Journal of Perinatology (2006) 26, 498–500

www.nature.com/jp

ORIGINAL ARTICLE

Does intensive phototherapy produce hemolysis in newborns of 35 or more weeks gestation?

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Objective: Because there is some *in vivo* and *in vitro* evidence that standard phototherapy might produce hemolysis, we wished to know whether intensive phototherapy produces hemolysis.

Study design: We measured end-tidal carbon monoxide (CO) concentration corrected for ambient CO (ETCOc) in 27 newborn infants ⩾35 weeks gestation receiving intensive phototherapy (average irradiance 43 μW/cm^2/nm).

Results: There was a steady decrease in the mean ETCOc over the course of the phototherapy.

Conclusion: Intensive phototherapy did not produce hemolysis in infants ⩾35 weeks gestation.
Journal of Perinatology (2006) **26,** 498–500. doi:10.1038/sj.jp.7211552; published online 8 June 2006

Keywords: phototherapy; newborn infant; hyperbilirubinemia; intensive phototherapy; hemolysis; end-tidal carbon monoxide

Introduction

Although phototherapy lowers the serum bilirubin level, in one study of 24 preterm neonates[1] standard phototherapy (irradiance of 5 to 10 μW/cm^2/nm) produced a modest, but statistically significant increase in the mean end-tidal carbon monoxide (CO) concentration corrected for ambient CO (ETCOc). ETCOc provides a direct index of heme turnover and bilirubin production,[2] one molecule of CO being formed for each molecule of heme catabolized.[2,3] Thus, the increase in ETCOc suggests the possibility that phototherapy could produce hemolysis. In addition, there is some *in vitro* evidence that phototherapy can increase erythrocyte osmotic fragility[4] and produce lipid peroxidation of the red cell membrane,[5] leading to hemolysis.

If standard phototherapy does, indeed, increase heme catabolism, then one would anticipate a similar, or greater, effect from intensive phototherapy.[6] As we routinely use intensive phototherapy for infants ⩾35 weeks gestation (as recommended by the American Academy of Paediatrics),[7] we wished to know whether intensive phototherapy (irradiance of at least 30 μW/cm^2/nm) would produce hemolysis and therefore interfere with the bilirubin lowering effect of phototherapy. If this effect were confirmed, it might be desirable to use a less intense form of phototherapy.

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Received 28 March 2006; revised 25 April 2006; accepted 9 May 2006; published online 8 June 2006

Materials and methods

We studied a convenience sample of 27 infants, ⩾35 weeks gestation, born between 1 June and 31 October 2001 who received phototherapy. Twenty-two infants received phototherapy in our well-baby nursery during their birth hospitalization and five infants received phototherapy following readmission to the pediatric service. The decision to use phototherapy was made by the individual attending pediatrician. Phototherapy was provided above the infant by eight, 24-inch special blue fluorescent tubes (General Electric 20W F20T12/BB). This produced an average irradiance of 43.0±7.4 μW/cm^2/nm at 425–475 nm, measured with an Olympic Bilirubin Meter Mark II (Olympic Medical, Seattle, WA) at the surface of the infant. All infants also lay on a fiberoptic blanket – the Biliblanket (Ohmeda, Columbia, MD) or the Wallaby (Fiberoptic Medical Products Inc., Allentown, PA) and the irradiance measured at the surface of the blanket ranged from 18 to 21 μW/cm^2/nm. We measured the ETCOc using the Natus CO-Stat® End Tidal Breath Analyzer (Natus Medical, San Carlos, CA). Measurements were obtained 0.7±0.9 hours before commencing phototherapy and then at 8.3±3.2 and 22.2±3.3 hours (mean±s.d.) after phototherapy was started. The final measurement was made 2.6±3.5 hours after phototherapy was discontinued. In three infants, the first ETCOc measurement was obtained after phototherapy commenced. This study was approved by the Hospital Human Investigation Committee and informed consent was obtained from one parent of each infant.

For controls, we performed ETCOc measurements during the same 5-month period in 104 infants of similar age who did not receive phototherapy.

Results

The gestational age of the infants studied ranged from 35 1/7 to 41 1/7 weeks and 14 (15.9%) were ⩽38 weeks gestation. The mean age at the time of initiating phototherapy was 63.5±30.4 hour (range 6.4 to 128 hour). The mean bilirubin level before phototherapy was 14.6±3.15 mg/dl (range 8.8–21.0 mg/dl) and 10.9±2.2 (6–14.9) mg/dl when phototherapy was discontinued. Seventeen out of twenty-seven (63%) infants had blood typing performed and 10 were ABO incompatible with their mothers, but only two were Coomb's positive. Twenty-one out of twenty-seven (78%) were exclusively breastfed. Mean ETCOc before commencing phototherapy was 2.83±0.49 parts per million (p.p.m.), significantly higher than the ETCOc of a group of 104 infants of similar age who did not receive phototherapy (1.79±0.47 p.p.m., $P = 0.000$, two-sample *t*-test). There was a steady decline in the mean ETCOc over the course of the phototherapy (Table 1), although two infants showed a modest increase in ETCOc (Figure 1).

