

Side Effects of Phototherapy on Neonates

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Abstract

Phototherapy in neonates for treatment of pathological jaundice is an effective therapeutic tool that is widely used in neonatal units. Over the past years, a greater concern has emerged about the effects on the immune and inflammatory system and its potential genotoxic and side effects, especially the late ones, possibly associated with childhood diseases, showing that this treatment is not as harmless as previously believed. Numerous studies assessing these possible adverse effects of phototherapy on neonates have been published over the past years. Through this review, we seek to analyze what we know about the side effects of phototherapy in the neonatal period. The main causes of jaundice, phototherapy techniques, acute and late side effects, and effects on the immune and inflammatory system were reviewed. It was concluded that phototherapy is not a treatment free of side effects and further studies need to be conducted to elucidate its harmful effects on neonates.

Keywords

- ▶ jaundice
- ▶ hyperbilirubinemia
- ▶ neonate
- ▶ phototherapy
- ▶ side effects

Jaundice due to indirect hyperbilirubinemia affects more than 60% of neonates. A large number of the causes of hyperbilirubinemia in full-term neonates are benign and reversible and do not need therapeutic intervention.^{1,2} The most feared toxic effect, potentially irreversible and secondary to hyperbilirubinemia, is bilirubin encephalopathy, also known as kernicterus.¹⁻⁴

The main treatment for jaundice is performed using phototherapy, following the criteria recommended by the American Academy of Pediatrics.¹ Since the 1950s, phototherapy has been the therapy of choice for neonates suffering from indirect hyperbilirubinemia. It reduces the plasma levels of unconjugated bilirubin, preventing kernicterus and decreasing the need for exchange transfusion.

Side effects may occur in the short or long run.⁵ Among the short-term effects, we could mention the interference in the maternal–infant relationship, thermal and hydroelectrolytic imbalance, skin lesions, bronze baby syndrome, hematological alterations, paralytic ileus, patent ductus arteriosus, ocular effects, and circadian cycle disorders.⁴ Among the

long-term side effects are neoplasms, nevi, café au lait spots, and allergic diseases such as asthma, rhinitis, and conjunctivitis.

Several studies trying to correlate phototherapy with damage to the newborn have been published. Some studies have assessed the immune and inflammatory response by analyzing the expression of adhesion molecules, cytokines, and lymphocyte surface markers. Others have evaluated DNA damage in neonates subjected to phototherapy. The association of phototherapy in the neonatal period to several childhood diseases has been investigated.

This article aimed to carry out a review of the literature covering the knowledge of neonatal jaundice, phototherapy treatment, and the side effects of the phototherapy treatment. A review of the literature was performed in the PubMed database, including the keywords “neonatal jaundice,” with 8,177 studies, “neonatal jaundice phototherapy,” which returned 1,649 studies, and “neonatal jaundice phototherapy side effects,” with 327 studies. Initially, the titles and abstracts available at PubMed were reviewed. Articles not

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related to neonatal period were excluded. Sixty articles (cohort studies, case-control studies, systematic review, and case report) were selected. Some references found in these articles were included. The text was organized in topics for a better understanding of the subject, and the focus of the evaluated population were late premature and term newborns due to established diagnosis guidelines for this group.⁴

Definition of Neonatal Hyperbilirubinemia

Neonatal hyperbilirubinemia in newborns at a gestational age ≥ 35 weeks can be defined as an increase in the levels of bilirubin above the 95th percentile of the Bhutani nomogram. The yellowish color of the skin and/or conjunctiva of the neonate is caused by the deposition of bilirubin.^{4,5}

Severe hyperbilirubinemia is defined as a total bilirubin level higher than 25 mg/dL. It is associated with an increased risk of bilirubin-induced neurological dysfunction, which occurs when bilirubin crosses the blood-brain barrier and deposits on brain tissue. Acute bilirubin encephalopathy is usually described as an acute manifestation of bilirubin-induced neurological dysfunction, and kernicterus is usually described as a chronic, permanent sequela of the bilirubin-induced neurological dysfunction.⁴

