Pediatric RESEARCH

COMMENT

Repetitive bilirubin measurements in preterm infants prior to phototherapy: is it wise to use the rate of rise?

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In this issue of *Pediatric Research*, Hahn et al.[1] report on the use of the rate of rise (ROR) of total serum bilirubin (TSB) concentration (TSB-ROR) in very low birth weight (VLBW) preterm infants until the start of phototherapy.[1] They used data retrospectively collected during a 3-year time period from 467 infants with a birth weight <1500 g admitted to the neonatal intensive care unit (NICU). Based on the clinical characteristics of this group, the authors conclude that a lower gestational age (GA), a lower birth weight, and a lower Apgar score at 5′ predispose to a steep TSB-ROR defined as a TSB-ROR above the 90th percentile. The approach used to calculate TSB-RORs is original since data on the postnatal course of TSB in preterms are numerous.

What does this manuscript add to the existing knowledge on the management of unconjugated hyperbilirubinemia in preterm infants? For instance, would it be possible to use a TSB-ROR for early identification of those VLBW preterm infants at risk to develop severe hyperbilirubinemia or for a more individualized timing of reassessment of hyperbilirubinemia, and eventually treatment? To answer these questions, several aspects of the management of unconjugated hyperbilirubinemia unique for preterm infants are important to address.

Ubiquitously applied nomograms of risk of hyperbilirubinemia in VLBW infants do not exist, in contrast to the widely used risk nomogram for term or near-term appropriate for GA newborns infants.[2] This nomogram has even resulted in a so-called BiliTool, that is, "designed to help clinicians assess the risks toward the development of hyperbilirubinemia or 'jaundice' in newborns over 35 weeks GA" (http://www.bilitool.org/). The nomogram includes the key message that when plotting a TSB in a risk zone of the nomogram, this risk refers to the risk of a subsequent bilirubin level in that infant >95th percentile for age. As early discharge is not an issue for VLBW preterm infants admitted to a NICU, one could argue that such risk nomograms are not helpful. On the other hand, risk factors are clinically useful in the management of jaundice in preterm infants. Due to their prematurity, all preterm infants have neurotoxicity risk factors, but well-known hyperbilirubinemia risk factors may not always be present. In contrast to those VLBW preterms who appear relatively healthy, others may suffer from multiple hyperbilirubinemia risk factors with an unpredictable effect on TSB concentrations. Thus, it would be of interest if TSB-ROR might prove to be an additional predictor of hyperbilirubinemia in VLBW preterm infants.

Many VLBW preterm infants admitted to NICUs are treated with phototherapy. Hahn et al.[1] reported that 89% of the VLBW infants were treated with phototherapy, which was started at a median postnatal age of 30 h. In a recent Norwegian study, the overall incidence of phototherapy in all infants admitted to one of the 21 national NICUs was 27%.[3] Incidence and duration of phototherapy was highest in infants with a birth weight <1000 g and with a GA <28 weeks (86 and 82%, respectively with a mean (SD) duration of 39 (32) and 37 (32) h, respectively). Data on phototherapy at two NICUs in the USA showed that 82% of infants with a GA between 23 and 35 weeks received phototherapy with a median (interquartile range) duration of 50 (27–85) h.[4] Here, 94% of infants with the lowest GA (23–$27^{6/7}$) and birth weight <1000 g received PT for 74 (42–111) and 70 (42–104) h, respectively. In 10 Dutch NICUs, 88% of preterm infants <32 weeks (mean BW of 1250 g) received PT with a mean (SD) duration of 74 (50) h.[5] From these data, it is clear that considerable variation exists in the frequency and duration of PT mainly related to the use of different treatment guidelines. For the management of jaundice in preterm infants <35 weeks gestation, NICUs either follow nationally developed recommendations or may have adopted the American approach.[6] Yet, even within one country variation in PT practices exists: PT may be started earlier (i.e., when approaching the treatment threshold based on an anticipated rather than calculated TSB-ROR) or continued longer than indicated by the guideline.[7] Under the assumption that the TSB-ROR contributes to an individualized risk prediction of rapidly rising TSB concentrations in preterm infants, a TSB-ROR >90th percentile could be interpreted not only as a hyperbilirubinemia predictor but could also affect time to follow-up of the next TSB measurement. A TSB-ROR >90th may predict the need to measure TSB earlier than usually planned with the aim to start PT treatment at the most appropriate time (when TSB is at or just above the treatment threshold) and to keep the duration of phototherapy as short as possible. Eventually, but not studied here, the TSB-ROR in infants under phototherapy might be used to consider intensified PT.

Hahn et al.[1] were able to calculate TSB-ROR as TSB was reported by their instrument used for blood gas and blood glucose analysis, when this was indicated. At many NICUs, TSB is replaced by transcutaneous (TcB) measurements. According to Maisels et al.[8] "routine screening with TcB measurements in a level III NICU can identify infants who do or do not require a TSB to rule in or out the need for phototherapy and can eliminate the need for many heel stick blood samples." In analogy to TSB-ROR, TcB-ROR has been found useful to identify (near) term infants at risk for severe hyperbilirubinemia.[9,10]

The main message of the paper by Hahn et al.[1] is that the use of TSB-ROR in clinical practice is still premature. We must also realize

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that the study was not powered to assess the predictive value of other known hyperbilirubinemia risk factors and the data were derived from a single center. The clinical course of neonatal jaundice may vary in a different population with different hyperbilirubinemia risk factors. Although provocative, the data need to be prospectively confirmed in a larger study in more NICUs to prove (or disprove) that TSB-ROR is useful to predict severe hyperbilirubinemia in VLBW preterm infants.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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