Risk Assessment For Readmission For Phototherapy in Neonates With ABO Hemolytic Disease

Chuncai Xu  
Women's Hospital, School of Medicine, Zhejiang University

Yingying Bao  
Women's Hospital, School of Medicine, Zhejiang University

Yuanyuan He  
Women's Hospital, School of Medicine, Zhejiang University

Jingxin Zhao  
Women's Hospital, School of Medicine, Zhejiang University

Fengjuan Ji  
Women's Hospital, School of Medicine, Zhejiang University

Mingyuan Wu  
Women's Hospital, School of Medicine, Zhejiang University

Jiajun Zhu (✉ jiajunzhu@zju.edu.cn)  
Women's Hospital, School of Medicine, Zhejiang University

Research Article

Keywords: ABO hemolytic disease of the newborn (ABO HDN), Direct Antiglobulin Test (DAT), readmission, rebound hyperbilirubinemia

Posted Date: November 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1086673/v1

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Abstract

Background: ABO hemolytic disease of the newborn (ABO HDN) is a main risk factor for neonatal hyperbilirubinemia, which is one of the most common causes for readmission in neonates after discharge. Our objective is to assess the risk factors for readmission in neonates with ABO hemolytic disease for phototherapy.

Methods: 291 neonates at gestational age ≥ 35 weeks were enrolled with the diagnosis of ABO hemolytic disease by collecting their clinical and laboratory data retrospectively. All these infants were born in Women's Hospital School of Medicine Zhejiang University between 2018 and 2019. Among these neonates, 36 cases were readmitted due to hyperbilirubinemia, which is defined as the study group, while the other 255 cases as the control group.

Results: The study and control groups were similar on maternal and infants basic parameters (P > 0.05), as well as the complications of both infants and mothers (P > 0.05). However, we found significant differences in the concentration of initial total serum bilirubin, the onset age for phototherapy, the positive direct antiglobulin test (DAT) between two groups (P < 0.05). Logistic regression analysis suggested that the age for onset phototherapy and the initial level of total serum bilirubin were both independent risk factors for readmission in neonates with ABO hemolytic disease.

Conclusions: For neonates with hyperbilirubinemia due to ABO HDN, positive direct antiglobulin test (DAT), small age for phototherapy and high initial level of bilirubin can increase the risk of readmission for phototherapy.

Introduction

ABO HDN is the main cause of severe neonatal hyperbilirubinemia, which might lead to neurological impairment without effective management. A recent study reported that 71% neonates with rebound hyperbilirubinemia in was due to hemolysis[1]. As effective monitoring and appropriate treatment are essential for hyperbilirubinemic neonates with ABO HDN[2], a longer time for hospitalization is usually recommended for these patients [3]. However, the prolonged-hospital–stay strategy brings concerns about several problems including the separation of mothers and infants, which can impede breastfeeding process. Hence, it’s quite important to identity those neonates who might potentially develop severe rebound hyperbilirubinemia and indeed need more observation time before discharge in case of readmission, instead of indistinguishably extending the hospital stay for all hyperbilirubinemic neonates. This article aimed to evaluate the risk factors related to readmission for rebound hyperbilirubinemia through retrospective analysis in the neonates with ABO HDN.

Materials And Methods

1.1 Participants
A total of 291 neonates with ABO HDN were included who were hospitalized in the department of neonatology of Women's Hospital School of Medicine Zhejiang University between 1 February 2018 and 30 April 2019, with gestational age at birth ≥ 35 weeks.

**Inclusion criteria:** Maternal blood type is O type, neonatal blood type is non-O type, and ABO HDN was diagnosed after delivery.

**Exclusion criteria:** 1). severe infectious disease; 2). severe birth asphyxia; 3). long-term respiratory support after birth; 4). severe congenital birth defects; 5). the existence of inherited metabolic disease; 6). accompanied with RH incompatibility; 7). hemolytic jaundice due to defects in enzymes or membranes in red blood cells, such as glucose-6-phosphate dehydrogenase deficiency (G-6-PD), pyruvate kinase deficiency and other inherited blood diseases; 8). The rebound hyperbilirubinemia for readmission caused by other diseases except ABO HDN, such as infections.

### 1.2 Methods

The neonates were divided into readmission group and control group according to the need for phototherapy after discharge. The following indicators were compared between the two groups: general conditions, related comorbidities, the laboratory tests and jaundice relevant parameters.

