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A pilot randomized controlled trial to improve sleep and fatigue in children with CNS tumors hospitalized for high dose chemotherapy

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Abstract

Objectives: To determine whether a sleep intervention compared to standard of care (SOC) was successful in preserving nighttime sleep in children with central nervous system cancers hospitalized for high dose chemotherapy (HDCT) and autologous stem cell rescue, and to explore associations between sleep and fatigue during treatment.

Methods: An unblinded, randomized, controlled, multi-component intervention (NCT00666614) including evidence-based cognitive and behavioral strategies to improve sleep was implemented in 33 children (age 4-12y) and adolescents (age 13-19y) during hospitalization. Children wore an actigraph to measure sleep and wake, and reported fatigue scores daily. Parents concurrently kept a sleep diary and reported fatigue scores for their children.

Results: Mean age was 9.5±3.9 years, 81.8% were White, and 60.6% were male. Sleep in all children was seriously disturbed throughout the study. Children in the intervention group maintained their longest nighttime sleep across the study, while it declined in children receiving SOC (p=0.009 for interaction). There were few other differences in sleep between groups.

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CONFLICT OF INTEREST

Dr. Sonia Ancoli-Israel is a consultant for Eisai Inc., Eli Lilly and Co., Merck, Pfizer and Purdue Pharma, although has no conflicts of interest related to this research. All other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Controlling for age and baseline fatigue, higher nighttime activity score and lower percent sleep were significantly associated with higher next day adolescent-reported fatigue ($p<0.05$); longest sleep was significantly positively associated with next day child-reported fatigue ($p=0.018$).

Conclusion: In this sample of children undergoing HDCT, a multi-component sleep intervention modestly preserved nighttime sleep duration, although overall sleep was poor in both groups. Sleep is an integral component of health, and may influence outcomes of children receiving HDCT. Further investigation into methods of preserving sleep in children undergoing intensive cancer therapy is warranted.

Keywords

actigraphy; CNS tumor; chemotherapy; children; adolescents; sleep

INTRODUCTION

Central nervous system (CNS) cancers are the most frequently occurring solid tumors in children and most common cause of cancer deaths among children 0-14 years of age.[1] Despite improvements in survival, morbidity remains high.[2,3] Sleep disturbances are frequently reported during treatment and survivorship.[4–7] Damage to the circadian pacemaker in the hypothalamus during surgery, and irradiation of the hypothalamic-pituitary axis disturb secretion of hormones regulating sleep and wake such as melatonin.[8] Hospitalization for cancer treatment disrupts children's sleep pattern through changes in routines, environmental light and noise, pain, chemotherapy side effects and awakenings for care provision.[5,9] High dose chemotherapy (HDCT)/stem cell transplantation appear to confer particularly severe sleep problems, in the short-term during transplant and over the longer-term in survivors.[10–12]

Sleep disturbances are associated with significant long-term morbidities. Short duration and poor quality sleep are associated with suboptimal neurodevelopmental outcomes in healthy children,[13,14] and with development of cardiovascular and metabolic disease and obesity.[15] Sleep also plays a key role in immune system function.[16,17] Thus, maintaining healthy sleep in children who also have cancer becomes even more important.

Feasibility and effectiveness of sleep interventions designed around components of cognitive behavioral therapy for insomnia such as sleep education, stimulus control, relaxation and sleep hygiene have been demonstrated in school-aged children[18] and adolescents with insomnia,[19,20] adolescents with insomnia and physical or psychiatric comorbidities,[21,22] and adolescent and young adult cancer survivors.[23] Little is known about how sleep might be preserved during intensive cancer therapy in the hospital. In one of the few hospital-based intervention studies, Hinds, et al.[24] successfully implemented an enhanced physical activity intervention (peddling a stationary bicycle) in children 7-18 years of age hospitalized for treatment of solid tumors or leukemia. Sleep efficiency of children in the intervention group was significantly better than controls when modeled using ANOVA, although was not replicated in mixed model analyses. In another study, Ekti Genc et al.[25] implemented a multi-component intervention including daytime walking, limited napping, and bundled nighttime nursing care to preserve sleep in hospitalized children aged 7-12 years with

leukemia and lymphoma receiving chemotherapy.[25] Although sleep was not reported, fatigue was significantly lower in the intervention group than in controls. This sparse literature highlights the challenges of delivering sleep interventions in a hospital setting. Given the relationship of sleep to physiological function and neurocognitive development of children, preserving sleep during treatment may be important to improving outcomes of children with cancer.

