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ORIGINAL ARTICLE

Caffeine preserves quiet sleep in preterm neonates

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Abstract

Caffeine is widely used in preterm neonates suffering from apnea of prematurity (AOP), and it has become one of the most frequently prescribed medications in neonatal intensive care units. Goal of this study is to investigate how caffeine citrate treatment affects sleep-wake behavior in preterm neonates. The observational study consists of 64 preterm neonates during their first 5 days of life with gestational age (GA) <32 weeks or very low birthweight of < 1500 g. A total of 52 patients treated with caffeine citrate and 12 patients without caffeine citrate were included. Sleep-wake behavior was scored in three stages: active sleep, quiet sleep, and wakefulness. Individual caffeine concentration of every neonate was simulated with a pharmacokinetic model. In neonates with GA ≥ 28 weeks, wakefulness increased and active sleep decreased with increasing caffeine concentrations, whereas quiet sleep remained unchanged. In neonates with GA < 28 weeks, no clear caffeine effects on sleep-wake behavior could be demonstrated. Caffeine increases fraction of wakefulness, alertness, and most probably also arousability at cost of active but not quiet sleep in preterm neonates. As such, caffeine should therefore not affect time for physical and cerebral regeneration during sleep in preterm neonates.

KEYWORDS

apnea of prematurity, caffeine, preterm neonates, sleep

1 | INTRODUCTION

Preterm birth, defined as birth before 37 weeks of gestational age (GA), affects 1 in 10 newborns worldwide and is associated with reduced life expectancy and increased morbidity.[1] Increased perinatal morbidity in preterm neonates often appears with breathing disorders, among which apnea of prematurity (AOP) is the most frequently observed.[2,3] AOP is likely the result of increased arousal threshold during sleep and reduced ventilatory response to increasing CO_2 in preterm neonates.[4]

Aside from respiratory assistance (non-invasive and invasive), pharmacological support with caffeine citrate (1,3,7-trimethylxanthine) has been successfully employed in the treatment of AOP in preterm neonates. Nowadays, caffeine citrate (hereafter

Abbreviations: AOP, apnea of prematurity; AS, active sleep; BW, birth weight; GA, gestational age; NICU, neonatal intensive care units; NREM, non-rapid eye movement; PK, pharmacokinetic; PNA, postnatal age; QS, Quiet sleep; W, wakefulness.

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shortened to caffeine) is administered to all preterm neonates suffering from AOP, and it has become one of the most frequently prescribed medications in neonatal intensive care units (NICU) in the last 40 years.[5-7]

Independent of its form of administration (oral or intravenous), caffeine is absorbed with minimal-to-no first pass metabolism, reaches a high bioavailability, and achieves peak plasma concentration within a few hours.[7-10] However, due to immature hepatic metabolism in preterm neonates, caffeine clearance is strongly reduced leading to a prolonged half-life of up to 100-150 hours,[11] in contrast to 4-5 hours in adults.[9,12] Current standard caffeine dosing regimen consists of a loading dose of 20 mg/kg followed by a maintenance dose of 5-10 mg/kg per day.[5,13] It was recently demonstrated by pharmacometric modeling and simulation[14] that a fixed maintenance dose is associated with decreasing caffeine concentrations as a result of a maturation-related increase in caffeine clearance.

Caffeine overcomes biological membranes because of its hydrophobic nature; thus, it also passes the blood-brain barrier to enter the central nervous system.[3] Therein, the major molecular target sites are the adenosine receptors, due to its similar molecular structure with adenosine. More precisely, caffeine competitively antagonizes the endogenous adenosine A_1 and A_{2A} receptor subtypes.[3,10]