### 1.3 Relative definitions and the standards for diagnosis and treatment

**1.3.1 Transcutaneous bilirubin monitoring and indications for treatment** All neonates in our hospital were monitored for transcutaneous bilirubin level every 12 hours since the first day of birth. The total serum bilirubin (TSB) test was performed when the transcutaneous bilirubin level detected by the hourly bilirubin nomogram increased to the standard for phototherapy intervention. When the TSB result reached the phototherapy threshold according to the guideline from the American Academy of Pediatrics (AAP) management for hyperbilirubinemia in 2004, the neonate was admitted for treatment, receiving double-sided phototherapy and sometimes other managements as clinically warranted. When the TSB level reached the threshold of exchange transfusion, both intensive phototherapy and infusion of immunoglobulin (1 g / kg / d for 2 days) were applied.

**1.3.2 Indications for termination of phototherapy** The phototherapy was stopped when the TSB level decreased to 2 standard deviations of the phototherapy threshold.

**1.3.3 Discharge criteria and follow-up** Neonates with total serum bilirubin below the 75th percentile of the nomogram in the AAP management for hyperbilirubinemia in 2004 were allowed for discharge. At the time, the follow-up plan was made based on the age and the serum bilirubin level when discharging. In order to make it easy to follow up these neonates after discharge, it is necessary to make their parents clear the risk of hyperbilirubinemia and continue the monitor in communities or local hospitals.
1.3.4 Readmission criteria: Neonates were readmitted for treatment when total serum bilirubin levels reached or exceeded the threshold of phototherapy again during the monitoring process after discharge.

1.4 Statistical analysis

All statistical analysis were performed by the Statistical Package for the Social Sciences (SPSS) software, version 21.0. Continuous variables were presented as mean, standard deviation and median with interquartile range using t test. Categorical variables were presented as frequency using $\chi^2$ test mainly and rank sum test for the data those not normally distributed. The risks of readmission were estimated by logistic regression analysis. $P$ values less than 0.05 were considered as the indication of statistical significance.

Results

2.1 Comparison of general conditions and related comorbidities. There’s no statistically significant differences between the readmission group and the control group in neonates’ general conditions, including gestational age, birth weight, gender, feeding methods, delivery methods, in-vitro fertilization (IVF), multiple fetuses, and maternal complications during pregnancy ($P > 0.05$). In addition, the incidence of hypoglycemia, cephalohematoma, polycythemia, intraventricular hemorrhage (IVH), neonatal anemia, and bruising of body regions after birth were also similar among the two groups ($P > 0.05$). See Table 1.
**Table 1**
Comparison between demographic features and complication of both groups

| Variables                        | Readmitted group (n=36) | Control group (n=255) | P value* |
|---------------------------------|-------------------------|-----------------------|----------|
| Gestational age                 |                         |                       |          |
| [M(P25-P75), weeks]             | 39.00(38.04-40.11)      | 39.14(38.43-40.14)    | 0.761    |
| Birth Weight (X±S, g)           | 3314.17±403.22           | 3311.61±439.39        | 0.974    |
| Male (n, %)                     | 12(33.3)                | 120(47.1)             | 0.122    |
| Caesarean (n, %)                | 3(8.3)                  | 50(19.6)              | 0.101    |
| Breast feeding (n, %)           | 25(69.4)                | 174(68.2)             | 0.884    |
| Length of hospitalization       |                         |                       |          |
| [M(P25-P75), days]              | 7(5-8)                  | 6(5-8)                | 0.284    |
| Macrosomia (n, %)               | 2(5.6)                  | 13(5.1)               | 1.000    |
| LBW (n, %)                      | 0(0)                    | 7(2.7)                | 0.603    |
| IVF (n, %)                      | 2(5.6)                  | 6(2.4)                | 0.259    |
| Multiple fetuses (n, %)         | 0(0)                    | 6(2.4)                | 1.000    |
| SGA (n, %)                      | 1(2.1)                  | 9(2.4)                | 1.000    |
| Cephalohematoma (n, %)          | 0(0)                    | 5(2.0)                | 1.000    |
| Hypoglycemia (n, %)             | 1(2.8)                  | 6(2.4)                | 1.000    |
| IVH (n, %)                      | 0                       | 0                     | NA       |
| Anemia (n, %)                   | 6(16.7)                 | 25(9.8)               | 0.337    |
| Polycytemia (n, %)              | 0(0)                    | 0(0)                  | NA       |
| Bruising of body regions (n, %) | 0(0)                    | 0(0)                  | NA       |
| Maternal complications (n, %)   |                         |                       |          |
| PROM                            | 8(22.2)                 | 51(20.0)              | 0.756    |
| GDM                             | 5(13.9)                 | 47(18.4)              | 0.505    |
| ICP                             | 0(0)                    | 8(3.1)                | 0.602    |
| Intrauterine infection          | 1(2.8)                  | 8(3.1)                | 1.000    |
| GBS infection                   | 0(0)                    | 3(1.2)                | 1.000    |

