Abstract

Objective: to review the recent medical literature on the treatment of neonatal jaundice, focusing on practical aspects that are relevant to pediatricians and neonatologists.

Sources: an extensive review of the related literature was performed, also including the author’s clinical experience in this field of investigation.

Summary of the findings: jaundice is very common among infants during the first days of life. Several factors such as maternal and neonatal history have to be considered before implementing treatment. Significant advances have been made in the past few years concerning the treatment of jaundiced newborn infants. This review focuses on three forms of treatment of neonatal hyperbilirubinemia: phototherapy, exchange transfusion and the use of drugs to reduce serum bilirubin concentration.

Conclusions: nowadays, the in-depth knowledge about the mechanism of action of phototherapy, the development of intensified phototherapy units and the use of drugs to reduce bilirubin formation, have contributed to significantly decrease the need for exchange transfusion.


Introduction

Hyperbilirubinemia is the most frequent pathology in the neonatal period. It is estimated that around 60% of newborns develop serum bilirubin levels higher than 5mg%. In most cases, the etiology of this disorder is multifactorial. Treatment depends on the type and intensity of hyperbilirubinemia.

Several factors must be considered before treatment is begun in icteric newborns. First, it is important that the obstetric history of the mother and delivery be analyzed to allow identification of the factors that may be contributing to the occurrence of hyperbilirubinemia, such as drugs taken by the mother (diazepam, oxytocins), type of delivery (forceps, pelvic, cesarean section), delay in umbilical cord clamping, blood type, Rh factor, and maternal Coombs’ test.

Neonatal history must be carefully investigated. The physician must verify whether the newborn has already eliminated meconium, and if this elimination was early or late. If the newborn is breastfeeding, the possibility of problems on the part of the mother must be investigated, as well as the frequency with which the newborn is sucking. Usually, mothers submitted to C-sections are kept away from the newborns, and breastfeeding is not frequent during the first days after delivery.

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The loss of weight since birth should also be considered. An excessive loss (> 10%) may indicate insufficient water and calorie intake. The onset and evolution of hyperbilirubinemia must be analyzed. Was the onset early or late? Is progression fast or gradual?

The newborn must be submitted to a detailed physical examination, with determination of weight and gestational age. The general state should be observed, as well as level of activity and reflexes. The presence of visceromegaly, brain hematomas, and petechiae should be investigated. The hypothesis of infection should be ruled out.

Only after analysis of the history (maternal, newborn, and breastfeeding) and physical examination will the blood be collected for analysis. Basically, laboratory tests are as follows: 1) total and partial serum bilirubin concentration; 2) blood type and Rh factor and direct Coombs’ test; 3) hematocrit or hemoglobin.

This information will enable determination of hyperbilirubinemia as physiologic or pathologic. Pathologic bilirubinemia is characterized by: a) being clinically detectable during the first 24 hours after birth; b) an increase in serum bilirubin concentration higher than 5mg% /day; c) direct fraction higher than 2mg%; d) total serum bilirubin level higher than 15mg%; e) presence of clinical signs of hyperbilirubinemia for more than 1 week in term newborns or 2 weeks in preterm babies. Once the type and intensity of hyperbilirubinemia are determined, treatment can be defined.

Due to the high incidence of this disorder in the neonatal period, the present article will only address the treatment of indirect, or unconjugated hyperbilirubinemia. Possible treatments include phototherapy, exchange transfusion, and adjuvant drug therapy (for example, with heme-oxygenase inhibiting metalloporphyrins, phenobarbital, and endovenous immunoglobulin).

The objective of the present article is to review the current literature and offer a critical analysis of these treatments, focusing on practical aspects that may be useful for pediatricians and neonatologists.

