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Follow-up of neonatal jaundice in term and late premature newborns

Fernando Perazzini Facchini,[1] Maria Aparecida Mezzacappa,[2] Izilda Rodrigues Machado Rosa,[2] Francisco Mezzacappa Filho,[3] Abimael Aranha Netto,[4] Sergio Tadeu Martins Marba[4]

Abstract

Objective: To report on the results of a project following term and near term newborn infants who were jaundiced during the neonatal period.

Methods: Neonates were referred to the follow-up clinic with weight ≥ 2,000 g and/or gestational age ≥ 35 weeks, and jaundice at discharge was initially assessed with an Ingram icterometer or Bilicheck and, if indicated, with a Unistat bilirubinometer (Leica). These newborn infants had bilirubinemia at or above the 40th percentile on the nomogram developed by Bhutani. All infants treated with phototherapy while in hospital were reassessed by laboratory methods 24 hours after withdrawal of treatment. Patients were rehospitalized for intensive phototherapy if their level was greater than or equal to 20 mg/dL.

Results: From a total sample of 11,259 neonates, 2,452 (21.8%) were referred to the follow-up clinic, 87.2% (2,140) of whom did return. Eighty returned neonates were readmitted. Return appointments were set for 2,452 patients, 180 (7.3%) of whom had bilirubinemia ≥ 15 mg/dL at discharge. Of these 180, 151 returned for follow-up. Twenty (13.2%) were readmitted for treatment. Of the total number of readmitted patients, two newborn infants had levels ≥ 25 mg/dL and none ≥ 30 mg/dL. All responded rapidly to intensive phototherapy, and there was no need for exchange transfusions.

Conclusions: Our results suggest that the regime adopted is effective for detecting and preventing hyperbilirubinemia at risk of causing bilirubin-induced encephalopathy in term and near term newborn infants.

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Introduction

Although almost always benign, indirect hyperbilirubinemia can, if excessively elevated, cause damage to the nervous system of newborn infants (NB) (kernicterus). This entity, which appeared to have been extinct for years, began to be recognized in a small, but growing number of NB in the USA.[1-5] Early discharge has been associated with significant hyperbilirubinemia, particularly during the first week of life.[5,6] The earlier the discharge, without adequate outpatients follow-up, the greater the probability of more severe jaundice cases going unnoticed by family members, who, in general, are not able to evaluate this complication. In

1. Professor colaborador voluntário, Setor de Neonatologia, Departamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brasil.
2. Doutora. Professora assistente, Setor de Neonatologia, Departamento de Pediatria, Faculdade de Ciências Médicas, UNICAMP, Campinas, SP, Brasil.
3. Professor assistente, Setor de Neonatologia, Departamento de Pediatria, Faculdade de Ciências Médicas, UNICAMP, Campinas, SP, Brasil.
4. Doutor. Professor assistente, Setor de Neonatologia, Departamento de Pediatria, Faculdade de Ciências Médicas, UNICAMP, Campinas, SP, Brasil.

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this manner a small number of neonates will develop very severe hyperbilirubinemia which, if not treated in appropriate time, could result in serious sequelae.

Other important factors that were linked with the reemergence of kernicterus were a lack of concern with the level of bilirubinemia at hospital discharge, possible risk factors for increased levels, less aggressive treatment of hyperbilirubinemia and delayed postnatal follow-up (2 weeks of life).[4,7] These factors are even more important for the care of borderline premature NB (between 35 and 36 6/7 weeks' gestational age) who, if treated in the same manner as full term NB, with bilirubinemia not assessed at discharge and insufficient post-discharge follow-up, have a high risk of kernicterus.[7]

Aiming to solve this problem, some authors have used bilirubin assay results during the first hours of life to develop indicators of risk of significant hyperbilirubinemia that allow to identify those NB who require more careful follow-up post-discharge to be identified.[8,9]

Based on the work of this group of authors, our service set up a follow-up clinic to monitor neonatal jaundice during the first week of life, aiming to monitor bilirubinemia in neonates who exhibit, according to the publications cited, a possibility of developing dangerous hyperbilirubinemia levels.

This study reports on the results of the outpatients follow-up of full term and borderline preterm NB, selected by means of bilirubinemia assessment, conducted systematically before discharge.

Methods

This study covers all neonates born between April 1st, 2001 and August 31st, 2005 with birth weight ≥ 2,000 g and gestational age, by the Capurro method ≥ 35 weeks,[10] transferred to the rooming-in ward and, therefore, with no complications detected during the first hours after birth. At our service all NB were breastfed and, in certain situations, due to clinical indications, received supplementation with artificial formula. Routine hospital discharge was after 48 hours of life for full term NB delivered vaginally and 72 hours for caesarian births.