Adenosine is an endogenous sleep factor and serves as an energy regulator. In the case of cell-threatening conditions such asphyxia, the increased level of adenosine provides neuroprotection as it decreases cellular metabolism via the generally dominant, inhibitory A_1 receptors.[15-17] Adenosine has its sleep-inducing effect for two reasons: the wake-promoting neurons are inhibited by adenosine at the A_1 receptors in the cholinergic basal forebrain; the sleep-active neurons are activated by adenosine at the A_{2A} receptors in the subarachnoidal space below the rostral forebrain.[16,17] As an adenosine antagonist, caffeine suppresses the sleep-inducing effect of adenosine promoting wakefulness (W) and sleep fragmentation in adults.[18]

From an ontogenic perspective, one of the most important functions of sleep is early brain development at preterm age. During the phase of prematurity, the largest portion of sleep consists of active sleep (AS), the predecessor of rapid eye movement sleep. This sleep stage is most important for brain development and maturation.[19,20] The highest relative amount of AS is observed at extremely premature age and decreases gradually up to term.[19,20] Quiet sleep (QS), the predecessor of non-rapid eye movement (NREM) sleep, is the sleep with the slowest wave activity in the EEG. Furthermore, QS is crucial for physical and cerebral regeneration, and development of the immune system.[21] The amount of QS remains stable during the phase of prematurity to term age.[20] Hence, every sleep stage plays a crucial role during prematurity and it is essential to understand caffeine-related effects on these different stages.

In this study, we investigate how caffeine treatment affects sleep-wake behavior in preterm neonates by addressing the following three research questions: (i) Does caffeine treatment affect the three sleep-wake stages AS, QS, and/or W? (ii) Is there a relationship between caffeine concentrations and magnitude of caffeine-related effects on sleep-wake stages? (iii) Does GA and/or postnatal age (PNA) influence caffeine-related effects on sleep-wake behavior in preterm neonates?

2 | METHODS

2.1 | Study subjects

Recruitment and measurements of preterm neonates were carried out in the neonatal intensive care unit (NICU) at the University Children's Hospital Basel, Basel, Switzerland between 2013 and 2015. The study was approved by the local ethical committee (EKBB-Nr: 37/12), and conducted according to the principles of the Declaration of Helsinki. A detailed description of the study setting can be found in previous reports.[22-25] Enrolled preterm neonates met the following inclusion criteria: written informed consent of their parents; very preterm birth (GA < 32 weeks), or very low birthweight (<1500 g). Exclusion criteria were perinatal asphyxia (either arterial cord blood pH < 7.0, base deficit > 12 mmol/l, or serum lactate > 5 mmol/l during first hour of life) or major congenital malformations. None of the neonates had received antiepileptic drugs during the days of measurement. Data from a total of 52 preterm patients treated with caffeine (caffeine cohort) and 12 preterm neonates without caffeine (no-caffeine cohort) were included.

2.2 | Study design

Monitoring and administration of treatments for all preterm neonates followed standard operating procedures of the NICU. As a standard of care, caffeine was administered routinely in all neonates born below 32 weeks GA and was given at the same time on subsequent days. The timing of the daily caffeine administration was dependent on the time of birth and clinical routine procedures and was not influenced by the study protocol.

2.3 | Sleep-wake behavior measurements in preterm neonates

Videographic recordings of sleep-wake behavior were performed over the first 5 days of the neonates' life for 3 hours between 8:00 AM and 11:30 AM. Two cameras (Microsoft 1080 HD Sensor) filmed the preterm neonates (dressed only in a diaper) in their actual position. One camera filmed the face and eye movements through the incubator doors and the other camera focused on body movements through the incubator roof. Nursing disturbances were avoided as much as possible during videographic recordings.