**Mechanisms of action**

The success of phototherapy depends on the photochemical transformation of bilirubin in areas exposed to light. This reaction alters the molecular structure of bilirubin and allows photoproducts to be eliminated by the kidneys and liver without being metabolically transformed. Therefore, the basic mechanism of action of phototherapy is the use of photoenergy to transform bilirubin into more hydrosoluble products.6

Bilirubin absorbs light in the region from 400 to 500nm. The light emitted in this spectrum enters the epidermis and reaches subcutaneous tissue. Thus, only bilirubin found close to the skin surface (2 mm) is directly affected by light7,8.

Two mechanisms have been proposed to explain the action of phototherapy for reducing serum levels of bilirubin: photoisomerization and photooxidation.9

**Photoisomerization**

Once irradiated by light, bilirubin molecules originate two types of isomers: a geometric or configurational isomer and a structural isomer, or lumirubin. The geometric isomer forms quickly and can reverse back to a bilirubin molecule; its excretion is slow in newborns. The formation of structural isomers is slower than that of geometric isomers; however, this is an irreversible reaction. Since it is soluble in water, lumirubin is quickly eliminated through bile, and especially through the urine of affected newborns submitted to phototherapy, with no need for conjugation.

**Photooxidation**

In aerobic environments, a small part of the active bilirubin molecule suffers a process of oxidation, leading to the production of pyrrolic complexes, soluble in water and eliminated in urine. The quantitative contribution of photooxidation for the decrease of serum bilirubin levels has not been completely elucidated. However, it seems that this contribution is small.

**Efficacy of phototherapy**

The efficacy of phototherapy depends on several factors, such as the initial, pretreatment bilirubin concentration, the body surface exposed to light, the dose and irradiance emitted, and the type of light used (Figure 1). The main factors influencing phototherapy are discussed below.

**Initial serum concentration of bilirubin**

The higher the initial serum bilirubin levels the more pronounced and faster the decrease. Weise has shown, by means of mathematical calculation, that the phototherapy...
Figure 1 - Variables that interfere with the effectiveness of phototherapy

- Type of jaundice
- Type of light
- Initial serum bilirubin concentration
- Body surface area exposed to phototherapy
- Irradiation dose
- Distance between light source and patient

**Figure 1** - Variables that interfere with the effectiveness of phototherapy

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dose required to decrease the serum bilirubin concentration from 20mg% to 7mg% is the same dose required to decrease the concentration from 10mg% to 5mg%.10

The efficacy of phototherapy decreases with the decrease in bilirubin levels. With a serum concentration equal to or smaller than 5mg%, the efficacy of phototherapy is minimal.11

**Body surface exposed to light**

Since phototherapy acts on the patient’s skin, it is fair to suppose that the amount of body surface exposed to light is an important determinant of its efficacy. The largest the irradiated area, the more effective the therapy.12

The use of diapers in icteric newborns submitted to phototherapy significantly decreases the surface exposed to light, and therefore should be avoided. Reflecting surfaces (parabolic mirrors, reflecting films, aluminum foil, or white fabric) placed below or laterally in relation to the newborn have been successfully used to increase the body surface exposed to light.13 The use of these artifacts increases exposure to light in up to 35%.14 However, it is important to keep in mind that the use of these materials decreases visibility of the patient, in addition to increasing the risk for overheating. Another way of increasing the exposed surface is using additional sources of light (double or triple phototherapy).15-17

**Distance between light source and patient**

The photoenergy that reaches the newborn varies inversely with the distance between the source and the patient.12,16 In early times, before several mechanisms of action had been elucidated, it was recommended that the light source be placed around 50 cm away from the patient. Currently, it is known that irradiance (dose of photoenergy) may be significantly increased by placing the lamps as close as possible to the patient. In relation to conventional phototherapy using white fluorescent lamps, irradiance, measured on the skin of the newborn, is about 4µw/cm²/nm when placed 30cm above the patient. Irradiance increases to 8 and 12µw/cm²/nm when the light source is placed 20 and 10cm, respectively, away from the patient.12

