Update on phototherapy in jaundiced neonates.

Running title: Update on phototherapy

*Finn Ebbesen[a,b], Thor Willy Ruud Hansen[c,d] and M.Jeffrey Maisels[e]

[a] Department of Pediatrics, Aalborg University Hospital, Aalborg, Denmark.

[b] Institute of Clinical Medicine, Aalborg University, Aalborg, Denmark.

[c] Department of Neonatal Intensive Care, Division of Paediatric and Adolescent Medicine, Oslo University Hospital – Rikshospitalet, Oslo, Norway.

[d] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway.

[e] Department of Pediatrics, Oakland University William Beaumont School of Medicine, Beaumont Children's Hospital, Royal Oak, Michigan, USA.

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*Corresponding author: Finn Ebbesen, Department of Pediatrics, Aalborg University Hospital, P.O.Box: 561 9100 Aalborg, Denmark.

Phone: 004597663331.

E-mail: fe@rn.dk.

ABSTRACT

Background: Even relatively low serum bilirubin concentrations can cause neurodevelopmental impairment in extremely low birth weight (EBWL) infants, while sequelae from hyperbilirubinemia in late preterm and term infants are rare and occur only at very high serum bilirubin levels. Phototherapy is the current treatment of choice.

Objective: To present an update on the most important issues involved in phototherapy for jaundiced infants.

Results: Light absorption by bilirubin in the skin transforms the native *Z,Z*-bilirubin to conformational photoisomers *Z,E*-bilirubin and *E,Z*-bilirubin and structural photoisomers *E,Z*-lumirubin and *E,E*-lumirubin. Formation and excretion of *Z,E*-bilirubin and *E,Z*-lumirubin are both important routes of elimination of bilirubin through bile and urine, although the precise contributions of the various photoisomers to the overall elimination of bilirubin are unknown. It appears that the photoisomers of bilirubin are predominantly formed in the plasma, and the rate of formation is affected by the hemoglobin concentration. Phototherapy lights with an emission spectrum of 460-490 nm provide the most efficient bilirubin-reducing light. LEDs should replace fluorescent tubes and halogen spotlights as the preferred light sources. Recent data raise concerns that sick ELBW infants under prolonged phototherapy may have an increased risk of death, though sur-

vivors may benefit from reduced rates of neurodevelopmental impairment. Comparison of the efficacy of cycled vs. continuous phototherapy has given divergent results. Changing the infant's position does not increase the efficacy of phototherapy.

Conclusion: During the last decade we have made progress in our understanding of how and where phototherapy works and in its practical applications.

Abbreviations:

PT: phototherapy; ELBW: extremely low birth weight; TSB: total serum bilirubin: LEDs: light emission diodes

INTRODUCTION

Jaundice occurs in more than 80% of late preterm and term infants [1,2]. Although in these infants it is generally harmless, on rare occasions the presence of significant hyperbilirubinemia can lead to acute bilirubin encephalopathy. With extreme elevations of total serum bilirubin (TSB), deposition of unconjugated bilirubin in the central nervous system can cause chronic bilirubin encephalopathy (kernicterus) [3]. Conversely, in extremely low birth weight (ELBW) infants, chronic bilirubin encephalopathy can be seen even at low and modestly elevated TSB [4-8]. Phototherapy (PT) is the current treatment of choice due to its efficacy and apparent safety, although recent reports of an increase in mortality in sick ELBW infants exposed to prolonged PT have raised questions about its safety [6,7]. Exchange transfusions are rarely needed.

The efficacy of phototherapy depends on the irradiance and spectrum of the light, the exposed body surface area, and the TSB level [9]. Other things being equal, the efficacy is also inversely related to birth weight, as with increasing weight the ratio of body surface area to weight decreases [10].

OBJECTIVE

We aim to provide an update on the most important issues involving phototherapy for jaundiced neonates.

FORMATION OF PHOTOISOMERS OF BILIRUBIN

Light absorption by bilirubin in the skin transforms the native toxic non-polar *Z,Z*-bilirubin to more polar and water soluble photoisomers of bilirubin: the configurational bilirubin isomers *Z,E*-bilirubin and *E,Z*-bilirubin, and the structural bilirubin isomers *E,Z*-lumirubin and *E,E*-lumirubin. The photoisomers of bilirubin can be excreted in bile and urine without conjugation.

