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Evaluation of two guidelines for the management of hyperbilirubinemia in newborn babies weighing less than 2,000 g

Maria das Graças C. Leite,[1] Fernando P. Facchini[2]

Abstract

Objective: To evaluate the use of two phototherapy guidelines for the treatment of hyperbilirubinemia in newborn babies weighing less than 2,000 g.

Methods: Eighty-one newborn infants with birth weight less than 2,000 g were studied. They were divided in two groups: the "early" group, which started phototherapy 12 hours after birth, undergoing treatment for at least 96 hours; and the "late" group, which received phototherapy whenever the transcutaneous bilirubin reached 8 mg/dl and phototherapy suspended when bilirrubin levels fell to 5 mg/dl. The following factors were analyzed: maintenance of transcutaneous bilirubin levels below 10 mg/dl, mean value of daily transcutaneous bilirubin, the highest transcutaneous bilirubin value and the period it first occurred, and duration of treatment.

Results: In the early group, 20% of all patients showed transcutaneous bilirubin level higher than 10 mg/dl compared to 60% of patients in the late group. The highest daily mean rate of transcutaneous bilirubin in the early group was 6.6 mg/dl, which happened on the 7th day. In the late group, it was 8.6 mg/dl on the 2nd day after birth. The median duration of phototherapy treatment used in the early group was 96 hours (minimum of 96 and maximum of 156 hours) and in the late group, 51 hours (minimum of zero and maximum of 120 hours). None of the babies needed changes in the treatment (double phototherapy or exchange transfusion).

Conclusion: The use of early phototherapy treatment for babies weighing less than 2,000 g is safer when compared to the late group, considering satisfactory the maintenance of transcutaneous bilirubin levels below 10 mg/dl.

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Introduction

Neonatal jaundice is characterized by yellow coloration of the skin in newborns due to bilirubin levels greater than 5 to 7 mg/dl.[1,2] Two thirds of newborns develop jaundice in their first week of life. A wide series of situations (e.g.: prematurity) may cause bilirubin levels to increase excessively, and bilirubin then leaks into several tissues, including the central nervous system. The large amount of bilirubin for long periods may permanently damage structures such as the globus pallidus, subthalamic nuclei, hippocampus, and oculomotor nucleus, among others, resulting in the so-called kernicterus.[3]

Premature infants often are subject to this disease due to factors such as low albumin level;[4] a less stable bilirubin-albumin binding;[5] reduced hepatic glucuronidation;[6] immature blood-brain barrier;[7] hyperbilirubinemia, as well as associated diseases such as asphyxia, infections, hypercarbia and hyperosmolarity, which increase the permeability of the blood-brain barrier,[7,8] and the metabolization of bilirubin by the central nervous system via oxidation is underdeveloped in premature infants.[9]

1. M.Sc., School of Medicine, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil.
2. Ph.D.; Professor, Department of Pediatrics, School of Medicine, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil.

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Controversy still exists among experts over the high bilirubin levels that could cause injury to premature babies. There have been reports of kernicterus at very low levels among newborns. It is advisable to prevent the exposure of infants to bilirubin levels greater than the physiological ones.[10]. Levels below 10 mg/dl are seemingly safe, although it is commonly known that other factors are implicated in the development of kernicterus in preterm babies.

Phototherapy has been the treatment of choice in the last 30 years[11] because of its efficiency in the management of preterm babies and also because it has no severe side effects. Two types of treatment have been used: "prophylactic", which should be preferably called early treatment, since it does not prevent jaundice, which develops within the first 12 to 24 hours of life and usually lasts for 96 hours, and "therapeutic", or late treatment, implemented according to a certain bilirubin level until lower values are obtained. Both treatments have their advantages and disadvantages, and because of that, no common agreement has been reached on which treatment should be used.

The determination of bilirubin levels has improved substantially, having become "miniaturized", simpler, less invasive and cheaper.

By applying new and noninvasive methods for bilirubin measurement and very efficient phototherapy equipment, the present study aims at comparing the early and late treatments of jaundiced newborns weighing less than 2,000 g, defining which treatment is more satisfactory, allowing lower exposure to high bilirubin levels, lower costs and more comfort to patients.