In total, videographic recordings of 172 observation intervals performed on 64 neonates were available (minimal = 1 and maximal = 5 per neonate within the first 5 days of life). A total of 135 recordings were performed on neonates receiving caffeine (caffeine cohort), and 37 recordings on neonates not treated with caffeine (no-caffeine cohort). In the caffeine cohort, 20 caffeine

administrations were within the 3-hour observation interval, and 115 before or after. State determination of sleep-wake behavior was done with a VLC media player (Version 2.2.1) using a two- to fourfold playback speed. Results were registered on CSV files in bins of 10 s. States were attributed to one of the following stages: AS, QS, and W. We took into consideration that sleep in neonates is initiated by AS and continues with QS. Sleep scoring criteria were taken from Anders et al[26,27] and Grigg-Damberger,[28] and based on behavioral observations looking at eye movements/facial expressions, respiration regularity, and body movements. The terms "indetermined" or "translational" sleep were not employed because behavioral observations were not combined with EEG recordings. Situations in which any disturbance occurred (eg, opening of incubator doors, external activity like nursing procedures and medical interventions) were discarded when the neonate was clearly compromised. In addition, observers were blinded with regard to caffeine treatment. Position of the neonates during the study period was noted as prone, supine, or in lateral position. As the attribution of behavioral sleep-wake stages has subjective aspects, some of the videos (n = 11) were evaluated twice by different members of the study group, and all uncertain cases were discussed with a pediatric sleep expert.

2.4 | Caffeine concentration profiles in preterm neonates

Individual caffeine concentration profiles over the first 5 days of life were simulated for each of the preterm neonates applying a previously published mathematical pharmacokinetic (PK) model[14] that takes birth weight (BW), GA, and PNA into account. This caffeine PK model was developed based on two clinical studies[29,30] with a total of 185 preterm neonates. The caffeine PK model characterizes initial caffeine concentration increase caused by drug accumulation during the first week of life and predicts the peak caffeine concentration after 7 days. Furthermore, the model characterizes decreasing caffeine concentration due to maturating clearance. Due to immature hepatic metabolism, caffeine clearance is strongly reduced in preterm neonates leading to a prolonged half-life of up to 100-150 hours.[8,11,31] As such, caffeine concentrations remain close to constant during an observation interval of 3 hours as employed in this study. Therefore, the average caffeine concentration (C_{avg}) in this observation interval was used, see Figure 1C. For completeness, the overall caffeine concentration dynamic is shown for the first 5 days of life, see Figure 1A. It should be noted that caffeine concertation remains nearly constant during the 3-hour observation interval, while sleep-wake behavior is a dynamic process, see Figure 1B.

2.5 | Statistical methods to address our three research questions

To investigate the effect of caffeine concentrations on the behavioral sleep-wake stages (dependent variable) expressed as a percentage of the total observation period and C_{avg} as independent variable (research question (i)), a linear mixed effects model with random effects was fitted including a random intercept for each study participant. Goodness of fit was determined using standard residual analysis. In terms of descriptive statistics, the Mann-Whitney-Wilcoxon test for non-normally distributed continuous variables was performed for the other research questions.

All analyses were conducted with the statistical package R (R Core Team 2013. R: A language and environment for statistical

