

Clinical Course and Prognosis of Hemolytic Jaundice in Neonates in North East of Iran

Hassan Boskabadi¹, Gholamali Maamouri², Shahin Mafinejad³, Farzaneh Rezagholizadeh⁴

^{1,2}Neonatal Research Center, Department of Pediatrics, Ghaem Hospital, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran; ³Department of pediatric, Fellowship of Neonatology, MUMS, Mashhad, Iran; ⁴Department of pediatric, Ghaem Hospital, MUMS, Mashhad, Iran

ABSTRACT

Citation: Boskabadi H, Maamouri G, Mafinejad S, Rezagholizadeh F. Clinical Course and Prognosis of Hemolytic Jaundice in Neonates in North East of Iran. *Maced J Med Sci.* 2011 Dec 15; 4(4):403-407. <http://dx.doi.org/10.3889/MJMS.1957-5773.2011.0177>.

Keywords: jaundice; newborn; hemolysis; Blood group incompatibility.

Correspondence: Dr. Hassan Boskabadi. Neonatal Research Center, Department of Pediatrics, Ghaem Hospital, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran. Tel.: 0985118412069; 0989155153987; Fax:985118409612. E-mail: BoskabadiH@MUMS.ac.ir

Received: 28-Apr-2011; Revised: 20-Jul-2011; Accepted: 22-Jul-2011; Online first: 16-Nov-2011

Copyright: © 2011 Boskabadi H. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Competing Interests: The authors have declared that no competing interests exist.

Background: Hemolytic jaundice is the most serious cause of hyperbilirubinemia among neonates. It may develop to kernicterus due to misdiagnosis or inappropriate treatment. The aim of this study is to determine the prevalence rate of hemolytic jaundice, predisposing factors and assessment of treatment and complications in hemolytic jaundice.

Methods: This prospective descriptive study has been performed on 1568 newborns with jaundice as their chief complaint, in a seven-year period at Ghaem hospital in Mashhad, Iran. 795 neonates were included in our study (237 infants with hemolytic jaundice and 558 infants with idiopathic jaundice). Complete physical examinations and laboratory tests were performed and data were recorded. Statistical analysis was carried out, using SPSS 11.5 statistical package.

Results: In the present study, significant differences were determined between two groups of hemolytic and idiopathic jaundice for total serum bilirubin, hematocrit, time of jaundice appearance, age of admission, hospitalization period and incidence of kernicterus ($p < 0.001$). Newborns with ABO incompatibility (17%), Rh disease (7%), G6PD deficiency (6%) and minor blood group immunization (2%) were developed to hyperbilirubinemia, respectively. Among the newborns affected with kernicterus, 12 cases were placed in group with ABO hemolytic disease (9%), 3 cases were in Rh isoimmunization group (5.5%), 4 cases were in G6PD deficiency group (8.9%) and 9 cases were idiopathic (1.6%).

Conclusion: Jaundice due to hemolysis is associated with a higher serum bilirubin and more complications like kernicterus. ABO incompatibility was the most common reason of hemolytic jaundice among neonates in north east of Iran. Special attention to ABO incompatibility and G6PD enzyme screening may decrease complications and improve the prognosis.

Introduction

Hyperbilirubinemia is a common and in most cases, benign problem in neonates. Jaundice is appeared during the first week of life in approximately 60% of term and 80% of preterm infants. Hyperbilirubinemia may increase in 8-11% of newborns to higher than 95% of percentile and requires evaluation and treatment [1]. Jaundice is the most common reason for admission

during the 1st month of life [2, 3]. Multiple variables (maternal, infantile, during labor and environmental factors) affect the course and severity of jaundice. Unfortunately, early discharging of mother and baby from obstetric ward is recently increased. High risk infants who became symptomatic in the hospital should be followed up as outpatient; otherwise they will usually develop into severe jaundice and complications [2, 3].