Methods

We carried out a controlled, clinical randomized study at the Center for Women's Health (CAISM) and Hospital Estadual de Sumaré (HES), public tertiary institutions affiliated with Universidade Estadual de Campinas-UNICAMP. Serum bilirubin concentration was assessed in 81 neonates, born consecutively between July 31st and November 2nd, 2001, with birthweight less than 2,000 g. The patients were placed in two groups (randomly drawn out) within the first 12 hours of life. The exclusion criteria included any evidence of hemolysis, characterized by hemolytic disease due to Rh incompatibility or rare antigen, with positive indirect Coombs' test in maternal serum or positive direct Coombs' test in the newborn;[12] hemolytic disease due to ABO incompatibility with an indirect bilirubin level greater than 8 mg/dl in the first 24 hours of life and reticulocytosis according to the criteria established by Blanchette & Zipursky[13]; G6PD deficiency; malformations; intestinal obstruction; cholestasis; congenital infections; maternal or neonatal use of phenobarbital; transcutaneous bilirubin (TB) level greater than 15 mg/dl at any age, due to the necessity to change the treatment (double phototherapy or exchange transfusion). Eleven patients were excluded: ten of them died and one had a positive direct Coombs' test.

In the early-treatment group, newborns were submitted to phototherapy 12 hours after birth, regardless of their bilirubin concentration, up to 96 hours of life. In the late-treatment group, phototherapy was started only when bilirubin concentration reached 8 mg/dl and was discontinued when it fell to 5 mg/dl or less. The first measurement of bilirubin levels was performed before phototherapy in both groups, and every day during seven days, using the Bilicheck bilirubin analyzer (SpectRx Inc.-Norcross, Georgia, USA), in the frontal region, which was covered with aluminum foil to protect the patient from the phototherapy. Bilical calibration tips were used for each measurement, according to the manufacturer's instructions.

To control the measurements performed by Bilicheck, capillary blood was regularly collected and direct spectrophotometry was made using the Leica Unistat bilirubinometer. A bilirubin calibration standard containing 25.9±0.98 mg/dl was used, as recommended by the Joint Committee Report.[14,15] The bilirubinometer was calibrated every day with the default optical standards, and after that, it was calibrated by this calibration standard in triplicate, so that its reliability could be checked.

We used eight FANEM Mod 007 devices equipped with seven Philips TL20W/52 fluorescent lamps (special blue), at the wavelength of 400 to 540 nm and with a peak output of 450 nm. The equipment was placed 1 cm far away from the overhead heater unit, and spectral irradiance was measured using a custom-made radiometer (International Light - IL 1700), calibrated according to the recommendations of the U.S. National Institute of Standards and Technology, containing an SED 033/tblu sensor, at the wavelength of 345 to 530 nm and with a peak output of 460 nm. Irradiance was measured at nine different spots at the level of the incubator mattress, for calculation of average spectral irradiance, as recommended.[16,17] Average spectral irradiance was measured 200 hours after the use of the lamps, with an average of 14.4 μW/cm^2/nm. A 20% decrease in average spectral irradiance was tolerated at the beginning of phototherapy.[18]

The analyzed variables were: peak bilirubin concentration, the mean value of daily bilirubin levels, expressed in mg/dl; and length of phototherapy, expressed in hours. The control variables used to check the randomization of groups were: prematurity (gestational age < 37 weeks), birthweight, appropriateness for gestational age, gender, race, type of delivery, previous child with jaundice, maternal diabetes and smoking (>3 cigarettes/day), birth trauma, polycythemia (ht > 65%), perinatal anoxia (Apgar at 5 min < 5), sepsis, hypoglycemia (blood sugar level < 40 mg/dl), peri-intraventricular hemorrhage, hypoxemia (pO_2 < 50 mmHg), metabolic acidosis (pH < 7.20), respiratory distress syndrome, presence of fasting, type of enteral nutrition and use of parenteral nutrition.

Seventy newborns were necessary for this study, based on a previous calculation made by Brown.[19] The results were logged into a database using Epi-Info 6 and

the statistical analysis was made using SAS version 8.02. Bilirubin curves were plotted for both groups, and the difference between groups was determined by repeated measures ANOVA. A box-plot was constructed with phototherapy hours for both groups, and the difference between the groups was verified using Wilcoxon's test. A significance level of $\alpha = 0.05$ was established.

The study was approved by the Research Ethics Committee of the School of Medicine of UNICAMP, and an informed consent form was signed by parents before the inclusion of their children in the study.

Results

Twenty-three control variables regarding mothers and their respective newborns were analyzed (Table 1), revealing that both groups are apparently homogeneous.

Bilirubin levels reached or exceeded 10 mg/dl in seven newborns of the early-treatment group (20%) and in 21 newborns of the late-treatment group (60%), p = 0.0015.

