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Updates on phototerapy in full-term and pre-term neonates with non-hemolytic jaundice

Atualizações sobre fototerapia em neonatos a termo e pré-termo com icterícia não-hemolítica

Actualizaciones sobre fototerapia en infantes a término y prematuros con ictericia no-hemolítica

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Corresponding Author:
Pedro Henrique A. de Oliveira Santos
Email: ppppedro52@gmail.com

Pedro Henrique Albuquerque de Oliveira Santos[1]
Bruna Tavares Oliveira[2]
Andrea Marques Vanderlei Fregadolli[3] Orcid Id: https://orcid.org/0000-0002-6496-8438

[1] Medical student, Federal University of Alagoas, Maceió, AL, Brasil.
[2] Medical student, University center CESMAC, Maceió, AL, Brasil.
[3] Medical school professor, Federal University of Alagoas, Maceió, AL, Brasil.

Abstract

Phototherapy is a low-invasive procedure used in the treatment of jaundice, a clinical manifestation resulted by an increase of total serum bilirubin concentration (TsB). It affects the majority of newborns (NB), especially the premature ones. To assembly the major benefits, consequences and updates about phototherapy treatment in non-hemolytic jaundiced full-term or late preterm (with gestational age ≥ 35 weeks) neonates. This is a systematic review that examines the literature with permutations of the following descriptors: jaundice; phototerapy; and newborn; considering Spanish, English and Portuguese languages and only publications ranging from 2015 to early 2020. Moreover, the boolean operator “AND” was used. The consulted databases were: SciELO, Lilacs, PubMED, MedLine, CAPES periodicals and WorldWildScience. Among the 314 articles founded, 36 were adequate for this study’s theme understanding. The phototherapy is a photocatalyst process able to convert bilirubin molecules into luminirubin, using artificial or solar light. This substance will be more easily excreted, in order to avoid neurotoxic damages. It is considered safe and efficient, even considering individual characteristics and risk factors such as age group, genetics and maternal profile. Thus, phototherapy is deservedly the gold standard in neonatal non-hemolytic jaundice treatment, nevertheless, it deserves wariness in the prescription and commencement, due to the possibility of broad-spectrum side effects. It is also necessary adequate management and infrastructure.

Descriptors: Jaundice; Newborn; Phototerapy; Term; Pre-term.

Resumo

A fototerapia é um procedimento pouco invasivo utilizado no tratamento da icterícia, uma manifestação clínica decorrente do aumento da concentração de bilirrubina sérica total (BST). Acomete a maior parte dos recém-nascidos (RN), especialmente os prematuros. Elencar os principais benefícios, consequências, e atualizações acerca da fototerapia para tratamento de neonatos com icterícia não-hemolítica nascidos a termo ou pré-termo tardio (com idade gestacional ≥ 35 semanas). Trata-se de uma revisão sistemática que vasculha a literatura com permutações dos seguintes descritores: jaundice; phototerapy; e newborn; considerando os idiomas português, inglês e espanhol, e a data das publicações a partir de 2015. Além disso, fez-se uso do operador booleano AND. As bases de dados consultadas foram: SciELO, Lilacs, PubMED, MedLine, periódicos CAPES e WorldWildScience. Dos 314 artigos encontrados, 36 se adequaram ao entendimento do tema abordado. A fototerapia é um processo fotocatalisador capaz de converter moléculas de bilirrubina em luminirrubina a partir da luz solar ou artificial. Essa nova substância será excretada com maior facilidade, de forma a evitar danos neurotóxicos. É considerada segura e eficiente, mesmo levando em conta características individuais e fatores de risco como prematuridade, genética, e perfil materno. Portanto, a fototerapia é merecidamente o padrão ouro para o tratamento da icterícia neonatal não-hemolítica, mas exige cautela em sua prescrição e aplicação, visto que há a possibilidade de efeitos colaterais de amplo espectro. Também se faz necessário infraestrutura e manejo adequado.

Descritores: Icterícia; Recém-nascidos; Fototerapia; A termo; Pré-termo.

