ARTICLE

Decreased Response to Phototherapy for Neonatal Jaundice in Breast-fed Infants

K. L. Tan, FRCPE, FRACP, DCH

Objective: To evaluate the efficacy of phototherapy for nonhemolytic hyperbilirubinemia in breast-fed and formula-fed infants and infants receiving formula and breast milk.

Design: Prospective study.

Setting: Nursery for healthy infants.

Method: Full-term healthy infants with nonhemolytic hyperbilirubinemia (bilirubin concentration, >255 µmol/L [14.9 mg/dL] or 222 µmol/L [13.0 mg/dL] at ages younger than 48 hours) were treated with conventional phototherapy by using daylight fluorescent lamps. Three groups of infants were studied: group 1, formula-fed infants; group 2, breast-fed infants; and group 3, infants receiving formula and breast milk. All patterns of feeding started at birth. Phototherapy was terminated only when bilirubin concentrations had decreased to less than 185 µmol/L (10.8 mg/dL); the minimum exposure period was 24 hours.

Results: A total of 163 infants were studied: group 1, 79; group 2, 34; and group 3, 50. The age at the start of exposure was comparable in all groups. The mean ± SD weight loss as a percentage of birth weight was as follows: group 1, 2.8% ± 5.0%; group 2, 6.1% ± 3.4%; and group 3, 3.2% ± 2.6%. The duration of exposure to phototherapy was as follows: group 1, 54.1 ± 20.8 hours; group 2, 64.6 ± 25.1 hours; and group 3, 54.9 ± 21.5 hours; the 24-hour rate of decrease in the bilirubin concentration was as follows: group 1, 18.6% ± 11.7%; group 2, 17.1% ± 9.6%; and group 3, 22.9% ± 9.4%. The overall rate of decrease in the bilirubin concentration for the duration of exposure to phototherapy was as follows: group 1, 0.8% ± 0.3% per hour; group 2, 0.6% ± 0.3% per hour; and group 3, 0.8% ± 0.3% per hour. Weight loss at the start of phototherapy was significantly greater in group 2 compared with group 1 ($P<.001$) and group 3 ($P<.001$), although the hemoglobin and hematocrit values were comparable. The duration of exposure to phototherapy was not significantly different in the 3 groups ($P = .06$); however, the duration of exposure of group 2 infants was 10 hours more than that of the other 2 groups. The 24-hour rate of decrease in the bilirubin concentration in group 3 was significantly better than that of group 2 ($P = .007$) and group 3 ($P = .02$); the rates of decrease for groups 2 and 3 were similar ($P = .52$). The overall rate of decrease in the bilirubin concentration during the duration of exposure to phototherapy in group 2 was significantly less than that of group 1 ($P = .002$) and group 3 ($P<.001$); the rates for groups 1 and 3 were similar ($P = .35$). The postexposure rebound bilirubin concentrations were comparable in all groups during the first 2 days; however, the duration of moderate jaundice in group 2 was more prolonged.

Conclusions: The response to phototherapy of group 2 infants was significantly slower than that of group 3 and group 1 infants; this response was still of adequate efficacy. The addition of formula to the feedings for totally breast-fed infants, without suspension of breast-feeding, would enhance the efficacy of phototherapy and reduce exposure time.

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Editor's Note: For me, the take-home message from this study is that a clinician never (dangerous word!) needs to stop a mother from breast-feeding because of neonatal jaundice caused only by human milk. I just know someone will come up with a case that will force me to drink my words.

Catherine D. DeAngelis, MD

From the Department of Neonatology, National University Hospital, Singapore, Republic of Singapore.

BREAST-FEEDING IS associated with more frequent and more severe jaundice,[1,2] which is also of earlier onset and frequently of longer duration. Although bilirubin is an effective antioxidant and, thus, may be beneficial,[3] in high concentrations it is not innocuous but is capable of causing bilirubin encephalopathy, even in the breast-fed infant.[4] Hence, severe hyperbilirubinemia in breast-fed infants requires treatment just as in other infants.

Phototherapy is safe and effective in the management of neonatal hyperbilirubinemia[5,6]; its efficacy has been demonstrated in several studies, including a study by Tan and Boey[7] of 3999 neonates with nonhemolytic hyperbilirubinemia treated with daylight fluorescent lamps. It is the standard method of management for neonatal hyperbilirubinemia in Singapore, Republic of Singapore. Although

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PATIENTS AND METHODS

Full-term healthy infants with nonhemolytic neonatal hyperbilirubinemia[8] evidenced by absence of blood group isoimmunization, a negative direct Coombs test result, a hemoglobin level of more than 140 g/L, a hematocrit of more than 0.45, a normal hemogram, and a normal glucose-6-phosphate dehydrogenase status,[9] were recruited for this study. The infants were divided into 3 groups according to mode of feeding: group 1, formula-fed infants (n = 79); group 2, breast-fed infants (n = 34); and group 3, mixed-fed infants (received formula and breast milk, n = 50). The group 3 infants received additional formula feedings if breast-feeding seemed inadequate; sometimes formula feedings were substituted for breast-feeding at the mother's request. Only infants with consistent patterns of feeding from birth were included.

