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Commentary

Phototherapy for neonatal hyperbilirubinaemia: Unresolved aspects & future directions

Although hyperbilirubinaemia is a leading cause of neonatal admissions and phototherapy is the most commonly used treatment, many aspects of phototherapy remain ambiguous due to paucity of evidence. Addressing one such area, the study published by Gottimukkala SB *et al*[1] in this issue has compared the efficacy and safety of intermittent phototherapy (IPT) versus continuous phototherapy (CPT) in non-haemolytic hyperbilirubinaemia in neonates born at ≥35 wk gestational age. The trial showed that IPT was non-inferior to CPT, since the difference in the rate of reduction of serum bilirubin was within the non-inferiority margin of 0.04 mg/dl/h[1].

The rationale for IPT is the hypothesis of two-step bilirubin clearance during phototherapy[2]. In step 1, light photons act on bilirubin molecules deposited in dermis and the photoproducts migrate to bloodstream. This step is completed within nanoseconds. In step 2, further bilirubin molecules migrate from the bloodstream to the dermis. Step 2 takes 1-3 h and is probably the rate-limiting step in the action of phototherapy. Since the amount of bilirubin clearance that occurs during step 2 is probably meagre, IPT may be as effective as CPT. However, recent studies propose a different theory, suggesting that phototherapy acts on circulating bilirubin molecules in dermal capillaries and not on bilirubin bound to dermal tissues[3,4]. This is based on observations that turning the neonate's positions does not increase the rate of bilirubin clearance[3] and that photoproducts appear in circulation just minutes after starting phototherapy[4].

Although the two-step bilirubin clearance during phototherapy is controversial, the rate of excretion of bilirubin photoproducts may support IPT. Phototherapy acts by converting bilirubin into water-soluble photoproducts that can be excreted directly without hepatic metabolism. The products of structural (lumirubin) and configurational isomerization (bilirubin isomer 4Z, 15E) have excretion half-lives of 1.9 and 13 h, respectively. These photoproducts are speculated to be non-neurotoxic based on the observations that these are polar and do not cross blood–brain barrier, and the apparent reversibility of acute bilirubin encephalopathy with timely aggressive therapy[5,6]. This speculation remains unproven, lacking direct scientific evidence[5,6]. Hence, until the photoproducts are excreted, further conversion of bilirubin may not be of much use.

There are a few other studies that have compared IPT versus CPT[7-9]. The schedules of IPT used in these studies were highly variable, ranging from 15 min on and 15 min off to 12 h on and 12 h off[7-9]. In the present study, the authors chose one hour on and two hours off to match the 2-3 h time duration taken for step 2 in the two-step hypothesis described above and showed that IPT is non-inferior to CPT[1].

Does this mean that the results of this study by Bhushan *et al*[1] can be incorporated into daily practice? Extrapolation of the results of this study, however, needs to be considered in the light of a few factors. The mean bilirubin at enrolment in this study was only 14 mg/dl in both groups at a median age of 68-70 h. The investigators used a bilirubin cut-off of two less than the recommended thresholds for phototherapy in the American Academy of Pediatrics guidelines[10]. Whether phototherapy is required at all at such lower bilirubin concentrations is questionable and may even cause more harm than good. Furthermore, only infants born at ≥35 wk gestation with normal birth weight were recruited into this trial. Hence, the answer that is most needed, *i.e.,* is IPT effective in babies with

clinically significant jaundice and in preterm/very low birth weight babies, remains unanswered.

This study raises the question as to at what threshold one should start phototherapy for non-haemolytic jaundice. Although there are many guidelines for treatment of neonatal jaundice, but those have been developed mainly based on expert opinion and consensus[10-14]. There is little evidence from randomized trials or systematic observational studies on bilirubin thresholds for phototherapy or exchange transfusion. There is wide disparity in the bilirubin thresholds used for phototherapy among neonatal centres across the globe[6]. The bilirubin levels at which neurotoxicity is reported in the literature are also highly variable[15-17].

