Third World Issues

Efficacy of phototherapy in non-haemolytic hyperbilirubinaemia

K L TAN, K W BOEY

Abstract

Clinical experience of phototherapy for non-haemolytic hyperbilirubinaemia in 3999 infants in Kandang Kerbau Hospital, Singapore, is documented. Phototherapy was most effective in extremely preterm infants with very low birth weight (gestation ≤ 32 weeks, birth weight ≤ 1500 g) and least effective in full term infants with very low birth weight (gestation ≥ 37 weeks, birth weight ≤ 1500 g) and large preterm infants (gestation < 37 weeks, birth weight > 2270 g). Overall, phototherapy was effective in almost all the infants, with a failure rate of only 2.00/1000 infants. No characteristic features common to all the failures could be detected. The bilirubin rebound was usually mild; repeat phototherapy was required in only 30 infants (7.50/1000), with the response to the second exposure comparable to that to the first. No infant required a third exposure.

All the infants tolerated phototherapy well, none developing any illness that could be attributed to the treatment. This clinical experience shows that phototherapy for the treatment of non-haemolytic hyperbilirubinaemia is effective and safe.

Introduction

Phototherapy is now an accepted method for treating neonatal jaundice; its clinical efficacy has been confirmed by many studies.¹ Clinical experience of phototherapy in a large number of infants in a single neonatal unit, however, has yet to be documented. In the Kandang Kerbau Hospital, Singapore, where neonatal jaundice is a common complication in neonates,² phototherapy has been used for more than 10 years; many infants have been treated in this manner during this period. Phototherapy has completely replaced exchange transfusion in the management of neonatal jaundice. Though various light spectra and intensities have been used in the unit, the usual mode of phototherapy for most infants uses an open 7 daylight lamp (Philips TL 54/20W).

We report our clinical experience of phototherapy in about 4000 infants who had non-haemolytic hyperbilirubinaemia.

Patients and methods

In the Kandang Kerbau Hospital, Singapore, infants requiring phototherapy, whether they have deficient or normal activities of glucose-6-phosphate dehydrogenase (as screened by a modification of Bernstein's method³), are investigated as previously described.⁴ Birth weights and

gestational ages are recorded. The gestational age is obtained by assessing physical and neurological characteristics⁵ as well as maternal history; if a discrepancy is observed clinical assessment of gestational age is used.

The usual form of phototherapy uses the open 7 overhead daylight lamp (Philips TL 54/20W) which, for infant skin, provides an average radiance of 295 $\mu\text{W}/\text{cm}^2$ in the 400-480 nm range, 250 $\mu\text{W}/\text{cm}^2$ in the 425-475 nm range, and 140 $\mu\text{W}/\text{cm}^2$ in the 440-480 nm range and a total light intensity of 4630 lx. The method of measurement has been described previously.⁴ The lamps are changed regularly after 2000 hours of use, by which time the radiance is still 80% of the original.⁶

Phototherapy is given to infants who are clinically well but suffering from non-haemolytic hyperbilirubinaemia as evidenced by the absence of blood group isoimmunisation, a negative result of a direct Coombs test, haemoglobin concentration > 140 g/l, and a normal haemogram as well as normal glucose-6-phosphate dehydrogenase activity. Phototherapy is started when bilirubin concentration is ≥ 256 $\mu\text{mol/l}$ (15 mg/100 ml) regardless of the time of the day. In infants with a very rapid onset of jaundice (< 24 hours postnatal age) phototherapy is started when bilirubin concentrations rise to ≥ 222 $\mu\text{mol/l}$ (13 mg/100 ml) in the first 48 hours of life. The infants are exposed to continuous phototherapy completely unclothed with their eyes covered.

Capillary blood is sampled at the start of phototherapy and at intervals of six or 12 hours thereafter; the lights are switched off and infants removed from the cots for blood sampling. Phototherapy is stopped when bilirubin concentrations have decreased to < 187 $\mu\text{mol/l}$ (11 mg/100 ml), the minimum period of exposure being 24 hours. At the end of phototherapy another capillary blood sample is taken for determination of bilirubin concentration. The duration of phototherapy is recorded. Bilirubin concentrations after phototherapy are determined daily, the minimum period being two days. The haemoglobin and at a later stage packed cell volume values are also determined one day after treatment has stopped. Infants with rebound bilirubin values greater than or equal to concentrations before phototherapy are again exposed to phototherapy, following the same guidelines as in the first exposure.

