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Management of hyperbilirubinemia in preterm infants in Turkey

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Background/aim: Prematurity is a significant risk factor for developing unconjugated hyperbilirubinemia. This study investigated the current approach to managing hyperbilirubinemia in preterm newborns in Turkey.

Materials and methods: A study-specific questionnaire on the management of jaundice in preterm infants was sent to 100 level III neonatal intensive care units in Turkey.

Results: Responses were obtained from 84 centers from all regions of Turkey. Of the centers, 75.3% used the Turkish Neonatology Society guidelines for deciding to start phototherapy, and 24.7% used different guidelines. The monitoring of bilirubin varied among the participants. Of the participants, 53.6% believed that prophylactic phototherapy was necessary if the infant's birth weight was below 1000 g. The participants reported 6 cases of kernicterus in preterm infants in recent years.

Conclusion: There is no single standard approach for managing neonatal hyperbilirubinemia in preterm infants in Turkey. Prophylactic phototherapy for extremely low birth-weight infants might be added to the guidelines for Turkey.

Key words: Hyperbilirubinemia, preterm

1. Introduction

Bilirubin levels increase soon after birth, and neonatal hyperbilirubinemia is common in newborns. However, high levels of unconjugated bilirubin can enter the central nervous system and cause kernicterus. Because early identification can prevent severe hyperbilirubinemia, in 2004, the American Academy of Pediatrics (AAP) Subcommittee on Hyperbilirubinemia published guidelines for managing hyperbilirubinemia in newborn infants of ≥35 weeks gestational age (1).

Premature infants develop more significant jaundice due to poor bowel motility, decreased oral intake, and immaturity of the hepatic conjugating system. Consequently, prematurity is a significant risk factor for developing hyperbilirubinemia, requiring therapy (2,3).

This study investigated the current approach to managing hyperbilirubinemia among preterm newborns in Turkey. The results may contribute to national guidelines for better management and prevention of hyperbilirubinemia among preterm newborns.

2. Material and methods

We conducted a survey of the management of hyperbilirubinemia in preterm infants in Turkey. By email or a letter, 100 clinical directors of level III neonatal intensive care units (NICUs) in all regions of Turkey in different hospital types (public, private, teaching, and university) were invited to complete a questionnaire on the management of jaundice in preterm infants. After 2 weeks, all nonresponders were contacted again with second and third copies of the questionnaire. Another phone call was made to clinicians who failed to respond to the last call.

The questionnaire examined the approach to preterm infants with hyperbilirubinemia in NICUs. We asked the participants about the approaches used to assess jaundice clinically, monitoring the total serum bilirubin (TSB), rebound bilirubin measurement, age-specific phototherapy threshold, and which devices they used to treat preterm newborns.

3. Results

We received responses from 84 of the 100 hospitals surveyed. Of these, 21.4% (n = 18) were located in western Turkey, and 26.2% (n = 22), 20.2% (n = 17), 19% (n = 16), and 13.1% (n = 11) were in the central, southern, northern, and eastern parts of Turkey, respectively. Of the centers, 31% were public hospitals, 44% were training or university hospitals, and 25% were private hospitals.

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Approximately 19,800 infants under 35 gestational weeks and 5800 extremely preterm newborns were monitored in the hospitals over the last year. In total, 91.7 % (n = 77) of the participants felt that extremely preterm infants were at high risk for developing bilirubin encephalopathy. Of the respondents, 53.6% believed that prophylactic phototherapy was necessary if the infant's birth weight was below 1000 g.

Of the participants, 42.9% stated that phototherapy was initiated when the TSB concentration reached the threshold level. An initial TSB measurement was performed routinely in 50 hospitals (59.5%). In these centers, the first TSB measurement was done within 6 (n = 13), 12 (n = 5), 12–24 (n = 7), or 24 (n = 25) h. In 40.5% of the hospitals, routine measurements were not made, and the first measurement was based on clinical assessment by the doctors in the unit. The majority of respondents (56%) sent venous blood samples to their central laboratories for the first check of bilirubin, and 40% of the centers measured bilirubin by spectrophotometry in capillary blood samples. In 22% of the centers, transcutaneous bilirubinometers were used, although only 4 centers used these for the first bilirubin check.

Postphototherapy rebound bilirubin was checked in 27.4%, 27.4%, and 28.6% of the units at 6, 12, and 24 h, respectively. Of the participants, 10.7% considered rebound bilirubin measurement unnecessary.

Of the centers, 75.3% used the Turkish Neonatology Society (TNS) guidelines to decide when to start phototherapy and to perform exchange transfusion, whereas 24.7% of the centers used different guidelines.

