J. Perinat. Med.
3 (1975) 198

Time-limited phototherapy of term newborns in ABO hemolytic disease and hyperbilirubinaemia

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Received September 12, 1974. Accepted December 2, 1974.

The National Academy of Sciences, USA [1], has published a preliminary report concerning the phototherapy of newborn infants. Despite 16 years of favorable experience with this "empirical therapeutic procedure" it was suggested that this therapy "to be kept to a minimum until more is known about its long-term effects". LUCEY [10] called for a more balanced approach. It has to be admitted, that **there are no uniformly accepted indications for phototherapy** at present and that its role in the prevention and treatment of neonatal jaundice is still not clear. Earlier studies have reported on prophylactic light treatment of preterm babies when irradiation was started immediately after birth [11, 18]. Later the 10 mg/100 ml serum indirect bilirubin level was proposed as an indication [5, 6]. Efficacy was assessed by the change in the means of daily serum bilirubin levels, compared to controls and the frequency of the necessity in performing an exchange transfusion despite irradiation [7, 21].

1 Purpose of the study

At the Ist Department of Pediatrics, SEMMELWEIS University Medical School, Budapest, a controlled clinical study was set up to find **reasonable indications for the phototherapy of term newborns**. In view of the controversy on long-term side effects [3, 9], irradiation was limited. Though an appropriate spectroradiometer [12, 15] was not available, accurate registration

Curriculum vitae

Dr. J. ROSTA graduated at the Budapest (now SEMMELWEIS) University Medical School in 1950. Since then working there at the Ist Department of Pediatrics and 2nd Department of Obstetrics, in the last 12 years as Head of the Neonatal Unit. Elected in 1964 as secretary, later first secretary of the Hungarian Pediatric Association. Editor of Hungarian and international journals and textbooks on neonatal medicine. Main research interest in jaundice of newborns. Thesis, more than 100 publications, papers given at international congresses and panels deal mostly with perinatal bilirubin metabolism and body composition.

of methodological details paved the way for future retrospective dosimetry.

2 Material and methods

Our material consisted of **term babies with a birth weight above 2500 g** (including 3 cases between 2350 and 2500 g) and a **gestational age over 37 completed weeks**. Under such circumstances phototherapy was indicated only at a serum bilirubin value **4–6.0 mg/100 ml** lower than the critical level calling for exchange transfusion according to our previously designed diagram for the indication of exchange transfusion [17]. In both indicational programs separate limits were offered according

to the various types of jaundice, intrauterine development, postnatal age and neurological findings (Fig. 1).

Fig. 1. Indications for phototherapy in term and near-term jaundiced infants.

The diagram covers the first five days of life as later irradiation was not initiated.

Our guide-lines were based on the hypothesis that they provide sufficient time for the light to exert its effect by reversing or at least decelerating bilirubin accumulation and reducing serum levels, whereby exchange transfusions can be avoided.

If a bilirubin level surpassed the limit for the indication of an exchange transfusion, phototherapy was considered inefficient and thus contraindicated. Light therapy was not used on febrile newborns, if septicemia or hepatitis was suspected or when metabolic disease was present. In such cases glucose-albumin infusions were preferred.

For phototherapy a MEDICOR KFL-21 instrument equipped with eight 20 W blue TUNGSRAM lamps (450 nm wave-length peak emission) was used. The lamps were fixed 80 cm from the bed level. Ultraviolet waves (below 380 nm) were shielded by a Plexiglas plate or by the top of the incubator [22]. The eyes of the infants were protected with thick gauze pads or dark glasses.

Irradiation was done for 18 hours daily consisting of three 6-hour periods with two-hour intervals until a marked drop in the serum indirect bilirubin level was noted. The change back and fro from prone to supine position, rectal temperature, bowel movements, voiding

of urine, fluid intake (5% glucose water) and any unusual events were recorded every hour on a flowsheet. Serum bilirubin levels were determined at least twice daily during irradiation and every 48 hours afterwards, to follow serum bilirubin concentrations.

During the first year of "limited" phototherapy (May 1, 1973 to May 1, 1974) 33 newborns were treated according to the above criteria. Their serologic and hematologic findings proved in 17 cases ABO-hemolytic disease, whereas 16 cases without any sign of hemolytic disease were grouped as "hyperbilirubinemia". Treatment of Rh-hemolytic babies is not discussed in this paper.

Selected data of the patients and their treatment are given in Tab. I.