*Significant P value < 0.05.
2.2 Comparison for jaundice relevant risk factors between the two groups. In the readmission group, there’s a tendency of higher TSB level at the enrollment, younger age at the initial phototherapy and higher rate of the following issues: positive DAT result and treatment of intensive phototherapy with the differences statistically significant (p <0.05). There’s no significant differences between the two groups in terms of the administration of Chinese medicine and excessive weight loss after birth. (p> 0.05) See Table 2.

| Variables                        | Readmitted group(n=48) | control group(n=379) | P value* |
|----------------------------------|------------------------|-----------------------|----------|
| Age at phototherapy beginning    |                        |                       |          |
| [M(P25-P75), hours]              |                        |                       |          |
| ≤24                              | 16.50(11.75-19.00)     | 20.00(13.00-23.00)    | 0.029    |
| 24-48                            | 31.00(28.00-42.00)     | 39.00(32.75-44.25)    | 0.033    |
| 48-72                            | 55.00(51.50-64.00)     | 64.00(56.00-70.00)    | 0.036    |
| TSB at enrollment[M(P25-P75), umol/L] |                       |                       |          |
| ≤24                              | 183.70 (161.18-196.48) | 150.35 (131.73-175.38)| 0.005    |
| 24-48                            | 229.90 (212.45-284.30)| 212.50 (197.85-230.28)| 0.026    |
| 48-72                            | 268.10 (257.70-279.05)| 249.50 (236.80-268.70)| 0.045    |
| TSB at discharge                 |                        |                       |          |
| [M(P25-P75), umol/L]             | 175.28(156.04-189.38) | 174.42(160.74-186.39)| 0.252    |
| DAT positive (n, %)              | 17(47.2)               | 74(29.0)              | 0.027    |
| Intensive phototherapy (n, %)    | 12(33.3)               | 22(8.6)               | 0.000    |
| Exchange transfusion (n, %)      | 0(0)                   | 0(0)                  | NA       |
| Weight loss from birth≥10%( n, %)| 2 (5.5)                | 15(5.9)               | 1.000    |
| Yinzhihuang oral liquid (n, %)   | 23(63.9)               | 159(62.4)             | 0.859    |

*Significant P value < 0.05.

2.3 Readmission risk assessment. The Logistic regression analysis suggested that the age at onset phototherapy and the initial serum bilirubin level at first enrollment were independent risk factors for
readmission of neonates with ABO HDN. See Table 3.

| Variables                  | β      | SE     | P value | 95% CI for EXP(B) Lower | Upper |
|---------------------------|--------|--------|---------|-------------------------|-------|
| Gestational age           | 0.000  | 0.000  | 0.768   | 0.999                   | 1.001 |
| Birth Weight              | -0.061 | 0.174  | 0.724   | 0.669                   | 1.323 |
| Age at phototherapy begin  | -0.061 | 0.016  | 0.000   | 0.913                   | 0.971 |
| TSB at enrollment         | 0.020  | 0.005  | 0.000   | 1.011                   | 1.030 |
| DAT positive              | 0.661  | 0.406  | 0.104   | 0.873                   | 4.294 |

**Discussion**

Hyperbilirubinemia is one of the most common causes of neonatal readmission. Although many disorders can lead to neonatal hyperbilirubinemia, such as infection, G-6-PD deficiency, delayed meconium excretion, insufficient feeding, premature delivery ABO HDN is still the main factor\textsuperscript{12–15}. In the neonatal period, about 60% of term infants and 80% of premature babies have a process of jaundice, and 5% -10% of them need phototherapy for treatment. Although hyperbilirubinemia is mostly a benign disease, severe hyperbilirubinemia in some neonates can cause permanent damage of the brain, especially in those with ABO HDN \textsuperscript{16–18}. In 2013, neonatal jaundice has been taken into the catalog of the main causes of early neonatal death \textsuperscript{19}, suggesting that timely and effective treatment is in great importance for the good prognosis of neonates with hyperbilirubinemia.