The capillary blood samples are placed in labelled red coloured drinking straws and kept in a lightproof box till bilirubin concentration is determined, under standard conditions, with an AO bilirubinometer, which is checked regularly against known standards. The bilirubin concentrations in paired samples of capillary blood are also randomly monitored to determine the reliability and reproducibility of the estimations. Direct acting bilirubin concentration is determined in random samples as well as in those from infants not responding to phototherapy as previously described.⁷ The data are compiled and stored in an IBM 3081 computer in a fixed input format and analysed with the statistical package for social sciences.⁸

Results

Altogether 3999 infants with non-haemolytic hyperbilirubinaemia, divided into seven groups (table I), were exposed to phototherapy. During this period 179 465 infants were delivered in the hospital, but, as most healthy babies and their mothers were discharged within 24 to 48 hours after delivery, these infants with non-haemolytic hyperbilirubinaemia exposed to phototherapy might not represent the total number, as not all the infants developing hyperbilirubinaemia after discharge were referred back to this hospital.

The infants were apparently well and free from any detectable clinical illness at the start of treatment. There were relatively few infants with a very low birth weight (≤ 1500 g), owing partly to the low incidence of such infants and partly to the fact that relatively few infants with a very low birth weight

National University of Singapore, Singapore

K L TAN, FRCPED, FRACP, professor of paediatrics

K W BOEY, PHD, DCP, senior lecturer, department of psychological medicine

Correspondence to: Professor K L Tan, Neonatal Unit, Kandang Kerbau Hospital, Singapore 0821.

are free from clinical illness. The haemoglobin concentrations were higher in the two groups of growth retarded infants (table I, groups 4 and 7). All the infants remained well during and after exposure, except for one extremely preterm infant (gestation ≤ 32 weeks) with very low birth weight (group 6) who developed sepsis and another full term infant with very low birth weight (group 7) who aspirated; these infants were excluded from their respective groups. The normal sized infants (>2270 g) were able to maintain normothermia during phototherapy, but those with a low birth weight (1501-2270 g), especially the very low birthweight infants, needed extra heat from incandescent lamps with minimum light radiance in the range effective for phototherapy⁹ to maintain normothermia. Increased fluid intake was also needed to ensure adequate hydration.

TABLE I—Data on infants exposed to phototherapy and decreases in bilirubin concentration in response to phototherapy. Values are means (SE) unless otherwise stated

	1 Normal,* full term	2 Large, preterm	3 Low birth weight, preterm	4 Low birth weight, small for date	5 Very low birth weight, small for date	6 Very low birth weight, preterm	7 Very low birth weight, full term
Total	2813	590	318	187	24	25	43
M:F	1629:1184	347:243	179:139	98:89	12:12	9:16	25:18
Birth weight (g)	3124.33 (8.61)	2920.83 (19.80)	2020.34 (10.21)	2121.97 (9.60)	1396.58 (25.30)	1242.15 (50.24)	1344.60 (17.23)
Gestational age (weeks)	39.17 (0.02)	34.88 (0.06)	34.32 (0.12)	38.67 (0.12)	33.96 (0.20)	29.80 (0.46)	39.09 (0.25)
Age at phototherapy (days)	3.86 (0.02)	3.88 (0.04)	4.19 (0.08)	4.10 (0.08)	4.00 (0.27)	3.42 (0.30)	3.74 (0.13)
Haemoglobin concentration (g/l):							
At the start of phototherapy	184.7 (0.4)	185.5 (0.9)	183.2 (1.3)	190.1 (1.8)	183.9 (5.5)	172.4 (5.8)	194.8 (3.3)
At the end of phototherapy	177.5 (0.4)	180.8 (1.1)	178.5 (1.4)	184.7 (1.6)	177.8 (5.0)	166.4 (6.2)	188.7 (4.1)
Packed cell volume (%):							
At the start of phototherapy	56.56 (0.13)	56.60 (0.28)	56.26 (0.39)	58.23 (0.57)	55.95 (2.05)	Insufficient data	58.44 (0.99)
At the end of phototherapy	54.26 (0.14)	55.30 (0.30)	55.00 (0.38)	57.30 (0.46)	55.49 (1.85)	Insufficient data	57.15 (1.63)
Serum bilirubin concentration ($\mu\text{mol/l}$):							
At the start of phototherapy	265.2 (0.5)	266.9 (1.3)	263.5 (1.7)	261.6 (2.7)	265.5 (8.7)	256.8 (5.8)	263.8 (6.5)
After 24 hours of phototherapy	213.2 (0.5)	213.9 (1.3)	193.0 (1.7)	199.0 (2.5)	205.2 (8.9)	177.5 (5.1)	212.0 (6.1)
At the end of phototherapy	165.2 (0.5)	168.7 (1.2)	154.2 (1.5)	157.0 (1.7)	162.6 (6.1)	146.3 (6.1)	162.6 (5.1)
Decrease in bilirubin concentration after 24 hours:							
$\mu\text{mol/l}$	52.5 (1.0)	53.2 (1.7)	71.1 (3.0)	62.0 (2.5)	60.3 (10.2)	83.1 (9.7)	51.1 (6.6)
%	20.44 (0.34)	19.25 (0.60)	27.56 (0.99)	23.21 (0.96)	21.52 (5.99)	31.86 (3.35)	18.64 (2.53)
Decrease in bilirubin concentration at end of phototherapy:							
$\mu\text{mol/l}$	100.0 (1.0)	98.3 (1.7)	109.2 (2.4)	102.4 (3.2)	102.9 (10.7)	109.9 (8.3)	94.9 (6.6)
%	36.86 (0.26)	35.87 (0.61)	40.47 (0.79)	38.08 (1.01)	37.17 (3.24)	42.28 (2.61)	35.28 (2.75)
Duration of phototherapy (hours)	59.00 (0.48)	60.51 (1.04)	51.46 (1.90)	50.07 (1.49)	49.67 (4.05)	41.48 (4.00)	56.37 (3.44)
% Decline in bilirubin concentration/hour	0.70 (0.01)	0.66 (0.02)	0.91 (0.03)	0.84 (0.03)	0.90 (0.10)	1.29 (0.15)	0.70 (0.06)