Neonatal Jaundice Treatment

Aiming at the prevention of kernicterus cases, the treatment of neonatal jaundice focuses on preventing hyperbilirubinemia by identifying neonates at risk and starting preventive therapeutic interventions when necessary, namely, phototherapy and exchange transfusion.^{4,6}

Indications and Guidelines for Phototherapy in Term and Preterm

The decision of when to initiate therapy and the choice of intervention are based on the probability of developing severe hyperbilirubinemia, using hour-specific plasma bilirubin, gestational age, and the presence or absence of risk factors that increase the risk of brain damage. These factors include isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, or albumin < 3 g/dL.^{2,3} This approach to assess severity is consistent with the practice guideline developed by the American Academy of Pediatrics.⁴

Phototherapy Mechanisms

Phototherapy exposes the skin of the newborn to a light with a specific wavelength, which reduces bilirubin levels through three mechanisms⁷: structural isomerization to lumirubin (bilirubin is converted to lumirubin via irreversible structural isomerization. Lumirubin is a more soluble substance than bilirubin and is excreted unconjugated in the bile and urine. This is probably the main mechanism for reducing the plasma concentration of bilirubin through phototherapy);

photoisomerization to a less toxic bilirubin isomer (the 4Z,15Z bilirubin isomer is converted to the 4Z,15E isomer, which is more polar and less toxic. Like lumirubin, the 4Z,15E isomer is excreted unconjugated in the bile, but photoisomerization is reversible and its clearance is low. Therefore, this pathway may have a small effect on reducing bilirubin levels, but it reduces 15% of toxic bilirubin to the nontoxic form); photo-oxidation to polar molecules (photo-oxidation reactions convert bilirubin to a colorless polar component, which is primarily excreted in the urine. This is a low process and occurs to a small extent during the elimination of bilirubin).

Phototherapy Techniques

During phototherapy, the area covered with diapers must be minimized. The eyes must be protected with opaque visors. Devices with fluorescent lights must be preferably used in open cradles. With levels of bilirubin > 20 mg/dL, phototherapy must be administered continuously without interruptions. When the value is < 20 mg/dL, phototherapy can be discontinued for breastfeeding and parents' visits.

The dose of phototherapy, called irradiance, determines its effectiveness. The measurement is performed in $\mu\text{W}/\text{cm}^2$ of the body surface of the exposed area/nm of the wavelength. Irradiance depends on the type of light used, the distance between the light and the patient, and the area of exposed skin. In conventional phototherapy, irradiance ranges from 6 to 12 $\mu\text{W}/\text{cm}^2/\text{nm}$. In intensive phototherapy, irradiance is higher than 30 $\mu\text{W}/\text{cm}^2/\text{nm}$.⁸ For phototherapy to be intensive and effective, the irradiance levels should reach the largest surface area of the newborn as possible and the light should be placed at a distance of 10 to 30 cm from the patient, depending on the manufacturer's recommendation and the combination of optical fiber, light-emitting diode (LED), or special blue light.⁶ Although it is not necessary to measure the irradiance spectrum prior to each phototherapy session, periodic checks to determine if the appropriate irradiance is being used are important.⁴

Intensive phototherapy reduces the levels of bilirubin to 2 to 3 mg/dL within 4 to 6 hours. Within 24 hours, bilirubin may decline by 30 to 40%.⁹ Conventional phototherapy, on the other hand, reduces bilirubin by 6 to 20% within the first 18 to 24 hours. The rate of bilirubin decline during phototherapy depends on numerous factors, such as degree of irradiance, exposed body surface, and initial bilirubin levels (the higher, the faster the rate of decline). The effectiveness of the treatment also depends on the neonate's pathology, being less effective in neonates with cholestasis and those with hemolytic disease with a positive direct Coombs' test.⁴