Hemolysis is the most important and most serious cause of hyperbilirubinemia in newborns. Jaundice due to hemolysis can be diagnosed easily and is preventable by early treatment [4, 5]. Neurologic injury, kernicterus, may be resulted by inadequate preventive management and treatment delay [6].

Kernicterus causes 10 percent of death and 70 percent of disorders related to hyperbilirubinemia. Asian ethnicity is more affected to kernicterus [7]. The aim of this study is to determine the prevalence rate, time of jaundice appearance, severity of jaundice, maternal and infantile predisposing factors, duration of treatment and complications of hyperbilirubinemia due to hemolysis.

Material and Methods

This descriptive analytic study has been done from October 2002 to September 2009 and evaluated causes, contributing factors, signs and symptoms and complications of hyperbilirubinemia in newborns with jaundice. Clinical jaundice is diagnosed by yellowish color of sclera, mucosal and skin. Newborns who were admitted for jaundice aged 1 to 29 days. This study has been accomplished over seven years, on 1568 newborns admitted to NICU and pediatric emergency room in Ghaem hospital in Mashhad, Iran.

Laboratory tests were performed for two groups of infants. First, infants who were clinically jaundice to more extent of mid-abdomen with normal physical examination and second group who was defined as high risk jaundice infant. High risk infant was determined as Rh or ABO incompatibility, prematurity, history of jaundice and hospitalization in prior baby and symptomatic jaundice. The ethic committee of Mashhad University of medical science approved this study and all patients signed informed consent. Information were collected and recorded by neonatal fellowship and neonatologist.

Maternal data like history of pregnancy and delivery, age, blood group, disorder of pregnancy, type of delivery, duration of hospitalization after delivery and gestational order were all recorded.

Newborn's data like time of jaundice appearance and discharge from hospital, signs and symptoms on admission, duration of hospitalization and treatment plan were recorded and complete physical examination was done. Finally, laboratory tests were performed (hematocrit, indirect and direct bilirubin, coombs test, reticulocyte count, blood type and G6PD).

In current study, 795 infants with jaundice were included and categorized in two groups, 237 neonates with hemolytic jaundice (Rh, ABO, minor blood group incompatibility and G6PD deficiency) and 558 infants with idiopathic hyperbilirubinemia (Fig. 1). Then, they were compared with each other. 773 jaundice babies were excluded due to non hemolytic- non idiopathic causes of hyperbilirubinemia, non compliant parents and symptomatic disease (Fig. 1).

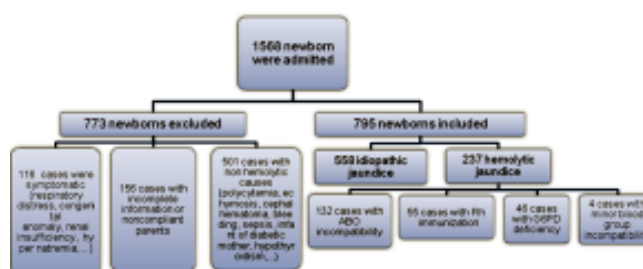


Figure 1: Flowchart of the study.

Rh isoimmunization was determined by either mother's Rh negative and infant's Rh positive, both with positive direct antiglobulin test and/or decreased hematocrit. ABO incompatibility was defined by either mother's O blood group and infant with A or B blood group with two or more of the following were present: 1- jaundice appears in the first day 2-positive direct antiglobulin test 3-positive indirect antiglobulin test 4-presence of microspherocytosis in peripheral blood smear.

Provided Rh or ABO isoimmunization ruled out and direct antiglobulin test become positive, it is interpreted as minor blood group incompatibility. G6PD enzyme was measured by the fluorescent spot method.

Statistical analysis was carried out using SPSS 11.5. The Student T-test, Fissure test and Chi-square test were performed on quantitative and qualitative variables. P-value less than 0.05, was considered statistically significant.