*In Singapore infants weighing >2270 g are deemed to be of normal birth weight.
Conversion: SI to traditional units—Serum bilirubin: $1 \mu\text{mol/l} \approx 0.058 \text{ mg/100 ml}$.

The bilirubin concentrations decreased steadily during phototherapy in all groups (figure). The rate of decrease was assessed in two ways: firstly, the 24 hour reduction in bilirubin concentrations was expressed as a proportion of the initial concentrations, this being a valid method for assessing the initial response in all the infants, as they were all exposed to phototherapy for at least 24 hours, and, secondly, the overall decrease in bilirubin concentrations was related to the total exposure time, expressed as percentage decrease/hour (table I). When assessed by the 24 hour reduction method the smallest decrease occurred in the full term infants with very low birth weight (group 7) followed by the big preterm infants (group 2), the order being reversed when the overall decrease was related to the total exposure time. Student's *t* test showed significant differences in response among the various groups of infants (tables II and III). The rate of decrease in the extremely premature infants with very low birth weight (group 6) was significantly greater than that in the other groups both when the overall proportionate

TABLE II—Comparison (*t* values) of % decrease in bilirubin concentration over 24 hours among groups

Group No	2	3	4	5	6	7
1	0.20	8.83***	4.17***	0.61	4.13***	0.20
2		7.30***	3.56***	0.57	4.03**	0.25
3			2.57*	1.21	1.74	3.04**
4			0.42	2.69**	1.76	
5					2.08*	0.63
6						3.38**

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

TABLE III—Comparison (*t* values) of rate of % decrease in bilirubin concentration (% decrease/hour) among groups

Group No	2	3	4	5	6	7
1	2.48*	7.44***	5.03***	1.99*	4.04***	0.00
2		8.01***	5.83***	2.37*	4.29***	0.64
3			1.81	0.10	2.56*	3.14**
4				0.58	3.03**	2.10*
5					2.20*	1.71
6						3.73**

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

decrease was related to total exposure time and when the 24 hour decrease was compared (except in comparison with group 3).

The overall failure rate was 2.00/1000; there were only three failures in group 1 (1.06/1000), four in group 2 (6.77/1000), and one in group 7 (23.25/1000). We could not detect any definite characteristic features common to all these failures, and all the infants had direct acting bilirubin concentrations $\leq 17 \mu\text{mol/l}$ (1 mg/100 ml). All the infants were transferred to high intensity phototherapy as previously described,⁷ with prompt response.

The rebound after phototherapy (figure) was mild, only 30 infants (7.50/1000) requiring phototherapy again. The response to the second exposure was comparable to that to the first. No infants required phototherapy for a third time.

The direct acting bilirubin concentration did not exceed $17 \mu\text{mol/l}$ (1 mg/100 ml) in all the random samples analysed.