Formation and excretion of both *Z,E*-bilirubin and *E,Z*-lumirubin are important routes for elimination of bilirubin in neonates [11] and thus account for the therapeutic effect of PT measured as a decline in TSB, although the precise contributions of the various photoisomers to the overall elimination of bilirubin are unknown.

Lumirubin formation is irreversible [12], the plasma half-life of *E,Z*-lumirubin is relatively short (about 2 h), and lumirubins have limited accumulation in the plasma [13]. The concentrations of lumirubins in bile and urine are far higher than the concentrations of configurational isomers [14]. The half-life in plasma of *E,Z*-lumirubin is inversely, but weakly, correlated with gestational age [15].

Conversely, formation of configurational photoisomers of bilirubin is reversible [12]. *Z,E*-bilirubin is excreted slowly, its plasma half-life is about 14 hours and it accumulates in plasma [16]. If there is sufficient irradiance, the formation of *Z,E*-bilirubin is rapid and within about 4 h of the initiation of phototherapy an equilibrium is reached between *Z,E* and *Z,Z*-bilirubin [17-19], at which time *Z,E* bilirubin constitutes about 25% of TSB [18,19]. It has been speculated that this early accumulation of *Z,E* photobilirubins (before there is a measurable decline in the TSB) may be “brain protective”, but this attractive hypothesis needs verification [18,19].

Isolated photobilirubins formed *in vitro* may be biologically inert and non-toxic to neuroblastoma cells [20]. This finding is consistent with chemical and biological arguments, which posit that photoisomers of bilirubin must be less toxic than the predominant native *Z,Z*-bilirubin. In addition to their lack of cellular toxicity, their more polar characteristics make them less prone to cross biological membranes. However, as recently reviewed by Hansen [21], the sum of extant evidence at this time is still equivocal and *in vivo* experimental proof is lacking.

CHANGING THE POSITION OF THE INFANT, AND WHERE PHOTOTHERAPY ACTS

Phototherapy in newborns was described as a result of Sister Ward's initial observation that jaundiced skin blanched when exposed to light [22], and changing the infant's position every second to third hour during PT has been a routine in many neonatal departments [23,24]. By turning the infant from supine to prone and vice versa, jaundiced skin that has not been exposed to light will now receive such exposure.

Recently, in a randomized controlled trial, Donneborg *et al.* [24] demonstrated that intensive phototherapy (a) reduced the transcutaneous bilirubin level (i.e. the bilirubin in the skin and subcutaneous tissues) by 65% in 2.5 hours and (b) reduced the TSB by 50% in 24 hours. But rotating the infant from prone to supine or supine to prone (thus exposing unblanched skin to the light) had no effect on the rate at which the bilirubin level was lowered. These observations confirm the data from 3 studies (25-27) all of which demonstrated that turning the infant does not improve the efficacy of phototherapy. Thus, while phototherapy certainly decreases the bilirubin in the skin and subcutaneous tissues, this effect cannot be responsible for the ability of phototherapy to decrease the bilirubin in the plasma.

Furthermore, Mreihil *et al*. [18,19] have shown that photoisomers are detectable in the blood within 15 minutes after starting phototherapy, too soon to be accounted for by isomerization in the skin. All of this evidence

strongly suggests that the primary site responsible for the bilirubin-lowering effect of phototherapy is the blood in the superficial capillaries in the skin.

CYCLED (INTERMITTENT) PHOTOTHERAPY

Studies of cycled (intermittent) versus continuous phototherapy, exposing the same body surface to light, have produced conflicting results [28-36], although the majority of these studies show no benefit (or harm) of cycling [32-35]. Most recently, in preliminary studies of ELBW infants, cycled and continuous phototherapy were equally effective in preventing elevation of TSB levels [37].

The questions regarding the difference in TSB reduction related to turning the infant, or using phototherapy in a cycled fashion, are not identical. Turning the infant has to do with alternately exposing jaundiced (unbleached) skin to phototherapy, while cycled phototherapy simply has to do with the intermittent (as opposed to continuous) use in an on-off sequence.

