



## Light-dark cycle in the neonatal intensive care unit

Chronobiology is the study of the interaction of external temporal signals with regular and predictable periods called “zeitgebers”, which can impose their period and phase on physiological variables; The most important temporal signal is the light-dark cycle that projects from the retina to the suprachiasmatic nucleus (SCN) of the hypothalamus through the first retinohypothalamic tract. The SCN is considered the master clock of the circadian system and synchronizes it to close periods to 24 hours and allows the generation of an adaptive response to changing but predictable environmental conditions.

Most chronobiology studies place special emphasis on light as the main environmental signal for the regulation and proper functioning of the circadian system. However, we should not ignore the importance of darkness as a temporal signal with the same importance as light. In such a way it should be considered that the most important thing for the circadian system is the alternation between these two signals, to keep circadian temporal stability in all bodily functions, so constant lighting conditions could be considered not proper for the circadian system.

Currently, it is considered that the hospital environment is the most appropriate space to characterize the probable harmful effects of the use of constant light, since almost all hospital units worldwide are kept on 24 hours a day with the light constantly on to allow healthcare personnel, adequate supervision of hospitalized patients, constant light conditions in most inpatient services around the world has no scientific basis [1].

Neonatal intensive care units (NICU) are areas that are kept in conditions of constant lighting, and the lack of other temporal signals that function as zeitgebers, for newborns who are hospitalized, many of whom are preterm babies and who can remain in these constant lighting conditions for prolonged periods of hospitalization.

It is important to mention that the fetal suprachiasmatic nucleus (SCN) is functional from the last trimester of pregnancy and can generate circadian rhythms, as well as synchronize with the mother's circadian signals [2,3]. That is, it is under the maternal influence, receiving humoral circadian signals from the mother that cross the placenta and keep it synchronized until the moment of birth. When the baby is born, it requires rapid physiological adaptation to respond to the multiple sensory signals it receives from the environment, for example: temperature, noise, lighting, and feeding.

In the review by Lewis et al., 2024 [4] in this issue, problem is reviewed with the following question: “What is the evidence for health effects of neonatal exposure to light-dark and/or other chronobiological factors?”, to answer this question, they carried out a systematic review where they included 56 works that studied newborns, in an age range that goes from 25 to 37 weeks of gestation at the beginning of the study, that is, studies carried out on preterm newborns and term babies without

congenital anomalies and in stable condition; Interestingly, in this review, in addition to the chronotherapeutic intervention or exposure for neonatal health, mainly light and dark cycles, feeding, noise, feeding and time of day of birth, the results in each intervention are compared.

In the studies included in Lewis et al., 2024 [4], the main aim was the use of the light-dark cycle in NICU on neonatal health. Unlike the two Cochrane versions of 2013 and 2016 [5,6], this work includes a greater number of studies, and the “clinically most relevant” results are discussed, such as weight gain, reduction in days until enteral feeding, shorter duration of assisted ventilation, fewer days of oxygen supply or reduction in hospital stay.

Another question raised by Lewis et al., 2024 [4] is whether “should an increased day vs. night difference be considered evidence in favour of LD over DD?” Importantly, no study was included in the review (as the authors comment) “Importantly, no study indicated that LD would be detrimental compared to LL or DD.” Therefore, such a lighting condition could be said to be relevant to the immediate health of a hospitalized newborn but could be relevant to fostering the neurodevelopment of the circadian system in the newborn.

In the studies included, no day-night differences were found in sleep-wake patterns, a result that had already been revealed, where only rhythms with ultradian periods were found, but no clear circadian rhythms [6,7]. However, it should be noted that maternal feeding schedules and physical contact during newborn care influence the baby's temperature, heart rate, and activity patterns and therefore mask circadian rhythms.

It is important to note that the findings of some studies depend mainly on the NICU conditions that the newborns are in, for example: in all studies included in this review, the light levels in the NICU to which they are exposed newborns are not equally controlled, a great dispersion is observed between the direct lighting intensities used, ranging from ~1 lux to 700 lux, which logically makes a difference in the results found between studies. As mentioned above, it is considered important to expose the newborn to external cyclical events to promote and stimulate the development of the circadian system. However, due to the in-hospital surveillance needs and protocols of the NICU, it is difficult to implement general light-dark lighting in neonatal intensive care; however, some strategies could be adapted, such as those reported in two of the works included in this review, where personalizes the light-dark cycle through cephalic helmets [8,9].

Also, in this review [4], this last question is asked: “Can preterm infants translate LD into similar circadian signals that they receive in utero?” However, only three studies included in the review use the comparison of the light-dark cycle with constant dark conditions with short-term results. It is suggested that preterm babies especially may

develop better in a dark environment than in one with constant light [10]. However, babies are exposed in utero to the mother's rhythms synchronized with the light-dark cycle, which indirectly causes the newborn to be synchronized with this light-dark signal [11]. Consequently, this shows that the use of light-dark cycles after birth could be the best choice for the newborn.

However, as the authors comment, "very few studies are missing to reach conclusions and many questions remain" (to be answered), in addition, more experimental clinical studies are needed in this area where a lack of consensus has been generated on the use of the light-dark cycle as routine in the NICU.

Current evidence on the benefits of the light-dark cycle is still premature and inconclusive, probably due to the lack of standardization in the chronobiological stimuli used, for example: the intensity of lighting, how many lux to use in the subjective day phase, and how many lux use during the subjective night, the amounts of nutrients and types of formula in the diet, the temperature at which newborns should be housed, so the generalization of the findings is limited.

Many of the studies reviewed in this article focus on the response of the circadian system in the first stages of development, it is important to include long-term analysis of light-dark cycle stimulation in later stages of development. The moment where research work has focused is the postnatal stage, where the newborn interacts with new direct environmental signals. At this stage the circadian system is still in maturation, it responds with the generation of ultradian rhythms in both full-term and premature babies. Failure to see circadian rhythms in the first stages of birth does not rule out the potential importance of a light-dark cycle in the hospital environment. There is sufficient data mentioned above to show that there is no justification for continuing a chaotic non-circadian environmental approach in neonatal hospital units.

The study and characterization of the effect of the light-dark cycle on the development and maturation of homeostatic regulation systems should be expanded with more clinical studies that explore other favored variables, and especially the existing results should be considered as an integral part of newborn care. This review mentions that the exposure of newborns to a light-dark cycle favors, to a certain extent, rapid weight gain and a reduction in hospital stay. This implies benefits for the baby who quickly joins the family, and the reduction in hospital stay reduces the risk of exposure to nosocomial diseases. In addition, direct and indirect economic costs in health are also reduced.

Finally, we can say that the work of Lewis et al. highlights the need to

carry out studies with rigorous experimental designs in this field, which can improve neonatal health in hospitals.

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