Pearl W. Chang et al \textsuperscript{6} analyzed 7048 neonates with hyperbilirubinemia and found that about 4.6% neonates had rebound hyperbilirubinemia after phototherapy. However, there is a higher incidence of rebound hyperbilirubinemia about 14.5% in premature infants and those neonates with positive direct DAT result. Sachdeva M et al. found that hyperbilirubenemic neonates with specific high-risk factors had a higher rate of rebound hyperbilirubinemia after phototherapy and required close follow-up after discharge \textsuperscript{20}. Our study found that hyperbilirubinemia due to ABO HDN in 34.4% (100/255) of neonates occurred within 24 hours after birth, and 12.4% of them were readmitted after discharge. Our results were consistent with the previous study. The serum bilirubin level tends to rebound after phototherapy in neonates with hyperbilirubinemia due to ABO HDN. We also found that neonates with higher total serum bilirubin concentration at the beginning of phototherapy, with initial jaundice (especially within 24 hours after birth), or with positive DAT result were more likely to be readmitted for phototherapy, and the differences between the two groups were statistically significant. Therefore, it’s reasonable to perform close follow-up after discharge with high-risk factors as listed above for the neonates due to ABO HDN, in case of left neurological sequelae resulted from severe hyperbilirubinemia.
Barak M et al. suggested those neonates with high-risk factors had a longer hospital stay [21]. Neonatal hyperbilirubinemia caused by ABO hemolysis also resulted in a long hospital stay [1, 6]. However, in recent years, breastfeeding, which could be hindered by neonates admission, has been advocated for its irreplaceable advantages. In China, it is much difficult to get breastfeeding for those neonates with ABO HDN who are in hospital for phototherapy. Therefore, it is crucial for these infants during admission period to perform individualized management to reduce the separation time between mother and their babies. Moreover, our study suggested that the initial age for phototherapy and the serum bilirubin at enrollment are independent risk factors for readmission in neonates with ABO HDN. Saeko Tsujimae et al. have found that in early-onset neonatal hyperbilirubinemia, ABO HDN is the main reason, which is consistent with our study [22]. Thus, we speculate that not all neonates with ABO HDN need extended hospitalization, despite of its widespread application. In terms of jaundice management for neonates with ABO HDN, it might be more appropriate to limit the pronged hospitalization strategy to those with early jaundice appearance and high serum bilirubin level, especially the ones received photography within 24 hours after birth, instead of delaying discharge for all the patients in this population. In addition, follow-up after discharge should be strengthened [23]. The new strategy is supposed to reduce the possibility of readmission, the frequency of follow-up after discharge, the incidence of cross-infection in outpatient follow-up process and the financial burdens of the families.

With the further improvement of the guidelines, the management for neonatal hyperbilirubinemia is becoming more and more standardized. Based on the AAP guidelines and its native features, Japan has developed its own guideline for full-term infants and preterm infants respectively in jaundice management, and so have Canada, Brazil, and the United Kingdom [4, 5, 24-26]. To date, we have not established a unified guideline of management and follow-up plan for neonatal hyperbilirubinemia after discharge in China, especially with ABO HDN. Our study is of great significance in providing scientific data for the future guideline, although with some deficiencies like the insufficient sample size.

In conclusion, not all neonates with ABO HDN need prolonged hospitalization. We suggest that it is necessary to extend the length of hospital stay and to implement close follow-up after discharge only for those with early jaundice appearance or high serum bilirubin at enrollment. We suppose this strategy will reduce the separation of mother and infant, the rate of readmission, the frequency of follow-up after discharge, the family’s economic burdens and will increase the rate of breastfeeding and improve the combination between mothers and infants.

**Abbreviations**

ABO HDN: ABO hemolytic disease of the newborn; DAT: Positive direct antiglobulin test; G-6-PD: Glucose-6-phosphate dehydrogenase deficiency; TSB: The total serum bilirubin; AAP: American Academy of Pediatrics; IVF: In-vitro fertilization; IVH: Intraventricular hemorrhage; LBW: Low birth weight; SGA: Small for gestational age; PROM: Premature rupture of membranes; GDM: Gestational diabetes; ICP: Intrahepatic cholestasis of pregnancy; GBS: Streptococcus agalactiae
Declarations

Ethics approval and consent to participate: This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from one of the parents of all neonates in the study.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no potential conflicts of interest to disclose.

Consent for publication: Not applicable.

Funding: This study is supported by a grant from the Major scientific and technological projects of medical and health in Zhejiang Province (WKJ-ZJ-2032) for the analysis and interpretation of data by the third organization, also for the submission and publication the manuscript.

Authors’ contributions:

• JJ: conceptualized and designed the study, coordinated and supervised data collection, performed the data analysis, reviewed and revised the manuscript and approved the final manuscript as submitted.

• CC, YY: designed the data collection instruments, enrolled the patients, collected the data, drafted the initial manuscript and approved the final manuscript as submitted.

• YY, JX, FJ, MY: collected the data, drafted the initial manuscript and approved the final manuscript as submitted.

Acknowledgements: Not applicable.

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