**Turn off the lights and the oxygen, when not needed:**

**phototherapy and oxidative stress in the neonate**

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In this issue of the Journal of Pediatrics, Aycicek and Erel1 publish an article that highlights the potentially serious harmful effects of “light therapy” on newborns’ defenses against oxidative stress. This is the first report showing a correlation between serum oxidative and antioxidant parameters in full-term newborns treated with phototherapy. It is surprising how little is known about the damage caused by phototherapy and its probable mechanisms, and that so little attention has been paid to the possible adverse effects of such a frequently applied therapy. Who could have imagined that exposing healthy full-term newborns to just 48 hours of phototherapy soon after birth could cause metabolic disturbances in their underdeveloped and still poorly functioning defenses against oxidative stress? What the authors describe emphasizes my motto regarding oxygen therapy and newborn health risks:

"More important than what we see is what we don't see." After the light shed by this article, we

are left to ask: What does light do that leaves us in the dark? Based on the findings of these authors, it appears that phototherapy causes oxidation in full-term babies. In that case, what happens to those premature newborns who are placed under the light "just in case" and also receive much more oxygen than necessary?

What a potentially bad combination: a therapy that reduces antioxidants and another that

increases oxidants! Unfortunately, most healthcare professionals administer both therapies to newborns, either together or separately, without any proven need and without any known benefit. Causing hyperoxia in a newborn while simultaneously reducing their immune system.

What potential for damage from oxidative stress! The two therapies together can aggravate DNA damage, cause brain, eye, and lung damage, and perhaps even childhood cancer.

**Oxidative Stress in Newborns**

Increased oxidative stress is dangerous. This study should clarify that, in full-term newborns, a

short exposure to phototherapy in the first week of life for approximately 48 hours reduces serum concentrations of vitamin C and uric acid and increases total oxidative status (TOS),

lipid hydroperoxide levels, and the oxidative stress index (OSI). These new findings may be associated with possible serious and long-term clinical consequences, even lifelong consequences, as other studies have shown.

Furthermore, a recent study conducted with 90 full-term newborns, also in Türkiye, shows that neonatal hyperbilirubinemia is related to high blood pressure levels. significantly lower levels of oxidants and higher levels of antioxidant enzyme activity (superoxide dismutase, catalase, and glutathione peroxidase), concluding that neonatal hyperbilirubinemia is associated with lower oxidative stress.

I wonder if the fundamental reason we all have physiological neonatal hyperbilirubinemia

is that we develop an innate defense mechanism during our transition to extrauterine life.

Oxidative stress can affect the entire body. We recently reviewed some morbidities related to

inadequate neonatal oxygenation.

Adequate SpO2 monitoring with SET technology (Masimo®) prevents hyperoxia and reduces morbidity.

However, we cannot measure oxidation caused by phototherapy in clinical practice.

We still don't know for sure whether phototherapy administered during the first 2-3 weeks of life is toxic or not for newborns with antioxidative mechanisms and underdeveloped cells. However, I wouldn't be surprised if it were demonstrated in the future that oxidation induced by phototherapy in newborns can cause DNA damage and alter gene expression, just as

excess oxygen does. It's true that numerous other possible consequences of oxidation are still unknown, such as programming growth and development and disease processes later in life.

Once total antioxidant capacity is reduced and/or EOT and IEO are increased, the disorder can last for a long time before being completely resolved, unless we eat dark chocolate and drink (quality) red wine. But we can't give these to babies, "because it's dangerous." However, the more we learn about oxygen, phototherapy, and oxidative stress, we may discover that

dark chocolate and red wine are less toxic than oxygen therapy and phototherapy, two therapies sometimes which we unfortunately subject babies to all too often and often unnecessarily.

**Phototherapy**

About 80% of premature newborns develop hyperbilirubinemia, which is typically treated with phototherapy, used for decades to prevent bilirubin encephalopathy and kernicterus. The main effect is the conversion of the pigment into more polarized, water-soluble isomers, which can be easily eliminated without conjugation in the liver. This, along with the photooxidation of

bilirubin, decreases the total concentration of bilirubin in the body and reduces plasma levels. Short-term side effects are generally not serious and include rashes, abdominal distension, mild hemolysis, mild thrombocytopenia, and fluid loss due to impaired absorption of water, sodium chloride, and potassium. Radiation with wavelengths in the 480 to 500 nm range is very effective; but above approximately 550 nm it is useless. The dose of phototherapy is determined by the wavelength of the light, its intensity (irradiation; suggested by some as > 15 μW/cm2

/nm), the distance between the light and the newborn and the exposed body area. In the study by Aucicek & Erel1, the newborn was placed naked under six fluorescent lamps with luminosity of 12–16 μW/cm2/nm at a distance of 40 cm. Phototherapy was continuous for 48 hours. It can be inferred that the greater the irradiation and the longer its duration, the worse the impact on the EOI reported by the authors.

