

Published: July 10, 2023

Citation: Mendelson S, 2023. Neonatal Phototherapy Adverse Effects in Infants: A Scoping Review, Medical Research Archives, [online] 11(7). <https://doi.org/10.18103/mra.v11i7.1.4099>

Copyright: © 2023 European Society of Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI
<https://doi.org/10.18103/mra.v11i7.1.4099>

ISSN: 2375-1924

REVIEW ARTICLE

Neonatal Phototherapy Adverse Effects in Infants: A Scoping Review

Sherri Mendelson

Email: sherri.mendelson@providence.org

ABSTRACT

Objective: To determine what adverse effects of neonatal phototherapy have been identified and the general breadth of the research.

Data Sources: A search for relevant sources was conducted using PubMed, The Cochrane Database, Ovid, and Clinical Key via EBSCO Discovery Search from January 2013-January 2023.

Study Selection: Sources were included if participants had undergone phototherapy for hyperbilirubinemia during their first weeks of life, including term and preterm infants. Twenty-three sources met the inclusion criteria.

Data Extraction: Extraction included citation, design, context, aim, participants, outcomes, and main results.

Data Synthesis: General concepts leading the synthesis included adverse effects of neonatal phototherapy. In addition, specific subgroups of adverse effects explored included childhood allergies, childhood cancers, patent ductus arteriosus (PDA), migraine headaches, attention deficit hyperactivity disorder, autism spectrum disorder, eye disorders and acoustic disorders.

Conclusion: While the quality of studies varies, more rigorous research on adverse effects of neonatal phototherapy would benefit from careful selection of methods and reference standards, direct measures of each adverse outcome identified in adults and children, and prospective cohort studies linking early neonatal exposure with each adverse outcome outcomes throughout childhood and adolescence.

Elucidating the effects of hyperbilirubinemia versus neonatal phototherapy on each potential adverse outcome will help to determine if new treatment methods for infants with hyperbilirubinemia need to be developed.

Background

Per algorithm recommendations of The American Academy of Pediatrics (AAP), and many other professional organizations, newborn infants with elevated levels of unconjugated bilirubin are treated with phototherapy. Research and development of algorithms by Bhutani, et al. has improved the care of newborns with hyperbilirubinemia by through appropriate testing and treatment as needed with phototherapy.¹ Phototherapy is typically provided using special blue light. Double phototherapy consists of special blue light with the addition of fiberoptic phototherapy. For the past twenty years AAP has recommended an irradiance of $\geq 30\mu\text{W}/\text{cm}^2\text{nm}^{-1}$ and a wavelength of 430-490nm for treatment of hyperbilirubinemia.²

The dose of phototherapy is a key factor in how quickly it works; dose in turn is determined by the wavelength of the light, the intensity of the light (spectral irradiance), the distance between the light and the baby, and the body surface area exposed to the light (irradiance footprint). Commercially available phototherapy systems include those that deliver light via fluorescent bulbs, halogen quartz lamps, light-emitting diodes, and fiberoptic mattresses. It has been used for this purpose for newborns since the 1950s when the first publication on phototherapy for treatment of neonatal hyperbilirubinemia was published.³

The newest clinical practice guidelines on management of neonatal hyperbilirubinemia were released by the American Academy of Pediatrics (AAP) in July 2022.² These guidelines have raised the transcutaneous bilirubin (TCB) level for infants ≥ 35 weeks gestation prior to recommended use of phototherapy based on gestational age, days of life and risk factors with the intent to avoid adverse effects of phototherapy while providing safe care for infants with hyperbilirubinemia.

Sunlight is also known to help with bilirubin breakdown but is not generally recommended when phototherapy devices are available due to harmful ultraviolet light and infrared radiation, with potential for sunburn, skin damage, and hyperthermia or hypothermia.

Approximately 50% full-term newborns and 80% preterm newborns will present with hyperbilirubinemia usually between day 2-4 of life.⁴ Bilirubin in higher amounts can be toxic to cells of the brain. In a large retrospective cohort study by Tsao, et al. the risks of long-term adverse neurodevelopmental outcomes including cerebral palsy, hearing loss and developmental delay, were 2-3 times higher in infants with significant neonatal jaundice, irrespective of treatments

including phototherapy, intense phototherapy, and exchange transfusion.⁵

If a baby has severe jaundice, there's a risk of bilirubin passing into fat cells of the brain, a condition called acute bilirubin encephalopathy. Prompt treatment may prevent significant lasting damage. Permanent damage to the brain due to acute bilirubin encephalopathy is known as kernicterus. Phototherapy is a method for breaking down bilirubin by transforming bilirubin into water-soluble isomers for elimination via urine and stools without conjugation in the liver. Phototherapy is used for newborns with elevated levels of bilirubin to prevent bilirubin encephalopathy. In a study by Auger, N., et al., of 32,314 infants born between 2006-2016, 4.1% of newborns were exposed to phototherapy for treatment of jaundice.⁶

