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The Effect of Sleep Continuity on Pain in Adults With Sickle Cell Disease

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Abstract: This analysis examined the influence of quantifiable parameters of daily sleep continuity, primarily sleep duration and sleep fragmentation, on daily pain in adults with sickle cell disease. Seventy-five adults with sickle cell disease completed baseline psychosocial measures and daily morning (sleep) and evening (pain) diaries over a 3-month period. Mixed-effect modeling was used to examine daily between- and within-subjects effects of sleep continuity parameters on pain, as well as the synergistic effect of sleep fragmentation and sleep duration on pain. Results revealed that nights of shorter sleep duration and time in bed, increased fragmentation, and less efficient sleep (relative to one's own mean) were followed by days of greater pain severity. Further, the analgesic benefit of longer sleep duration was attenuated when sleep fragmentation was elevated. These results suggest that both the separate and combined effects of sleep duration and fragmentation should be considered in evaluating pain in adults with sickle cell disease.

***Perspective:** Subjective parameters of sleep continuity (eg, sleep duration, fragmentation, and efficiency) predict clinical pain in individuals with sickle cell disease. Additionally, sleep duration should not be considered in isolation, and its association with pain may be qualified by sleep fragmentation. Research and practice should include assessments of both when addressing pain severity.*

***Key words:** Daily diaries, pain, sickle cell disease, sleep fragmentation, sleep continuity.*

Sleep is disrupted among individuals with chronic pain conditions, with daily diary studies finding abnormal sleep onset (>30 minutes), fragmented sleep (1–2 awakenings during the night and for >30 minutes), and inefficient sleep (80–85% sleep efficiency).[10,20,21,35]

A growing body of evidence suggests that poor sleep prospectively predicts increases in clinical and experimental pain.[8] Specifically, a limited number of studies have demonstrated that indices of sleep continuity, such as decreased sleep duration,[17,35] delayed sleep onset latency (SOL, >30 minutes),[17,35] and increased sleep fragmentation (ie, wake after sleep onset [WASO]) predict increased pain severity.[17] Investigations of sleep continuity are important because they provide an estimate of the association of sleep and pain that is less susceptible to retrospective heuristic biases than ratings of sleep quality, which may be influenced by feeling states present at the time of reporting.[15,27]

A few studies have identified sleep fragmentation (eg, high WASO) as a particularly harmful characteristic of sleep continuity. Smith et al[28] demonstrated that experimentally disrupting sleep continuity (ie, increasing WASO) significantly decreased endogenous pain inhibition and increased spontaneous pain in healthy participants. In 2 observational studies, increased sleep fragmentation significantly predicted higher next-day pain among adolescents and adults with chronic pain.[1,18] Although evidence generally supports the notion that sleep fragmentation increases vulnerability to pain, it is not known if sleep fragmentation interacts with other aspects of sleep continuity in predicting pain. For example, it would be important to know if the effects of sleep duration on pain are more pronounced or less pronounced in the context of fragmented sleep (relative to nonfragmented sleep), thereby elucidating the value of acquiring both longer and consolidated sleep.

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We elected to study sleep continuity and pain in adults with sickle cell disease (SCD) for several reasons. First, pain is the most commonly reported symptom of SCD and exhibits day-to-day variability.[19,31] Second, up to 70% of patients with SCD report sleep disturbances, including difficulty initiating and maintaining sleep.[14,34] Sleep continuity has not been quantified among nonsleep clinic adults with SCD; however, sleep-disordered breathing (eg, obstructive sleep apnea)[6,9] and pain[12,13,33] are common etiologies. Although disturbed sleep correlates with greater SCD pain,[12,13,33] and sleep is impaired during a vaso-occlusive crisis,[12,13] little is known about day-to-day variations in sleep, as well as the extent to which disrupted sleep continuity influences daily SCD pain.

