LETTER TO THE EDITOR
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Caffeine therapy in preterm infants: effects in 2nd and 3rd childhood

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To the Editor,

The immediate postnatal period is the moment for the individual's cardiopulmonary adaptation. It is necessary for the neonate's organic systems to mature so that the hemodynamic and respiratory transformation occurs in a physiological manner.[1] The cardiopulmonary and neurological immaturity of premature newborns requires caffeine to reduce the need for invasive ventilatory support, facilitate extubation and promote better cognitive outcomes. It is worth noting that the action of caffeine occurs due to its structural similarity to adenosine, acting as a competitive antagonist against the depressant effects of this molecule, through its binding to adenosine A1 and A2A receptors, which leads to beneficial results, especially in cardiac, lung and brain development.[2]

While reading the manuscript "Late effects of caffeine use on sleep of infants born prematurely" by Oliveira et al.,[3] volume 42, 2024, methodological gaps were found in the analysis of variables regarding wake-up time and total daily sleep time in premature babies undergoing caffeine therapy in the neonatal period.

Therefore, we identified in the study by Oliveira et al.[3] that the comparison of groups regarding the variables mentioned above is done through variance analysis with Tukey post-hoc, which is considered inadequate due to the imbalance between the groups. This may inflate the type I error due to the post-hoc selection, which should be Hochberg's GT2.[4]

Oliveira et al.[3] also do not present an effect measure for findings with significant differences, which limits understanding of their clinical usefulness. It is necessary to develop a measure of effect in order to expose the relevance of the findings. Based on this, using the descriptive statistics of the variables "wake-up time" and "total daily sleep time", an effect measure called Cohen's d was created for unbalanced groups.[5] It reveals that the difference between the preterm (PCG) and at term (TG) groups presents d=1.78, equivalent to a very large effect. The same was evident for the variable "total daily sleep time", with d=1.69.

In view of the above, the considerable differences in effect magnitudes indicate that caffeine administered to neonates may have considerable long-term effects on sleep in childhood. In addition to confirming these findings, it would also be interesting to observe the likely implications related to social interaction and learning that could arise in school-going children due to the longer duration of their sleep. These are the imaginable paths for future investigations into the therapeutic use of caffeine.

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AUTHORS' RESPONSE

Reply: Late effects of caffeine use on sleep of infants born prematurely

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We fully agree with the positive impact of caffeine on the cardiorespiratory function of preterm infants. However, we would like to highlight that its widespread use precedes most of the evidence on the latter positive effects in neurodevelopment.[1,2] Even though positive neurodevelopment outcomes can be related to caffeine effects beyond adenosine receptor antagonism, this inhibition could have specific and unpredictable effects on sleep neuronal circuitry development, much less explored.[3]

We were surprised by the criticism regarding using the Tuckey *posthoc* test due to different groups' sample sizes. We use it in normally distributed samples with homogeneous variances between groups. Levene test was applied in both wake-up time (p=0.133) and total daily sleep time (p=0.248) analysis. We recognize the impact of group sample size on the homogeneity of the distributions, but we could not find any references supporting the prioritization of one criterion over the other.

As for the in-between group comparisons, differences observed between individuals born at term (TG) and those born preterm and exposed to caffeine in the neonatal period (PCG) do not equal the caffeine effect.

Although the differences in "wake-up time" and "total daily sleep time" reached statistical significance, we did not interpret these differences as clinically significant, not justifying additional statistical analysis, which we judge, in this case, to be statistical preciosity.

Our results regarding total daily sleep time are in accordance with the normal populational sleep time distribution,[4] and it is unlikely that in-between group differences in the normal range of sleep time duration would affect social interaction and learning in the studied population.

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