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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 Jornal de Pediatria, Aycicek & Erel[1] publish an *illuminating* article on the potentially serious detrimental effects of "therapy with light" on neonatal defenses against oxidant stress. This is the first report showing an association between serum oxidant/antioxidant parameters in phototherapy-treated term infants. It is amazing, indeed, that little is known about the potential damage of phototherapy and its possible mechanisms and that so little attention has been paid to possible adverse effects of such a commonly used therapy. Who would have imagined that only 48 hours of exposure to phototherapy soon after birth in full term healthy neonates may lead to metabolic derangement of the already poorly functioning and underdeveloped neonatal defenses against oxidant stress? What the authors describe emphasizes my motto in relation to oxygenation and neonatal health hazards: "More important than what we see is what we do not see." Through the *illumination* of this manuscript, we must now wonder: What is the light doing that leaves us in the darkness? Based on these authors' findings, it seems that phototherapy oxidizes term babies. If this is so, what happens to preterm infants who are placed under the light 'just in case' and are also given oxygen in excess of what they need? What a potentially really bad combination: one therapy which decreases antioxidants and one which increases them! Sadly, most of the time healthcare providers give both these therapies to an infant, in combination or separately, without any proven need and to produce no known benefit. Making a newborn hyperoxic and

See related article on page 319

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at the same time decreasing his/her defenses against oxidative stress (when it is not needed) does not sound as good medical care. What a potential for oxidative stress damage! Both therapies together may lead to worse DNA damage, brain, eye and lung injury, and perhaps even childhood cancer.

Oxidative stress in the newborn

Increased oxidative stress is dangerous. This study should illuminate us that in healthy term newborns a short exposure to phototherapy for about 48 hours at about one week of age lowers serum vitamin C and uric acid concentrations and increases total oxidant status (TOS), lipid hydroperoxide and oxidative stress index (OSI) levels. These novel findings may be associated with potentially serious and long-term, even lifelong, clinical consequences based on other studies. Besides, a recent study in 90 term newborns, also from Turkey, demonstrates that neonatal hyperbilirubinemia is associated with significantly lower oxidant levels and higher antioxidant enzyme activities (superoxide dismutase, catalase and glutathione peroxidase), concluding that neonatal hyperbilirubinemia is associated with lower oxidative stress.[2] I wonder if the ultimate reason why we all have neonatal *physiologic* hyperbilirubinemia is to have an innate defense during our transition to life outside of the womb.

Oxidative stress can affect the whole organism. We have recently reviewed some of the associated morbidities of inappropriate neonatal oxygenation.[3] Adequate SpO2 monitoring with signal extraction technology (SET; Masimo®) prevents hyperoxia and decreases morbidity.[4,5] However, we cannot measure phototherapy-induced oxidation in clinical practice. It is not yet fully known whether or not phototherapy during the first 2-3 weeks of life is toxic to infants with underdeveloped antioxidant mechanisms. Nevertheless, I would not be surprised if it is shown in the future that phototherapy-induced oxidation in the newborn could potentially damage DNA and alter gene expression, just like too much oxygen does. Many other potential consequences of oxidation are obviously not yet known, such as programs for growth and development and disease processes later in life. After total antioxidant capacity is reduced and/or TOS and OSI is increased, the derangement can last for a long time before it becomes fully compensated, unless we eat and drink dark chocolate and (good) red wine. But we do not give these to babies, "because this is dangerous." However, the more we learn about oxygen, phototherapy and oxidative stress, it may turn out that dark chocolate and red wine are less poisonous than oxygen and phototherapy, two therapies that we unfortunately feed babies so frequently and many times unnecessarily.

Phototherapy

Around 80% of preterm infants develop hyperbilirubinemia, which is most commonly treated with phototherapy, used for decades for prevention of bilirubin encephalopathy and kernicterus. The principal effect is conversion of the pigment into more polar water-soluble isomers that can be more readily eliminated without conjugation in the liver. This, coupled with some *photo-oxidation* of bilirubin, diminishes the overall pool of bilirubin in the body and lowers plasma levels. Short-term side effects are in general not serious and include skin eruption, abdominal distention, mild hemolysis, mild thrombocytopenia and fluid loss due to impaired absorption of water, sodium chloride, and potassium. Radiation wavelength in the region of 480 to 500 nm is most effective; above approximately 550 nm it is useless. The dose of phototherapy is determined by the wavelength of the light, its intensity (irradiance; suggested by some as > 15 μW/cm^2 /nm), the distance between the light and the infant, and the exposed body surface area. In the study by Aycicek & Erel,[1] the naked newborn was 40 cm below six white fluorescent tubes with a light energy of 12-16 μW/cm^2/nm. Phototherapy was continuous for 48 hours. One can speculate that the higher the irradiance and the longer its duration, the worse would be the impact on OSI reported by the authors.