The problems related to placing the light source too close to the patient include blocking the view of the patient, making the handling of the patient difficult, and excessive heating. The recommendation is that light sources in phototherapy be placed 30cm above the patient. However, it is important to note that only equipment using fluorescent lamps should be placed close to the patient. Halogen lamps, discussed below, must be kept about 50 cm away from the patient, due to the significant risk for burns.18

**Irradiance**

The efficacy of phototherapy depends directly on the amount of energy liberated (irradiance). The higher the dose administered to the newborn, and the larger the illuminated surface, the more effective the phototherapy.19 In clinical practice, the irradiance emitted by phototherapy units is measured using radiometers or dosimeters, which measure the amount of photoenergy emitted between 400 a 500nm. Currently, phototherapy equipment emits significantly more energy than the equipment available in the 1970s. The energy recommended by several authors, as measured on the newborn’s skin, is significantly higher than the amounts recommended in the past.19,20

The ideal therapeutic dose for phototherapy has not yet been defined. However, taking into consideration the wealth of clinical and laboratory investigations, it is evident that the objective of phototherapy is to provide icteric newborns with a therapeutic dose sufficient to reduce serum bilirubin concentrations as fast as possible. The fact that the importance of the light dose is often not considered is doubtless one of the factors behind the wide variation in the efficacy of phototherapy in nurseries. The administration of phototherapy without determining irradiance is commonly ineffective.

Based on experiments conducted at the end of the 1970s, several authors have suggested a minimal phototherapy dose of 4 µw/cm²/nm.1,12,21 This minimal effective dose would be the cutoff point below which the photoreaction of bilirubin is too small to justify phototherapy. Unfortunately, despite current clinical and laboratory evidence, numerous newborns are still submitted to subtherapeutic doses of phototherapy.
Facchini et al. carried out 20 assessments of irradiance in conventional phototherapy equipment in four maternity wards in the city of Campinas, Brazil, and found levels below 4 μw/cm²/nm in all the units assessed. De Carvalho and Lopes assessed phototherapy units in 21 public hospitals in Rio de Janeiro, and found a mean irradiance, measured in the blue spectrum, of 2.4 μw/cm²/nm (ranging from 0.6 to 4.4μw/cm²/nm). From the 102 units, only one presented irradiance above 4μw/cm²/nm measured on the newborn’s skin. A recent study carried out in a maternity ward in São Paulo observed irradiance ranging from 2 to 3.2 μw/cm²/nm in conventional phototherapy equipment.

Type of light used in phototherapy

There are several reasons why our conventional phototherapy equipment emits, at the level of the newborn’s skin, irradiance below minimum recommended levels. Among them are the insufficient number of lamps per unit; often, the use of equipment with burnt bulbs; the lower intensity of daylight fluorescent lamps manufactured in Brazil when compared to those manufactured in the U.S.; and the positioning of the light sources far from the patient.

White light

This has been the most commonly employed in phototherapy throughout the years. It is the only type of light whose safety was tested in a large population of newborns followed during the first 6 years after birth. The problem with this type of light is that it has a very wide emission spectrum (380 to 770nm). Since the light absorption spectrum by the bilirubin molecule is relatively short (350 to 500nm), that means that, in theory, the light emitted outside this spectrum would not have any role in the photochemical reaction.

The irradiance emitted in the band corresponding to the absorption of bilirubin is low - thus the need to equip phototherapy units with an adequate number of fluorescent lights (usually 7 to 8). When the phototherapy unit equipped with white fluorescent lights is positioned 50 cm away from the patient, the photoenergy reaching the newborn is below the minimum levels (4μw/cm²/nm) recommended in the literature.

A frequent question among pediatricians and neonatologists that deal with phototherapy equipment using white fluorescent lamps is when to change them. Since irradiance tends to decline with time, it is recommended that this energy be periodically determined with photodosimeters, and that the lamps be replaced whenever irradiance falls below the minimum effective level. However, photodosimeters were not available in Brazil until 1989. Currently, these dosimeters are found in very few institutions.