Therefore, a randomized, controlled pilot study was implemented in children and adolescents with CNS cancers during hospitalization for HDCT followed by autologous hematopoetic stem cell rescue (aSCR). The main aims were to determine the feasibility and preliminary efficacy of a multi-component sleep intervention. A secondary aim was to explore the relationship between sleep and fatigue.

METHODS

Study design and participants

This was a single-site, unblinded, randomized controlled sleep intervention trial (ClinicalTrials.gov, NCT00666614). It was implemented in conjunction with St. Jude Children's Research Hospital (St. Jude) Protocol SJMB03, a phase III trial recruiting children with medulloblastoma or histologically similar CNS tumors.[26] Under SJMB03, participants underwent surgery and six weeks of craniospinal radiation. This was followed by hospital admission for HDCT/aSCR, which repeated every four weeks for four courses. Participation in the sleep intervention began on the day of admission (Day 0) for the second or third course and ended on the day of aSCR (day 5). Alignment of the two studies is depicted in Figure 1. Eligibility beyond that of SJMB03 included children aged 4-19 years able to self-report symptoms, and English speaking parent and child. This study was approved by the St. Jude Institutional Review Board prior to data collection. The present secondary data analysis was granted exempt status by the University of Maryland Human Research Protections Office.

Sleep intervention

The intervention was implemented between May, 2008 and August, 2011. Outcomes of nighttime sleep and mood have been published.[11] Methods are described here briefly, with a detailed description in Appendix S1. Study arms included the sleep intervention (INT) and standard of care (SOC) control groups. A group randomized design, randomizing by month of the year, was used to minimize condition contamination. The INT group received multi-component cognitive and behavioral interventions delivered by one of three trained research staff, including verbal and written age-appropriate sleep education, and relaxation training delivered on Day 0. Following training, parents implemented a relaxation technique (e.g. storytelling, book reading, massage) selected by the participant nightly before lights-out. Stimulus control measures, delivered daily throughout the study, were aimed at decreasing nighttime environmental sleep disruptors. They included establishing a lights-out time (including turning off electronic equipment) and morning lights-on time; choice of white noise program; thick black fabric placed over room windows to minimize light entry; and 90-minute protected sleep periods with bundled care between periods, instituted by nursing

staff from lights-out to lights-on. Compliance was verified by an entry/exit log completed by staff and family. The protected time frame was chosen to fit within the protocol of voiding every 2 hours following cyclophosphamide administration. The SOC group received standard nursing care for HDCT/aSCR, with the addition of personal time spent each evening with research staff, as an attention-control measure.

Integrity of the intervention was maintained through development of a manual detailing step-by-step guidelines for each encounter with patients/parents (Appendix S2). Research staff were trained on study protocol and implementation, with demonstration/return demonstration of study competencies. Quarterly refresher in-services, and observations of live study implementation with families using a standardized checklist were performed with each team member. Meetings between research and nursing staff occurred regularly to strategize protection of sleep periods. A research team member verified implementation of white noise programs, window covers, lights-out, and placement of a protected sleep sign outside the room each evening. They returned each morning to initiate lights-on and remove window covers and sign.

Measures

Actigraphy: A Micromini actigraph (Ambulatory Monitoring, Inc., Ardsley, NY) was worn on the non-dominant wrist continuously throughout hospitalization. These accelerometers measure movement, from which sleep and wake variables are estimated using manufacturer software (Action-W version 2.7). Actigraphy provides a valid estimate of sleep in typically sleeping children,[27] but is not validated in hospitalized children. Therefore, we made data editing decisions based on available literature to best capture children's sleep/wake patterns. Nighttime was considered the period from 9 PM to 9 AM, and daytime the period from 9 AM to 9 PM. Normal nighttime sleep periods with diary-reportable bedtimes and wake times were absent for nearly all children. Instead, episodic sleep and wake occurred throughout the 24-hour periods. Therefore, variables were chosen that reflected differences in sleep and wake between the daytime and nighttime periods. These included percent sleep, number of sleep/wake episodes, mean duration of sleep/wake episodes, longest sleep/wake episode and activity score (defined in Table 1), calculated for daytime and nighttime periods. Total sleep time was calculated for comparison to minimum recommended sleep guidelines.[28] A minimum of 72 hours of valid actigraphy data were required, excluding four participants. Periods with more than 2 hours of missing data (off-wrist or artifact) were excluded.[29] This resulted in a mean 4.8 days of actigraphy data per participant.