Phototherapy was started when the bilirubin concentration was more than 255 µmol/L (14.9 mg/dL) or 222 µmol/L (13.0 mg/dL) if the infant was younger than 48 hours of age,[10] regardless of the time of the day. A bilirubin concentration of more than 255 µmol/L (14.9 mg/dL) depresses the brainstem auditory evoked response[11]; this is fortunately reversible. Phototherapy was continuous except during feeding, providing nursing care, and bathing the infants.

Phototherapy using 7 overhead fluorescent lamps (Philips TL18W/54, Philips Lighting, Roosendaal, the Netherlands) provided an average irradiance on the infant skin of 403 µW/cm^2 in the 400- to 480-nm range, 205 µW/cm^2 in the 425- to 475-nm range, 107 µW/cm^2 in the 440- to 480-nm range, and 202 µW/cm^2 in the 440- to 500-nm range. The method of measurement has been described.[12] The lamps were changed regularly after 2000 hours of use, at which time the irradiance was about 80% of that at the start.[6]

Capillary blood was sampled at the start of exposure and at 12-hour intervals; the lights were off and the infants were removed from the cot during the sampling. Phototherapy was terminated when the bilirubin concentrations had decreased to less than 185 µmol/L (10.8 mg/dL) on 2 consecutive determinations; the shortest duration of exposure was 24 hours; this considered the diurnal variation of bilirubin concentrations and minimized laboratory errors. The duration of phototherapy was recorded.

If the bilirubin concentration increased on 2 consecutive determinations during exposure beyond the starting value, the direct bilirubin concentration was determined; if this was minimal (<10 µmol/L [0.6 mg/dL]), phototherapy was deemed to have failed, and the infant was transferred to "high-intensity" phototherapy, as described in previous studies.[12-15] The concentration of direct bilirubin also was determined in random samples.

The postphototherapy bilirubin concentration was monitored daily; the minimum period was 2 consecutive days. If the rebound bilirubin concentration exceeded the prephototherapy concentration, phototherapy was started again according to the same guidelines. The hemoglobin and hematocrit values were determined at the start of and 1 day after cessation of exposure to phototherapy. The infants were weighed at the start and end of phototherapy.

The labeled capillary samples were kept in a light-tight box until the moment of the determination of the bilirubin concentration, which was done under standard conditions using a meter (AO Bilirubinometer, American Optical Co, Southbridge, Mass) that was regularly calibrated against known standards. The concentration of direct bilirubin was determined as previously described.[8]

Data were analyzed by using the Windows program for the Statistical Program for the Social Sciences (SPSS Inc, Chicago, Ill). Analysis of variance (ANOVA) was used to determine whether significant differences occurred among the 3 groups and where they occurred; the Student *t* test was used to analyze intergroup differences. Informed consent was obtained. The study was approved by the director of medical affairs of the National University Hospital, Singapore.

hyperbilirubinemia in breast-fed infants seems to respond well to phototherapy, as far as I am aware, no objective study evaluating the effect of breast-feeding on the efficacy of phototherapy in healthy full-term infants with hyperbilirubinemia has been reported. It was therefore deemed that such a study would be timely.

RESULTS

A total of 163 infants were studied (**Table 1**). All infants were healthy and well before, during, and after exposure to phototherapy. They were comparable in all relevant aspects. The age at the start of exposure was apparently younger in group 2; this difference was not significant among the 3 groups (ANOVA, $P = .30$). The weight loss was significantly different among the 3 groups (overall loss, $P = .02$; loss per day, $P = .01$); the loss was more in group 2 than in groups 1 and 3 (Table 1). The hemoglobin and hematocrit values were, however, comparable. There was weight gain during exposure in all 3 groups; the lowest weight gain occurred in group 1; the differences, however, were not significantly different among the 3 groups ($P = .10$). The weights at the end of exposure to phototherapy were similar to the birth weights in all 3 groups: group 1, 97.8% of the birth weight; group 2, 96.4% of the birth weight; and group 3, 99.0% of the birth weight; however, the weight deficit in group 2 was still the greatest of the 3 groups. The group 2 infants were initially fed frequently (15-60 minute intervals); the frequency, however, varied with the enthusiasm of the mothers. During exposure, however, with lactation presumably already established, the intervals averaged about 3 hours, as was the case for group 1 and group 3 infants, who were fed about every 3 hours from birth.