So as to find an alternative to this problem, most pediatric services in Brazil adopt the practice of replacing phototherapy lamps after a certain time, varying from 200 to 2,000 hours. An extensive literature review has not provided any elements for inferring the emitted irradiance (and, consequently, the efficacy of phototherapy) based on the time of use of white fluorescent lamps. De Carvalho and Lopes, analyzing phototherapy equipment with different brands of white fluorescent lamps observed a decrease in irradiance of about 20% after 2,000 hours of uninterrupted use. Therefore, it seems that irradiance should be measured periodically, and that lamps should be exchanged whenever this irradiance, measured at the skin of the newborn, is below clinically levels.

Blue light

Several studies have shown that blue light lamps produce a faster and more pronounced decrease in serum bilirubin levels than the light obtained with white fluorescent lamps. However, blue fluorescent light is not often used in nurseries due to the undesirable effects associated with this type of light. It is common to hear medical professionals complain of dizziness, nausea, and vomits after prolonged exposure to blue light. Another inconvenience is that under blue light, the newborn appears extremely cyanotic, making clinical assessment more difficult.

Blue light (special blue) was introduced in clinical practice in 1972. Since then, several studies have shown that these lamps produce a faster and more pronounced decrease in serum bilirubin than white fluorescent light. They emit around 45% more energy in the band between 400 and 490nm than do white fluorescent lamps, and are considered by some investigators as the most effective light source for use in phototherapy. Unfortunately, these special blue lamps are not manufactured in Brazil.

Green light

Green light seems to be more effective than white fluorescent light. In a study with 100 icteric newborns, Vecchi et al. showed a more pronounced decrease in serum bilirubin concentration after 24 hours in patients submitted to phototherapy with green light than in those submitted to white fluorescent light (20% vs. 16%). However, there seems to be no difference in terms of efficacy between green light therapy and blue light therapy. Most works show that both the decrease in the concentration of bilirubin and the total duration of phototherapy are not different with blue or green lamps.
Despite an extensive number of works showing that green fluorescent light is efficient to reduce serum bilirubin levels, its exact mechanism of action remains unknown. Similarly to blue light (although less frequently), green light may cause erythema in newborns, in addition to nausea and dizziness in the medical staff.\(^{34}\)

**Light emitting diodes**

Light emitting diode (LED) are sources of light with an extremely short emission spectrum. Currently, they are available in the market for a variety of applications (traffic indicators, commercial signs, etc.). LEDs are extremely small, with a diameter of 5 mm, weighing, on average, 0.3 g. For the treatment of neonatal hyperbilirubinemia, LEDs are grouped in plates containing 100, 200 or 300 units. These plates must be placed in direct contact with the patient or at variable distances.\(^{35}\) When in direct contact with the patient, irradiance reaches values higher than 200 \(\mu W/cm^2/\text{nm} \).\(^{36}\)

**Types of phototherapy**

So as to increase treatment efficacy, new types of equipment have been introduced in the market. Below is a description of the main types of phototherapy equipment used in Brazil.

**Conventional phototherapy**

Conventional phototherapy equipment usually employs six to seven daylight-type 20 W fluorescent lamps. With the light source placed 50 cm away from the patient, irradiance with this conventional equipment is about 3 to 4 \(\mu W/cm^2/\text{nm} \). The total illuminated body surface is large, since the entire body of the newborn (front or back) is irradiated. The irradiance emitted is very low and this is not compensated by the large surface area exposed to light. The final efficacy is lower than that expected for phototherapy equipment. In fact, several clinical studies have shown the low efficacy of conventional phototherapy equipment employing national fluorescent lamps.\(^{23,26,37}\)

With the aim of improving the efficacy of this type of phototherapy, the following is recommended: a) position the unit about 30 cm away from the patient; b) keep the acrylic surface of the incubator and the protection of the phototherapy unit clean; c) verify that all lamps are on; d) use equipment with seven or eight lamps; e) replace two white fluorescent lamps with two blue lamps (position them in the center of the unit); f) periodically check the irradiance emitted (measured on the patient’s skin); g) the newborn must be exposed to phototherapy without clothes, to ensure that maximal exposure of the body to light; h) whenever possible, maintain enteral feeding.