A study by Jasprova, et al.⁷ utilized in vitro and ex vivo experimental models of photo-oxidative products of hyperbilirubinemia. Exposure to bilirubin oxidative products, even at high levels did not affect cell viability in vitro. However, there was an increase in pro-inflammatory cytokines that may be implicated in negative neurological outcomes according to the study. Concerns about adverse effects of phototherapy have been expressed since its inception. After almost seventy years as the primary treatment for neonatal jaundice, these questions regarding neonatal phototherapy persist.

Following incidental comments on public blogs regarding adverse effects of phototherapy for infants, a scoping review of the recent literature was undertaken to determine what adverse effects have been identified and the general breadth of the research. For infants treated with phototherapy what is the rate of complications? Is it the hyperbilirubinemia or the phototherapy that caused the problem? What is known and what aspects need further investigation? It is unclear what kind of information is available in the literature about adverse effects of phototherapy and ultimately safety of this treatment to prevent bilirubin encephalopathy. As the primary treatment for a potentially devastating sequelae, if there are significant risks of phototherapy to the infant, they need to be better understood so that research on mitigation or alternative treatments can be developed. Additionally, in discussing risks versus benefits with the infant's parents, determining what risks exist is critical. For these reasons, a scoping review was conducted to systematically map the research done in this area, as well as to identify any existing gaps in knowledge on adverse outcomes related to neonates with hyperbilirubinemia treated with

phototherapy to determine the extent phototherapy safety research has been undertaken and the prevalence and health outcomes associated with neonatal phototherapy.⁸

Design

A scoping review of adverse effects of neonatal phototherapy was undertaken. Scoping reviews are a type of knowledge synthesis. This methodology begins with a topic and follows a systematic approach to identify knowledge gaps by mapping evidence on a topic and identification of main concepts, theories, and sources.⁸ A checklist was developed with guidance from the EQUATOR (Enhancing the QUALity and Transparency Of health Research) Network. The checklist comprises 20 reporting items and 2 optional items and is known as the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews). The intent of the PRISMA-ScR is to help readers (including researchers, publishers, commissioners, policymakers, health care providers, guideline developers, and patients or consumers) develop a greater understanding of relevant terminology, core concepts, and key items to report for scoping reviews⁹ (see Figure 1).

Online databases including PubMed, The Cochrane Database, Ovid, and Clinical Key were searched via EBSCO Discovery Search from January 2013-January 2023. A general search for adverse effects of neonatal phototherapy was conducted. In addition, specific subgroups of adverse effects explored included neonatal phototherapy as well as; childhood allergies, childhood cancers, nevis or rashes, patent ductus arteriosus (PDA), migraine headaches, attention deficit hyperactivity disorder, autism spectrum disorder, eye disorders and acoustic disorders. All English language studies that included term or preterm infants with jaundice treated with phototherapy with exploration of adverse effects were included in the review. Excluded from the review were studies that were completed earlier than 2013 or were not prospective or retrospective studies conducted directly involving infants that received phototherapy.

Results

Summary

There were 25 studies included in the scoping review (see Table 1). Allergic reactions appear to be significantly increased in infants exposed to phototherapy for treatment of hyperbilirubinemia. Causation of PDA in preterm infants by phototherapy and the role of chest-shielding for prevention of PDA are not confirmed in the

literature. Mixed results were found for phototherapy and childhood cancer rates. ADHD rates were increased with exposure to phototherapy and higher bilirubin rates. ASD rates were not significantly increased with hyperbilirubinemia although phototherapy was not a specific objective this study. Phototherapy was not found to cause significant negative ophthalmologic outcomes. Adverse neurological and hearing loss outcomes appear to be increased by use of phototherapy for neonatal hyperbilirubinemia according to Erdevi, et al.¹⁰ and Tsao, et al.⁵ but were not found to be significant by Can, et al.¹¹ Phototherapy dose dependent changes were found for magnesium levels in one study and in another study without dose of phototherapy as a variable. There were decreased sodium levels demonstrated in preterm and low birth-weight infants that underwent phototherapy in another study. Potassium levels were not found to be influenced by phototherapy. No research literature was found for the selected timeframe that explored the relationship between migraine headaches and neonatal phototherapy use.