Phototherapy was highly effective in reducing the bilirubin concentrations in all 3 groups of infants; however, its efficacy in group 2 was poorer compared with the other 2 groups (**Figure**). Statistical analysis by ANOVA demonstrated no significant difference in the duration of exposure to phototherapy ($P = .06$), but significant differences in the 24-hour decrease in the bilirubin concentration ($P = .03$) and the overall decrease in the bilirubin concentration ($P = .001$). In group 2, the 24-

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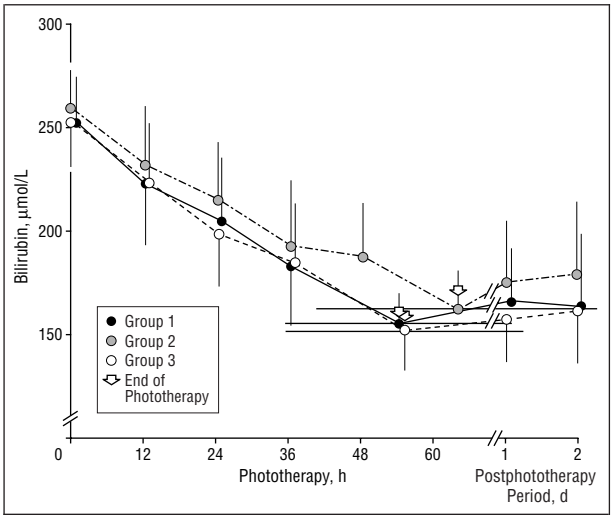
Table 1. Clinical Data of Infants Studied*

	Group 1 (n = 79)	Group 2 (n = 34)	Group 3 (n = 50)
Sex, M/F	43:36	17:17	28:22
Age			
Gestational, wk	38.7 ± 1.5	38.3 ± 1.6	38.0 ± 1.5
Postnatal (at start of phototherapy), d	4.09 ± 1.1	3.94 ± 0.9	4.34 ± 1.4
Weight, g			
Birth	3162 ± 374	3196 ± 314	3162 ± 315
Start	2978 ± 595	2997 ± 356	2958 ± 400
End	2995 ± 618	3079 ± 419	3032 ± 423
Weight loss at start of phototherapy, %			
Overall	2.8 ± 5.0†	6.1 ± 3.4‡	3.2 ± 2.6
Per day	0.7 ± 1.1†	1.5 ± 0.9§	0.8 ± 0.8
Weight gain during exposure to phototherapy, %	0.9 ± 5.0‖	2.7 ± 6.2	2.5 ± 3.5
Hemoglobin, g/L			
Start	178.7 ± 22.0	175.4 ± 21.1	172.3 ± 19.2
End	169.9 ± 22.1	167.8 ± 21.1	161.4 ± 18.1
Hematocrit			
Start	0.55 ± 0.07	0.54 ± 0.08	0.53 ± 0.06
End	0.52 ± 0.07	0.52 ± 0.07	0.49 ± 0.05
Bilirubin concentration, µmol/L (mg/dL)			
Start	253 ± 22 (14.8 ± 1.3)	259 ± 20 (15.1 ± 1.2)	253 ± 23 (14.8 ± 1.3)
End	155 ± 15 (9.1 ± 0.88)	162 ± 19 (9.5 ± 1.1)	152 ± 19 (8.9 ± 1.1)
Duration of exposure to phototherapy, h	54.1 ± 20.8	64.5 ± 25.1	54.9 ± 21.5

*Values are given as mean ± SD. "Start" and "End" refer to the initiation and discontinuation, respectively, of phototherapy. See "Patients and Methods" section for a description of the groups.
†P<.001, compared with group 2.
‡P<.001, compared with group 3.
§P=.001, compared with group 3.
‖P=.11, compared with group 2.