Since there are no reports of gonadal alterations associated with phototherapy, we do not recommend routine protection of the gonads. The usual wavelength used in phototherapy penetrates only 2-3 mm into the skin of the newborn, and therefore does not reach the gonads. Eye protection, however, should be observed.

**Biliblanket phototherapy**

This is a contact phototherapy, in which the newborn is placed on a fiber optic pad. The light source uses a special halogen lamp. Light travels from the source in the light pad through a fiber optic cable. The pad is a small rectangle measuring 13 cm x 10 cm. This skin of the newborn is in direct contact with the pad. The biliblanket has a system of filters that enable only the passage of light in the band between 400-500 nm.\(^{37}\)

The irradiance emitted by the biliblanket is between 35 and 60 \(\mu W/cm^2/\text{nm} \). Despite the high irradiance, efficacy is compromised by the small surface of the body exposed to light, and mainly by the mobility of the newborn. In clinical practice, the newborn often falls off the luminous pad and, as a result, the contact with light is decreased. In premature newborns, the biliblanket is more effective, since more body surface is exposed to light, and these patients are not very active. Currently, the biliblanket is used mainly as an adjuvant in double phototherapy, i.e., the newborn lies on the biliblanket while receiving conventional phototherapy.\(^{15,39-41}\)

**High intensity phototherapy**

In the 1990s, new phototherapy devices began to appear. These emitted high radiance distributed along a large body surface. Initially, these units employed 16 special blue fluorescent lamps disposed along a cylinder. The patient was, then, placed inside this cylinder in such a way that the lamps would be around the patient’s body, at a distance of about 15 cm (360° phototherapy). Under these circumstances, the irradiance reaching the newborn is higher than 100 \(\mu W/cm^2/\text{nm} \), reducing serum bilirubin levels in about 70% in the first 6 hours of treatment.\(^{16,42}\)

Recently, De Carvalho et al.\(^{43}\) created a high intensity phototherapy unit using white fluorescent lamps.\(^{43}\) This consists in a set of seven daylight white lamps distributed on an acrylic crib (60 cm length x 35 cm width), so that the acrylic basin remains around 5 cm away from the lamps. It is commonly used in nurseries and collective wards. This set of lamps emits light from the bottom up, crossing the inferior wall of the acrylic crib and reaching the newborn lying there. For increased comfort, a small silicone pad made of clear material (to avoid blocking the light) is placed inside the acrylic crib.

To profit from the peripheral light that would normally be lost, the crib’s walls are covered with semitransparent reflecting film. The upper opening features an arched acrylic lamp, also covered with reflecting film, so as to direct the light that would normally be lost back to the patient’s body.
Thus, the newborn will receive direct light from the bottom, and reflected (indirect) light from the lateral walls and upper dome of the crib (total integral phototherapy). The heat generated by this set of lamps is dissipated through a system of ventilation and exhaustion. The direct irradiance emitted by the unit is about 19μw/cm²/nm. The indirect irradiance, coming from the walls and reflecting dome, is 2-3μw/cm²/nm.

A controlled, randomized, prospective clinical study has shown that, after 24 hours, the decrease in serum bilirubin levels is about six times higher in newborns treated with this high-intensity phototherapy than in those exposed to conventional phototherapy (29% x 4%).

Currently, in our service, newborns with severe jaundice (TB >20mg%) are treated with high intensity phototherapy associated with two bilispots projecting light over the patient (the dome of the acrylic crib is removed). This type of triple phototherapy enables the baby to receive high intensity light over the entire body. Invariably, serum bilirubin levels decrease significantly a few hours after the start of treatment (we have observed a reduction of about 40% in basal serum levels of bilirubin in the first six hours of treatment). As a result, we observed an extraordinary reduction in the incidence of exchange transfusion in our service.