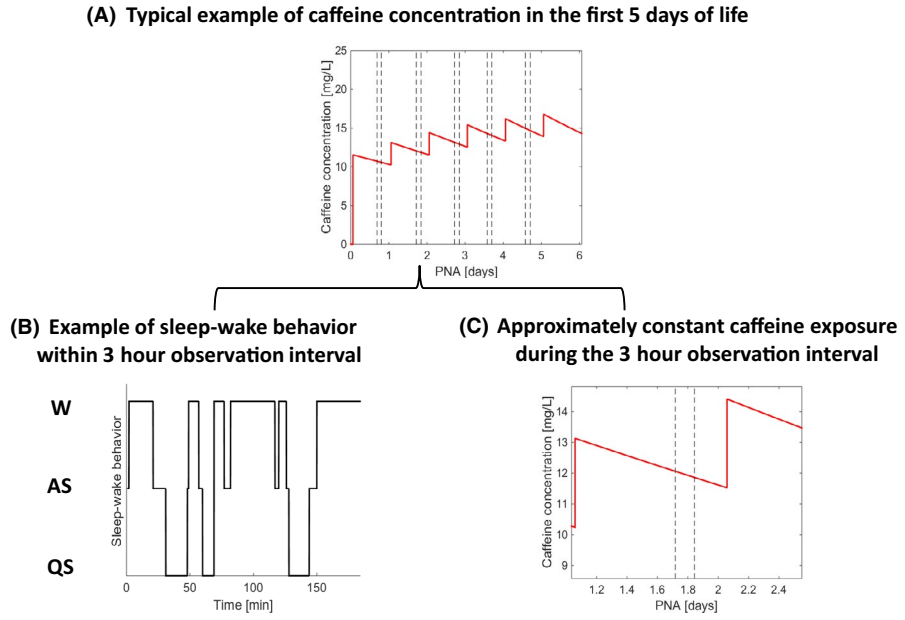

FIGURE 1 Example of caffeine concentration (red solid line) over the first 5 days of life (panel A) with the 3 hour observation intervals (indicated with dashed lines). Example for sleep-wake behavior (wakefulness, active sleep, and quiet sleep) (panel B) and the approximately constant caffeine exposure (panel C) in one of the observation intervals is shown

computing. R Foundation for Statistical Computing, Vienna, Austria) and a $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study participants

Demographic characteristics of study participants were as follows (see also Table 1). A majority of neonates received caffeine treatment (n = 52) with a median GA of 30.6 weeks and a median birth weight of 1380 g. Neonates not receiving a caffeine treatment (n = 12) had a median GA of 33.0 weeks and a median birth weight of 1335 g. Data from a total of 35 male and 29 female preterm neonates were available and 40 neonates had a GA ≥ 28 weeks.

3.2 | Interrater reliability

Interrater reliability was assessed for attributing active and non-active states within 11 videographic recordings as registered by two observers independently. It showed an agreement of 79% with a Cohen's kappa of 0.57 which is reasonable. A revaluation by one observer of a videographic recording indicated an uncertainty of about ±10% in the attribution of the behavioral sleep-wake stages.

3.3 | Results of the three research questions

In the following sections, we present results regarding our three research questions. (i) Does caffeine treatment affect the three sleep-wake stages AS, QS, and/or W? (ii) Is there a relationship between caffeine concentrations and magnitude of caffeine-related effects on sleep-wake stages? (iii) Does GA and/or PNA influence caffeine-related effects on sleep-wake behavior in preterm neonates?

(i) Caffeine treatment affects AS and W but not QS

W significantly increased ($P < .05$) with higher average caffeine concentrations in preterm neonates with GA ≥ 28 weeks. Since no caffeine concentration-related effect on QS was found, the increase in W is at the cost of significantly decreased AS, or the other way around, see Figure 2. Given available data, no caffeine-concentration-dependent effect on sleep-wake behavior was found in preterm neonates with GA < 28 weeks (data not shown).

(ii) Magnitude of caffeine-related effects depends on caffeine concentrations

In the group of neonates with GA ≥ 28 weeks, a significant decrease in AS (56.9% vs 38.2%, $P < .05$) and an increase in W (22.8% vs 45.8%, $P < .05$) was found when comparing the first and fifth day of life, compare Figure 3. For neonates without caffeine treatment, no PNA effect was seen on sleep-wake behavior, compare Figure 3. Magnitude of caffeine-related effects on AS and W increased with increasing caffeine concentration C_{avg}. These observations correspond to the sleep-wake behavior seen for C_{avg}, compare Figure 2. Caffeine concentrations increase with increasing PNA (Figure 1) in the first 5 postnatal days. No additional caffeine-independent PNA effect on sleep-wake behavior was found (Figure 3).

(iii) GA does influence caffeine-related effects

We found a difference in the effect of caffeine on sleep-wake behavior between the group of neonates with GA < 28 weeks compared to neonates GA ≥ 28 weeks for the first 5 postnatal days. In the group of neonates with GA ≥ 28 weeks, a significant decrease in AS and an increase in W under increase in caffeine concentration was found when comparing the first and fifth day of life, see Figure 3 and (ii). This was not the case for the group of neonates with GA < 28 weeks where no such reduction of W could be seen. As aforementioned, no PNA-related effect on sleep-wake behavior was found.

