Journal of Perinatology (2012) 32, 649–651

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EDITORIAL

Let there be light—but should there be less?

Journal of Perinatology (2012) **32,** 649–651; doi:10.1038/jp.2012.80

The account of the serendipitous discovery of the beneficial effects of light on jaundiced infants is a classic in medical history.[1,2] Of note, the 1957 and 1958 communications from the light therapy group at Southend Hospital in England initially met with concern. In letters to *The Lancet*, *BMJ* and *Gastroenterology*, Franklin[3] and Blondheim *et al.*[4,5] were worried about the possible toxicity of bilirubin photoproducts, and cited a lack of effect in their own preliminary clinical trials, which were stopped.

The next English language study of phototherapy did not appear until 1965. Broughton *et al.*[6] had combined clinical studies in infants and animal studies in Gunn rats with *in vitro* studies in rat brain and liver mitochondria. This study addressed both questions of effect and toxicity, and appears to be the first study of phototherapy to have employed both a randomization technique and statistical analysis of the data. The study found a clear clinical effect and no evidence of *in vivo* or *in vitro* toxicity.

In the 1970s, a large US collaborative study was conducted to investigate the effectiveness of phototherapy in preventing exchange transfusions.[7,8] Being a landmark in the field, this study concluded that phototherapy was effective both in preventing and in controlling neonatal jaundice. An apparent trend toward higher mortality in the phototherapy-treated low birth weight infants was discounted in the discussion because it was not found to be significant.[8]

Since then, and in spite of the acknowledged role of bilirubin as an important physiological antioxidant,[9] the reduction of which might possibly have side effects, phototherapy has been considered a largely innocuous treatment. In support of this concept, both the physicochemical characteristics of bilirubin photoisomers, that is, their increased polarity, as well as *in vitro* studies of the toxicity of these isomers, have pointed to the possibility of a protective effect of phototherapy even in the absence of significant reductions in total serum bilirubin values.[10,11] The practical application of phototherapy has earlier been shown to vary greatly,[12] and this still appears to be the case.[13–15]

Recent data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network comparing 'aggressive' vs 'conservative' phototherapy in extremely low birth weight (ELBW) infants[16] gave us reason to rethink our approach to neonatal jaundice, particularly in the smallest and most immature babies. They found that aggressive phototherapy significantly reduced the rate of neurodevelopmental impairment at 18 to 22 months of age, almost all of which was due to a reduction in profound impairment. However, a preplanned subgroup analysis of infants with birth weight 501 to 750 g suggested that mortality was increased in this group, although with the statistical method employed this apparent difference did not reach significance.

This issue of the Journal contains two important papers, both of which address this therapeutic conundrum, but from different perspectives. The Neonatal Research Network have taken a new look at their data using a Bayesian approach to the statistical analyses.[17] They now find that the relative risk of death in the 501 to 750 g birth weight subgroup treated with aggressive phototherapy was 1.19 (95% confidence interval 1.01 to 1.39), with a 99% estimated probability of increased mortality. On the other hand, the likelihood of impairment or profound impairment was significantly reduced in both weight groups (501 to 750 and 751 to 1000 g). The investigators conclude that 'phototherapy should not be assumed to have the same risks and benefits in the smallest and sickest infants as in more mature infants', and recommend efforts to develop other treatment approaches including phototherapy with lower irradiance levels.

In the other paper, four of the world's leading experts on neonatal jaundice provide suggestions for management of this condition in preterm infants born at <35 weeks gestation.[18] In their introduction, they make it clear that our knowledge in this area is too scant to allow for the formulation of truly evidence-based guidelines. However, we need a pragmatic approach that recognizes that every day in neonatal intensive care units around the world jaundiced premature infants are going to be treated. That being the case, should decisions about treatment be at the whim of individual physicians, or are the babies better served with more uniform practices? The results from the Neonatal Research Network[16,17] remind us that we need to start thinking about phototherapy as a 'drug' to be administered in appropriate dosage, as is indeed our approach to most other things we do for sick infants.

Maisels *et al.*[18] provide a thorough review of the extent and limitations of our knowledge, as far as the many aspects that underlie our treatment decisions, and present their treatment suggestions in tabular format with several user-friendly comments that supplement the actual numbers. As openly discussed by the authors, the recommendations are expert opinions, but several pragmatic choices have been made. Thus, both the use of a tabular

format and linking recommendations to gestational age rather than birth weight are such choices. The 2004 AAP guidelines for infants born at >35 weeks gestation used graphs but linked those to gestational ages.[19] Others have also chosen graphs[15,20] or used birth weights in lieu of gestational ages.[15]

The recommendations are clearly influenced by the results from the Neonatal Research Network,[16,17] and recommend phototherapy at lower levels than others have opted for.[15] Also, in infants with birth weight <750 g, the authors recommend starting phototherapy with lower irradiance, and to increase irradiance only if the initial irradiance fails to keep the serum bilirubin at safe levels. This highlights some of the challenges in understanding and interpreting the network results.[16,17]

The Neonatal Research Network enrolled almost 2000 premature infants, and few, if any, others in the world have the capability to execute a study of this size. Nevertheless, it was necessary to employ innovative statistical tools to arrive at a conclusion of increased mortality in the 501 to 750 g birth weight group. Also, the decision not to adjust for multiple comparisons is contrary to what many of us were taught in 'Statistics 101'. I confess inadequate insight into the pros and cons of the chosen approach, but suggest that some caution may be needed in the interpretation.

The aggressive vs conservative phototherapy groups differed in the bilirubin levels at which phototherapy was instituted, whereas the target irradiance was the same for both groups (15 to 40 $\mu W\,cm^{-2}\,nm^{-1}$). Not surprisingly, the duration of phototherapy was significantly longer in the 'aggressive' group (88 ± 48 vs 35 ± 31 h, $P<0.001$).[16] In the older Collaborative Phototherapy Trial, all the infants randomized to phototherapy were treated for 96 h.[7,8] The irradiance was apparently not measured, but with the phototherapy equipment extant at that time was probably considerably lower than the target irradiance in the Neonatal Research Network study.[16,17] Maisels[21] later calculated the relative risk for mortality among ELBW infants in the Collaborative Phototherapy Trial as 1.49 (0.93 to 2.40).

Based on these two studies, it may not be unreasonable to suggest that if there is indeed an increased risk of mortality associated with phototherapy for neonatal jaundice in ELBW infants, the association is more likely to be with duration of phototherapy than with irradiance. With this in mind, the recommendation to start phototherapy at lower irradiance in ELBW infants <750 g birth weight may need further discussion.[17,18] Indeed, the same may be true for the use of prophylactic vs targeted phototherapy, because this would also result in longer light exposure. Conversely, could it be argued that treatment for neonatal jaundice should be as brief as possible, but maximally effective during periods of exposure?

The papers presented in this issue of the Journal further attest to the complexity of the interaction between neonatal jaundice and the therapies we apply.[17,18] These papers undoubtedly add further to our understanding of these issues. However, as is so often the case in science, important questions still remain unanswered.

Conflict of interest

The author declares no conflict of interest.

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