There is a need for systematic and prospective collection of large-scale data to develop evidence-based guidelines on bilirubin thresholds to initiate treatment in term and preterm infants. Moreover, as many other factors modify the bilirubin threshold for neurotoxicity, we need data to systematically analyse their individual and combined predictive utility for bilirubin neurotoxicity. Until then, the disparities in bilirubin thresholds to initiate treatment will persist.

Since phototherapy reduces the need for exchange transfusion and is non-invasive and apparently free from side-effects, it is considered as a safe therapeutic option by neonatal health workers. This often leads to its overprescription. Though most side-effects of phototherapy such as skin rash, diarrhoea, increased insensible water loss and hyperthermia are transient and benign, there are other potential, more serious side-effects. Phototherapy may cause hypocalcaemia and disturbances in circadian rhythm leading to irritability. Both these adverse effects are probably due to inhibition of melatonin secretion[18]. Phototherapy causes arterial smooth muscle relaxation through activation of nitric oxide–cyclic guanosine monophosphate pathway and through calcium-dependent potassium channels. This may cause reopening of ductus arteriosus and other haemodynamic disturbances such as increase in peripheral blood flow and reduction in mean arterial pressure[18].

There is evidence for association between aggressive phototherapy and increased mortality in extremely low birth weight infants, and this is attributed to heat absorption and oxidative stress caused by phototherapy in such infants[19]. There is also evidence for association between phototherapy during neonatal period and long-term complications such as seizures, childhood cancers and melanocytic naevi[20,21].

Given the potential complications of phototherapy, it should be considered as a drug and needs to be prescribed at an optimal dose before being initiated for a neonate. The total irradiance received by the neonate should be just adequate to prevent severe hyperbilirubinaemia and neurotoxicity. This requires an individualized regimen of phototherapy in every neonate, taking into account the initial bilirubin level, a quantitative estimate of bilirubin production rate, the safe bilirubin target and the speed at which the safe level needs to be attained[22].

IPT may be one step towards this, since the major advantage of IPT is reduction in the total irradiance received by the neonate, which in turn may reduce the risk of complications. Though the current study shows no reduction in complications such as rash, diarrhoea, fall in calcium levels and increase in vitamin D and nitric oxide levels with IPT, the previous study by Zhou *et al*[23] showed a significant reduction in such complications. Other studies have not reported complications rate[7-9]. There are no data on the risk of serious complications with IPT compared to CPT.

The other aspect this study addressed is the acceptability of IPT versus CPT for mothers and nurses. While mothers found it satisfying, nurses found it more difficult to keep the schedule and handle the parents. This has implications in implementing the practice in resource-poor settings of low- and middle-income countries, where a nurse might have to look after several neonates and may not have the time to rigorously practice IPT. One could extrapolate these results into clinical practice by allowing mothers, whose infants are on phototherapy for mild hyperbilirubinaemia, to stop phototherapy during breastfeeding or skin-to-skin contact. Day-care IPT (12 h on and 12 h off) as done by Sachdeva *et al*[7] may be considered as an option for well neonates who otherwise do not need admission. This could be helpful in resource-limited settings that have constraints for nursery beds and nursing staff.

In this trial, the authors used both compact fluorescent lights (CFL) and light-emitting diode (LED) phototherapy[1]. LED phototherapy is potentially

more effective than CFL since it provides higher irradiance, narrower wavelength band that coincides with the absorption spectrum of bilirubin, and it can be placed closer to the baby due to less heat production. However, the study by Kumar *et al*[24] has shown that LED and CFL have similar efficacy. In the current study, CPT was better than IPT in the LED subgroup and the difference in the bilirubin reduction (0.06 mg/dl/h) was greater than the non-inferiority margin (0.04 mg/dl/h). This needs to be studied further in future trials, and the reason needs to be elucidated. IPT needs to be evaluated in other devices that are used to provide phototherapy in neonates such as halogen spotlights and fibre-optic blankets.

To summarize, though IPT seems to be promising, it needs to be evaluated further in diverse clinical settings before it can be recommended for routine clinical use. We need further data on bilirubin thresholds for neurotoxicity and bilirubin kinetics during phototherapy to enable judicious and evidence-based use of phototherapy.

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