Discussion

A weakness of this study is the absence of concurrent controls with four ECTOc measurements obtained at the same time and over the same intervals as the infants receiving phototherapy. Before receiving phototherapy, however, the elevated mean ETCOc in these infants (compared with infants who did not receive phototherapy) suggests that hemolysis played a significant role as a cause of their hyperbilirubinemia. Nevertheless, we found no evidence that intensive phototherapy at a high irradiance increased heme turnover or bilirubin production. In one study of preterm neonates,[8] 96 hour of phototherapy (irradiance not stated) produced a significant increase in blood thiobarbituric acid-reacting substances (TBARS, a measure of lipid peroxidation), suggesting that phototherapy induces oxidative stress. On the other hand, Kaplan *et al*.[9] found no increase in TBARS or plasma protein carbonyls (representative of protein oxidation) in 41 preterm infants, ⩽35 weeks gestation, during the first 24 hours of phototherapy (average irradiance 18 μW/cm^2/nm). They did, however, find an increase in the percentage change in blood carboxyhemoglobin levels in infants <1.5 kg birthweight when compared with those ⩾1.5 kg, suggesting the possibility of some hemolysis in this very low birthweight subgroup. Nevertheless, phototherapy reduced the serum bilirubin levels in all of these infants.

In a study of 24 preterm neonates (gestation 32.7±2.3 weeks), Aouthmany[1] demonstrated an increase in the mean ETCOc using much lower irradiances (5–10 μW/cm^2/nm) than used in our study. We studied term and near-term infants whereas Aouthmany[1] studied preterm infants. In his study, results were based only on ETCOc measurements obtained before and after phototherapy and no comparison was made with similar infants not receiving phototherapy. In our study, we measured ETCOc four times – before, during (at 8 and 22 hours of phototherapy) and after phototherapy. Thus, it is possible that the increase in ETCOc reported by Aouthmany was merely coincident with, but not caused by, phototherapy. Most recently, Barak *et al*.[10] studied 38 infants

Table 1 ETCOc levels before, during and after intensive phototherapy

	Time of measurement (hours) Mean±s.d.	*ETCOc (p.p.m.) Mean±s.d.*
Before phototherapy	−0.7±0.9	2.83±0.49
During phototherapy	8.3±3.2	2.80±0.50
During phototherapy	22.2±3.3	2.57±0.68
After phototherapy	+2.6±3.5	2.49±0.62

Abbreviations: ETCOc, end-tidal carbon monoxide concentration corrected for ambient CO ; p.p.m., parts per million; s.d., standard deviation.

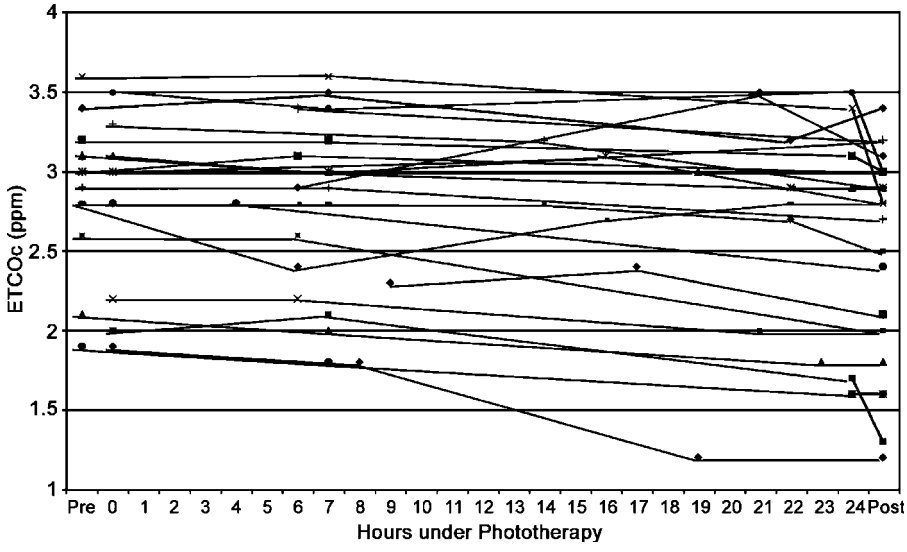

Figure 1 ETCO, levels before, during and after intensive phototherapy.

⩾35 weeks gestation and, similar to our observations, demonstrated no effect of phototherapy on ETCOc.

If phototherapy increases heme catabolism, it would have an impact on the efficacy of phototherapy. As there is no doubt that phototherapy reduces serum bilirubin levels, if it also increases hemolysis in some newborns, this effect must be quite small. Perhaps, there is a subgroup of infants who, for unknown reasons, (e.g. genetic) tend to hemolyze when exposed to phototherapy. If we could identify these infants, they would be good candidates for the use of tin mesoporphyrin, a drug that inhibits bilirubin production.[11]

Finally, it is possible that preterm infants react differently from term infants to intensive phototherapy. We are currently conducting a study of preterm infants to evaluate this possibility.

Acknowledgments

This work was supported by a grant from Natus Medical, San Carlos, California. The CO-Stat End Tidal Breath Analyzer is no longer produced by this company. We thank Drs Tom Newman, Michael Kaplan and Jon Watchko for their helpful comments.

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