Resumen

La fototerapia es un procedimiento mínimamente invasivo utilizado para tratar la ictericia. Una manifestación clínica resultante del aumento de la concentración de bilirrubina sérica total (TsB). Afecta a la mayoría de los recién nacidos (NB), especialmente a los bebés prematuros. Describir los principales beneficios, consecuencias y actualizaciones sobre la fototerapia para el tratamiento de neonatos con ictericia no hemolítica nacidos a término o prematuros tardíos (con edad gestacional ≥ 35 semanas). Se trata de una revisión sistemática que busca en la literatura permutaciones de los siguientes descriptores: jaundice; phototerapy; y newborn; considerando los idiomas portugués, inglés y español, y la fecha de las publicaciones desde 2015. Además, se utilizó el operador booleano AND. Las bases de datos consultadas fueron: revistas SciELO, Lilacs, PubMED, MedLine, CAPES periódicos y WorldWildScience. De los 314 artículos encontrados, 36 eran adecuados a la comprensión del tema abordado. La fototerapia es un proceso de fotocatalizador capaz de convertir moléculas de bilirrubina en luminirrubina de la luz solar o la luz artificial. Esta nueva sustancia se excretará más fácilmente para evitar daños neurotóxicos. Se considera seguro y eficiente, incluso teniendo en cuenta las características individuales y los factores de riesgo como la prematuridad, la genética y el perfil materno. Por lo tanto, la fototerapia es merecidamente el estándar de oro para el tratamiento de la ictericia neonatal no hemolítica, pero requiere precaución en su prescripción y aplicación, ya que existe la posibilidad de efectos secundarios de amplio espectro. También se necesita infraestructura y gestión adecuadas.

Descriptores: Ictericia; Recién nacidos; Fototerapia; Término; Pretérmino.

INTRODUCTION

Jaundice, according to DeCs (Health Science Descriptors) (1), is hyperbilirubinemia's clinical manifestation, characterized and diagnosed by a high concentration of non-conjugated serum bilirubin, which persists at least 24 hours. It is the most common newborn (NB) disease, being present in 60% of full-term neonates (gestational age (GA) ≥ 37 weeks) and in 80% of late-premature ones (in this study we considerate as "late" 35≤ gestational age <37). It is self-limited and usually disappears after the first month (2,3).

It has a greater incidence in masculine children; with Asian ethnicity; with another congenital abnormality; premature or post-mature ones; or who presented extremely low birth weight; in addition of maternal risk factors such as: age group, smoke habit, record of fertility-related diseases, diabetes and financial fragility (4–6). This disorder can be classified as physiological or pathological, the latter including hemolytic and non-hemolytic diseases. The pathological ones are habitually more severe and precocious (6).

Jaundice does not always need a therapy and is notorious for, among other symptoms, presenting a characteristically yellowish tone on the skin and in other parts of the patient (7). Without proper medical intervention in the most serious cases, it can result in irreversible damages to the infant's nervous system. It is worthy highlighting beforehand that, according to recent literatures, these sequelae do not manifest exclusively and obligatory as a cognitive reduction, leading to other conditions such as dystonia, for example (8).

The Golden Standard used against non-hemolytic jaundice is phototherapy, exclusively administered or combined with other interventions. It is an effective; safe; and relatively inexpensive procedure, that nevertheless requires prescription; infrastructure; and proper handling, like any other procedures, and not being exempt of side effects as well (9). A study estimates that 7,6% of all babies receive this treatment in the initial days of life (10).

The phototherapy action mechanism consists in transforming non-conjugated bilirubin molecules – toxic and insoluble- in isomers excreted in urine and gastrointestinal tract without requiring submission to hepatic conjugation. The principal ones are E,Z-luminirubin and E,E-luminirubin, produced throughout a process of photoisomerization, which is directly influenced by the wavelength of the light source used, with blue 460 nm or 476 nm being the most common (3,7,11).

As a systematic review, the objective of this study is to compile holistically what is known about the phototherapy management in the treatment of non-hemolytic jaundice in newborns with gestational age later than 35 weeks, so that the researcher optimizes his/her search for information. It is noteworthy that some generalizations can be made, with caution, to the other subgroup of the disease and to other populations of infants, requiring additional clinical and literary acquaintance from the reader's knowledge.