Sleep diary: This was a 16-item parent-report of their child's sleep patterns, and circumstances disrupting sleep.[30] Parents completed sleep diaries daily, concurrently with actigraphy.

Fatigue: Three questionnaires measured fatigue. Intensity of fatigue symptoms was reported using a 5-point Likert-type scale scored from 1-5 for all measures. Higher scores indicated greater fatigue. The reduced Fatigue Scale-Child is a 10-item measure completed by children aged 7-12 years. Reported Cronbach's alphas range from 0.72-0.81[31] and in this

study was 0.84. A cut-point of 12, based on Likert scale responses from 0-4, indicates risk for significant fatigue,[32] thus the cut-point was adjusted to 22 for this study. The reduced Fatigue Scale-Adolescent is a 13-item self-report measure for ages 13-18 years. Reported Cronbach's alpha range from 0.89-0.95[33] and in this study was 0.91. A cut-point of 31 indicates risk for significant fatigue.[34] The Fatigue Scale-Parent is a 17-item parent-report of their child's fatigue. Reported Cronbach's alpha range from 0.88-0.92[31,33] and in this study was 0.94. No cut-point has been established. Children under seven years of age did not self-report. Age-appropriate questionnaires were completed daily.

Demographic and treatment history: Collected variables included age, race, sex, total body radiation, tumor location and tumor risk classification. Age was dichotomized into children (4-12 years) and adolescents (13-19 years). Tumor location was categorized as infratentorial, supratentorial, or spine only. Risk classification included average risk (localized tumor) or high risk (metastatic disease/residual tumor).

Statistical analysis

Descriptive statistics (mean±standard deviation, range, percent) were used to describe the sample and their sleep. To evaluate whether children were meeting sleep recommendations, 24-hour total sleep time averaged across the study was subtracted from each participant's age-group sleep recommendation.[28] Assumptions (e.g., normality) and missing data patterns were checked. Independent t-tests or Mann-Whitney tests were employed to test differences between groups on sleep/wake variables. Cohen's d effect sizes[35] were calculated for group differences on sleep/wake variables. Generalized linear mixed models (LMMs) were used for exploratory analyses of group differences in change across time for sleep/wake variables, controlling for age group (Aim 1); and the effect of daytime fatigue on that night's sleep and nighttime sleep on next day fatigue using separate models for each sleep variable, controlling for age group and baseline (Day 0) fatigue (Aim 2). Analyses were carried out using IBM SPSS Statistics, Version 21 (Armonk, NY: IBM Corp.) and STATA 15 (StataCorp. 2017). Significance was a p-value <0.05. No corrections were made for multiple comparisons.[36]

RESULTS

Participants

Fifty-six families were recruited and 43 consented. Six children were later excluded due to increased acuity. Four children were excluded for inadequate actigraphy data, resulting in 33 participants (INT=17, SOC=16). Mean age of the sample was 9.5±3.9 years. Twenty-four (72.7%) participants were children and nine (27.3%) were adolescents. Twenty (60.6%) were male; and 27 (81.8%) were White, five (15.2%) were Black/African American and one (3.0%) was Asian. Tumor location included 25 (75.8%) infratentorial, seven (21.2%) supratentorial, and one (3.0%) spine only. Sixteen (48.5%) participants were classified as average risk and 17 (51.5%) as high risk. Study groups did not differ on age, sex, race, tumor location, risk classification or total radiation dose.