4 | DISCUSSION

For a good understanding of alertness, sleep, brain development as well as cerebral, mental, and physical regeneration at preterm age, knowledge about caffeine-related effects on sleep-wake behavior at that age is crucial. The strengths of this study are as follows: (i) the incorporation of dynamical time-related sleep-wake behavior data over the first 5 postnatal days, (ii) the capability of predicting individual caffeine concentrations based on BW, GA, and PNA leveraging a pharmacometric model, (iii) the large number of patients, and (iv) the availability of patients without caffeine treatment. Key findings in this study permit us to address our three pre-specified research questions as discussed in the following paragraphs.

TABLE 1 Demographic characteristics (mean, standard deviation, median, minimum, maximum, 25% and 75% quantiles) of the study participants (n = 64, female = 29)

	Mean	SD	Median	Min	Max	25% quantile	75% quantile
Caffeine cohort (n = 52, female = 22)							
Gestational age (weeks)	29.9	1.96	30.6	24.7	32.4	28.6	31.5
Birth weight (grams)	1287	375	1380	420	1900	990	1553
No-caffeine cohort (n = 12, female = 7)							
Gestational age (weeks)	33.4	1.75	33.0	30.6	37.0	32.7	34.0
Birth weight (grams)	1401	149	1335	1240	1700	1293	1490

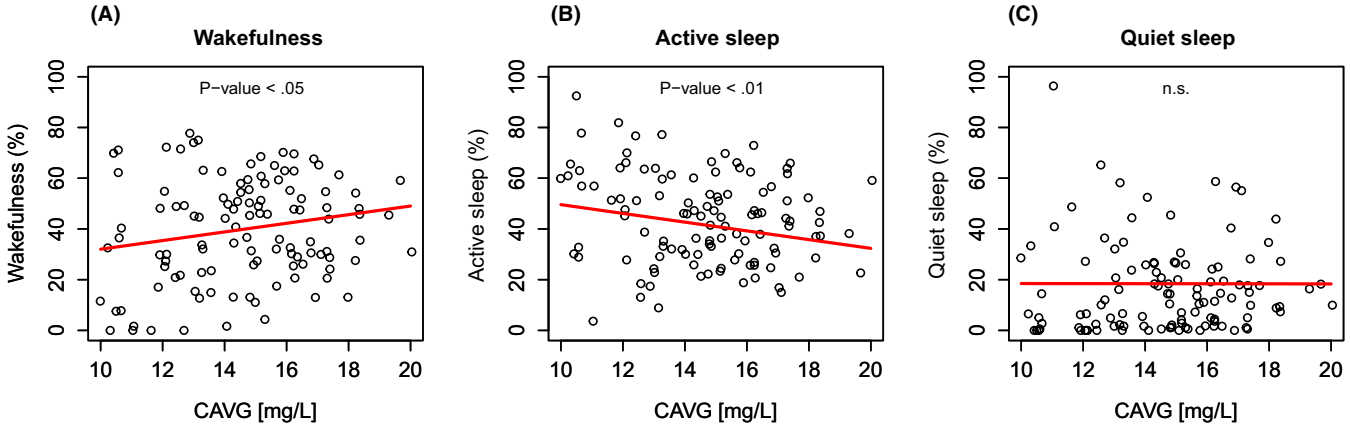

FIGURE 2 Sleep-wake behavior (wakefulness, active sleep, and quiet sleep expressed as percentage) for the caffeine cohort with GA ≥ 28 weeks in dependence of average caffeine concentration (C_{avg}). Significant changes with increasing C_{avg} are observed for wakefulness (panel A) and active sleep (panel B), whereas no change appears for quiet sleep (panel C). The red lines present the result from linear mixed effects regression