The papers selection criteria and the motivating question were defined using the PICO system: Population (full-term neonates and late preterm, which means, gestational age later than 35 weeks, with any birth weight); Intervention (usufruct of phototherapy in the jaundice treatment); Comparison (jaundiced babies that were not treated with phototherapy) and Outcomes (improvement in jaundice control).

METODOLOGY

The database research took place from March to April 2020, merging the Boolean operator AND with descriptors consulted in MeSH and DeCs. The following databases were addressed (Table 1): PubMED, Medline, CAPES Periodicals, WorldWideScience, SciElo e Lilacs. Filters of species (restricted to human only), relevance, and language (English, Portuguese and Spanish) were used when available, also only articles that were published since 2015 were considered, with the exception of the guideline of the American Academy of Pediatrics (AAP, 2004), and the collection of Stanford University, which were included to engender some specific comparisons.

Table 1 – Search Strings used in each database.

Search String	Databases
jaundice AND phototerapy	PubMED
	Medline
	CAPES Periodicals
	WorldWideScience
jaundice AND newborn	Scielo
	Lilacs

Despite not using types of study's filters, case reports were disregarded during the survey, and articles with broader aims than this project were not excluded. A pre-selection was executed judging the titles and abstracts of the documents rescued in the previous process, which were handled with the assistance of the software Mendeley, that has an organizational function. In the course of the process, the authors independently analyzed each paper, and disagreements about inclusion of works were resolved with consensus meetings and with consultation to the work's orientation.

Subsequently, for the discussion, the results contained in the abstract of each article were compiled, translated to English if necessary, and inserted in the online word counter of the developer Zygomatic, which works by indicating the weight of a word in this compilation of the abstracts, based on their frequency in the text. This list contributed to the construction of some discursive categories, in order to establish a logical and hierarchical sequence of the debate.

The following criteria of exclusion were adopted: Words that are part of the title or motivating question of this project, including synonyms, as this recurrence is evident and with little categorizing essence; adjectives of any nature, except when the context of use is easily deduced; and verbs or generic nouns, for instance: study (s), article (s), finding, discovery, analyzed, indicated, difference, etc. Ultimately, all terms with a weight equal to or above 4 were considered.

RESULTS

It is delicate to establish updates for the ideal use of phototherapy in the treatment of jaundice, insofar as several variables have not yet been elucidated, such as the

complete pathophysiology of nerve damage by bilirubin, and the optical properties of the skin and blood of each newborn (NB), leaving aside the kinetics and dynamics of all bilirubin photoisomers.

Moreover, there is a lack of uniformity on the approach of various technologies available in the market and their influence on the results obtained, and also a certain lack of concern regarding the availability of information variables of value, such as the exclusive breastfeeding rate of the groups under study, and the frequency of measurement of bilirubin concentration and constancy of phototherapy devices, which hinder to compare results and may generate bias. These data are at least partially absent in almost all scientific productions on the matter.

The results of the searches in the bibliographic bases cited on the Methodology of this work were summarized in Table 2. After applying the filters, the number of papers decreased considerably, and these were selected based on the criteria and processes described, the duplicates were eliminated unconsciously by the Mendeley software. A single article was left unselected due to difficulties in acquiring the right to read, and another 12 articles were excluded after a complete analysis for bringing redundant information or for revealing itself unqualified to the eligibility requirements.

Table 2 – Quantity of papers selected

Search string	Databases	Total publications without filters	Total publications after applying all filters	Texts used after analysis
jaundice AND phototerapy	PubMED	1930	281	35
	Medline	1	1	1
	CAPES Periodicals	5	3	0
	WorldWideScience	9	8	0
jaundice AND newborn	Scielo	96	21	7
	Lilacs	361	36	12
Total	-	-	-	49

DISCUSSION

Phototherapy is a jaundice treatment technique that uses photons to isomerize the bilirubin molecules in subcutaneous tissues, converting them into isomers such as luminirubin, facilitating their excretion through the urinary and gastrointestinal tracts, in addition to hindering their resorption. The baby must be undressed in an incubator, with eye and genital protection and must have frequent inspection of hygiene and the correct position of these protections by the responsible nurses (12).