Types of Phototherapy Devices

Bilirubin absorbs light more strongly in the blue region, in the spectrum near 460 nm. There are several types of devices for phototherapy, with variable types of light, different wavelengths, and different degrees of irradiance.^{8,10} Light sources include fluorescents tubes, halogen white light, fiberoptic blankets or pads, and blue LEDs. Fluorescent tubes

have been shown to be effective in lowering plasma bilirubin levels because they deliver light in the blue–green spectrum, which penetrates the skin well and is absorbed maximally. Halogen white lamps are hot and can cause thermal injury. They should be placed at the distance from the patient recommended by manufacturer. Fiberoptic blankets or pads generate little heat and can be placed close to the infant, providing higher irradiance than fluorescent lights.¹¹ However, blankets are small and rarely cover sufficient surface area to be effective when used alone. They can be used as an adjunct to overhead fluorescent or halogen lights. LEDs deliver high-intensity narrow band light in the absorption spectrum of bilirubin and are as effective as conventional fluorescent blue light.^{10,12}

Side Effects of Phototherapy

Molecular Alterations by Phototherapy

Phototherapy may have a toxic effect on DNA. Yahia et al¹³ demonstrated that phototherapy causes DNA damage and induces apoptosis in the lymphocytes of full-term newborns. Aycicek et al¹⁴ showed damage to the DNA of endogenous mononuclear leukocytes in icteric full-term newborns undergoing phototherapy. El-Abdin et al,¹⁵ Karakukcu et al,¹⁶ and Tatli et al¹⁷ also demonstrated the genotoxic effects of phototherapy.

Some studies have demonstrated the influence of phototherapy on the concentration of cytokines in neonates, in an attempt to correlate their findings with effects on the immune and inflammatory systems. Procyanoy et al¹⁸ demonstrated decreased levels of interleukin (IL)-6 after 24 hours of phototherapy, suggesting a possible anti-inflammatory effect of phototherapy. Sirota et al¹⁹ found an increase in IL-2 and IL-10 and a decrease in IL-1 β in neonates after phototherapy, demonstrating that it affects the immune system function. Zarkesh et al²⁰ found an increase in IL-6 levels and leukocyte counts in neonates after phototherapy, also suggesting that alterations in the function of the neonatal immune system may be triggered by phototherapy.

Studies demonstrating alterations in the expression of lymphocyte surface antigens in neonates submitted to phototherapy have also been conducted. Rashedy et al²¹ studied the effect of phototherapy on the levels of CD4, CD8, and NK lymphocytes after 72 hours of phototherapy and found no significant change in relation to the controls. Eyada et al²² also found no correlation among the levels of CD19, CD4, and CD8 in the lymphocytes of neonates after 72 hours of phototherapy, nor the occurrence of infections after a 6-month follow-up. Elfeky et al²³ found lower CD3 and CD19 levels after 72 hours of phototherapy and followed up these patients for 6 months. Patients with a higher CD3 decline had an increase in the number of hospital visits.

Studies have compared oxidative stress and effects on antioxidant/oxidant balance in term and preterm newborns after conventional, LED, and fiberoptic phototherapy. They indicated that phototherapy disturbs the oxidant/antioxidant balance in favor of oxidants and induces an oxidative stress.^{24–27}

Acute Side Effects of Phototherapy

Interference in the Mother–Child Relationship

The phototherapy treatment separates the neonate from his mother. Unless jaundice is very severe, phototherapy can be safely discontinued for breastfeeding and parents' visits.²⁸ Family-centered phototherapy strongly supports the rooming-in, skin-to-skin contact, and breastfeeding.²⁹ Jaundice and phototherapy treatment are a factor of risk for vulnerable child syndrome, first coined by Green and Solnit in 1964: "parental reactions to an acute, life-threatening illness in a child may have long-term psychologically deleterious effects on both parents and children."³⁰

Thermal and Hydroelectrolytic Imbalance

Phototherapy changes the neonate's thermal environment and may lead to insensible water loss, hypothermia or hyperthermia, and dehydration.³¹ It may also trigger diarrhea, possibly due to increased intestinal secretion, and alteration of the transepithelial electric potential difference. The absorption of water, sodium, and potassium may be impaired in neonates receiving phototherapy, but this effect is transient and resolves once treatment has been discontinued.²⁸ An increase in the water supply to the neonate undergoing phototherapy by 10 to 15 mL/kg/d is recommended to prevent dehydration. No intravenous hydration is required if severe dehydration is not present.³²