Given the limitations of previous investigations, the goals of the present analyses were to examine the direct effect of parameters of sleep continuity during the night (sleep duration, latency, and fragmentation) on SCD pain experienced between waking and going to bed the following day (ie, next-day pain). We also examined the interacting, or synergistic, effect of sleep fragmentation and sleep duration on next-day pain in the course of daily life in adults with SCD. For the second goal, we hypothesized that the synergistic effect of decreased sleep duration and greater sleep fragmentation would be associated with the highest next-day pain severity.

Methods

Participants

Participants in these analyses are from a larger National Institutes of Health–funded study investigating dimensions of pain among individuals with SCD. Participants for the parent study were recruited through SCD clinics as well as posted flyers and advertisements. Individuals with SCD were eligible to participate in the parent study if they were 1) 18 years or older, 2) diagnosed with an SCD hemoglobinopathy genotype (HbSS, HbSC, HbS/β-thalassemia), 3) on a stable dose of nonsteroidal anti-inflammatory drugs, acetaminophen, or opioids (ie, no change in pain management regimen made by a clinician during the weeks prior to enrollment), 4) without a vaso-occlusive crisis within the past 3 weeks, and 5) willing to provide informed consent. Individuals with SCD were excluded from participation if they 1) were an active substance abuser, 2) had a significant cognitive impairment or mental disorder, 3) had current infection, 4) had received a diagnosis of an autoimmune disorder, 5) had human immunodeficiency virus infection with a neuropathy, or 6) were currently pregnant, lactating, or planned to become pregnant in the subsequent 6 months of the study. A total of 236 individuals with SCD were screened by phone for participation in the parent study; 84 were eligible after the phone screen, and 84 provided study consent.

Only participants with SCD from the parent study who completed the electronic daily diary assessment portion of the study (n = 78) were used in the present analyses. The diary assessment period was intended to be approximately 3 months; however, the total number of diary days varied among participants. We excluded participants (n = 3) who completed less than 1 week (<7 days) of diary entries and/or had a diary completion ratio (an index of diary adherence calculated as number of diaries completed out of the total number of days the participant carried the personal digital assistant) of less than or equal to 25%. At least 1 week of diaries is recommended for examining variations in sleep.[4] Additionally, large intervals between reporting days would decrease our ability to examine day-to-day variations in sleep. In total, 75 adults (96% of all participants with SCD who completed the electronic diary portion of the study protocol) were included in the subsequent analyses.

Procedure

An institutional review board at the study site approved all study procedures. Written informed consent was obtained from each study participant at the baseline study session. During the baseline session, psychosocial measures (eg, Center for Epidemiologic Studies Depression Scale [CES-D] and Pain Catastrophizing Scale [PCS]), demographic questions, and a medical and psychiatric history were collected.

At the conclusion of the baseline session, participants were provided with and trained on the use of an electronic handheld diary. The electronic diary included 2 reporting segments (morning for sleep and evening for daily pain) and was used to record daily experiences over the subsequent 3-month period.

Measures

Daily Measures

Electronic morning (sleep) and evening (pain) diaries were completed on a personal digital assistant (Palm personal electronic organizer; Palm Inc, Sunnyvale, CA) using a customized application. Responses to each sleep and pain item were logged into customized menus and data entry screens with the use of a stylus pen. Participants did not receive daily reminders to complete entries; however, participants were scheduled for a 1-week and as-needed follow-up to answer any questions about the diary and to identify any technical issues regarding its use in order to enhance compliance with data entry procedures. Participants received financial incentives based on the number of diaries completed.

During data cleaning, entries that were not completed within 12 hours of waking or bedtime were removed to decrease recall bias. Of the 5,839 days in which a personal digital assistant was carried across participants (average of 78 days per participant), 4,411 morning diaries (average of 59 entries per participant) and 4,549 evening diaries (average of 61 entries per participant) were included in our analysis.

Sleep Diary. Immediately on waking, participants were instructed to record what time they went to bed that night, their final awakening time, and what time they got out of bed that morning. Participants were also asked to estimate how long it took them to fall asleep (ie, SOL) and the total amount of time they spent