Few studies were able to differentiate results from phototherapy versus hyperbilirubinemia.

Immune or Inflammatory/Childhood Allergies

Five studies were included that sought to determine if neonatal phototherapy may lead to immune and inflammatory reactions potentially resulting in childhood allergies. In the systematic review by Das and Naike¹² a significant increase in allergic asthma and rhinitis following neonatal hyperbilirubinemia and neonatal phototherapy was demonstrated and hospitalization due to asthma after neonatal phototherapy was increased [OR 3.56 (95% CI 2.93–4.33)]. There was a significant positive correlation found by El Sheikh between total serum bilirubin and both eosinophil count and eosinophil % ($r = 0.281$ and $r = 0.339$), respectively ($P < 0.001$) after PT.¹³ A significant positive correlation was also found between both tumor necrosis factor alpha and eosinophil % after PT ($r = 0.545$, $P < 0.001$)¹³. The increased serum tumor necrosis factor-alpha and eosinophilic count following neonatal phototherapy indicates an allergic response. Faulhaber, et al. conducted a systematic review on adverse effects of neonatal phototherapy. This review that included five studies specifically exploring childhood allergies as an adverse outcome of neonatal phototherapy indicated a possible association between neonatal phototherapy and childhood allergies.¹⁴ Following LED neonatal phototherapy on 30

infants with severe hyperbilirubinemia Beken, et al. found significantly increased levels of eosinophil cationic protein which may lead to the development of allergic diseases.¹⁵ Aydin et al. demonstrated that bilirubin levels and/or phototherapy might be responsible for an increase in the peripheral eosinophil count in infants with elevated bilirubin levels treated with phototherapy.¹⁶

Patent Ductus Arteriosus (PDA)

Three studies were included exploring causation of PDA in preterm infants by phototherapy. The role of chest-shielding for prevention of PDA is not confirmed in the literature. A Cochrane Review by Bhola, et al. explored older studies that found that PDA is an adverse outcome from neonatal phototherapy in preterm babies.¹⁷ No conclusions could be drawn on the use of chest shielding to prevent this adverse outcome. In contrast, a meta-analysis by Mannan J, et al. found a decrease in PDA among preterm infants receiving phototherapy with chest shielding. With regards to PDA,¹⁸ Surmeli-Oney, et al. concluded from their prospective study that phototherapy does not cause PDA through altered prostaglandins levels.¹⁹

Migraine Headaches

Although there is incidental non-scientific blog discussions regarding neonatal phototherapy and migraine headaches, no research literature was found that explored the relationship between neonatal phototherapy use and migraine headaches.

Childhood Cancers

Mixed results were found for phototherapy and childhood cancer rates among the four studies included in this scoping review. A systematic review and meta-analysis that included 11 studies indicated that neonatal phototherapy might be a possible risk factor for childhood cancer in general, and specifically, leukemia. The findings of one study by Hemati, et al. show that phototherapy was significantly associated with an increased risk of all types of cancers (RR = 1.28; 95% CI (1.08, 1.51)).²⁰ A cohort study by Digitale, et al. included a sample of 139,100 infants <35 weeks gestation from 1995 to 2017, and followed through March 16, 2019, and a sample of 40,780 children with 5 years of follow-up from their previous report. In this large study no association with any cancer diagnoses at age >4 years of age was found.²¹

A retrospective cohort study by Auger, et al. with a sample of 786,998 infants determined that neonatal phototherapy may be associated with a

slightly increased risk of solid tumors in childhood.⁶ The study was not able to determine whether the slightly increased risk of solid tumors was an effect of phototherapy versus the effect of bilirubin. Sabzevari, et al. conducted a case control study to explore if there was a relationship between neonatal phototherapy and all cancer types in 116 children up to age four. The study results indicated that no correlation was found between neonatal phototherapy and childhood cancers.²²

Attention Deficit Hyperactivity Disorders (ADHD) or Autism Spectrum Disorder (ASD)

