

Phototherapy and Seizures: Should We Change Practice?

James A. Taylor, MD

It is axiomatic that for every treatment there are associated adverse events. For many medical conditions, the risk/benefit assessment of treatment is trivial, with an example being antibiotics for patients with bacterial meningitis. Even the risk of therapies leading to serious adverse events may be outweighed by the potential benefit, such as chemotherapy for a child with leukemia. However, the calculus becomes more difficult when the likelihood of an adverse outcome without treatment is small and/or the patients receiving the treatment are not sick but healthy.

Such is the case with phototherapy. In this issue of *Pediatrics*, Newman et al¹ analyzed data from a large and rich database and found an increased risk of subsequent seizures in newborns treated with phototherapy. Although the increased risk was small, with an adjusted hazard ratio (HR) of 1.22, and only truly apparent in boys, the results are troubling. Phototherapy is a common therapy for newborns; in the data evaluated by Newman et al,¹ ~8% of ~500 000 newborns received this treatment for hyperbilirubinemia. Most of the infants who were treated were term neonates without hemolytic disease; the risk of a bad outcome (ie, kernicterus) without phototherapy, although not 0, is low.^{2,3} Given this low risk of an adverse outcome without treatment, the small increased risk of a seizure disorder associated with phototherapy becomes relatively more important.

Because the results of the study by Newman et al¹ may be used to change clinical practice, it is critical to use

basic epidemiological principles to assess whether they are valid and indicative of a causative relationship between phototherapy and seizures.⁴ Assessing validity involves accounting for known confounders and the possibility that the results occurred by chance or because of unknown bias or confounding. As the authors point out, total serum bilirubin (TSB) levels were not accounted for in a previous study in which an association between phototherapy and seizures was found.⁵ TSB level is a classic confounder, associated both with the exposure (phototherapy) and outcome (seizures). Newman et al¹ rigorously accounted for TSB levels in their study and found that phototherapy was an independent predictor of subsequent seizures.

The possibility that the results occurred by chance or because of an unknown source of bias is harder to dismiss. The adjusted HR of 1.2 is modest. Epidemiologists caution against overinterpretation of risk ratios <2, or even <3, because of the chance of a spurious result.⁶ Cognizant of this, Newman et al¹ conducted multiple analyses and found no other explanation for their findings. Thus, to the limit of the available data and knowledge, the results seem valid.

Among the epidemiological criteria for assessing causation are consistency, a dose–response relationship, and biological plausibility.⁴ The adjusted HR of 1.2 and the finding that the increased risk was largely in boys is consistent with a Danish study in which the adjusted HR was 1.66 and was only significantly increased

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Department of Pediatrics, University of Washington, Seattle, Washington

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Address correspondence to James A. Taylor, MD, Department of Pediatrics, University of Washington, Box 354920, Seattle, WA 98195. E-mail: uncjat@uw.edu

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in male infants.⁵ Unfortunately, Newman et al¹ could not measure the “dose” of phototherapy, either in terms of duration or intensity; thus, it is difficult to evaluate whether “more” phototherapy was associated with a greater increased risk of seizures than “less” phototherapy. The authors did report that the HR for seizures with home phototherapy was 0.77 (95% confidence interval 0.43–1.27) compared with 1.74 (95% confidence interval 1.53–1.98) for those treated in the hospital; perhaps the intensity of home phototherapy was less than that provided in-hospital.¹ Finally, although Newman et al¹ speculated about possible mechanisms, there is currently no adequate biological model to explain the main study finding.

Given these caveats, should we change our management of newborn hyperbilirubinemia? There is a natural reticence to modify guidelines that have been successful in limiting the risk of a devastating outcome such as kernicterus. Concomitant with the implementation of the 1994 and 2004 American Academy of Pediatrics guidelines for management of neonatal hyperbilirubinemia, the rate of kernicterus has remained low and is currently estimated at 0.5 cases per 100 000 live births in the United States.^{7–10} However, as documented by Newman et al,¹ the use of phototherapy increased during this same period, and newborns are frequently treated at TSB levels below recommended thresholds.¹¹ Not only does this increase costs, there are other risks of phototherapy

such as reduced rates of exclusive breastfeeding after treatment.¹² Perhaps in the next iterations of neonatal hyperbilirubinemia guidelines, treatment thresholds should be modestly increased, with more focus on rigorous follow-up triage at hospital discharge and an emphasis on avoiding subthreshold phototherapy. Even a small increase in phototherapy thresholds might lead to a substantial reduction in its use, reducing both health care costs and the risk of adverse events, while not increasing the rates of kernicterus.

ABBREVIATIONS

HR: hazard ratio
TSB: total serum bilirubin

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