High intensity phototherapy using LEDs (described above), introduced experimentally in 2000, have been showing good results, but is not available in the market.

**What serum bilirubin levels indicate the need for phototherapy in icteric newborns?**

The indication for phototherapy will depend on the type of jaundice (hemolytic or not) and on specific characteristics of the newborn (term or preterm, presence of asphyxia, ecchymosis, etc.). The determination of serum bilirubin concentration is highly imprecise when conventional methods are used. Therefore, such a level does not exist in and of itself. It must be analyzed within a global context that includes several factors related to the newborn and to the newborn’s perinatal history (Figure 2).

In healthy term newborns presenting non-hemolytic jaundice (physiologic), the current trend is to delay the use of phototherapy until serum bilirubin reaches values considerably higher than those used in the past. The reason for this conduct is that several scientific publications show a lack of correlation between the serum levels of bilirubin and neurologic damage in terms newborns with non-hemolytic jaundice. The serum levels of bilirubin that are indicative of the need for phototherapy (non-hemolytic jaundice) used in our service, according to the weight range, appear in Table 1. In healthy term newborns with non-hemolytic jaundice, the recommendation of the American Academy of Pediatrics (AAP) appears in Table 2. According to the AAP, phototherapy must be started in term newborns with non-hemolytic jaundice presenting serum bilirubin levels of 15mg%. After more than 48 hours after birth, these levels would be between 18 and 20mg%. However, despite the recommendations of the AAP, most pediatricians and neonatologists still recommend phototherapy for patients with lower serum bilirubin levels.

**Exchange transfusion**

The main objective of exchange transfusion is to remove the excess of bilirubin, thus preventing its toxic effects. With this technique, about 85% of the circulating red cells are replaced when the volume of blood replaced is equivalent to twice the newborn’s volume (80ml/kg). Usually, the serum bilirubin concentration is reduced in 50%. Despite being a relatively safe procedure when performed by experienced professionals, the mortality associated with exchange transfusion is about 1%. The complications of exchange transfusion include, among others, thromboembolism, necrotizing enteritis, vascular perforation, hemorrhage, infection, and electrolyte, metabolic, and acid-base disturbances.

The indications for exchange transfusion must be individualized and based on an overall clinical assessment of patients with jaundice. In general, there are two types of exchange transfusion: early and late.

**Early exchange transfusion**

The criteria for indication of early exchange transfusion include less than 12mg% hemoglobin and more than 4mg% bilirubin in the umbilical cord and serum bilirubin levels at a rate of increase higher than 0.5mg%/hour.

Often, these newborns are hydropic and anemic. In addition, they may be hemodynamically unstable, and present heart failure. It is important to stress that, despite the anemia, these patients are not hypovolemic. Therefore, the performance of exchange transfusion with two blood volumes may worsen their cardiocirculatory instability.

In our service, we have chosen to treat hydropic and anemic newborns with an aggressive anticongestive therapy (diuretic, cardiotonic amines, and, if required, digitalization) before performing exchange transfusion. Once the patient is stable, we carry out exchange transfusion with one volume using high hematocrit blood (usually around 65%). Eight to 12 hours later, with the patient in a more stable condition and less anemic, we perform a second exchange transfusion (now with two volumes of total blood).

The administration of albumin before exchange transfusion, with the aim of increasing the removal of...
Circulating bilirubin is controversial and we do not use this routine in our service.

**Late exchange transfusion**

This is usually based on serum levels of bilirubin. However, the preestablished level of bilirubin should not be analyzed in isolation. Watchko and Oski describe a phenomenon they name as vigintifobia (twenty scare). In a magisterial article published in 1983, those authors show that there is no scientific basis to recommend exchange transfusion in term newborns without evidence of hemolysis only on the basis of a serum bilirubin level of 20mg%.51

The indication for exchange transfusion in newborns with 20mg% bilirubin and without hemolytic disease has become an everyday practice for pediatricians. It is extremely hard to change this hospital routine. We all seem to suffer from vigintifobia!