Three studies were included that explored either ADHD or ASDs. A retrospective observational study by Wei, et al. explored the adverse outcome of ADHD due to neonatal phototherapy. The study included 24,950 neonatal jaundice cases and 69,964 matched non-jaundice controls. The risk of ADHD increased for neonates with higher serum bilirubin levels that received phototherapy and had longer inpatient stays. It is not clear if hyperbilirubinemia or phototherapy is the cause. The hazard ratio was higher for male, preterm, and low-birth-weight infants.²³ The second study by Hung, et al. was a retrospective cohort study exploring a link between hyperbilirubinemia and ASD. This study included 67,017 neonates with and without hyperbilirubinemia. ASD rates were not significantly increased with hyperbilirubinemia although phototherapy was not a specific objective this study.²⁴ In the third study by Lozada, et al. a procedural treatment for jaundice was documented in 107 (3.7%) of children with ASD and 221 (2.5%) of controls (P < .001), suggesting a significant increase in ASD for children with a history of neonatal phototherapy for hyperbilirubinemia.²⁵

Ophthalmologic Disorders

One study was included in the scoping review related to adverse ophthalmologic effects of neonatal phototherapy. The study by Kara, et al. was a retrospective chart review of 100 infants with hyperbilirubinemia (57 phototherapy/43 no phototherapy) and follow-up with prospective ophthalmologic exams at 5-6 years of age. No significant difference was found between the groups in terms of the need for eyeglasses. Significant difference between the groups in terms of right cycloplegic spherical equivalent and left cycloplegic spherical equivalent was coincidental and clinically insignificant. Although convergence near point was statistically significant between the groups, it ranged from 2 to 5 cm, which remained in normal limits. This indicates that this statistical significance was clinically insignificant.²⁶

Neurological effects and hearing loss

Four studies were included that explored neurological adverse effects and hearing loss due to neonatal phototherapy exposure. In the study by Newman, et al. a significant increase in the rates of seizures were found for those exposed versus not exposed to neonatal phototherapy (crude IRR: 1.63; 95% CI: 1.44 to 1.85; $P < .0001$). The risk for seizures also was found to increase over time. Groups found in unadjusted analyses to be at higher risk of future seizures included male sex, African American race, lower gestational age, low birth weight, and being small for gestational age.²⁸ Rates of infantile cerebral palsy, hearing loss, and developmental delay were significantly higher within each cohort in the study by Tsao, et al. This study had a large sample size of 66,983.⁵ Results of the study by Erdeve, et al. showed neurological abnormalities (0.35%), and hearing loss (0.2%) without differentiating bilirubin versus phototherapy causation.¹⁰ Can, et al. found a non-significant difference in auditory neuropathy among late preterm infants with severe and non-severe hyperbilirubinemia.¹¹

Nevis and Rashes

The two studies exploring phototherapy as causation of nevis and rashes demonstrated mixed outcomes. Blue light phototherapy for neonatal hyperbilirubinemia was not found to result in a significant number of melanocytic nevis ($p=0.53$) in a study by Lai, et al.²⁸ Five studies were included in their systematic review and meta-analysis with a total sample of $n=2,921$ of which 642 received the phototherapy treatment.²⁸ In the systematic review by Olah, et al. six studies were included with 923 subjects. Four of the included studies found a relationship between neonatal phototherapy and nevis ($n=410$) while 2 studies did not ($n=513$).²⁹

Electrolytes

Three studies were included that explored adverse effects of neonatal phototherapy on electrolytes in the infant. In one observational study including 70 NICU babies on phototherapy by Khatab, et al. there was a significant decrease in magnesium levels from the pre-phototherapy levels to 48 hours and at the conclusion of phototherapy with a level of significance at each time of $p < 0.001$.³⁰ Potassium levels were not found to be influenced by phototherapy.³⁰ In a study by Eghbalian, et al. phototherapy dose dependent changes were found for serum total magnesium levels. The magnesium levels were significantly decreased with use of double phototherapy ($p=0.018$) but

not with single phototherapy.³¹ In a three cohort (infants at term, preterm and low birthweight) prospective observational study with a total sample of 100 by Chinnappa, et al. hyponatremia was significant in study infants that underwent phototherapy, especially in preterm and low birthweight infants. Potassium changes in the study by were non-significant.³²

Discussion

Immune and Inflammatory/Childhood Allergies

Allergic reactions appear to be increased in infants exposed to phototherapy for treatment of hyperbilirubinemia.^{12,13,14,15,16} Although the study by Das and Neike¹² was found to be of low quality, the consistency of the evidence for this adverse effect among all five studies included in this review, appears to indicate that children with a history of neonatal phototherapy immune should be screened for immune and inflammatory/childhood allergies during regular pediatric visits as a potential adverse effect of the neonatal phototherapy they received. There are not findings that consistently demonstrate causation of the adverse effects stemming from phototherapy versus hyperbilirubinemia versus a combination of the two.