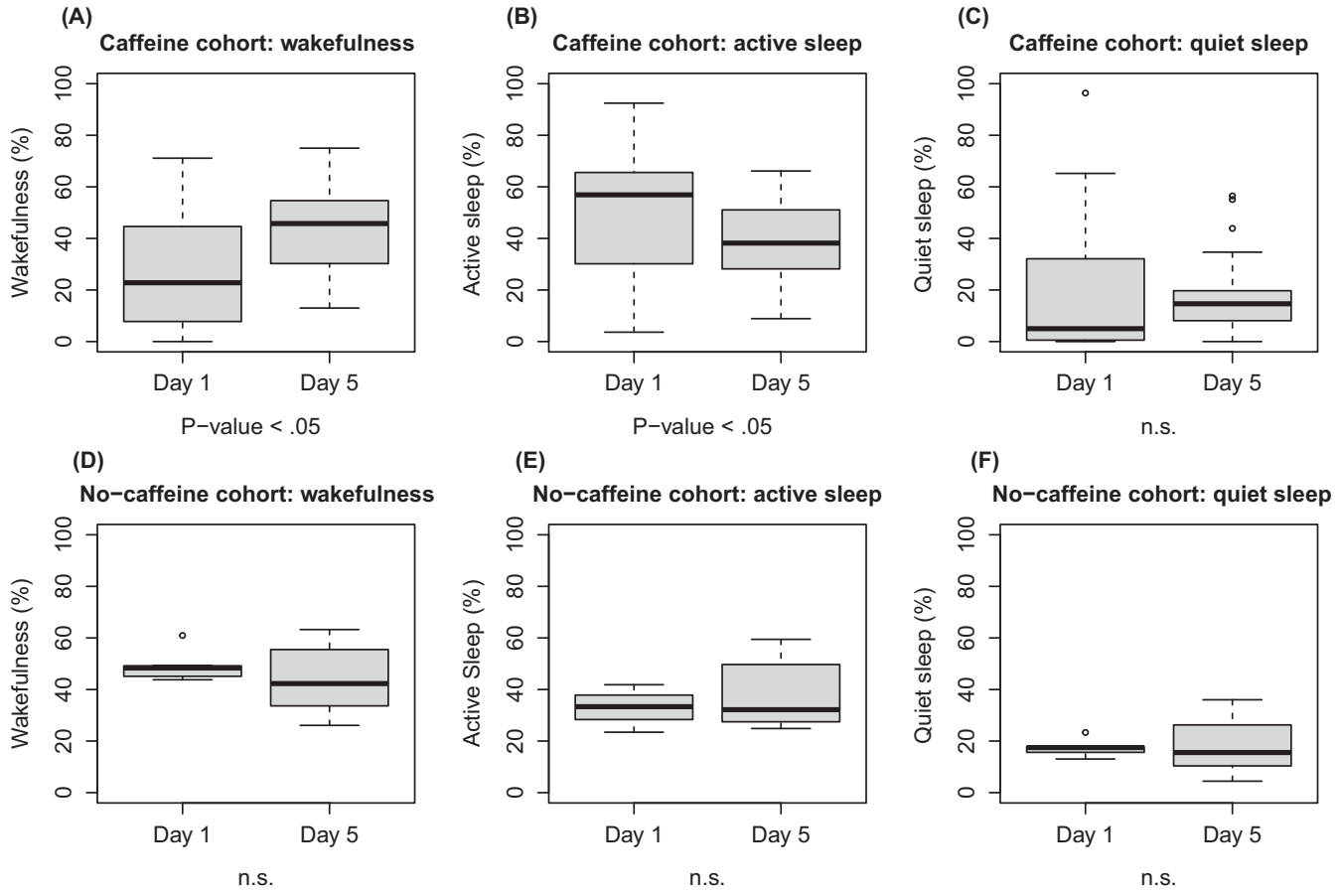

FIGURE 3 Sleep-wake behavior (wakefulness, active sleep, and quiet sleep expressed as percentage) for the caffeine cohort with GA ≥ 28 weeks (panels A–C) and for the no-caffeine cohort (panels D–F) in dependence of PNA day 1 and day 5. In the caffeine cohort, the caffeine concentration increases during the first 5 days of life

4.1 | Does caffeine treatment affect the three sleep-wake stages AS, QS, and/or W?