A control group of 44 comparable cases was gathered from newborns treated before May 1, 1973, along the same line, who did not receive phototherapy. The control babies were nearly identical in weight (± 250 g) and practically identical in serum bilirubin level (± 1.0 mg per 100 ml) with the treated ones at the point of time (± 6 hours) when irradiation of the latter was begun.

3 Results

Exchange transfusion, based on identical indications in both periods before and after May, 1973, was necessary in 13 of the 44 babies treated without, and only 3 of the 33 infants treated with phototherapy (Tab. II). One of the unsuccessful cases proved to be a metabolic disease later.

Means and standard deviations of serum bilirubin levels are shown in Fig. 2—3.

The bilirubin levels of the treated babies were lower during the period of irradiation. This difference was significant on the second and third day of life, in the cases of ABO-hemolytic disease, and from 4th day of life in cases of hyperbilirubinemia, respectively. The lower values of the standard deviation in treated babies are particularly important, as the indication for exchange transfusion is related to this value.

Successful irradiation lasted in the average 44 hours (30—72 hours) in cases of ABO-

Tab. I. Data of newborns subjected to phototherapy.

Patient No.	Sex	Birthweight [g]	Blood-group mother/child		Onset age [hours]	Phototherapy			Result*
						Duration [hours]	Indirect serum bilirubin level [mg/100 ml]		
							initial	maximum	
1	f	3200	0	B	28	72	16.5	20.5	pos
2	m	3100	0	A	72	33	18.2	idem	pos
3	f	3800	0	B	24	42	13.6	18.0	pos
4	f	2600	0	A	50	30	17.0	17.6	pos
5	f	2350 gem	0	A	96	42	21.2	idem	pos
6	f	3200	0	A	16	30	15.2	23.5	neg
7	m	3600	0	A	72	32	20.0	20.8	pos
8	f	2850	0	A	48	60	17.6	18.0	pos
9	f	2700	0	A	96	42	19.8	20.0	pos
10	f	3500	0	A	81	33	21.4	22.5	pos
11	f	3300	0	A	24	60	16.4	27.5	neg
12	f	2900	0	A	48	50	15.8	23.4	pos
13	f	2700	0	B	28	30	14.2	14.4	pos
14	m	3100	0	A	24	48	10.8	18.6	pos
15	m	3300	0	A	36	36	15.5	idem	pos
16	m	4100	0	B	48	48	18.4	21.4	pos
17	m	3150	0	B	72	60	20.0	20.4	pos
18	f	3100	0	0	116	34	20.8	idem	pos
19	m	3100	0	0	84	48	20.5	23.6	pos
20	f	3300	B	A	96	30	23.0	idem	pos
21	m	2800	A	A	86	48	17.8	19.8	pos
22	m	3800	B	0	72	36	16.4	18.0	pos
23	m	3800	A	A	96	34	18.7	idem	pos
24	m	2800	B	B	96	18	17.0	idem	pos
25	f	3650	AB	A	86	50	26.0	idem	pos
26	f	2400 sfd	A	A	74	30	18.5	20.0	pos
27	f	2650	A	AB	50	30	19.0	20.0	pos
28	f	2900	B	B	84	42	23.2	25.0	pos
29	f	2350 sfd	A	0	84	42	15.5	20.5	pos
30	m	2450 sfd	B	A	96	48	18.5	19.0	pos
31	m	3150	A	A	50	66	16.8	23.0	pos
32	m	3500	A	0	84	42	21.5	idem	pos
33	m	2600	0	0	96	12	19.5	24.5	neg

Comments:

Result*: pos = according to [17] no exchange transfusion was necessary

neg = exchange transfusion was performed

gem = twin

sfd = small for dates infant, gestational age over 37 completed weeks

hemolytic disease and 40 hours (18—50 hours) in cases of idiopathic hyperbilirubinemia, respectively.

4 Comment

Indication for phototherapy in term infants is a controversial issue. The committee report, cited already in the introduction [1], suggested serum indirect bilirubin values below the 20 mg/100 ml limit to be carefully considered before indicating

irradiation in term babies. In a diagram plotted by A. BROWN [2] and slightly modified by MAISELS [13] the following dye levels would invoke phototherapy: 5.0—9.0 mg/100 ml on the first, 10.0—14.0 mg/100 ml on the second, and 10.0—19.0 mg/100 ml on the 3rd and 4th day of life. According to this diagram the same indications are valid for babies with a birth weight below and above 2500 g. Some more recent papers [4, 14] on the other hand take

Tab. II. Number of exchange transfusions with and without phototherapy.