Patent Ductus Arteriosus (PDA)

There appears to be long-term evidence of PDA as an adverse reaction in preterm newborns with hyperbilirubinemia treated with neonatal phototherapy. However, the intent of the Cochrane Review by Bholra, et al. and the study by Mannan, et al. included in this scoping study, were intended to explore evidence for mitigation of this adverse outcome through use of chest shielding for preterm infants during phototherapy.^{17,18} The main weakness within the Cochrane Review was only two trials were included, and both were found to have a risk of bias.¹⁵ In use of chest shielding, there is a loss of surface area exposed to the phototherapy, in theory diminishing its effectiveness. In the study by Mannan, et al. chest shielding was found to be effective in PDA reduction. Therefore, although PDA may be increased in these infants, it is not confirmed whether the causation is the phototherapy, the hyperbilirubinemia, the preterm status, or a combination of these.¹⁸ The study by Surmeli-Oney, et al. found that phototherapy effects on prostaglandin does not mediate PDA as an outcome in preterm infants. However, no other causation was explored.¹⁹

Migraine Headaches

Although there was no research literature found for this review on migraine headaches as an adverse outcome from phototherapy, one interesting intersection within this review is the study by Khatab, et al. that found decreased magnesium levels with double phototherapy.³⁰ Magnesium supplements are a first line treatment for chronic migraines, indicating that lower magnesium levels and migraines are potentially related.³⁰ Long-term follow-up of infants that received phototherapy might be needed to determine the risk of this adverse outcome.

Childhood Cancers

Although two of the included studies showed significant results with increased risk of childhood cancers,^{20,6} two of the studies demonstrated no increased risk.^{21,22} As the role of confounding factors were not controlled in the four studies included in this scoping review, studies, future large cohorts are necessary in this regard. In addition, exploring the risk of cancer as an adverse outcome of neonatal phototherapy in a wider age range might present a clearer understanding of childhood cancers as a risk from neonatal phototherapy. The findings of the study by Hemati, et al. underscore the importance of greater adherence to scientific guidelines for thresholds of bilirubin for minimizing unnecessary exposure to phototherapy.²⁰

Attention Deficit Hyperactivity Disorders (ADHD) or Autism Spectrum Disorder (ASD)

All studies included for this category of neonatal phototherapy adverse effects had very large pools of subjects, strengthening their conclusions.^{23,24,25} The risk of ADHD was shown to increase with higher serum bilirubin levels that received phototherapy and had longer inpatient stays. It is not clear if hyperbilirubinemia or phototherapy is the cause. As infants with higher bilirubin levels might receive higher levels of phototherapy and for a longer time-period, this may be a subgroup with higher risk for ADHD versus all infants receiving phototherapy. With a higher hazard ratio found for males, preterm, and low-birth-weight infants²³, screening for ADHD might be indicated for these infants with a history of neonatal phototherapy. In the study by Hung, et al., ASD rates were not significantly increased with hyperbilirubinemia.²⁴ Although phototherapy was not a specific objective this study, many of the study infants did receive phototherapy. This would lend some credence to an unlikely connection between phototherapy and ASD. However, the study by Lozada, et al. with a large sample size,

found 47% increased odds of ASD in children who had required neonatal phototherapy (OR = 1.47; 95% CI = 1.16-1.86; P = .001).²⁵ The conflicting outcomes in these studies may be due to variation in population, study methodology, types of phototherapy utilized, or additional unidentified risk factors.

Ophthalmologic Disorders

The lack of significant adverse ophthalmologic effects of neonatal phototherapy may be due to the consistent practice of use of eye coverings for infants during treatment. In addition, only one study was found. The sample size consisted of 100 low birthweight infants; 57 with phototherapy and 43 in the control group who all had an ophthalmologic exam at 5 years of age or over. Fundoscopic evaluation of the retina was normal for all subjects. Electrophysiological evaluation was not done and was noted as a limitation. Other limitations included lack of information on the type of phototherapy that was used, small sample of infants with phototherapy, and inclusion of only low birthweight infants that did not account for gestational age or preterm infants with normal birthweights. These aspects may indicate a continuing gap in knowledge related to ophthalmologic disorders as a potential adverse event due to neonatal phototherapy.