The mean bilirubin levels reached by both groups were analyzed between the first and seventh days of life, and the curves of mean total bilirubin (TB) for both groups are shown in Figure 1. The highest TB mean in the early-treatment group, which occurred on the last day of the study, was of 6.6 mg/dl. In the late-treatment group, the highest mean (8.6 mg/dl) occurred on the second day of life, where p < 0.01 (Table 2). In terms of absolute values, the highest TB level was of 13 mg/dl and 14.6 mg/dl in the early- and late-treatment groups, respectively.

The total length of phototherapy (in hours) in both groups is shown in Figure 2, where the 25th, 50th (median) and 75th percentiles are observed. In the early-treatment group, the median was of 96 hours of phototherapy, coinciding with the minimum value, whereas the maximum value was of 156 hours. In the late-treatment group, the median was of 51 hours, and only one newborn did not need phototherapy since a bilirubin level of 8 mg/dl was not reached. The maximum use of phototherapy was of 120 hours in this group.

Table 1 - Distribution of newborns weighing less than 2,000 g in the early and late groups according to the control variables

Variable	Early		Late	
	n (35)	%	n (35)	%
Smoking mother (> 3 cigarettes a day)	5	14.3	7	20.0
Diabetic mother	0	0.0	1	2.9
Cesarean delivery	26	74.3	24	68.6
Kernicterus in previous child	3	8.6	3	8.6
Male	21	60.0	16	45.7
Caucasian	24	68.6	23	65.7
Preterm (GA < 37 weeks)	35	100.0	33	94.3
Preterm with GA < 34 weeks	27	77.1	26	74.3
Birth weight > 1,500 g	16	45.7	15	42.9
Small for gestational age	17	48.6	13	37.1
Apgar at 5 minute $\leq$ 5	0	0.0	1	2.9
Birth trauma	5	14.3	5	14.3
Hypoglycemia (glycemia < 40 mg/dl)	3	8.6	0	0.0
Polycythemia (ht > 65%)	8	22.9	5	14.3
Respiratory distress syndrome	15	42.9	10	28.6
Sepsis	5	14.3	2	5.7
Peri-intraventricular hemorrhage	0	0.0	2	5.7
Metabolic acidosis (pH < 7.20)	2	5.7	4	11.4
Hypoxemia (pO_2 < 50 mmHg)	5	14.3	8	22.9
Presence of fasting	3	8.6	3	8.6
Breastfeeding	7	20.0	10	28.0
Use of parenteral nutrition	25	71.4	22	62.8
Use of child formula	30	85.7	29	82.8

GA = gestational age.

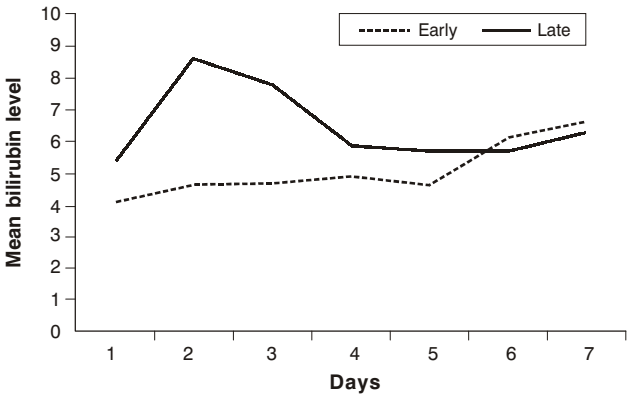

Figure 1 - Curves of mean total bilirubin (TB) for both groups

Discussion

Our study confirms that early treatment considerably reduced the number of newborns weighing less than 2,000 g, which had exceeded 10 mg/dl in the first week of life. This difference is quite expressive in percentage terms ($p < 0.01$) as it occurred in only 20% of newborns compared to 60% of those who received late treatment, a result that is inconsistent with previous studies.[20,21] The mean bilirubin concentrations were lower in the early-treatment group, being equal to and slightly higher than the values found for the late-treatment group on the sixth and seventh days of life. In the latter group, on the second day, the mean reached values greater than those which indicate the necessity for treatment, while in the early-treatment group levels of 8 mg/dl were not obtained. Again, these values differ from those found by Curtis-Cohen et al.[20] in 1985.