**Drug therapy for hyperbilirubinemia**

**Phenobarbital**

Studies with Rhesus monkeys have shown that phenobarbital increases the activity of glucuronyltransferase and, consequently, bilirubin conjugation. Based on that observation, phenobarbital is being used in pregnant women and newborns with the aim of preventing or minimizing neonatal hyperbilirubinemia. The use of phenobarbital in pregnant women considerably reduces the levels of bilirubin in newborns. However, according to Valaes et al., for this effect to be achieved, it is necessary that the pregnant woman take at least one 100mg tablet for at least 10 days.

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**Table 1 - Indicative levels for phototherapy in preterm newborns**

<table>
<thead>
<tr>
<th>Birthweight (kg)</th>
<th>bt (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.0</td>
<td>5</td>
</tr>
<tr>
<td>1.0 through 1.2</td>
<td>6</td>
</tr>
<tr>
<td>1.2 through 1.4</td>
<td>7</td>
</tr>
<tr>
<td>1.4 through 1.6</td>
<td>8</td>
</tr>
<tr>
<td>1.6 through 1.8</td>
<td>10</td>
</tr>
<tr>
<td>1.8 through 2.2</td>
<td>12</td>
</tr>
<tr>
<td>2.2 through 2.5</td>
<td>12–15</td>
</tr>
<tr>
<td>&gt; 2.5</td>
<td>&gt; 15</td>
</tr>
</tbody>
</table>

**Table 2 - Treatment of hyperbilirubinemia in healthy, full-term newborns, without hemolysis**

<table>
<thead>
<tr>
<th>Age</th>
<th>Consider phototherapy</th>
<th>Start phototherapy</th>
<th>Exchange transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 24 h</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>25 - 48 h</td>
<td>12 mg%</td>
<td>15 mg%</td>
<td>≥ 20 mg%</td>
</tr>
<tr>
<td>49 - 72 h</td>
<td>15 mg%</td>
<td>18 mg%</td>
<td>≥ 25 mg%</td>
</tr>
<tr>
<td>&gt; 72 h</td>
<td>17 mg%</td>
<td>20 mg%</td>
<td>≥ 25 mg%</td>
</tr>
</tbody>
</table>

American Academy of Pediatrics, 1994
The administration of smaller doses did not show to be effective in reducing the degree of jaundice in newborns. Therefore, it seems that both the dose of phenobarbital administered and the duration of the treatment play an important role in the process of stimulating enzyme activity. In practice, this has limited the prophylactic use of prenatal phenobarbital, since the beginning of delivery cannot be predicted. In addition, the drug can cause dependence in the mother and excessive sedation of the newborn. It could be that the prenatal administration of phenobarbital should be used only in risk groups.

The administration of phenobarbital to newborns after delivery or when jaundice is clinically visible is not effective to reduce serum bilirubin levels. The combination of phenobarbital and phototherapy in newborns does not reduce serum bilirubin levels faster than isolated phototherapy.

**Heme-oxygenase inhibitors**

Several studies have shown that metalloporphyrin, a potent heme-oxygenase inhibitor, reduces the conversion of the heme radical into bilirubin, and thus could have a role in the treatment of neonatal jaundice. The dose and interval of immunoglobulin administration varies from 0.5g to 1g. Alpay et al. treated 116 newborns with ABO and/or Rh hemolytic disease with 1g endovenous immunoglobulin (single dose). These patients required less phototherapy and fewer exchange transfusions, and spent less time in the hospital.

Although the use of endovenous gammaglobulin has become more common in the past years, a larger number of controlled studies are required before its routine use can be recommended for the treatment of hyperbilirubinemia caused by hemolytic disease (ABO or Rh) of the newborn.

**References**


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