Neurological Disorders and Hearing Loss

Auditory neuropathy spectrum disorder (ANSD) is a form of hearing loss in which some measures of cochlear function are relatively normal, yet the transmission of neural signals from the cochlea is impaired. Riboflavin depletion from bilirubin degradation and/or phototherapy has been identified as one potential pathway to ANSD by James, et al.³⁴ Use of neonatal phototherapy for hyperbilirubinemia appears to increase neurological adverse effects such as seizure disorders,^{5,27} infantile cerebral palsy,⁵ developmental delay,⁵ and hearing loss outcomes.^{5,10} Specific neurological outcomes in the study by Erdeve, et al. may be related to bilirubin encephalopathy versus phototherapy due to inclusion of these babies in the study.¹⁰ It appears from these studies that there is evidence that phototherapy might lead to adverse neurological outcomes. However, it is not entirely clear whether this is the result of hyperbilirubinemia, phototherapy, or a combination of both. In the one study by Can, et al. that found no significant difference in adverse effects of phototherapy between late preterm infants treated with phototherapy for severe and non-severe hyperbilirubinemia, the bilirubin levels for each

group was also accounted for and therefore, hyperbilirubinemia also did not appear to be a causative factor.¹¹

Nevis and Rashes

Inclusion criteria for this systematic review and meta-analysis by Lai included cohort, case-control, or cross-sectional study designs.²⁸ The age range varied in the five studies included. In one study the age range was 8-9 years and in another the age for all participants was 8 years. The other three studies had larger age ranges (2-7; 3-30 and ≥ 56). In consideration of the differences, the study designs and inclusion of older subjects helped to strengthen the results of the meta-analysis demonstrating no significant difference between infants that received phototherapy and those that did not in development of melanocytic nevi.²⁸

Electrolytes

Of the three studies that explored adverse effects of neonatal phototherapy on electrolytes in the infant, there were significant decreases in neonatal magnesium levels^{30,31} and in sodium levels.^{30,32} Two of the studies did not find evidence of significant changes in potassium levels.^{30,32} In the study by Eghbalian, et al. where phototherapy dose dependent changes were found for serum total magnesium levels, one aspect to consider in determination of phototherapy versus hyperbilirubinemia as the causation, is that infants with higher bilirubin levels generally are prescribed double phototherapy, while infants without risk factors and with lower levels needing phototherapy may be prescribed single treatment.³¹ Although the study results may provide information on an adverse effect of decreased magnesium levels with higher levels of neonatal phototherapy, it is important to consider the physiologic aspects of magnesium in the newborn.

According to Sapkota, N-methyl-D-aspartate (NMDA) is a glutamate receptor that has an important role in synaptic physiological functions and memory.³⁵ Overactivation of the glutamate receptor, degradation of its ion channel

complex in the membrane, and ultimately exertion of its neurotoxic effects may be due to bilirubin binding to the neural synapses of NMDA. Magnesium protects the nervous system against hypoxia and neurotoxic effects of bilirubin. It appears to apply these protective effects by blocking the NMDA receptors. The effect of double phototherapy in significantly decreasing magnesium levels may decrease protective mechanisms against neurological effects of hyperbilirubinemia.³⁵ This appears to indicate a phototherapy dose dependent reaction with magnesium levels. Future studies may be indicated to provide magnesium and sodium supplementation for neonates undergoing intensive phototherapy to mitigate its adverse effect on specific electrolyte levels.

Implications for Practice

As phototherapy continues to be the primary treatment for neonatal hyperbilirubinemia and has no evidence-based alternative treatments, use of this modality should be based on current American Academy of Pediatrics guidelines. Infants undergoing phototherapy should be evaluated for known adverse reactions to maximize timely interventions as needed. Future research on maximizing hyperbilirubinemia treatment while minimizing adverse events includes exploring aspects of phototherapy dose and potential new treatment modalities for improved safety.

Conclusions

While the quality of studies vary, more rigorous research on adverse effects of neonatal phototherapy would benefit from careful selection of methods and reference standards, direct measures of each adverse outcome identified in adults and children, and prospective cohort studies linking early neonatal exposure with each adverse outcome outcomes throughout childhood and adolescence. Elucidating the effects of hyperbilirubinemia versus neonatal phototherapy on each potential adverse outcome will help to determine if new treatment methods for infants with hyperbilirubinemia need to be developed.