In addition to the illuminating findings of this article, other related concerns have been reported in the last 2years. Phototherapy is associated with early changes in growth plate structure and oxidative stress-induced growth plate damage in rats newborns6, as well as mutagenic and gametocidal side effects on rat testes, with a decrease in the number of spermatogonia per seminiferous tubule, in- Tubular fertilization index and Sertoli cell index, which are the most reliable methods for assessing future fertility potential. 7

In a well-designed controlled study with 61 newborns, using real-time reverse transcriptase-polymerase chain reaction, blue light phototherapy had an effect on the expression of circadian genes in peripheral blood mononuclear cells and on plasma melatonin levels. 8 A phototherapy-mediated syndrome of inappropriate antidiuretic hormone secretion9 (SIADH) has been described, revealing an acute increase in serotonergic transmission due to intense illumination, suggesting that phototherapy could be the main environmental predisposing factor for iatrogenic neonatal SIADH syndrome. 9

Finally, intensive neonatal phototherapy is a strong risk factor for the development of nevi in ​​childhood. The high incidence of nevi is a recognized risk. of melanoma development, leading the authors to suggest that children exposed to phototherapy should undergo preventive dermatological measures and surveillance against the development of melanoma. 10

Other possible changes have been previously described, but we do not see them in daily neonatal clinical practice. For example, children treated with phototherapy have a higher risk of myeloid leukemia(OR = 7.5; 95% CI 1.8-31.9)11, increased production of

nitric oxide, a vasodilator involved in immune defense mechanisms, cytotoxicity, and neurotransmission. 12They also present alterations in cytokine production,with a 70% increase in IL-2 secretion and a 56% increase in IL-10 production, and concomitantly, a 43% reduction

in spontaneous IL-1beta secretion. 13 Furthermore, phototherapy affects cardiorespiratory activity during the active phase of sleep14, cardiac output, mean cerebral blood flow velocity, and renal vascular resistance15, as well as altering urinary calcium excretion16. In cultured cells, blue light phototherapy produced genotoxic effects. cos, inducing single-strand breaks in DNA, and the blue and green lights led to the formation of long-lasting toxic photoproducts. It remains to be seen whether the genotoxic effect observed in this study can occur in vivo.

There are no controlled, prospective, blinded trials that indicate that any of the above-mentioned effects occurs significantly more frequently in newborns "under the light" compared to those "left in the dark." On the other hand, the findings cited are evident and based on facts and cannot be ignored by conscientious physicians who wish to avoid causing some rare harm to a newborn. Absence of "evidence" (i.e., no randomized study shows that the problem exists) is not the same as "evidence of absence."

**Use of phototherapy in jaundiced newborns**

Phototherapy for hyperbilirubinemia is an effective way to therapy. On the other hand, according to a recent study, many pediatric practices are associated with an initial treatment

with phototherapy with parameters lower than those recommended by the American Academy of Pediatrics (AAP)18.

Even in Aycicek's study, it is possible that some of the full-term newborns undergoing phototherapy did not even need it (i.e., bilirubin > 13 mg/dL at 7 days of life). Furthermore, despite the long list of harmful effects of oxidative stress, we still use oxygen therapy unnecessarily. Unfortunately, phototherapy, like oxygen therapy, is used by neonatologists "just in case." *There are very few long-term follow-up studies of newborns treated with phototherapy.* Therefore, the possibility of detecting serious, albeit rare, side effects in future clinical studies related to findings published in this issue of the Jornal de Pediatria and in other studies cited above. Based on these findings, we recommend avoiding "prophylactic phototherapy," to prevent too many newborns from being irradiated in the neonatal intensive care unit and to continue treating only at-risk newborns, based on well-defined curves and serum values. From the findings of this study, it is clear that if we refrain from using phototherapy when it is not absolutely necessary, we can avoid harmful effects in newborns.

This is not the same as saying that we will abandon the use of phototherapy in cases where it is clearly indicated to prevent serious problems, avoiding repeating the frequent errors that have plagued neonatal treatment in the past and present. This means that we should not now create an idea of ​​"hyperbilirubinemia tolerance."

I am in no way suggesting leaving a newborn with hyperbilirubinemia untreated because of concerns about oxidative stress. The emphasis here is not to apply phototherapy unnecessarily "just in case," and not to prolong the use of light for another day "just in case." It is known that many healthcare professionals seek "quick fixes." This, coupled with the "extremist" attitudes of neonatologists, who oscillate from one extreme to the other without a balance based on scientific and clinical knowledge, leads to serious problems. Having issued these warnings, we must change our paradigm regarding phototherapy and view it as just another neonatal drug, and a very potent one at that, according to the findings reported in this article. We must also remember that no medication produces only the effect for which it was prescribed, but that it always affects other organs and functions. Anyone prescribing this drug should not do so "just as a precaution" or seek a rapid resolution of normally elevated bilirubin levels, but should take into account the findings of this study and carefully analyze each individual case, each newborn, in turn, to determine the actual likelihood or risk of bilirubin encephalopathy or kernicterus. rus, diseases that can be prevented and should always be avoided by prescribing this drug, and the possible long-lasting risks of unnecessary application of light.

**Abstract**

As conscientious clinicians, we know that, more often than not, generalizations and the widespread implementation of proposed solutions are part of the problem. Journal articles published in the last decade more often report adverse effects than real advances. Pascal wrote that "knowledge is like a sphere: the larger it becomes, the greater its contact with the unknown." In a Cartesian way, the study by Aycicek and Erel1 reminds us that the more we study, the more We become aware of our own ignorance. The study also helps me understand that what I know may be of much less importance than what I don't know. Other authors3-17 report cardiorespiratory and blood flow changes, effects on the endocrine and immune systems, damage to bone growth plates, development of nevi, mutagenic and gametocidal side effects, possible genotoxic effects with alterations in DNA and genes, aging, and myeloid leukemia and

childhood cancer. Based on this and the possible serious harm from too much oxygen3

, we should all turn out the lights and breathe deeply in the dark. We should seriously consider abandoning the clinical practice of subjecting newborns to unnecessary phototherapy and oxygen therapy until we know all the serious and possible consequences this entails in the short and long term. Let's work together in neonatology to May the obscure view of our therapeutic abilities described by François-Marie Arouet (Voltaire) in the mid-eighteenth century, that "doctors are men who prescribe medicines they know little about, to cure diseases they know even less about, for human beings about whom they know nothing," no longer be true in the future.

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