INFLUENCE OF THE HEMOGLOBIN CONCENTRATION ON THE EFFECT OF PHOTOTHERAPY

As the transformation of Z,*Z*-bilirubin predominantly takes place intravascularly, hemoglobin will compete with bilirubin for the absorption of light [38,39]. An increase in hemoglobin concentration decreased the percentage of *Z,E*-bilirubin in plasma in the first hour of PT but this effect disappeared later [19]. Theoretically, the hemoglobin concentration should have an effect on the percentage of *Z,E*-bilirubin until an equilibrium between *Z,E*-bilirubin and *Z,Z*-bilirubin is achieved [19]. The formation of lumirubins might be influenced by the hemoglobin concentration throughout the light exposure period, as an equilibrium between *E,Z*-lumirubin, *Z,Z*-bilirubin, and *E,Z*-bilirubin does not occur.

OPTIMAL EMISSION SPECTRUM OF THE LIGHT

Blue light with an emission spectrum matching the absorption spectrum of serum bilirubin with a peak emission around 460 nm is used worldwide, as it is considered to be the most effective [40]. Based on a skin optical model, Agati *et al.* [41] suggested that the greatest bilirubin reducing effect in neonates would be turquoise light in the spectral range 495±10 nm. Therefore, Ebbesen *et al.* [42] compared the bilirubin reducing effect in preterm infants of turquoise vs. blue fluorescent light with equal irradiance and with peak emissions at 490 nm and 452 nm, respectively. The turquoise light was more effective than the blue light indicated by the decrease of TSB.

As fluorescent tubes now are being replaced by narrow-spectrum light emitting diodes (LEDs), Ebbesen *et al.* [43] compared turquoise LED light centered at 497 nm vs. blue LED light centered at 459 nm, also with equal irradiance at the infant's body surface in late preterm and term infants. The two light sources were equally effective in reducing TSB. Using a skin optical model, Lamola *et al.* [38] recently predicted that LED light centered at 475-480 nm should be most effective in the treatment of neonates. These data suggest that the most effective light source will have an emission spectrum centered in the wavelength range of 475-490 nm [43], although clinical proof of this assumption is needed.

LIGHT SOURCES

In a multidirectional set up with blue fluorescent light Tan [44] appeared to find a "saturation point" at approximately 30 μW/cm^2/nm, above which there was no further decrease of TSB with increasing irradiance. But if lumirubins are the isomers responsible for the bilirubin-lowering effect of phototherapy, it is doubtful that such a "saturation point" exists. The conversion of *Z,Z*-bilirubin to lumirubins is irreversible and follows first order kinetics, and lumirubins are rapidly cleared in urine and bile [13,15]. Thus, neither an equilibrium nor a "saturation point" is ever reached, as has been demonstrated by Vandborg *et al.* [10]

The American Academy of Pediatrics defined intensive phototherapy as a light source in the spectrum range of 430-490 nm with an irradiance of at least 30 µW/cm^2/nm, exposing as much of the infant's surface area as possible (i.e. maximizing spectral power (irradiance x body surface area)) [40].

LEDs are replacing fluorescent tubes and halogen spotlights as light sources. LEDs have several advantages: a) their emission spectrum is narrower, i.e. they emit less unnecessary (and potentially harmful) wavelengths, b) they produce less heat so that the distance from the device to the infant can be reduced and the irradiance increased, c) their irradiance decreases very slowly over time, providing an extended lifetime of the light source and d) they do not cause significant transepidermal water loss, because they emit less infrared radiation [45]. In two meta-analyses it was concluded that LEDs and non-LED lights are equally effective in reducing TSB [46,47]. Late preterm and term infants have been exposed to LED blue light from above with irradiances as high as 120 µW/cm^2/nm [48]. The overhead PT can be combined with PT from below in the form of fiberoptic blankets, and several studies have shown that such double PT is more effective in reducing TSB than a single light [49,50]. Using blue LED light from above, Vandborg *et al*. [10] found a linear relationship between in-

creasing light irradiances from 20- to 55 µW/cm^2 /nm and a decrease in TSB.

Because high intensity treatment with LEDs is now being used worldwide in treatment of late preterm and term infants with very high TSB, rapidly increasing TSB, or signs of acute bilirubin encephalopathy, it is increasingly important to remain alert to the possibilities of unidentified short- and long- term adverse effects.