References

- Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a pre-discharge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103(1):6-14. doi:10.1542/peds.103.1.6
- Slaughter JL, Kemper AR, Newman TB. Technical Report: Diagnosis and Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics*. 2022;150(3):e2022058865. doi:10.1542/peds.2022-058865
- Cremer RJ, Perryman PW, Richards DH. Influence of light on the hyperbilirubinaemia of infants. *Lancet*. 1958;1(7030):1094-1097. doi:10.1016/s0140-6736(58)91849-x
- Woodgate P, Jardine LA. Neonatal jaundice: phototherapy. *BMJ Clin Evid*. 2015;2015:0319. Published 2015 May 22.
- Tsao PC, Yeh HL, Shiau YS, et al. Long-term neurodevelopmental outcomes of significant neonatal jaundice in Taiwan from 2000-2003: a nationwide, population-based cohort study. *Sci Rep*. 2020;10(1):11374. Published 2020 Jul 9. doi:10.1038/s41598-020-68186-w
- Auger N, Laverdière C, Ayoub A, Lo E, Luu TM. Neonatal phototherapy and future risk of childhood cancer. *Int J Cancer*. 2019;145(8):2061-2069. doi:10.1002/ijc.32158
- Jašprová J, Dal Ben M, Hurný D, et al. Neuro-inflammatory effects of photodegradative products of bilirubin. *Sci Rep*. 2018;8(1):7444. Published 2018 May 10. doi:10.1038/s41598-018-25684-2
- Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:10.7326/M18-0850
- Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-784. doi:10.7326/M14-2385
- Erdeve O, Okulu E, Olukman O, et al. The Turkish Neonatal Jaundice Online Registry: A national root cause analysis. *PLoS One*. 2018;13(2):e0193108. Published 2018 Feb 23. doi:10.1371/journal.pone.0193108
- Can E, Verim A, Başer E, İnan N. Auditory neuropathy in late preterm infants treated with phototherapy for hyperbilirubinemia. *Int J Audiol*. 2015;54(2):89-95. doi:10.3109/14992027.2014.938779
- Das RR, Naik SS. Neonatal hyperbilirubinemia and childhood allergic diseases: a systematic review [published correction appears in *Pediatr Allergy Immunol*. 2021 Jan;32(1):210]. *Pediatr Allergy Immunol*. 2015;26(1):2-11. doi:10.1111/pai.12281
- El-Sheikh MR, Ahmed AY, ELMashad AEM, Talaye II, El-Hawary EE. Eosinophil count and tumor necrosis factor α in response to phototherapy treatment of neonatal hyperbilirubinemia: a cross sectional study. *Ital J Pediatr*. 2022;48(1):103. Published 2022 Jun 20. doi:10.1186/s13052-022-01302-w
- Faulhaber FRS, Procianny RS, Silveira RC. Side Effects of Phototherapy on Neonates. *Am J Perinatol*. 2019;36(3):252-257. doi:10.1055/s-0038-1667379
- Beken S, Aydin B, Zenciroğğlu A, et al. The effects of phototherapy on eosinophil and eosinophilic cationic protein in newborns with hyperbilirubinemia. *Fetal Pediatr Pathol*. 2014;33(3):151-156. doi:10.3109/15513815.2014.883456
- Aydin B, Beken S, Zenciroğğlu A, Dilli D, Okumuş N. Blood eosinophil levels in newborns with severe indirect hyperbilirubinemia treated with phototherapy. *Iran J Pediatr*. 2014;24(3):267-272.
- Bhola K, Foster JP, Osborn DA. Chest shielding for prevention of a haemodynamically significant patent ductus arteriosus in preterm infants receiving phototherapy. *Cochrane Database Syst Rev*. 2015;2015(11):CD009816. Published 2015 Nov 3. doi:10.1002/14651858.CD009816.pub2
- Mannan J, Amin SB. Meta-Analysis of the Effect of Chest Shielding on Preventing Patent Ductus Arteriosus in Premature Infants. *Am J Perinatol*. 2017;34(4):359-363. doi:10.1055/s-0036-1592079
- Surmeli-Onay O, Yurdakok M, Karagoz T, et al. A new approach to an old hypothesis; phototherapy does not affect ductal patency via PGE2 and PGI2. *J Matern Fetal Neonatal Med*. 2015;28(1):16-22. doi:10.3109/14767058.2014.899575
- Hemati Z, Keikha M, Khoshhali M, Kelishadi R. Phototherapy and risk of childhood cancer: A systematic review and meta-analysis. *Journal*