	Number of patients	Number of exchange transfusions
ABO hemolytic disease with phototherapy	17	2
without phototherapy (controls)	28	9
Hyperbilirubinemia with phototherapy	16	1
without phototherapy (controls)	16	4

Fig. 2. Serum indirect bilirubin levels — means and ± 1 SD — in ABO hemolytic disease with and without phototherapy. Fig. 3. Serum indirect bilirubin levels — means and ± 1 SD — in cases of hyperbilirubinemia with and without phototherapy.

phototherapy into consideration if serum bilirubin values fall into the intermediate zone on POLACEK's diagram for indicating an exchange transfusion [16].

Our phototherapy diagram is similar to that of POLACEK and differs from BROWN's by giving **continuously rising limit-curves** and not stepwise changing ones. The sudden rise of 5.0 mg/100 ml at the end of each 24 hours of postnatal life makes BROWN's diagram difficult to adapt to these special periods.

Another advantage of our diagram is the **possibility of using separate guide-lines according to the etiology of jaundice and the gestational age (maturity)** of the newborn infant. It has to be stressed, however, that babies not reaching their completed 35 weeks of gestation or weighing less than 2000 g have to be judged for phototherapy or exchange transfusion individually and according to another diagram.

In cases where the risk of kernicterus is high (if hypoxia, acidosis, hypothermia is present, or drugs competing for albumin binding sites were used), **phototherapy should be begun at lower indicative values.**

There are few papers dealing with phototherapy in ABO-hemolytic disease. SISSON et al. [19] and KAPLAN and coworkers [7] reported favorable results. Our experience confirms their observations.

TABB et al. were the first to suggest a **time-limited phototherapy of 12–48 hours to prevent hyperbilirubinemia** in preterm infants [20]. We have attained a good effect with **therapeutic irradiation of ABO-isoimmunized and hyperbilirubinemic term infants**, when therapy was begun only at relatively high serum bilirubin levels. The originally proposed irradiation, lasting 144 hours seems excessive in term infants [8].

Short term phototherapy has two corner-stones: reserved indications and the lifting of irradiation as soon as an evident fall or harmless stagnation of bilirubin level is observed. We were never forced to resume phototherapy on account of a re-elevation of the bilirubin level, when the irradiation was once finished.

Summary

"Limited" phototherapy was used to treat full term babies with and without ABO-isoimmunization. Serum indirect bilirubin levels calling for irradiation during the first five days of life are summarized in a diagram (Fig. 1). Separate indications were given for babies with different etiologies of jaundice, maturity (gestational age and birth-weight) and indicational levels were correlated with the postnatal age (days and hours) of the infant.

After a fall or harmless stagnation of bilirubin levels irradiation was stopped.

Clinical assessment of the treatment of 17 babies with ABO-isoimmunization, and 16 newborns without it and with hyperbilirubinemia is given in detail (Tab. II and Figs. 2 and 3).

Results were compared with the outcome of treatment of 44 newborns who received the same care in every

respect, but phototherapy. These control cases, selected by pairs, were similar.

Exchange transfusion, based on identical indications, was necessary in 13 of the 44 babies treated without, and only 3 of the 33 infants treated with phototherapy. The bilirubin levels of the treated babies were lower during the whole course of the irradiation. The difference in favor of the treated babies was significant on the second and third days of life in cases of ABO-hemolytic disease, and from the 4th day of life in cases of hyperbilirubinemia. The values of standard deviations, important in view of the indication for exchange transfusion were also lower in the light treated babies.

Successful irradiation required on average of 44 hours (30—72 hours) in cases of ABO-isoimmunization and 40 hours (18—50 hours) in cases of hyperbilirubinemia, respectively. Re-elevation of the bilirubin level after finishing phototherapy was not observed.

Keywords: ABO-hemolytic disease, hyperbilirubinemia, neonatal jaundice, phototherapy.

Zusammenfassung

Zeitlich begrenzte Phototherapie bei reifen Neugeborenen (hämolytische Erkrankung im ABO-System und Hyperbilirubinämie)

Die zeitlich begrenzte Phototherapie wurde eingesetzt um am Termin geborene Kinder mit und ohne ABO-Isoimmunisierung zu behandeln. Die indirekten Serum-Bilirubinspiegel, welche für die Bestrahlung während der ersten 5 Lebensstage maßgeblich waren, sind in einem Diagramm zusammengefaßt (Fig. 1). Neugeborene mit Gelbsucht verschiedener Ätiologien wurden in getrennten Indikationsgruppen zusammengefaßt, desgleichen jene mit unterschiedlicher Reife, unterschiedlichem Gestationsalter und differentem Geburtsgewicht. Die Indikationsgruppen wurden zum postnatalen Alter des Neugeborenen (in Tagen und Stunden) korreliert.

