.75±16.99	69.83±31.08	16.04±1.45	5.97±2.55
No cause for reticulocytosis	18	54.06±14.81	56.17±19.32	15.96±2.09	7.43±6.6
Total	**67**	**54.04±16.58**	**67.67±27.12**	**18.82±6.63**	**7.23±4.8**

Table 3: Comparison of clinical variables in relation to reticulocytosis.

Causes for reticulocytosis	No of babies	Percentage	Onset of jaundice in hours	Duration of phototherapy (hours)	Peak bilirubin (mg/dl)	Mean reticulocyte count (%)
Blood group incompatibility	32	47.76	52.94±17.82	71.63±29.02	21.62±8.6	7.70±4.46
Sepsis/ cephalhematoma	5	7.5	45.00±10.15	78.6±22.02	17.84±1.87	6.52±3.98
With dehydration	12	17.9	60.75±16.99	69.83±31.08	16.04±1.45	5.97±2.55
With no cause	18	26.87	54.06±14.81	56.17±19.32	15.96±2.09	7.43±6.6
P value (ANOVA)			0.314	0.187	0.008	0.744

ANOVA: Analysis of variance

Table 4: Comparison of risk factors, sibling and family history of jaundice in relation to reticulocytosis in neonatal jaundice (NJ).

Number(N)Risk factors	Physiological jaundice n = 87	Dehydration only cause for NJ n = 39	Blood group incompatibility causing NJ n = 32	Reticulocytosis other than blood group incompatibility causing NJ n = 35	NJ due to causes other than reticulocytosis n = 7	P value
Only Major	2	2	3	0	0	0.58
Only minor	51	27	16	18	0	0.79
Major+ minor	19	6	11	13	4	0.24
No risk factors	15	4	2	4	3	0.79
Sibling history of jaundice	12	0	6	1	2	0.05
Family history of jaundice	7	0	3	2	3	0.93

Fischer exact test

Only 32 of the 67 babies with reticulocytosis, had ABO or Rh incompatibility on further evaluation. The remaining 35 of 67 babies did not have membrane defects on peripheral smear or G6PD deficiency. Out of 67 babies, 4 babies had features of sepsis, one baby had cephalhaematoma and 12 babies had dehydration also along with reticulocytosis. 18 babies (9%) had only reticulocytosis (cause) on evaluation (Table 2). Table 1 shows the comparison between idiopathic, dehydration, reticulocytosis and non-physiological jaundice due to other causes with respect to peak bilirubin, mean duration of phototherapy and mean onset of significant jaundice.

Table 3 shows comparison of etiologies of reticulocytosis in neonatal jaundice with respect to mean onset, duration of phototherapy and peak bilirubin. No significant correlation was found between the caste and community of origin, baby blood group for the 30 babies who had

only reticulocytosis as aetiology for jaundice (p = 0.287). No significant correlation was found with presence of risk factors (Table 4). No significant correlation was found with presence of family history of jaundice or blood transfusion (Table 4). Mildly significant correlation was found with sibling history of jaundice (P = 0.052).

DISCUSSION

Neonatal jaundice occurs due to mismatch between production and elimination of bilirubin, with many factors affecting each step of the process. An imbalance in the production and elimination of bilirubin more than what is anticipated can cause neurological sequalae in the baby (kernicterus).[8] Jaundice requiring phototherapy is the most common cause for prolonged hospital stay or readmission in the first week after birth.[9,10]

Most of the neonates that require phototherapy in the first week of life, have no identifiable etiology for their jaundice and are classified as idiopathic jaundice.[11] In this study 43.5% babies had no identifiable cause for jaundice requiring phototherapy and hence were labelled as idiopathic. 19.5% babies had only dehydration (weight loss more than 10% of birth weight) as the cause for jaundice (breastfeeding jaundice).[12,13] Idiopathic jaundice is proposed to be secondary to interplay between polymorphic genes involved in production and metabolism of bilirubin (glucose-6-phosphate dehydrogenase, uridine diphosphate glucuronosyl transferase 1A1 and solute carrier organic anion transporter polypeptide 1B1).[14]

Reticulocyte count more than 4% on day 3 of life is considered as reticulocytosis.[5] 33.5% (67) of the 200 babies had reticulocytosis (haemolytic cause for jaundice). Babies with reticulocytosis had earlier onset of jaundice (p = 0.001), though the peak bilirubin and duration of phototherapy were similar to that of neonates without reticulocytosis, as expected. 32 of these 67 (47.76%) babies had ABO and Rh incompatibility. 4 babies had sepsis contributing to reticulocytosis and one baby had cephalhaematoma. Most cases of haemolytic jaundice could be identified by combining family history with laboratory investigations and morphological picture on peripheral blood smear.[4]

30 babies (44.78%) had no further identifiable etiology for the reticulocytosis. Screening for other causes for hemolysis (glucose 6 phosphate dehydrogenase levels, peripheral blood smear for membrane defects and thyroid stimulating hormone for hypothyroidism) were negative. This is in contrast to available literature where G-6-PD causes 6-8% of haemolytic neonatal jaundice.[15] Since this is the first study evaluating reticulocytosis in jaundiced neonates to our knowledge, we do not have data from other studies to compare. However in a study done by Cheng SW et al to identify the etiology of hyperbilirubinemia, no etiology was found in 53.8 % of jaundiced babies. The reticulocyte count was not done for all jaundiced babies in that study.[16] Similar results were obtained by Sgro et al.[2,17]

Other than Rh and ABO incompatibility, moderate to severe cases of neonatal jaundice attributed to other minor group antibodies has been described in Asian population in the last ten years.[18,19] Genetic studies and screening of mother for irregular antibodies were not done in the study, due to financial constraints. Further genetic studies should also be considered, in those cases where no identifiable etiology are found.[20]

Babies in whom an etiology was found for the reticulocytosis, had a significantly higher peak bilirubin (p = 0.008) as compared to babies in whom no cause was found for reticulocytosis. In this study no significant correlation was found between presence of reticulocytosis; with caste and community of origin, baby blood group, presence of risk factors or family history of jaundice or blood transfusion. This could not be explained. Mildly significant correlation was found with sibling history of jaundice (p = 0.052). Further studies with larger groups of jaundiced neonates may throw better light on correlation with factors contributing to reticulocytosis.

Latest American association of paediatrics does not suggest routine testing of reticulocyte count in all babies with jaundice requiring phototherapy.[21] The results of this study stresses the importance of doing reticulocyte count in all babies with jaundice requiring phototherapy for further evaluation (peripheral blood smear, G-6-PD assays, other relevant tests), prognosticating the course of jaundice and better management of babies requiring phototherapy.

We suggest screening of all jaundiced babies with reticulocytosis with negative coomb's test; for irregular antibodies to detect rare variants in blood group.[22,23] We also suggest further genetic studies for academic interest if feasible so as to identify the cause of reticulocytosis in these jaundiced babies. The finances for the above suggestions being immensely expensive will need to be worked out, for arranging funds and formulating protocol.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Xavier R, Manoj VC, Kumar STM, Cherian VJ. Reticulocytosis: the unevaluated parameter in neonatal jaundice requiring phototherapy. Int J Contemp Pediatr 2016;3:1430-4.