Bilirubin Levels Measurement

The terms Mean; Serum; Bilirubin; Level; The acronym TsB (Total Serum Bilirubin); and the measurement unit mg/dl dominated the ranking, which highlights the relevance of the discussion on the methods and frequency of measurement of serum bilirubin in the texts. The bases of the American Academy of Pediatrics (AAP) (13) indicates that the measurement must be evoked with the diagnostic experience of the health professionals present, even though this opens up space for failures in this type of conduct. The most common methods are: traditional serum; transcutaneous; diazo-reagent; and exhaled CO.

The latter assumes the equimolarity between bilirubin (or heme, in a more regressive analysis) and the production of CO gas. The diazo reagent analysis is based on the absorbance of the product of its reaction with bilirubin, azobilirubin. On the transcutaneous measurement, more detailed research has been done in recent decades about its large-scale viability, since it is sparser and more frugal for the health institutions' exchequer. They point to satisfactory acceptability in healthy babies, but that can be questioned with prematurity, low body weight of the newborn, and some other factors. Due to the amount of material produced in recent years, this concern suggests separate systematic reviews (14–16).

The Total Level of Serum Bilirubin (TsB) indicated for the start of treatment is a dilemma that depends on factors such as gestational age (GA); newborn (NB) weight; hours or days of postnatal life; and cause of jaundice. Furthermore, it is necessary to evaluate the rate and the binding capacity of serum albumin, which indicates the child's susceptibility to bilirubin damage (17). Some guidelines from low-income countries outline the initiation of the procedure at TsB levels as low as 12.5 mg / dL, however, the American Academy of Pediatrics (AAP) uses the value of 20 mg / dL (8).

In addition, the most relevant guidelines establish that the frequency of measurement of total serum bilirubin levels should be guided according to the clinical experience of the professionals, who should be aware of the risk of lack of allegiance of this data, and that one should seek to avoid excessive blood sampling, for there is evidence on this inducing losses such as: increased intracranial pressure; heart rate; decreased oxygen saturation; and behavioral consequences, such as crying and squinting. Furthermore, long-term consequences were found, like prolonged response to altered pain, and potential epigenetic effects (18).

It is prudent to state that prophylactic phototherapy should not be prescribed, even in spite of the AAP discussing an "optional" threshold of phototherapy at home (19), and that, at very high bilirubin levels, the patient may require exchange transfusions, as phototherapy becomes insufficient in more austere conditions, while the risks of brain damage escalate unacceptably. Although there is no consensus among the international guidelines, the most important ones advise to suspend treatment as soon as the baby reaches adequate

levels of TsB, 13 to 14 mg/dL according to the AAP, or any value below the threshold of initiation (20 mg/dL). dL) according to other recommendations (6,9,18,20).

As mentioned above, AAP establishes the possibility of performing less canonical interventions in children with lower serum bilirubin levels and, therefore, less risk of nerve damage. In this context, homemade phototherapy may be requested by some puerperal mothers. According to Chang and Waite, the home modality results in less mitigation of blood bilirubin by treatment time. That means that researches with larger scope should be done as soon as possible to ensure the feasibility of the guideline.

Therefore, the measurement method is a much more ponderous than absolute praxis: the method and the frequency itself depends on factors like the patient's profile, the severity of the condition, and especially the physician's clinical experience, in addition to more casual ones such as availability of nurses, and hospital infrastructure. The health professional should also take into account the advice of current guidelines to organize his practice.

Light Source

With weights between 4 and 10, the terms light; irradiance; μW / cm2 / nm; pad; and LED also boasts popularity in the table. In the light of the American Aassociation of Pediatrics, it is recommended to use LED or fiber optic lamps, in the blue spectrum and with adequate distance from the neonate, so that a radiometer should be used to check the constant intensity between 10 to 30 μW/cm2/nm from the center of the light impression. Photons act as an active principle in the conversion of toxic bilirubin molecules into photoisomers that can be excreted more easily.