Screening and assessment of bilirubinemia during hospital stay and at hospital discharge

All NB were screened systematically, from 12 hours of life, for the presence of clinical jaundice by means of an Ingram® icterometer (Cascade Health Care Products, Salem, USA), observing the color of the skin at the tip of the nose, with sufficient pressure to make it bloodless.[11] When readings were > 2 (estimated mean bilirubinemia + 2 SD = 5.5-8.7 mg/dL) during the first 24 hours of life or ≥ 3 (estimated bilirubinemia = 10.0-14.5 mg/dL) after this point, total bilirubin (TB) was assessed by direct spectrophotometry, with a Unistat® bilirubinometer (Leica, Reichert Inc., Depew, USA).

When we added Bilicheck® (Respironics Inc. Murrysville, USA) to our routine, some of the readings that had been taken with the bilirubinometer were then taken with the Bilicheck®, using measurements from distinct points on the skin of the frontal region and following the recommendations in the manual. All results were the mean of two measurements. The calibration capsule was changed daily, rather than for every test, since this does not alter the results.[12] When transcutaneous estimates returned values ≥ 11 mg/dL,[13] then TB was confirmed by serum bilirubin assay (bilirubinometer Unistat®), using a blood sample taken at the same time as neonatal screening for phenylketonuria and congenital hypothyroidism. The bilirubinometer was calibrated daily with an optical standard provided by the manufacturer and with test assays in triplicate, employing a standard solution prepared in accordance with recommendations in the literature.[14] This standard was stored at 70 °C negative, and the range of reliability, within which the standard assays should remain, was determined periodically. The coefficient of variation of this apparatus is < 0.05, and therefore it meets the quality standards for this type of assay.[15]

Newborn infants treated with phototherapy were assessed with Bilicheck® only after 72 hours had elapsed from withdrawal of treatment.

Selection of patients for postnatal follow-up clinic

At discharge, all children had the intensity of their jaundice measured with the icterometer, with Bilicheck® and, when indicated, by bilirubinometer, as described above. The TB values obtained were then plotted against the graph published by Bhutani et al.[8] When TB was at or above the 40th percentile, children were made appointments to return to the clinic at times that varied from 24 hours after discharge to the end of the first week of life, depending on the percentile and, consequently, on the risk of developing significant hyperbilirubinemia. Those over P95 were asked to return in 24 hours (or remained in hospital for another TB assay 24 hours later). Infants with TB between P95 and P75 returned in 48 hours, and those from P75 to P40 returned between 72 and 168 hours of life. Those NB with TB values below P40 were referred to health centers, since, according to observations made by Bhutani et al.,[8] the risk of developing significant hyperbilirubinemia is null.

Inpatient treatment of hyperbilirubinemia

Children with early jaundice (< 24 h and TB > 8 mg/dL) were investigated for hemolytic disease of the NB and treated with phototherapy. Children with late jaundice (more than 24

hours old and icterometer ≥ 3) were treated according to clinical need, with TB assessments until discharge. Indications for phototherapy while in hospital during the immediate postnatal period were:

1) any level of TB in NB with suspected hemolytic disease and early jaundice until diagnosis is confirmed;
2) TB ≥ 10 mg/dL in NB with birth weight ≤ 2,500 g or gestational age < 37 weeks;
3) TB ≥ 20 mg/dL in full term NB without hemolytic disease, any time after birth.[16] Children subjected to intensive phototherapy for 6 hours whose bilirubinemia remained stable or increased should receive exchange transfusions.

In all NB, 24 hours after withdrawal of phototherapy, TB was assayed to detect any rebound.

Outpatient follow-up

All of the NB were monitored until bilirubinemia levels went into decline, with return consultations set at 24 to 72 hour intervals, depending on TB levels and which zone they related to on the graph by Bhutani et al.[8] During follow-up, TB was monitored by plasma assay or by transcutaneous assessment, the same as while in hospital. All patients who missed appointments at the clinic were reinvited to attend at least twice by our social service.

The criterion for rehospitalization for phototherapy was total bilirubinemia ≥ 20 mg/dL.[16] All patients readmitted were treated with double phototherapy beds, equipped with 14 special lamps (Philips TL52) which guarantee average spectral irradiation above 45 μW/cm^2/nm. Irradiance was controlled using a previously published method.[17]

Data collection and analysis

The variables studied were hours of life and weight at hospital discharge, degree of bilirubinemia at discharge (serum assay or transcutaneous estimate), frequency of patients returning, number of outpatients consultations, frequency of readmission and level of bilirubinemia on admission.