Results

Among 795 neonates, who were eligible in current study, we found 237 neonates with hemolytic jaundice and 558 neonates with idiopathic jaundice. We did not find significant differences in birth weight and weight on admission between two groups ($p > 0.05$, Table 1).

In this report, the prevalence rate of hemolytic jaundice was 30 percent (Fig. 2). Time of jaundice appearance, age of admission, serum bilirubin, hematocrit, hospitalization period, development of kernicterus, shows statistically significant differences between two groups ($p < 0.001$, Table1).

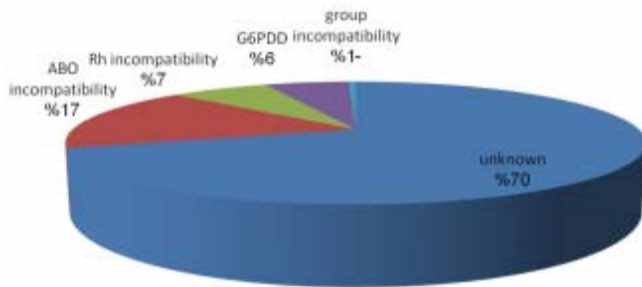


Figure 2: The prevalence rate of hemolytic jaundice in neonatal hyperbilirubinemia.

Jaundice in hemolytic disease group was developed by ABO hemolytic disease (56%), Rh isoimmunization (23%), G6PD deficiency (19%) and minor blood group incompatibility (2%), respectively. The current study showed that more infants with hyperbilirubinemia of at least 25 mg/dl were placed in hemolytic group in comparison with idiopathic group (37% vs 18%). Among jaundice newborns with ABO hemolytic disease, positive indirect coombs test was detected in 96 newborns (72.72%) and positive direct coombs test were reported in 36 infants (27.28%). Almost all newborns with Rh isoimmunization had positive direct coombs test.

Table 1: Characteristics of groups.

Variable	Subgroups	ABO incompatibility	RH isoimmunization	G6PD deficiency	Minor blood group incompatibility
Age of admission		5.4 ± 2.9	3.5 ± 3.2	5.9 ± 4.9	5 ± 2.4
Total Bilirubin		23.44 ± 7.3	25.1 ± 7.4	24.1 ± 9.1	23.6 ± 3.4
Direct Bilirubin		0.91 ± 0.9	1.2 ± 1.6	1.1 ± 0.9	0.45 ± 1.2
Hematocrit (%)		42.8 ± 7	38.4 ± 8.2	43.3 ± 9.5	46.2 ± 9.4
Platelet count (×1000)		236 ± 122	322 ± 132	248 ± 65	153
Infant's hospitalization period		3.9 ± 2.6	4.8 ± 2.6	4.8 ± 2.3	4 ± 1.7
Mother's hospitalization period		1.4 ± 0.6	1.7 ± 1.2	1.4 ± 0.5	1
Time of jaundice appearance (day)		1.2 ± 0.7	1.1 ± 1	1.8 ± 1.2	2

Median serum bilirubin and hematocrit were measured 34.3 ± 10 mg/dl and 40.3 ± 8%, respectively in neonates who developed into kernicterus. Kernicterus was defined by early clinical aspects like opisthotonus, seizures and high pitched cry and/or sensorineural deafness within next follow up. Among the newborns affected with kernicterus, 12 cases were placed in group

with ABO hemolytic disease (9%), 3 cases were in Rh isoimmunization group (5.5%), 4 cases were in G6PD deficiency group (8.9%) and 9 cases were idiopathic (1.6%).

Table 2: Clinical and paraclinical manifestations of newborns with hemolytic jaundice.