- of *Neonatal Nursing*. 2022;28(4):219-228. doi:10.1016/j.jnn.2022.01.007
21. Digitale JC, Chang PW, Li SX, Kuzniewicz MW, Newman TB. The effect of hospital phototherapy on early breastmilk feeding. *Paediatr Perinat Epidemiol*. 2021;35(6):717-725. doi:10.1111/ppe.12794
 22. Sabzevari F, Sinaei R, Bahmanbijari B, Dehghan Krooki S, Dehghani A. Is neonatal phototherapy associated with a greater risk of childhood cancers?. *BMC Pediatr*. 2022;22(1):356. Published 2022 Jun 22. doi:10.1186/s12887-022-03412-0
 23. Wei CC, Chang CH, Lin CL, Chang SN, Li TC, Kao CH. Neonatal jaundice and increased risk of attention-deficit hyperactivity disorder: a population-based cohort study. *J Child Psychol Psychiatry*. 2015;56(4):460-467. doi:10.1111/jcpp.12303
 24. Hung TW, Tsai JD, Pan HH, Chen HJ, Liao PF, Sheu JN. Is Neonatal Hyperbilirubinemia Exposure Associated with a Risk of Autism Spectrum Disorder? A Nationwide Cohort Study. *Am J Perinatol*. 2021;38(12):1244-1253. doi:10.1055/s-0040-1708033
 25. Lozada LE, Nylund CM, Gorman GH, Hisle-Gorman E, Erdie-Lalena CR, Kuehn D. Association of Autism Spectrum Disorders with Neonatal Hyperbilirubinemia. *Glob Pediatr Health*. 2015;2:2333794X15596518. Published 2015 Jul 21. doi:10.1177/2333794X15596518
 26. Kara S, Yalniz-Akkaya Z, Yeniaras A, Örnek F, Bilge YD. Ocular findings on follow-up in children who received phototherapy for neonatal jaundice. *J Chin Med Assoc*. 2017;80(11):729-732. doi:10.1016/j.jcma.2017.08.003
 27. Newman TB, Wu YW, Kuzniewicz MW, Grimes BA, McCulloch CE. Childhood Seizures After Phototherapy. *Pediatrics*. 2018;142(4):e20180648. doi:10.1542/peds.2018-0648
 28. Lai YC, Yew YW. Neonatal Blue Light Phototherapy and Melanocytic Nevus Count in Children: A Systematic Review and Meta-Analysis of Observational Studies. *Pediatr Dermatol*. 2016;33(1):62-68. doi:10.1111/pde.12730
 29. Oláh J, Tóth-Molnár E, Kemény L, Csoma Z. Long-term hazards of neonatal blue-light phototherapy. *Br J Dermatol*. 2013;169(2):243-249. doi:10.1111/bjd.12335
 30. Khatib A, Ashour N, Shehata M. Effect of phototherapy on serum magnesium level in newborn with hyperbilirubinemia. *Menoufia Medical Journal*. 2021;34(3):1004-1008. doi:10.4103/mmj.mmj_250_20
 31. Eghbalian F, Shabani S, Faradmal J, Jenabi E. Effects of Phototherapy on the Serum Magnesium Level in Neonates with Indirect Hyperbilirubinemia: A Prospective Cohort Study. *Int J Pediatr*. 2022;2022:5439630. Published 2022 Mar 22. doi:10.1155/2022/5439630
 32. Chinnappa AL, Rudrappa S. Study of changes in serum sodium and potassium levels in term and preterm neonates following phototherapy. *Int J of Contemp Peds*. 2022;9;9; 793-798. doi: <https://dx.doi.org/10.18203/2349-3291.ijcp20222115>
 33. Yablon LA, Mauskop A. Magnesium in headache. In R. Vink & M. Nechifor (Eds.), *Magnesium in the Central Nervous System* [internet]. University of Adelaide Press. 2011. <https://www.ncbi.nlm.nih.gov/books/NBK507271/>.
 34. James AL, Chakraborty P, Tomlinson C, Harrison RV. Does riboflavin depletion cause auditory neuropathy spectrum disorder in at risk neonates?. *Int J Pediatr Otorhinolaryngol*. 2020;137:110238. doi:10.1016/j.ijporl.2020.110238
 35. Sapkota NK. Effect of phototherapy on serum bilirubin and ionized magnesium level in hyper-bilirubinemic neonates. *Innovare J Medical Sciences*. 2017;5;1;29-30.