In addition to the illuminating findings of the article, other related concerns have been reported in the last 2 years. Phototherapy has been associated with early impairment of growth plate structure and oxidative-stress-induced growth plate injury in newborn rats[6] and with mutagenic and gametocidal side effects on the rat testicle with a decrease in spermatogonia numbers per tubule, tubular fertilization index and sperm Sertoli cell index, which are the most reliable methods in estimating future fertility potential.[7] In an elegant controlled study in 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 (SIADH) secretion has been described,[9] revealing an acute enhancement of serotonergic transmission by intense illumination, suggesting that phototherapy could be the ultimate environmental trigger for iatrogenic neonatal SIADH.[9] Finally, intensive neonatal phototherapy is a strong risk factor for nevus development in childhood. Having many nevi is a recognized risk for melanoma, leading the authors to suggest that exposed children should undergo dermatologic preventive measures and surveillance for the development of melanoma.[10]

Other potential derangements have previously been described, but we do not see them in daily clinical neonatal practice. For example, children who had been treated with phototherapy have increased risk for myeloid leukemia (OR = 7.5; 95%CI 1.8-31.9),[11] increased production of nitric oxide, a vasodilator involved in immunological defense mechanisms, cytotoxicity and neurotransmission,[12] and also have

alterations in cytokine production, with an increase of 70% in IL-2 secretion and 56% in IL-10 production together with a reduction of 43% in the spontaneous secretion of IL-1beta.[13] Furthermore, phototherapy affects cardiorespiratory activity during active sleep,[14] cardiac output, mean cerebral blood flow velocity and renal vascular resistance[15] and also alters urinary calcium excretion.[16] In cultured cells, blue light phototherapy produced genotoxic effects, inducing single-strand breaks in the DNA and blue and green light led to formation of long-lived toxic photoproducts.[17] It remains to be seen whether the genotoxic effect observed in this study can occur *in vivo*.

No controlled, prospective, masked randomized trials show that any of the above occurs significantly more frequently in 'illuminated' babies compared to those 'in the dark'. On the other hand, the above findings are evident and factual and cannot be ignored by concerned clinicians who want to avoid inducing a rare damage in a baby. Absence of 'evidence' (i.e.: no randomized study shows that the problem exists) is *not* the same as 'evidence of absence'.

Phototherapy use in jaundiced infants

Phototherapy for neonatal hyperbilirubinemia is an efficient form of therapy. On the other hand, according to a recent study, several pediatricians' practices are associated with initiation of phototherapy at lower than AAP recommended treatment parameters.[18] Even in the study by Aycicek, it is likely that some of the term infants who received phototherapy did not really need it (i.e. bilirubin > 13 mg/dL at 7 days of life). Additionally, in spite of the fact that the list of detrimental effects of oxidative stress is long, we still use oxygen unnecessarily. Unfortunately, phototherapy, just like oxygen, has been used by neonatologists "just in case." There are extremely few long-term follow-up studies of phototherapy-treated infants. Therefore, one cannot completely exclude the possibility that serious (albeit rare) side effects can be found in future clinical studies related to the findings published in this issue and in other studies cited above. Based on such findings, we recommend avoiding 'prophylactic phototherapy', to prevent having too many unnecessarily irradiated babies in the neonatal intensive care unit and to continue to treat only babies at risk, based on well described serum values and curves. From the findings of this study, it becomes evident that if we stay away from using phototherapy when it is not clearly necessary, we may be avoiding an adverse outcome in some infant. This is not the same to say that we will abandon the use of phototherapy in those cases when it is clearly indicated to prevent serious problems, avoiding repeating the frequent mistakes that plague the past and present of neonatal care. That is to say that we should not now come up with a concept of "permissive hyperbilirubinemia." By no means am I suggesting leaving untreated an infant truly at risk with hyperbilirubinemia because of concerns with oxidative stress. The emphasis should be on not starting *unnecessary* phototherapy 'just in case', and on not keeping the light one more day, "just in case." It is well known that many healthcare providers strive for "quick resolutions." This, together with the "extremist" behaviors of neonatologists, swinging the pendulum from one extreme to the other without the equipoise derived from scientific and clinical knowledge, leads to serious afflictions. With these caveats, we will have to change our paradigm in regard to phototherapy, considering it as another neonatal drug -and a powerful drug it is, according to the findings in this article. We then should remind ourselves that no drug produces only the effect for which it is prescribed; it invariably affects other functions and organ systems. Anyone indicating this drug should not use it 'just in case' or strive for quick resolution of *normally elevated* bilirubin levels, but be aware of the findings in this study and carefully analyze in each individual case, one baby at a time, the real likelihood or risk for bilirubin encephalopathy and kernicterus, preventable conditions that must always be avoided by giving such drug, and the potential for long-lasting risks of unnecessary illumination.

Summary

As concerned clinicians, we realize that too frequently the generalizations and broad implementation of proposed solutions have been part of the problem. Journal articles of the last decade report more frequently adverse effects than real advances. As Pascal wrote, 'knowledge is like a sphere; the larger it gets the larger the contact with the unknown'. In a Cartesian way, the study by Aycicek & Erel[1] reminds us that the more we educate ourselves, the more we discover our own ignorance. The study also helps me understand that what I know maybe be much less important than what I do not know. Other authors[3-17] told us about cardiorespiratory and blood flow changes, endocrine and immune effects, growth plate injury, nevus development, mutagenic and gametocidal side effects, possible genotoxic effects with DNA and gene alterations, aging, and childhood myeloid leukemia and cancer. Based on this and on the potential serious damage from excess oxygen,[3] we should all turn off the lights and take a deep breath in the dark. We must seriously consider stopping the clinical practices of providing *unnecessary* phototherapy and oxygen to any newborn infant as long as we do not know all of the potentially serious short- and long-term consequences of such practices. Let us work collaboratively in neonatology, so the dim view of our therapeutic capabilities described by François-Marie Arouet (Voltaire) in the mid-1700s, when he wrote that 'Doctors are men that prescribe medicines of which they know little, to cure diseases of which they know less, to human beings of which they know nothing', is no longer true in the future.

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