Variable	Subgroups	ABO incompatibility	RH isoimmunization	G6PD deficiency	Minor blood group incompatibility
Age of admission		5.4 ± 2.9	3.5 ± 3.2	5.9 ± 4.9	5 ± 2.4
Total Bilirubin		23.44 ± 7.3	25.1 ± 7.4	24.1 ± 9.1	23.6 ± 3.4
Direct Bilirubin		0.91 ± 0.9	1.2 ± 1.6	1.1 ± 0.9	0.45 ± 1.2
Hematocrit (%)		42.8 ± 7	38.4 ± 8.2	43.3 ± 9.5	46.2 ± 9.4
Platelet count (×1000)		236 ± 122	322 ± 132	248 ± 65	153
Infant's hospitalization period		3.9 ± 2.6	4.8 ± 2.6	4.8 ± 2.3	4 ± 1.7
Mother's hospitalization period		1.4 ± 0.6	1.7 ± 1.2	1.4 ± 0.5	1
Time of jaundice appearance (day)		1.2 ± 0.7	1.1 ± 1	1.8 ± 1.2	2

Values expressed as mean ± SD or number (%).

Discussion

The present study shows, the most common pathologic cause of hyperbilirubinemia in newborn, was due to hemolytic disease (30%). The prevalence rate of hemolytic jaundice was reported 23 percent in Canada [4]. High prevalence rate reported in this study may be explained by insufficient screening program, inadequate parents' information about early reexamination of newborns two days after discharge, early discharge and lack of serum bilirubin measurement or coombs' test in high risk newborns.

Among newborns with jaundice that were included in our study, hyperbilirubinemia caused by ABO incompatibility was the most common (17%), followed by Rh isoimmunization (7%), G6PD deficiency (6%) and minor blood group incompatibility (2%), respectively. In our study, the prevalence rate of ABO incompatibility (mother with blood group O and newborn's A or B) was reported 40.4 percent; therefore, high incidence of hemolytic jaundice due to inadequate screening test was predictable. Kaini's study in Nepal on 293 neonates with hyperbilirubinemia, reported, ABO and Rh isoimmunization were common causes of jaundice, 11 and 7.4 percent, respectively [8]. Only one-third of newborns with ABO incompatibility develop to hyperbilirubinemia [9]. The reason for high prevalence rate of ABO induced jaundice, reported in this investigation was that we have evaluated jaundice newborns but other publishes, evaluated all newborns.

In current study 18 percent of mothers had negative blood group, since their babies had positive Rh,

but hemolytic jaundice is occurred in 38 percent of cases.

Time of jaundice appearance was reported significantly earlier in hemolytic group. Jaundice appeared earlier in Rh isoimmunization, followed by minor blood group, ABO incompatibility and G6PD deficiency, respectively. According to higher level of serum bilirubin in Rh disease, earlier detection of jaundice is more possible. Inadequate screening for G6PD enzyme in our country may explain late determination of this group. Additionally, lack of follow up among newborns without Rh or ABO incompatibility may lead to underestimation of G6PD deficient cases. By screening all newborns for G6PD enzyme, we can detect the G6PD deficient cases, early enough to prevent its complications. Although, hyperbilirubinemia related to G6PD deficiency is known clearly but the exact mechanism of jaundice physiopathology is still unknown [10]. Hyperbilirubinemia among this group may be caused by insufficient hepatic conjugation and bilirubin secretion rather than an increase production of bilirubin due to hemolysis [11, 12]. Among Mediterranean ethnicity, the combination of glucose-6-phosphate dehydrogenase (G6PD) deficiency and genetic factors like Gilbert disease produces severe hyperbilirubinemia in the absence of hemolysis and anemia [13], which is consistent with our results.

Serum bilirubin was significantly higher in hemolytic jaundice group, in comparison with idiopathic group. This study reported significant jaundice and anemia through infants with positive direct coombs test. Same results were published by Risembery et al [14].