In administering caffeine, we aim to treat central apneas. An increase in cerebral cortical activity,[32,33] alertness, and responsiveness to rising CO2 levels, and increase in respiratory neuronal output as well as an improvement of respiratory muscle, lead to this stabilization of the respiratory system.[34] Central apneas appear in AS and QS[35] and caffeine should lead to a higher level of alertness and better arousability from deep sleep of QS into light sleep, from AS to W.

In preterm neonates with GA ≥ 28 weeks, we observed that W significantly increased with rising caffeine concentrations suggesting an elevated caffeine-related alertness (Figures 2 and 3). Every preterm neonate with a GA of less than 28 weeks did not show caffeine-concentration-dependent effects on sleep-wake behavior at all, and consequently no increase in alertness. Alertness has to be understood at different levels of sleep. Arousal from AS is easier than from QS. The level of awareness is higher in AS than QS. Therefore, we suggest arousal from AS easily leads to W, but arousals in QS lead to transitions from deep sleep to light sleep, and only then to W. The fact that QS fraction was stable with or without caffeine in the first 5 days of life in our study does not mean that we do not expect transitions from deep to light sleep within QS, but we cannot disentangle them with the current study setting as they do not automatically lead to W. In administering caffeine, we aim to treat central apneas. An increase in alertness and responsiveness to rising CO2 levels lead to this stabilization of the respiratory system.[34] Central apneas appear in AS and QS[35] and caffeine should lead to a higher level of alertness and better arousability from deep sleep of QS into light sleep, from AS to W. Due to the observational scoring technique in our study, arousal transitions from QS may remain undetected. Nevertheless, as the amount of QS remained stable in our study, so too should sleep associated regeneration and reorganization processes. Our data revealed a reduction in the amount of AS at the peak concentration of caffeine at day 5 from 57% to 38% (Figure 3). The high percentage of time spent in AS at premature age seems to be able to compensate for a certain amount of reduction of the latter through caffeine. Deprivation of QS/NREM sleep affects the cognitive system as well as physical health.

The effect of caffeine on neurodevelopmental outcome via a stabilization of respiration and reduction of apnea of prematurity has been proven to be positive at 18-21 months[5,6] with a reduction of clinical disabilities, cerebral palsy, and likelihood of death. At 5 years of age, the difference in the composite outcome and death between caffeine-treated and placebo-treated neonates was not visible anymore.[36] Nevertheless, at 11 years of age, a reduction of risk of motor impairment, behavioral problems, and an increase in academic performance were shown in caffeine-treated neonates compared to placebo-treated neonates.[37] Although difficult to prove, sleep quality for sure plays a major role to guarantee the best possible development in the population of preterm infants.

4.2 | Is there a relationship between caffeine concentrations and magnitude of caffeine-related effects on sleep-wake stages?

As shown with a mathematical PK model for caffeine concentrations after an initial loading dose and daily maintenance doses in relation to premature clearance, caffeine concentration increases with increasing PNA during the first 5 postnatal days and then tends to decrease.[14] A comparison of AS, QS, and W at PNA day 1 with day 5 showed similar results as for increasing caffeine concentrations, compare Figures 2 and 3.

4.3 | Does GA and/or PNA influence caffeine-related effects on sleep-wake behavior in preterm neonates?