Patient information was collected from an outpatients follow-up chart, specially drawn up for the purpose. Data were then input on Epi-Info, version 6.04. A descriptive statistical analysis was carried out employing frequencies, mean, median, standard deviations and P25 and P75. This study was approved by the institution's Human Research Ethics Committee.

Results

Over the 53 months covered by this study, 12,312 NB were born at our service. Of this cohort, 11,259 had birth weight ≥ 2,000 g and gestational age of 35 weeks or more. Of this total, 2,452 neonates (21.8%) were referred for outpatients follow-up. The return rate of these children was 87.2% (2,140 neonates). Just a single consultation was necessary for 79.7% (n = 1,706) of the NB, 11.4% returned twice, 2.7% returned three times and just 0.8% of the NB returned four or more times. During follow-up, 5.4% of the children (n = 115) abandoned treatment. Table 1 contains the birth weight, gestational and chronological ages total bilirubinemia values at discharge for returning NB and for those who did not attend any return appointments.

At discharge, 180 NB (7.34% of those referred to follow-up) had bilirubinemia levels ≥ 15 mg/dL. Means ± standard deviation for birth weight, gestational age and TB at discharge of these 180 NB were 3,326.3±492.6 g, 38.9±1.3 weeks and 16.1±0.9 mg/dL, respectively. Twenty-nine of these 180 NB did not return for follow-up appointments.

Eighty NB were re-admitted for treatment with phototherapy. This figure is 0.7% of the total NB cohort and 3.7% of those NB who returned. The mean TB level of these NB at rehospitalization was 19.0±2.9 mg/dL, with P25 at 17.7 and P75 at 20.3 mg/dL. Sixty percent of these rehospitalized children were male. Twenty (25%) of these NB had TB levels ≥ 15 mg/dL at discharge (Table 1). Two NB were readmitted with levels greater than 25 mg/dL, none of which were above 30 mg/dL. All patients responded rapidly to their treatment, with significant reductions in bilirubinemia. None of the patients required exchange transfusion. Neurological examinations at discharge were normal for the patients who were readmitted.

Just 0.6% of the NB who had bilirubinemia at discharge between percentiles 40 and 75 reached bilirubinemia levels ≥ 20 mg/dL.

Discussion

This study has demonstrated the practicality, in our milieu, of running a follow-up clinic on neonatal jaundice in the first week of life, based on a well-established bilirubinemia screening protocol applied before hospital discharge and employing instruments with a good level of accuracy. The follow-up consultation attendance rate of 87.2% can be considered excellent for our population, but without doubt it is dependent on the type and degree of guidance given to mothers prior to discharge and also on the social services recalling all mothers who do not attend their appointments.

While estimating bilirubinemia with an icterometer is dependent on a visual assessment and is, therefore, subjective, it has been considered adequate in published literature[11] and facilitates follow-up operations, restricting bilirubin collections to the most jaundiced NB, in addition to reducing costs, which is an extremely important factor in our country.

During the last year covered by this study, our service moved over to transcutaneous jaundice assessment for monitoring hyperbilirubinemia, which has greatly aided our activities because of the ease of execution and the speed and reliability of results.[13,18] Unfortunately, the high cost of this equipment may rule out its adoption by the majority of our maternity units.

The nomogram published by Buthani et al.[8] has proven itself an instrument that is easy to use and offers good accuracy for the identification of at-risk children, although we did not follow-up those NB who were in the lowest risk zone (below P40). It is important to point out that, for this standard of normality to be most applicable, the demographic characteristics of the population and its rates of exclusive breastfeeding should be similar. In the study carried out by Buthani et al.,[8] 40.8% of the NB were fed formula and 9.9% received supplementation. We were able to observe that, in common with other authors' reports,[19] the bilirubin levels that were assayed early (during the first 24 hours) frequently fell above P75 or P95; however, the majority of these NB, had benign outcomes during follow-up.