This discrepancy in efficiency may perhaps be explained by the fact that in these studies, although the authors waited for bilirubin levels to reach 5 mg/dl before starting phototherapy, these levels occurred quite near the beginning of early treatment, thus masking the increase we detected on the second and third days. The use of phototherapy equipment with efficient average spectral irradiance[16,22,23] caused the levels to be very close to those of early-treated infants in the study carried out by Curtis-Cohen et al.[20] If we had used the same criterion for

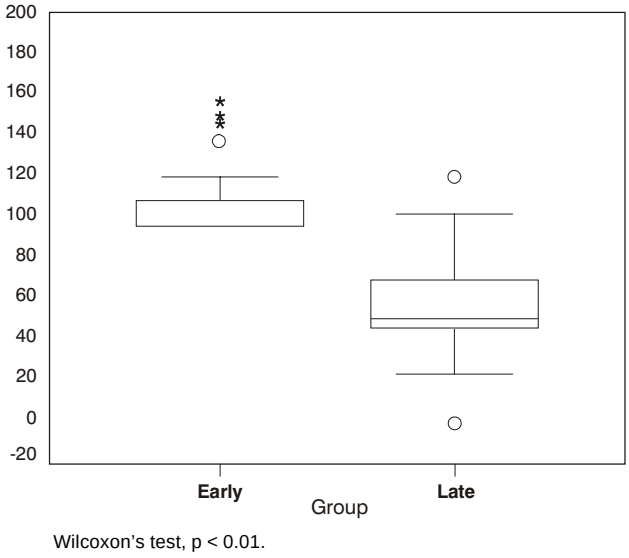

Figure 2 - Evaluation of total length of phototherapy (in hours) in both groups

Table 2 - Daily evaluation of mean total bilirubin (and standard deviation) in the early and late groups (in mg/dl)

	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
Group* early	4.1±1.38	4.6±1.93	4.7±2.54	4.9±2.26	4.6±1.82	6.1±2.31	6.6±2.84
Group* late	5.3±1.56	8.6±2.08	7.8±2.61	5.9±2.43	5.7±2.75	5.7±2.37	6.3±2.93

ANOVA * $p < 0.01$

the late-treatment group we would not probably have found any significant difference between the two groups tested. When both groups were divided into subgroups according to their weight (< 1,000 g, 1,000 to 1,500 g, and > 1,500 g), there was a clear difference as to the incidence of levels greater than 10 mg/dl, although the number of cases in each subgroup does not allow any statistical evaluation. For instance, in the early-treatment group, there were four patients weighing less than 1,000 g compared to eight patients with such weight in the late-treatment group, which could clearly influence the analysis of results if it were separately made in each weight subgroup. There is some agreement on the fact that preterm babies and very low weight children are at a greater risk for bilirubin-induced brain injury. These levels are not well-established due to the ethical impossibility of comparison with control groups. Some studies[10,24,25] recommend maintaining the levels below 10 mg/dl whenever possible. Therefore, they indicate exchange transfusion in newborns weighing less than 1,000-1,250 g with bilirubin levels above 10 mg/dl. This practice is still followed by many neonatology units, despite being economically prohibitive and risky.[26,27] Therefore we decided not to include it in our study.

So, if we intend to maintain bilirubin levels as close as possible to the physiological values observed in full-term newborns, early treatment is the recommended choice.[28] The hypothesis that the late indication of phototherapy could substantially reduce the number of treated infants was not confirmed, as only one newborn in this group did not have to be treated. The indication of phototherapy for most children with high levels of bilirubin also was observed by Curtis-Cohen et al.

The length of treatment of newborns in the early-treatment group was considerably longer (96 versus 51 hours). These data confirm the results of a previous study.[20] Longer duration of phototherapy obviously implies in higher exposure of the patients to its side effects. However, these side effects can be easily overcome.[29]

As for the costs of both treatments, the prolonged length of phototherapy does not increase costs incurred by the length of hospital stay, since newborns weighing less than 2,000 g usually cannot be discharged before seven days. The additional cost of phototherapy sessions (hours) will probably exceed the costs of TB measurements used for the monitoring of the late-treatment group. In services where noninvasive measurement of bilirubin levels is not available, repeated blood collections constitute a risk of infection, besides the discomfort of the needle prick for blood collection.

Given the difficulty in establishing the diagnosis of kernicterus based on specific tests and safe levels of serum bilirubin and the narrow relationship between high levels and their persistence, we consider early treatment with phototherapy to be the best option. After observing the levels obtained within the first 24 hours in both groups, there is no reason to start treatment before 24 hours. The cost and discomfort of prolonged phototherapy seem to be easily overcome.

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Corresponding author:
Maria das Graças da Cunha Leite
Rua Nacib Cury, 798/201
CEP 38060-380 - Uberaba, MG, Brazil
Tel.: +55 (34) 3312.6369 – Fax: +55 (34) 3332.7510
E-mail: mgcleite@terra.com.br