Discussion

We found that phototherapy with the open 7 daylight lamp was highly effective on about 4000 infants with non-haemolytic hyperbilirubinaemia; the failure rate was only 2.00/1000. The proportion of infants needing phototherapy again was also negligible. The response of these infants to repeat treatment was comparable to that to the first exposure.

The 24 hour reduction in bilirubin concentration during phototherapy expressed as a proportion of the initial bilirubin concentration was thought to be a reliable method of assessing the initial efficacy of phototherapy, as all the infants were exposed to

phototherapy for at least 24 hours. Moreover, problems caused by diurnal variation in bilirubin concentrations were effectively avoided by this method of assessment. The overall effectiveness of phototherapy was best assessed by relating the proportionate decrease in concentration during the whole period of exposure to the total duration of phototherapy, expressed as percentage decline/hour; by starting phototherapy at different times of the day the effect of diurnal variation of bilirubin concentrations on the overall bilirubin concentrations was virtually eliminated. These two methods of assessment of the efficacy of phototherapy therefore allow the initial and overall effects of exposure to be reliably determined and compared among the groups of infants.

Mean bilirubin concentrations during and after phototherapy. (a) ●=Group 1 (normal, full term). ○=Group 2 (large, preterm). (b) ●=Group 3 (low birth weight, preterm). ○=Group 4 (low birth weight, small for date). (c) ●=Group 5 (very low birth weight, small for date). ○=Group 6 (very low birth weight, preterm). □=Group 7 (very low birth weight, full term). Arrows indicate end of phototherapy.

Phototherapy was least effective during the first 24 hours in the full term infants with very low birth weight (group 7), followed by the large preterm infants (group 2) and the full term, normal sized infants (group 1). Over the whole period of treatment, however, phototherapy was least effective in group 2 followed by group 1 and group 7. This observation seems to implicate gestational age and size as important determinants in influencing the efficacy of phototherapy. The increasing thickness and opacity of the infant skin with increasing maturity might present a progressively resistant barrier to phototherapy; the relatively less opaque skin of the large preterm infants would probably be offset by their relatively thicker subcutaneous tissue, which could present a comparable barrier to phototherapy. The good flexor posture of the very low birthweight infants would compensate to some extent for their relatively greater surface area due to their small size; this, together with their opaque

skin, could possibly explain the reduced response to phototherapy. The higher packed cell volume with the resultant relatively greater rate of haemoglobin breakdown and increased bilirubin production could be another contributory factor.

The increased effectiveness of phototherapy in extremely preterm infants with very low birth weight could be due to their relatively greater surface area, which is further augmented by their hypotonic extended posture, thereby resulting in maximum surface area exposed to phototherapy; this virtually amounts to a relatively greater light dosage. This is further enhanced by the very thin translucent skin coupled with very scanty subcutaneous tissue, both of which might result in a greater "permeability" to phototherapy. These factors could account for the greater response to phototherapy in spite of the greater tendency of such infants to suffer from severe jaundice.

The results of previous studies have shown the lack of effect of birth weight and gestational age on the efficacy of phototherapy.^{10 11} These studies included smaller numbers of patients with much smaller differences in size and gestational age than in our study. In addition, in one study phototherapy was started at bilirubin concentrations not much greater than 85 μmol/l (5 mg/100 ml),¹⁰ the concentration below which phototherapy becomes relatively ineffective⁷; hence there was difficulty in detecting significant differences in response. In our study bilirubin concentrations were relatively high at the start of exposure, which, coupled with greater differences in birth weight and gestational age in the large groups of infants, allowed the differences in response to be readily detected. This was further enhanced by the method of assessment of the response to treatment: by evaluating the decrease in bilirubin concentration as a proportion of the initial concentration over 24 hours as well as the proportionate decrease in relation to the total duration of phototherapy reliable comparisons could be made among groups, especially as the concentrations before phototherapy were similar.

Phototherapy with daylight lamps with radiance comparable to that of our study seems to be highly effective in the management of non-haemolytic hyperbilirubinaemia in most infants, regardless of gestational age or birth weight. Rebound after phototherapy is also acceptable, with only a small proportion of infants requiring phototherapy again for rebound concentrations equalling or exceeding concentrations before treatment; re-exposure has proved to be just as effective as the first exposure.

With its efficacy, convenience, and relative freedom from major side effects phototherapy seems to be the treatment of choice for non-haemolytic hyperbilirubinaemia; inexpensive daylight lamps seem to be adequate in most cases.

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