In the first 5 days of life of our cohort, no PNA-related effect (ie, no caffeine-independent effects due to maturation) on sleep-wake behavior could be concluded. In the no-caffeine cohort, compared to the caffeine-treated neonates, no maturational effect could be seen on either W, AS, or QS. This supports the idea that the decrease in AS and increase in W of the caffeine-treated children were purely related to the increasing concentration of caffeine in the first 5 days (Figure 3). However, a difference in the effect of caffeine on sleep-wake behavior between the group of neonates with GA < 28 weeks compared to neonates GA ≥ 28 weeks was found for the first 5 postnatal days.

4.4 | Comparison with the literature

In the following, we relate our results to previous studies. Curzi-Dascalova et al[38] used polysomnographic recordings, and found no difference in the sleep-wake behavior between the caffeine cohort (n = 10) and the no-caffeine cohort (n = 5). In their study, GA was in a similar range but we emphasize the low number of patients (n = 15) compared to our study. Hayes et al[39] also investigated a small group of preterm neonates (caffeine n = 14, no-caffeine n = 10) using videographic and actigraphic recordings. They reported an increased number of arousals, longer time of W and a decrease in AS in neonates receiving caffeine what corresponds to our results. Interestingly, they found lower arousal rates and a suppression of sleep-related spontaneous movements after 5 days compared to non-treated neonates, and explained this phenomenon as a secondary effect of sleep deprivation due to cumulative activational effects of caffeine in the first 5 days after birth.

4.5 | Limitations of the study

Besides the strength of this study to observe a fragile population during their first days of life, some limitations should be mentioned. Due to ethical considerations, it was not possible to randomize neonates to receiving or not receiving caffeine. Therefore, neonates not receiving caffeine treatment were slightly older in terms of GA. In addition, it can be argued that precision of the results might be improved by including more neonates in the study. However, due to the intensive sampling process, this would have required more resources, but could be considered for a follow-up study. Caffeine concentrations are not measured in daily clinical routine, but only in exceptional cases because of the invasiveness of the procedure.

Therefore, a previously developed mathematical PK model was applied to simulate concentrations for every time interval. Sleep quality can be quantified as long periods of sustained sleep, good REM sleep fraction (brain development), stable NREM sleep fraction (regeneration) and as few arousals possible. In our study setting, we cannot prove that a stable percentage of QS under caffeine treatment should be in part responsible for the favorable outcomes and that in very preterm neonates a decrease in AS from 56.9% to 38.2% and an increase in W from 22.8% to 45.8% would be well tolerated. Given the known positive effects of caffeine on future neurodevelopmental outcome and the responsibility of the different sleep episodes described before, such a correlation can be assumed from our results. The purely observational method of sleep staging[27,28] can be clearly justified through the limitation of the EEG giving insufficient elements to determine the exact sleep staging before 32 weeks of gestation. Nevertheless, this method remains imprecise because it depends on the observational abilities of the visual scorer.

4.6 | Summary

Caffeine increases fraction of wakefulness, alertness, and likely also arousability at cost of active but not quiet sleep. As such, caffeine should not affect time for physical and cerebral regeneration during sleep in preterm neonates. Additional studies in preterm neonates are warranted to optimize and personalize caffeine citrate dosing with the ultimate goal to maximize the benefit of the treatment while further mitigating the risk for negative caffeine-related effects on sleep quality in preterm neonates.

ETHIC STATEMENT

The study was approved by the local ethical committee (EKBB-Nr: 37/12), and conducted according to the principles of the Declaration of Helsinki.

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DISCLOSURE

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AUTHORS' CONTRIBUTIONS

Participated in research design: Kerstin Jost, Sven M. Schulzke, and Alexandre N. Datta. Conducted experiments: Natalie Schönfeld, Kerstin Jost, and Alexandre N. Datta. Performed data analysis: Gilbert Koch, Natalie Schönfeld, Kerstin Jost, Andrew Atkinson, and Marc Pfister. Wrote or contributed to writing the manuscript: Gilbert Koch, Natalie Schönfeld, Kerstin Jost, Andrew Atkinson, Sven M. Schulzke, Marc Pfister, and Alexandere N. Datta.

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