The most common pathologic cause of blood incompatibility between mother and fetus is Rh isoimmunization. Despite ABO incompatibility is estimated among 20-25 percent of pregnancies, hemolytic disease is occurred only in 10 percent of these newborns. The reason for the milder nature of ABO hemolytic anemia may be one or more of the following: (1) the presence, in infants with A or B blood groups, of the antigen in all tissues in the body, effectively diluting and neutralizing transferred maternal antibody, (2) neutralization of maternal antibody by placental A and B antigen prior to its entry into fetal circulation, and (3) the relatively weak nature of A or B antibody, resulting in less intense hemolysis [15, 16].

Clinical jaundice appears earlier in hemolytic hyperbilirubinemia, shows the more severity of disease and longer hospitalization period. Boskabadi et al. reported infants with hyperbilirubinemia due to G6PD

deficiency, were almost visited in fifth day of life, which is consistent with our study [17].

Kernicterus is a serious complication of hyperbilirubinemia and may progress to neurologic impairment or death [6]. The present study determined the prevalence rate of kernicterus was 1.5 percent among jaundice newborns. This value may be underestimated due to misdiagnosing mild cases of kernicterus and inappropriate follow up. Our study was carried out only on term infants; therefore with addition of preterm jaundice infants, the incidence of kernicterus would be increased. Higher incidence rate of kernicterus in our report, comparing with worldwide incidence, indicates that, jaundice prevention system in our country is inefficient and needs close attention and consideration of health care providers and insiders.

The incidence rate of acute encephalopathy is estimated 1 out of 10000 neonates [18].

We found that, 62 percent of infants with kernicterus were related to Rh and ABO incompatibility, but idiopathic hyperbilirubinemia is the main cause of kernicterus in the world as kernicterus induced by hemolytic disease is significantly decreased.

This study showed that 14 percent of newborns with kernicterus had G6PD deficiency, although it is reported 21 percent in the USA, which is explained by decreased rate of Rh and ABO induced hyperbilirubinemia and appropriate prevention programs [19].

Evaluation of jaundice by clinical manifestations alone, without performing coombs test, may increase kernicterus, because parents have not been trained about early follow up and prevention program [4, 17, 20, 21].

In our hospital, evaluation of newborns blood group due to maternal O blood typing was not desirable and in addition, inappropriate outpatient follow up, both were resulted to increase ABO induced hyperbilirubinemia and performed approximately half of kernicterus cases.

In several countries, for a better management of jaundice and its complications, the screening system, diagnosing method, treatment and follow up program are always renewing [21].

In summary, jaundice due to hemolysis is associated with higher serum bilirubin and more complications like kernicterus. ABO incompatibility was

the most common reason of hemolytic jaundice among neonates in north east of Iran. Evaluation of maternal and neonatal blood group and Rh, measuring G6PD enzyme in all newborns is strongly advised; therefore reevaluating coombs test and hematocrit in newborns with Rh or blood group incompatibility may decrease severe jaundice and related complications.

Acknowledgements

This study was kindly supported by the Research Council of Mashhad University of Medical Science, Mashhad, Iran. Also we are thankful from Dr Soheil Salari for editing this manuscript.