Light-emitting diode (LED) phototherapy was used in 57.1% of the centers, and conventional phototherapy with fluorescent light sources was used in 14.3%. In 22.6% of the centers both LED and conventional approaches were used, and 3.6% of the centers used all devices, including fiber optics.

The participants reported 6 cases of kernicterus in preterm infants in recent years. Our questionnaire included no questions about the etiology or long-term follow-up of kernicterus cases. We sent e-mails to the 6 centers that reported a case of kernicterus, but only 3 replied. Two patients had ABO incompatibility and one patient had Rh disease. One patient with ABO disease had hearing loss at 1 year of age. There was no information on the long-term follow-up of the other patients.

4. Discussion

Based on this questionnaire study, we concluded that the management of neonatal jaundice in preterm infants varies greatly among hospitals in Turkey. Despite the common belief among participants that unconjugated hyperbilirubinemia is more dangerous for preterm infants, there is no universal approach to these vulnerable infants. The TNS recommendations for the treatment of jaundice in infants were published in 2002 (Table) (4). These guidelines suggest that birth weight and postnatal age should be used to determine TSB thresholds. New guidelines published in 2014 adopted the AAP hyperbilirubinemia guidelines for babies of gestation age 35 weeks or older, while the management of hyperbilirubinemia in preterm infants was not revised (5). Although most of the centers used the TSB threshold of the TNS for starting phototherapy, 6 preterm infants still developed kernicterus. There are no precise data on the prevalence of hyperbilirubinemia in newborns, and there are no reports on deaths due to acute bilirubin encephalopathy in the mortality statistics for Turkey. Although most studies have examined term and near-term infants, some studies have found that a few diseases that are common in Turkey (e.g., glucose-6-phosphate dehydrogenase (G6PD) deficiency) cause neonatal jaundice and that the high rate of consanguinity and consequent high rate of inherited diseases (e.g., galactosemia, G6PD deficiency) may also cause the

Table. The Turkish Neonatology Society's phototherapy and exchange transfusion threshold in newborns of less than 35 weeks gestational age.*

Birth weight (g)	24–48 h FT/exchange (mg/dL)	49–72 h FT/exchange (mg/dL)	>72 h FT/exchange (mg/dL)
<1000	4/10	5/11	6/12
1000–1499	5/12	7/14	8/16
1500–1999	7/15	9/16	10/17
≥2000	8/17	12/18	14/19

*If risk factors are present, consider phototherapy and exchange transfusion at a TSB level 2 mg/dL lower than those shown. Risk factors: isoimmune hemolytic disease, G6PD deficiency, perinatal asphyxia, significant lethargy, temperature instability, acidosis, sepsis, and albumin level of <3.0 g/dL.

increased incidence of neonatal hyperbilirubinemia. Additionally, hemolytic hyperbilirubinemia dependent on Rh incompatibility persists due to disruptions in maternal prophylaxis (5–10).

A study of the causes of jaundice in hospitalized infants conducted in southern Turkey reported that 20% were isoimmunized and 5% had G6PD (6). Another study conducted in eastern Turkey reported that the cause of hyperbilirubinemia was Rh incompatibility in 21.4% and G6PD deficiency in 9% (7).

Based on our results, half of the respondents thought that prophylactic phototherapy was necessary for extremely low-birth-weight (ELBW) infants. The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network compared the effects of aggressive and conservative phototherapy in ELBW infants. The death rate did not differ between the two treatments, although neurodevelopmental impairment was reduced significantly in the aggressive phototherapy group (11). Lasky et al. (12) reported that aggressive phototherapy in ELBW infants reduced brainstem auditory evoked response latencies. In our study, almost all of the participants agreed that LED phototherapy was more effective. Nevertheless, 14.3% of the participants used only conventional phototherapy for preterm infants because they had only conventional phototherapy devices in their units. Recently, Morris et al. (13) showed that fiber optic phototherapy devices were associated with a decreased risk of age-corrected mental development index (MDI) score of <85 compared with LED phototherapy at 18–22 months, whereas they found an increased risk of MDI of <85 with conventional phototherapy compared to LED phototherapy. Furthermore, conventional phototherapy resulted in increased risks of death and MDI of <85 compared with LED and fiber optic phototherapy.

Rebound bilirubin was not measured in 10.7% of the hospitals. The few studies that have determined the incidence and magnitude of the postphototherapy bilirubin rebound in preterm infants showed that preterm infants were at the highest risk of postphototherapy neonatal bilirubin rebounding to clinically significant levels (14,15).

In conclusion, there is no standard approach to the management of neonatal hyperbilirubinemia in preterm infants in Turkey. We highlight the importance of managing neonatal hyperbilirubinemia in preterm infants, which is generally considered a simple treatment. We also suggest that prophylactic phototherapy for ELBW infants might be added to the guidelines for Turkey.

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