Intervention feasibility

All children completed the study. No adverse outcomes resulted from the intervention; on the contrary, parents had many positive comments about how helpful the intervention was for improving sleep. Protection of the 90-minute sleep periods by hospital staff and parents was confirmed by room entry logs. Intervention delivery was confirmed through research team delivery for every participant every day. INT parents self-reported delivery of relaxation techniques on a Patient Activity Log (Appendix S2). All observations of intervention integrity were performed and documented per protocol. Thus, feasibility of the stimulus control components and intervention integrity monitoring was demonstrated. Compliance with relaxation delivery was confirmed on 39.5% of days and denied on 37.0% of days, with missing data on 23.5% of days. Retention of sleep education was not objectively verified.

Sleep and wake

Nighttime sleep was profoundly abnormal for all children. Only 48.5% of children achieved the minimum recommended 24-hour sleep duration[28] (Table 2), with the youngest children incurring the greatest sleep deficit. Common parent-reported sleep disruptors included nausea, vomiting and diarrhea; and awakenings by staff every two hours to void as part of a bladder-protective protocol. Others included pain, fever and intravenous pump beeping. There were no univariate group differences on any nighttime sleep/wake variable. Actigraphy data and Cohen's d are presented for daytime and nighttime periods by study group (Table 3).

Exploratory LMMs demonstrated a significant study group-by-study day interaction for longest nighttime sleep episode (b=9.85, 95%CI 2.49, 17.22, p=0.009). Post hoc analysis showed that longest sleep episode in the SOC group, which was longer at baseline relative to INT, declined across the study, while there was no significant change over time in the INT group. Study group-by-study day interaction for mean length of nighttime sleep episode (b=4.04, 95% CI −.48, 8.56, p=0.080) approached significance, with mean length of sleep decreasing over time in the SOC group while remaining stable in the INT group. These findings suggest the sleep intervention helped preserve sleep consolidation. Nevertheless, the percent of children who achieved at least one 90-minute nighttime sleep episode declined across days 0-3 (60.6%, 48.5%, 33.3%, 18.2%, respectively) and slightly increased (39.4%) on day 4, with no differences between groups.

Daytime wakefulness was also abnormal for most children, who spent the daytime sleeping intermittently. Overall mean number of daytime sleep episodes was 5.0±0.8. Few children did not sleep during the daytime (3, 3, 2 and 4 children across days 1-4, respectively). There were no differences between groups on any daytime variable. Figure 2 depicts the actogram of one participant, to demonstrate the abnormal sleep/wake pattern.

Fatigue

Overall, 53.3% of children and 77.8% of adolescents scored above the cut-point for risk of significant fatigue. There were no differences in fatigue between groups on any fatigue measure. For the secondary hypotheses, higher activity score (p=0.014) and lower percent

sleep (p=0.001) at nighttime were significantly associated with higher next day adolescent-reported fatigue (Table 4). Contrary to expectations, longest nighttime sleep episode was significantly positively associated with higher next day child-reported fatigue (p=0.018), suggesting that younger children may be particularly susceptible to sleep fragmentation, increasing their pressure to sleep[37] yet still increasing their fatigue. There were no effects of any sleep variable on next day parent-reported fatigue. Likewise, there were no effects of daily fatigue reports (child, adolescent, parent) on that night's sleep for any variable.

DISCUSSION

We found that implementing a sleep intervention was feasible in children and adolescents hospitalized for HDCT. Sleep did not meet daily recommendations for over half of participants, and was characterized by severe sleep fragmentation regardless of study group. Mean duration and longest nighttime sleep episode decreased across the study in the SOC group while remaining stable in the INT group, a significant interaction. Finally, higher fatigue was associated with higher nighttime activity and lower percent sleep in adolescents, but longer sleep episodes in children.

Sleep is integral to maintaining good mental health, a challenge for many cancer patients undergoing treatment. It also has a restorative function, supporting physiological processes including immune system function.[17] Our sample was at a major disadvantage for obtaining adequate duration and quality of sleep due to treatment factors (surgery, radiation, HDCT) and environmental factors (hospitalization). Some aspects of sleep appeared to be preserved by this sleep intervention, yet, despite our finding that many participants achieved at least the minimal recommended 24-hour sleep duration, sleep quality was poor for all children. Achieving merely the minimal sleep duration is unlikely to be adequate for children or adolescents undergoing HDCT who likely require more and higher quality sleep than their healthy counterparts to support immune function and achieve adequate recovery. Additionally, in our sample the youngest children had the greatest sleep deficits. While the reason for this is unclear, it is possible that younger children may be at greater risk for poor sleep in the hospital because they are more distracted by the busy hospital environment, or less able to sleep in an environment different than their own home, relative to adolescents.