References

- Bhutani VK. For a safer outcome with newborn jaundice. *Indian Pediatr.* 2004;41(4):321-6.
- Facchini FP, Mezzacappa MA, Rosa IR, Mezzacappa Filho F, Aranha-Netto A, Marba ST. Follow-up of neonatal jaundice in term and late premature newborns. *J Pediatr (Rio J).* 2007;83(4):313-22.
- Boskabadi H, Maamouri GH, Mafinejad Sh. The relationship between traditional supplements' intake (camelthorn, flix weld and glucose water) and idiopathic neonatal jaundice. *Iranian Journal of Pediatrics.* 2011(in press).
- Sgro M, Campbell D, Shah V. Incidence and cause of sever hyperbilirubinemia in Canada. *CMAJ.* 2006;175(6):587-90.
- Goulet L, Fall A, D'Amour D, Pineault R. Preparation for discharge, maternal satisfaction, and newborn readmission for jaundice comparing postpartum models of care. *Birth.* 2007; 34(2):131-9.
- Maamouri GA, Mokhtari AM, Boskabadi H, Khalesi H. Evaluation of Auditory Brainstem Response (ABR) in neonatal hyperbilirubinemia . *The Iranian Journal of Otorhinolaryngology.* 2008;20(51):27-32.
- Rostami N, Mehrabi Y. Identifying the Newborns at Risk for Developing Significant Hyperbilirubinemia by Measuring Cord Bilirubin Levels. *J Arab Neonatal Forum.* 2005;2:81-5.
- Kaini NR, Chaudhary D, Adhikary V, Bhattacharya S, Lamsal M. Overview of cases and prevalence of jaundice in neonatal intensive care unit. *Nepal Med Coll J.* 2006;8(2):133-5.
- Ozolek JA, Watchko JF, Mimouni F. Prevalence and lack of clinical significance of blood group incompatibility in mothers with blood type A or B. *J Pediatr.* 1994;125(1):87-91.
- Kaplan M, Hammerman C. Severe neonatal hyperbilirubinemia. A potential complication of glucose-6-phosphate dehydrogenase deficiency. *Clin Perinatol.* 1998; 25(3):575-90.
- Dhillon AS, Darbyshire PJ, Williams MD, Bissenden JG. Massive acute haemolysis in neonates with glucose-6-phosphate dehydrogenase deficiency. *Arch Dis Child Fetal Neonatal.* 2003;88(6):534-6.
- Kaplan M, Abramov A. Neonatal hyperbilirubinemia associated with glucose-6-phosphate dehydrogenase deficiency in Sephardic-Jewish neonates: incidence, severity, and the effect of phototherapy. *Pediatrics J.* 1992;90(3):401-5.
- Shah VA, Yeo CL. Massive acute haemolysis and severe neonatal hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient preterm triplets. *J Paediatr Child Health.* 2007;43(5):411-3.
- Risemberg HM, Mazzi E, Macdonald MG, Peralta M, Heldrich F. Correlation of cord bilirubin levels with hyperbilirubinemia in ABO incompatibility. *Archives of Disease in Childhood.* 1977;52:219-22.
- Stoll BJ. Digestive system disorder. In: Kelieman R, Behrman R, Jenson H, Stanton B. *Nelson Textbook of pediatrics.* 18th ed, Sanders: Philadelphia, 2008:770-73.
- Wong RJ, Desandre GH, Sibley E, Stevenson DK. Neonatal Jaundice. In: Martin RJ, Fanaroff AA, Walsh MC. *Neonatal Perinatal-Medicence.* 8th ed, Elsevier Mosby, 2008:1428-1430.
- Boskabadi H, Maamouri GH, Mafinejad Sh. Prevalence and Clinical Manifestation of Glucose-6-Phosphate Dehydrogenase Deficiency in Newborns with Hyperbilirubinemia in Mashhad, Iran. *Maced J Med Sci.* 2011; 4(1):93-98.
- Bhutani VK, Johnson LH, Jeffrey Maisels M, Newman TB, Phipps C, Stark AR. Kernicterus: epidemiological strategies for its prevention through systems-based approaches. *J Perinatol.* 2004;24(10):650-62.
- Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. *J Pediatr.* 2002;140(4):396-403.
- Riskin A, Abend-Weinger M, Bader D. How accurate are neonatologists in identifying clinical jaundice in newborns? *Clin Pediatr.* 2003;42(2):153-8.
- Boskabadi H, Maamouri GH, Kiani M, Abdollahi A. Evaluation of urinary tract infections following Neonatal hyper-bilirubinemia. *Journal of Shahrekord University of Medical Sciences.* 2010;12(2):95-100.
- Chowdhury AD, Hussey MH, Shortland DB. Critical overview of the management of neonatal jaundice in the UK. *Public Health.* 2007; 121(2):137-43.