Before starting the procedure, one should check and follow the manufacturer's instruction of the device used, if available. Generally speaking: a distance of 10 to 50 cm is maintained between the neonate and the light source, which will have an average intensity, measured at the center of the light cone impression, varying from 10 μW/cm2/nm for the conventional procedure up to 30 μW/cm2/nm for intensive treatment, in the range of blue 460 nm or blue-green 476 nm, over the largest possible body area, as well as an increase in water intake from 10 to 15 mL/kg/d (9,20,21). The decision for an intensive or conventional treatment will depend on the individual risk of each patient.

Furthermore, the continuous or non-continuous administration of phototherapy is also a complex and debatable topic, since the literature indicates that this decision generates different isomeric balances. For now, the intermittence shows similar results to the continuity with respect to total irradiation per time of exposure, in addition to allowing intervals for rest, breastfeeding, and skin-to-skin contact of the mother-child binomial. This is particularly encouraging for researchers in low-cost technologies that aim to use filtered sunlight as a phototherapy device, which obviously subjects the treatment to the duration of the day cycle (8).

However, depending on the case, this may be too high a price to pay, given the longer delay in converting the same amount of bilirubin compared to the continuous treatment, which runs counter to the logical decision to mitigate jaundice as soon as possible. This is compounded by the fact that it is not known whether bilirubin photoisomers can also cause neural damage or not. Also, some studies indicate that duration, not intensity, is the determining factor of the aggravation of side effects (22).

As for lamps, the main ones used are: halogens, fluorescents, optical fiber, and high and low power LEDs. The later three are more suitable by producing less heat, and providing a more constant and directed spectrum for conversion of bilirubin (9,23). A study with a small population of preterm indian babies also indicated less promotion of possible oxidative stress by LED (24). If available, dual light sources and reflective materials around the cradle also appear to increase the effectiveness of the procedure (25,26). Asides that, the most recommended lamps today are the blue monochromatic ones, with length between 460 to 490 nm and peak close to 475 nm (17). The risks of damage resulting from exposure to this type of luminescence, in the case of LED, both for the healthcare teams and for the other individuals who are in the same environment as the incubator appear to be low (12).

However, the effectiveness of blue has been subjected to tests, as some research has shown greater effectiveness of green 510 nm when a non-toxic photocatalyst is added to the infant's blood (27,28). In addition, another study demonstrated that the spectrum of the 497 nm turquoise light has similar efficacy, but generates different photoisomeric balances, which have a still mysterious clinical significance (11). To this day, blue continues to be the most used spectrum in phototherapy, but the recent research has questioned its absolute effectiveness, which may better establish a sort of optionality of the color used.

The discussion of light in phototherapy is, ironically, one of the topics with most lacunae of the theme. Several gaps were presented during this discussion and, finally, greater efforts are needed to unveil the biokinetics and biodynamics of all bilirubin photoisomers, and also to study the optical properties of newborn skin and serum. Further clarification and accessibility of today's technologies such as fiber optic blankets and serum photocatalysts is also eagerly awaited.

Risks

With 8 weights, the word Risk can refer to the side effects related to the administration of phototherapy. The Stanford University's publisher mentions in its FAQ (Frequently Asked Questions) (29) that the main side effects are some dermatological manifestations, and the bronze baby syndrome, marked by a tan discoloration in the infant's fluids and surfaces. It also points out the risk of phototherapy for the responsible health team as low.

It is an appropriate procedure for most neonates, as differences in the concentration of melanocytes or in the patient's gestational age - this last one influencing in the vascularity and thickness of the skin - have little impact on its final effectiveness. However, one data with direct influence on the efficacy of phototherapy is hematocrit, due to the competition between bilirubin and hemoglobin for the absorption of light over a wide spectrum, which is one of the

explanations for the short range of light frequencies really favorable to optimal absorption by bilirubin (17).

However, phototherapy can bring harm to the newborn, and that is the reason for the contraindication to prophylactic phototherapy. Among the short-term ones, there are: anti-inflammatory effects (increase in IL2, IL6, IL10 and decrease in IL1-beta); thermal, water and electrolyte imbalances; skin lesions; bronze baby syndrome; paralytic ileum; patent ductus arteriosus; eye effects; circadian cycle disorders; and diarrhea. Regarding long-term ones, allergic diseases stand out. Other more ambiguous effects in the literature are: nevi; DNA and immune system damage, seizures, epilepsy, oxidative stress, and cancer. The severity and incidence of these vary widely with the severity of jaundice, age, weight, and even sex of the newborn (5,9,30–36).