Response to phototherapy in group 1 (formula-fed infants), group 2 (breast-fed infants), and group 3 (infants receiving formula and breast milk). The values given are means, and vertical bars indicate SD. To convert the bilirubin values to traditional units (milligrams per deciliter), divide by 17.1.

hour decrease was significantly less than that in group 3, and the overall rate of decrease was much poorer than the rates in the other 2 groups (**Table 2**). The most pronounced response occurred in group 3; the 24-hour and overall decreases in the bilirubin concentration were the greatest; the 24-hour decrease was significantly better than that of group 1 ($P = .007$). No treatment failure occurred in any group. The postphototherapy rebound during the first 2 days was comparable in all 3 groups; no

Table 2. Efficacy of Phototherapy as Indicated by Percentage of Decrease in Bilirubin Concentration*

Group	24-h Decrease, %	*P*	Overall Decrease, %/h	*P*
1 (n = 79)	18.6 ± 11.7†	.52	0.8 ± 0.3‡	.002
2 (n = 34)	17.1 ± 9.6	.007	0.6 ± 0.3	<.001
3 (n = 50)	22.9 ± 9.4†		0.8 ± 0.3‡	

*Values are given as mean ± SD. For a description of the groups, see the "Patients and Methods" section.
†P = .02.
‡P = .35.

additional phototherapy for rebound hyperbilirubinemia was required, although the jaundice seemed to be much more prolonged in group 2, in some cases extending beyond 1 month of age, despite bilirubin concentrations that did not require additional phototherapy; the jaundice in group 1 and group 3 infants in contrast faded much more rapidly. It was no longer apparent 7 to 10 days after completion of exposure to phototherapy. This impression was, however, only subjective, since not all infants were available for long-term evaluation. None of the random blood samples examined had direct bilirubin concentrations of more than 10 µmol/L (0.6 mg/dL).

COMMENT

Breast-feeding has been established as one of the factors associated with hyperbilirubinemia, which in some cases can be very severe. If very severe, hyperbilirubinemia as-

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sociated with breast-feeding can cause bilirubin encephalopathy even in healthy infants[4]; indeed, my previous observation of bilirubin encephalopathy in healthy infants with severe nonhemolytic hyperbilirubinemia led to the conclusion that whatever the cause, severe jaundice could cause brain damage.[16] Hence, marked jaundice in breast-fed infants requires treatment as much as in other situations.

In view of the more rapid rate of increment and often more marked bilirubin concentrations experienced by breast-fed infants, the efficacy of phototherapy might not be adequate. The present study demonstrated that group 2 infants experienced hyperbilirubinemia earlier (about 3.8% and 10.2% faster than group 1 and group 3 infants, respectively) although the time difference was not significant ($P = .30$). However, phototherapy remained highly effective in controlling the hyperbilirubinemia, but with significantly less efficacy for group 2 compared with the other 2 groups: about 8% slower in the 24-hour rate of decrease in the bilirubin concentration and 24% slower in the overall rate of decrease compared with group 1, and 25% and 28% slower rates, respectively, compared with group 3. The duration of exposure to phototherapy was also longer. This difference was observed despite good weight gain during phototherapy, an indication of increasing maternal milk production during exposure, as is the norm after the first few days following delivery. Despite this, group 2 still had the greatest weight deficit at the end of exposure; this relative "dehydration," although mild, might be a contributing factor in reducing the response to phototherapy. However, the weight deficit was no longer significantly different from the weight deficits of the other 2 groups. It would thus seem that breast-feeding was probably the main reason for the reduced response. Of interest was the response of group 3; although the initial response seemed better than that of group 1, this difference disappeared when the duration of phototherapy was evaluated. Thus, while the efficacy of phototherapy in group 3 does not seem to be better than that in group 1 for the duration of exposure, it can be safely concluded that breast-feeding in combination with formula-feeding does not reduce the response to phototherapy as might have been expected. Indeed, in totally breast-fed infants with severe jaundice that requires phototherapy, the addition of formula feeding might enhance the response to phototherapy; no interruption of breast-feeding, even temporary, would be necessary.

The rebound bilirubin concentration of group 2 remained comparable with those of the other 2 groups with no need for additional phototherapy; however, a prolongation of the jaundice was observed compared with the other 2 groups, although it was at a moderate level.

Weight gain during phototherapy in group 2 had an apparently inverse relationship with weight loss before therapy, an indication that make-up weight apparently occurred when the need was greatest, although this correction was still not complete by the end of exposure.

Phototherapy with daylight fluorescent lamps was effective in reducing the bilirubin concentration in neonatal hyperbilirubinemia associated with breast-feeding; its efficacy was reduced significantly compared with formula feeding or with feeding a combination of breast milk and formula, although still of adequate efficacy; this reduction occurred in the presence of almost full correction of the greater weight loss at the start of exposure to phototherapy. The addition of formula feedings for totally breast-fed infants would be useful in enhancing the efficacy of phototherapy and reducing the exposure time to phototherapy.

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Reprints: K. L. Tan, FRCPE, FRACP, DCH, Department of Neonatology, National University Hospital, 5 Lower Kent Ridge Rd, Singapore 119074, Republic of Singapore.

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