AGGRESSIVE VS. CONSERVATIVE PHOTOTHERAPY IN ELBW INFANTS

Neurologic sequelae have been seen in sick ELBW infants exposed to low or modestly elevated bilirubin levels [4-8]. In a large, multicenter randomized study Morris *et al.* [6] compared aggressive with conservative PT in ELBW neonates. Aggressive therapy was defined as PT starting at a TSB >85 µmol/L, while in the conservative group PT was started at TSB >119 µmol/L. In both groups light irradiances were in the 15-40 µW/cm^2/nm range and were not by design different between the study groups. Infants in the aggressive group were exposed to phototherapy for an average of 88 ± 48 h and those in the conservative group for 35 ± 31 h. At 18-22 months, in sick infants of birth weight 500-750 g, there was a 5% reduction

in the rate of severe neurodevelopmental impairment (one or more of blindness, deafness, moderate or severe cerebral palsy, mental development index scores below 70) in the aggressively treated group, but a 5% increase in mortality in that group compared with the conservatively treated group. A Bayesian analysis of these data showed that among ventilated infants of 500-750 g birth weight, there was a 99% posterior probability of increased mortality and a similar probability of a decrease in profound neurodevelopmental impairment in those infants who survived [7].

The increased neurodevelopment impairment of the conservatively treated (vs. the aggressively treated) group could be explained by a direct neurotoxic effect of the higher concentrations of unbound bilirubin sustained over time. The higher mortality in the aggressively treated infants with birth weight 500-750 g and respiratory failure might be caused by oxidative damage due to a lower antioxidant level pursuant to lower bilirubin concentrations [51], or by oxidative stress produced by the PT [52-54]. These tiny, sick infants have thin gelatinous skin and greater body surface area in relation to weight (compared with larger infants) and therefore absorb more energy and heat from the PT. PT is also associated with changes in blood flow [55,56], and it is possible that the more prolonged periods of exposure to PT seen in the aggressively treated group exposed those infants to greater circulatory variation or instability. The results of this study

raise important and, as yet, unanswered questions about how we should be delivering PT to these ELBW infants.

An unexpected result in this study was a significant increase in the rate of bronchopulmonary dysplasia in the conservatively treated group [7]. As we have no biological explanation for this outcome, it seems most likely, as suggested by the authors, that it is simply a chance occurrence.

ADVERSE EFFECTS

Short-time adverse effects

As mentioned above, an increase in mortality has been described in sick, ELBW infants (birth weights 500 –750 g) who were receiving “aggressive” PT [6,7].

PT causes oxidative stress (52] and the total oxidative status in the plasma of neonates was increased during phototherapy [53,54]. Furthermore, PT caused changes in the erythrocyte membranes, although their mechanical properties were unchanged [57].

PT produced DNA damage in peripheral lymphocytes [53,54,58,59], though these changes were transient [58].

TNF-α, IL-1β, and IL-8 were increased in the serum of light-exposed infants [60], and production of IL-2 and IL-10 was increased while IL-1β

decreased in peripheral blood mononuclear cells from light exposed term neonates [61].

Due to the low heat generation by LEDs, hypothermia has been observed in naked term neonates [62]. On the other hand, hyperthermia has been described at very high light irradiances of 60-120 μW/cm^2/nm [48]. Thus, temperature monitoring is advised in all infants undergoing PT.

Long-time adverse effects

The potential impact of phototherapy on melanocytic naevus count, a risk factor for subsequent development of cutaneus melanoma, has been investigated with inconsistent results (63), but there is no evidence that neonatal phototherapy is a risk factor for skin cancer [64].

Most recently, Wickremasinghe *et al.* [65] found a small but significant association between neonatal phototherapy and the rates of overall cancer, myeloid leukemia and kidney cancer during the first year of life. However, in another study with a longer follow-up period, the same set of authors failed to find a significant association [66]. The different results might be due to residual confounding or different length of the follow-up [65]. Although these findings represent association and not causation, there are several criteria that do satisfy the possibility of causality [67]. While the overall results of the epidemiologic studies relating neonatal phototherapy

to cancer risk are divergent [66], there remains the possibility that phototherapy is not harmless and, as noted by the authors, “avoiding unnecessary phototherapy may be prudent.” [66]

Finally, Swedish studies have suggested that phototherapy may be associated with diabetes type 1 [68] and childhood asthma [69].

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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