Another small-scale Chinese study pointed out changes in glucose and cholesterol metabolism in children after phototherapy. Although this does not necessarily cause disturbances, once again it is necessary to focus on caution when prescribing and performing the procedure (3). Another one with term and normal weight babies under phototherapy with fluorescent lamps indicated subtle changes in the cardiac cycle and in the parasympathetic system, which, like most of the aforementioned side-effects, is also open to further investigation (37).

Among the indirect side effects, physical and psychological abuse to which the puerperal mother is subjected is worth mentioning, especially when the communication channel with health agents is deficient. Phototherapy may provoke a tension in the maternal instincts of baby protection, which is especially worrying when there is a possibility of the mother refusing to follow the treatment or beg for less distressing alternatives, such as drug intervention, that are not ideal (21). Thus, it is a fundamental role of the health team to propose humanized and informative care to the mother-child binomial, reinforcing psychological care (2).

On the present, prototypes of blankets adapted with fiber-optic and/or LED technology has appeared on the market, aiming to maintain the same haptic properties of a traditional blanket to be used, exclusively or along with a lamp under the head, as a weapon against jaundice. They allow greater comfort and respect for maternal-child bonds during the whole treatment, but they seem to generate considerable heat, which makes frequent temperature measurement mandatory (38). It is the role of the administrative sectors of public and private health, therefore, to overcome the rarity of this technology and at the same time make its ideal environment available for use in the national intensive care units (21).

Upon these theses, the large amount of scientific research produced over this discussion made appear a miscellaneous of collateral symptoms correlated to treatment with phototherapy, which may sound dantesque to an ear unaccustomed to scientific scrutiny. However, the procedure continues to see its benefits far outweigh the damage, so much so that it has very few explicit contraindications in the papers of relevant entities.

NICUs

Another possibly referable term is NICU, that corresponds to Neonatal Intensive Care Unit. Still according with the literature of Stanford School of Medicine, these units are specific areas of nursing centers that are equipped with more refined technology and labor, and that not necessarily covers only serious cases, but the ones urging some type of special intervention.

The studies by Mreihil et al., Borden et al., And Slusher & Vaucher dealt with the methodological diversity in the application of phototherapy with concern to distance, screening, and intensity in Neonatal Intensive Care Units on the following regions: Norway, United States, and countries of low income, respectively. The assessment indicated large discrepancies in all levels of regional differentiation, which have a varied impact on the success rate of the analyzed place. These studies should serve as a warning for Brazil, which has great regional inequalities as a pustular spot.

Despite discrepancies being expected as a reflection of the obvious regional idiosyncrasies related to culture; socioeconomics and politics; there is a call for more uniformity and allegiance of the procedure to the available guidelines, which in turn can also contribute to the erosion of this problem by making frequent and unison updates, that must fill indications too vague or that suggest excessive discretion by the part of the medical team, in order to maintain a balance between generalizable recommendations and provenances in very specific contexts.

CONCLUSION

Due to its effectiveness and safety, in contrast to the lack of evidence and/or risks of other techniques such as blood transfusion or metalloporphyrin injection, phototherapy is very likely to remain the gold standard for treating non-hemolytic neonatal jaundice. However, it is still necessary to assess each case individually. The technical and technological updates mentioned throughout this paper opposes the collateral damage of the procedure, in order to allow it further improvements.

COLLABORATION

The creative conception of this work arose from dialogues between authors 1 and 3, followed by an initial mapping of the literature and definition of the scope, made jointly by authors 1 and 2. The first author participated in the creative formulation, selection of papers, data interpretation, scientific writing, translation and, finally, correspondence to publication. The second author participated in the selection of articles, data interpretation, scientific writing, and translation. The third author, in short, served as a guide to the progress, acting, for instance, as a mediator of conflicts like the inclusion of references without consensus, the definition of categories, and the organization of paragraphs.

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