Asl et al³³ measured calcium excretion before and after 48 hours of phototherapy and, as a result, found an increase in urinary calcium excretion, although without evidence of hypocalcemia. Light can affect calcium homeostasis by inhibiting melatonin secretion by the pineal gland, consequently leading to hypocalcemia.³⁴ Calcium levels return to normal 24 hours after the end of phototherapy. No prophylactic calcium is required during phototherapy.^{28,35}

Bronze Baby Syndrome

The bronze baby syndrome is a rare complication that occurs in newborns with cholestasis (direct bilirubin > 2 mg/dL) undergoing phototherapy. It manifests itself through a gray-brown pigmentation of the skin, serum, and urine. Its specific etiology is unknown. Pigmentation returns to normal once phototherapy has been discontinued. This syndrome may be an additional risk for the development of kernicterus.³⁶ Neonates with mixed (direct and indirect) hyperbilirubinemia who undergo phototherapy should be monitored for the risk of this syndrome.³¹

Skin Lesions

Phototherapy may cause skin lesions such as macules, papules, and maculopapular rash. Surmeli-Onay et al³⁷ did not demonstrate differences in the incidence and extent of rashes in newborns undergoing conventional phototherapy compared with LED. There is a description of a phototherapy-induced purpuric eruption in neonates who received blood transfusion and intravenous immunoglobulin for the treatment of neonatal hemolytic disease.³⁸

Hematologic Alterations

Regarding leukocyte counts, Zarkesh et al²⁰ and Jahanshahifard et al³⁹ showed an increase in circulating leukocytes after phototherapy in icteric neonates, and Mrkaić et al⁴⁰ showed an increase in the total number of polymorphonuclear leukocytes, lymphocytes, and monocytes; however, these findings were temporary. The study by Mrkaić et al evaluated the effects of phototherapy on the immune system of newborn without signs of asphyxia or infection, which may explain this only temporary response, not being possible establish the consequences of phototherapy in the presence of baseline disease.⁴⁰

Neonatal thrombocytopenia is not commonly cited in pediatric textbooks as a complication of phototherapy.^{41,42} Bhargava et al studied the association of phototherapy for neonatal jaundice with thrombocytopenia in 96 newborns, finding mild to moderate thrombocytopenia after 48 hours of phototherapy, usually asymptomatic and transient.⁴¹ Khera and Gupta also studied the effect of phototherapy on the platelet levels of 100 neonates and the thrombocytopenia was observed in 74% of patients during the first 24 hours of phototherapy, being transient and not associated with complications such as bleeding.⁴²

Paralytic Ileus

The occurrence of paralytic ileus may be associated with phototherapy for neonatal jaundice according some studies. Kadalraja et al⁴³ performed a prospective observational study in 14 premature newborns and finding increased superior mesenteric artery end-diastolic blood flow velocity, may indicate photorelaxation of the mesenteric vascular smooth muscle during the phototherapy, and concluding that phototherapy may be a risk factor for ileus in preterm neonates. Raghavan et al⁴⁴ found a high proportion (63.4%) of extremely low-birth-weight preterm infants with paralytic ileus compared with newborn that did not receive phototherapy (9%), also concluding that phototherapy is an independent risk factor for paralytic ileus in extremely low-birth-weight neonates.

Circadian Cycle Disorders

The effects of neonatal phototherapy on the expression of circadian genes have been studied. Chen et al⁴⁵ demonstrated an increased expression of the *Cry1* gene and a reduction in the levels of melatonin and the *Bmal1* gene, altering the normal circadian rhythm and leading to abnormal behaviors in newborns under phototherapy for jaundice, such as crying and nervousness.