Nach einem definitiven Abfall oder bei gefahrloser Konstanz der Bilirubinspiegel, wurde die Bestrahlung gestoppt.

Die klinischen Behandlungsergebnisse von 17 Neugeborenen mit ABO-Isoimmunisation und von 16 Neugeborenen ohne dieselbe jedoch mit Hyperbilirubinämie werden in Tab. II und Fig. 2 und 3 im Detail angegeben. Die Resultate wurden mit dem Behandlungsergebnis von

44 Neugeborenen verglichen, die in jeder Hinsicht dieselbe Behandlung erfahren haben mit Ausnahme der Phototherapie. Diese Kontrollfälle, welche paarweise ausgelesen wurden, waren ähnlich.

Eine Austauschtransfusion wurde bei ein und derselben Indikationsstellung in 13 Fällen der 44 Neugeborenen ohne und nur in 3 von 33 Kindern mit erfolgter Phototherapie notwendig. Die Bilirubinspiegel der bestrahlten Neugeborenen waren während der gesamten Bestrahlungsperiode niedriger. Die Differenz zugunsten der behandelten Neugeborenen war signifikant beim Vergleich des 2. und 3. Lebenstages bei den ABO-Inkompatibilitäten und des 4. Lebenstages bei den Fällen mit Hyperbilirubinämie. Die numerischen Werte der Standarddeviationen, die hinsichtlich der Indikationsstellung für die Austauschtransfusion wichtig sind, waren ebenfalls niedriger bei den mit Licht behandelten Neonaten.

Die erfolgreiche Bestrahlung belief sich im Mittel auf 44 Stunden (minimal 30, maximal 72 Stunden) bei den Fällen mit ABO-Isoimmunisation, auf 40 Stunden (18 bis 50 Stunden) bei Fällen mit Hyperbilirubinämie. Ein Wiederanstiegen des Bilirubinspiegels nach Abschluß der Phototherapie wurde nicht beobachtet.

Schlüsselwörter: ABO-Inkompatibilität, Gelbsucht des Neonaten, Hyperbilirubinämie, Phototherapie.

Résumé

Photothérapie à temps limité des bébés nés à terme (maladie hémolytique ABO et hyperbilirubinémie)

La photothérapie «limitée» a été utilisée pour traiter les bébés nés à terme avec et sans isoimmunisation ABO. Les taux de bilirubine indirecte du sérum indiquant la nécessité d'irradiation durant les cinq premiers jours

après la naissance ont été classées dans un diagramme (Fig. 1). Des indications séparées ont été données pour les nouveaux-nés ayant des étiologies d'ictère différentes; maturité (âge de gestation et poids à la naissance) et les taux indicationnels ont été corrélationnés avec l'âge post-natal (jours et heures) de l'enfant.

L'irradiation a été stoppée après une baisse ou une stagnation non mauvaise des taux de bilirubine.

L'évaluation clinique du traitement de 17 **bébé**s avec iso-immunisation ABO et de 16 **nouveaux-nés** sans iso-immunisation ABO/hyperbilirubinémie est donnée de façon détaillée (Tab. II et Fig. 2 et 3).

Les **résultats** ont été comparés avec l'issue du traitement de 44 nouveaux-nés ayant reçu les mêmes soins moins la photothérapie. Ces **cas de contrôle**, **sélectionnés** par paires, étaient similaires.

La **transfusion d'échange**, basée sur des indications identiques, a été **nécessaire** chez 13 des 44 nouveaux-nés ayant été traités sans photothérapie et seulement chez 3 des 33 **bébé**s traités avec photothérapie.

Les **taux de bilirubine** des **bébé**s traités ont été moins élevés durant tout le temps de l'irradiation. La différence en faveur des **bébé**s traités s'est révélée significative les deuxième et troisième jours après la naissance dans les cas de maladie hémolytique ABO et à partir du quatrième jour dans les cas d'hyperbilirubinémie. Les valeurs des déviations standard, importantes pour l'indication d'une transfusion d'échange, ont donc été moins élevées chez les nouveaux-nés traités par photothérapie.

Une **irradiation réussie** fut **durée** respectivement à une moyenne de 44 heures (30—72 heures) dans les cas d'iso-immunisation ABO et de 40 heures (18—50 heures) dans les cas d'hyperbilirubinémie. Aucune remontée du taux de bilirubine après photothérapie n'a été observée.

Mots-clés: Hyperbilirubinémie, ictère néonatal, maladie hémolytique ABO, photothérapie.

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