We may state that the proportion of neonates in this study with birth weight ≥ 2,000 g and gestational age ≥ 35 weeks who were readmitted to be treated for hyperbilirubinemia, at 0.7%, was relatively low compared with other reports in the literature.[5,20] The probable cause of this low rate of readmissions is the fact that neonates of low weight or with gestational age < 37 weeks were given phototherapy when levels were ≥ 10 mg/dL, thus avoiding elevated levels of bilirubinemia. This hypothesis is supported by the finding that, of the total number of 80 NB who were readmitted for phototherapy, just nine cases had birth weight < 2,500 g and six had gestational age < 37 weeks, despite such children's elevated risk of hyperbilirubinemia. This conduct should

Table 1 - Description of the study population

	Returned (n = 2,140)	Did not return (n = 312)	Readmitted (n = 80)
Weight (g)			
Mean ± SD	3,190.2±477.1	3,130.4±499.4	3,099.4±494.2
Median	3,170.0	3,097.5	3,132.5
(P25-P75)	(2,870.0-3,495.0)	(2,800.0-3,425.0)	(2,760.0-3,382.5)
GA (weeks)			
Mean ± SD	38.9±1.5	38.7±1.6	38.3±1.4
Median	39.0	39.0	38.0
(P25-P75)	(38.0-40.0)	(37.0-40.0)	(37.0-40.0)
Age at discharge (h)			
Mean ± SD	69.4±33.3	70.2±2.9	76.2±45.6
Median	63.0	67.0	65.0
(P25-P75)	(54.0-73.0)	(56.0-77.5)	(54.0-81.0)
TB at discharge (mg/dL)			
Mean ± SD	11.1±2.6	11.0±2.8	13.1±2.6
Median	10.8	10.8	13.0
(P25-P75)	(9.5-12.6)	(9.5-12.5)	(11.1-15.0)

GA = gestational age; n = number of cases; P25 = 25th percentile; P75 = 75th percentile; SD = standard deviation; TB = total bilirubin.

possibly be reassessed, since it results in prolongation of hospital stays and increased utilization of phototherapy equipment and heightened maternal tension, together with its possible implications.[21] Well-respected authors have raised doubts as to whether this conduct reduces the risk to these children.[22]

An insignificant proportion of this large cohort of patients were lost to follow-up (5.4%) or did not attend return consultations (12.7%), although the similarity of their demographic characteristics with those of the patients who did return suggests that the possibility that this caused bias is small and that the results have a high degree of external validity.

A significant proportion of the cohort born with weight ≥ 2,000 g or gestational age ≥ 35 weeks (8,807 NB = 78.2%) was not reassessed by the jaundice clinic. This group was made up of NB whose jaundice did not reach level 3 on the icterometer and who, when assessed with Bilicheck or the bilirubinometer, were below the 40th percentile on the Bhutani curve.[8] At discharge, these children were referred to children's healthcare centers since the possibility of developing significant hyperbilirubinemia was nonexistent.[8] Just one of these children returned spontaneously with jaundice at a level requiring treatment. This failure was probably linked to an inadequate assessment at the time of discharge, since this patient was only observed clinically and was judged to be "discreetly" jaundiced. Some of these neonates were re-referred by the childcare doctors and, after reevaluation of their bilirubinemia, sent home once more, since none of them presented with levels that justified treatment or follow-up for longer periods. These facts reinforce the lack of precision of clinical assessments of hyperbilirubinemia.[23]

The fact that just 13.2% of the children who presented bilirubinemia ≥ 15 mg/dL at discharge were later rehospitalized for treatment confirms the observation that the majority of these patients will not reach levels ≥ 20 mg/dL.[24,25] Although some services do indicate phototherapy when bilirubinemia ≥ 15 mg/dL,[26,27] this conduct can result in unnecessarily prolonged hospital stays, with increased demand on therapeutic and laboratory resources,[28] in addition to the suffering of babies' families and its consequences.[21] This was reported by a survey carried out in the USA.[29] Nevertheless, the fact that 75% of those readmitted had bilirubinemia levels < 15 mg/dL when discharged, underscores the need to monitor moderately jaundiced patients until jaundice has abated. The rehospitalization of just two NB with levels > 25 mg/dL and none > 30 mg/dL confirms the adequacy of the screening system adopted. Using intensive phototherapy equipment with rehospitalized children allowed shorter duration treatments (< 48 hours), with reductions in length of hospital stay, costs and stress to family members with consequences for the future[21] and avoids exchange transfusions with the elevated costs and risks they involve.[30]

Finally, the adoption of the regime used at our service suggests that it is possible to significantly reduce the costs of monitoring jaundiced neonates without causing any increase to the risk they are submitted.

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Correspondence:
Fernando Perazzini Facchini
Rua Coronel Quirino, 910/101
CEP 13025-900 – Campinas, SP – Brazil
Tel.: +55 (19) 3251.4735, +55 (19) 8181.2028
Fax: +55 (19) 3521.9307
E-mail: fepefaca@fcm.unicamp.br