Patent Ductus Arteriosus

In the 1990s, Barefield et al⁴⁶ demonstrated a significant increase in the incidence of patent ductus arteriosus in very extremely birth weight preterm infants when compared with neonates who did not undergo phototherapy (76 and 53%, respectively), and Benders et al⁴⁷ showed the reopening of the ductus arteriosus in more than 50% of preterm infants

(<32 weeks and birth weight <1,400 g) under phototherapy. Numerous studies have shown that phototherapy may indirectly or directly cause patency of the ductus arteriosus by the effect of photorelaxation via prostaglandins. In 2015, Surmeli-Onay et al⁴⁸ demonstrated a new approach to an old hypothesis: phototherapy does not affect the patency of the ductus arteriosus via prostaglandins, and these are eliminated concomitantly with the closure of the ductus arteriosus. The photorelaxation effect possibly is not influenced by prostaglandin levels. Further studies are needed to verify that phototherapy is truly associated with patent ductus arteriosus.

Ocular Effects of Phototherapy

The retina is susceptible to light and animal studies indicate retinal degeneration after a continuous exposure to phototherapy.⁴⁹ In view of this, the eyes of neonates must be covered to protect their retina from light-induced damage. The staff should be careful to check the proper positioning of eye shields, avoiding the retinal damage that can be caused by light, and evaluate possible periorbital skin irritations due to these shields, as well as conjunctival infections that may arise from their use.²⁸

Late Side Effects of Phototherapy

Neoplasms

Two large cohort studies conducted in California^{50,51} associated phototherapy with an increased risk of developing childhood cancer, particularly acute myeloid leukemia (AML). Cnattingius et al⁵² also showed an association between phototherapy and AML in infants. Although the increase in the absolute risk is small, it is sufficient to cautiously judge when the phototherapy treatment should start.

Studies correlating phototherapy and melanoma have not demonstrated evidence of a statistically significant risk. Studies have not demonstrated an increased incidence of basal cell and squamous cell carcinoma in patients who underwent phototherapy in the neonatal period either.^{53,54}

Skin Lesions

Studies are not in agreement about the association between melanocytic nevi and phototherapy. Wintermeier et al⁵⁵ found no significant influence on the development of melanocytic nevi in preschool children who had been submitted to phototherapy for hyperbilirubinemia in the neonatal period but demonstrated an increase in café au lait macules. Lai and Yew⁵⁶ performed a systematic review and did not find evidence of an increased number of melanocytic nevi in newborns undergoing phototherapy. Mahé et al⁵⁷ found no increase in nevi count in 9-year-old children after neonatal phototherapy using a blue light. Matichard et al⁵⁸ demonstrated a high correlation between neonatal phototherapy and nevi count, especially 2 to 5 mm, in children aged 8 to 9 years. Csoma et al⁵⁹ investigated 747 schoolchildren aged 14 to 18 years who had undergone phototherapy and

associated it with the increased prevalence of common and atypical nevi.

Allergic Diseases

Some studies have demonstrated the association between neonatal hyperbilirubinemia and neonatal phototherapy with allergic diseases in childhood, such as allergic asthma, rhinitis, and conjunctivitis. Aspberg et al⁶⁰ demonstrated, in a large population-based study, the association between childhood asthma and neonatal phototherapy and/or jaundice. Das and Naik⁶¹ showed a significant increase in allergic asthma and rhinitis following neonatal hyperbilirubinemia and neonatal phototherapy. Beken et al⁶² demonstrated increased levels of eosinophils and eosinophil cationic protein after LED phototherapy and speculated that neonates treated with LED phototherapy showed increased levels of eosinophil cationic protein and this increase may play a role in the development of allergic diseases later. Aydin et al⁶³ demonstrated that the peripheral eosinophil count may be affected by bilirubin levels and/or phototherapy. Bottini and Bottini⁶⁴ showed an association between neonatal phototherapy and allergy (rhinitis and conjunctivitis).

Final Considerations

Phototherapy is the therapy of choice for neonates with neonatal jaundice, as it decreases the levels of indirect bilirubin and prevents kernicterus. Over the past years, concerns with its potential short- and long-term toxicities have arisen, and this review included numerous studies demonstrating the possible toxic effects of this treatment modality on the newborn. Many effects are transient. The use of neonatal phototherapy must be judicious and aimed only at neonates who really need it, following the recommended guidelines and always weighing the risks and benefits of the treatment for neonates. Phototherapy is not a treatment free of side effects and further studies need to be conducted to elucidate its harmful effects on neonates.

Conflict of Interest

None.

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