Sleep might also influence outcomes of stem cell therapies. One study, using a murine model of stem cell transplantation demonstrated that migration of intravenously infused stem cells into the bone marrow was slowed when the donor was sleep deprived.[38] In our patients who self-donate stem cells, even sleep prior to bone marrow harvest may be important for recovery of blood counts post-HDCT/aSCR. In addition, melatonin, a hormone of the pineal gland that helps regulate sleep-wake cycles, is a powerful free radical scavenger with oncostatic activity.[39] In pre-clinical and clinical studies, melatonin supplementation was shown to improve stem cell survival in recipients, and to ameliorate damage to multiple organs from radiation and HDCT.[40,41] It is unknown whether these findings apply to pediatric cancer patients. They do, however, suggest that measures to promote sleep and protect endogenous melatonin secretion may be important to the success of aSCR.

Clearly, bundling care and multi-component cognitive and behavioral strategies are inadequate to maintain healthy sleep in children undergoing HDCT, as many children failed to achieve a single 90-minute sleep period. Under current CNS cancer treatment protocols, healthy sleep may not be achievable. Future sleep interventions may be more impactful if aimed at establishing healthy sleep patterns prior to hospitalization, in preparation for intensive therapy, and at restoring sleep following hospital discharge to maximize treatment outcomes. Sleep may also be more amenable to intervention in hospitalized children undergoing less intensive treatment than HDCT/aSCR.

Treatment protocols that lessen toxicity yet maintain their efficacy, or adjunct therapies that help mitigate toxicities, may become a possibility in future treatment of childhood cancers and also hold potential for improving sleep during cancer treatment. For example, chronotiming of chemotherapeutic agents, which capitalizes on the circadian biology of an individual's tumor and their personal circadian variation in pharmacokinetic and pharmacodynamic actions on drugs is an active area of research. Chronopharmacology in cancer is still in its infancy, but has already been shown effective in lowering doses of some drugs while providing equal effectiveness and a better toxicity profile.[42] These studies have largely included adults, but should be extended to children. Current research on melatonin supplementation during cancer treatment is evaluating outcomes such as improving sleep, appetite, effectiveness of radiation therapy in brain tumor patients, and immunological and inflammatory markers; and decreasing neurocognitive deficits and breast cancer risk.[43,44] Nearly all study adult cancer patients, however, with only one trial on ClinicalTrials.gov involving children—a phase I dose finding study for melatonin in relapsed brain tumor patients. Further studies testing melatonin for sleep promotion and improvement of other cancer outcomes should be considered in pediatric cancer patients.

The potential for improving health outcomes through modifications in clinical care should also be considered. Sleep of all children with cancer can benefit from supportive interventions, even those hospitalized for intensive therapies. Hospitals should foster a commitment to promoting healthy sleep environments for patients. This could begin at admission, by taking a sleep history to assess home bedtime routines and environments conducive to sleep that could be modified for hospital application. Protected sleep periods that take patient safety and treatment requirements into consideration could be implemented, with proactive medication between periods for anticipated sleep-disrupting side effects of treatment. Additional measures could include regulating environmental light and noise levels during the designated nighttime period, and limiting patient and family use of electronic devices after bedtime. Finally, daytime activities could be organized by child life specialists and physical therapists to promote socialization and prevent excessive napping, which can disrupt nighttime sleep, tailored to the child's condition.

This study had several limitations. We did not have statistical power to compare differences between children and adolescents, whose sleep requirements differ. Thus, our results are preliminary and require verification with larger samples. The study took place in a single, research-based institution, limiting generalizability of these findings to other settings where staffing constraints and unit leadership may be less supportive of changes in established care routines. We did not measure the effect of certain components such as sleep education or

relaxation, thus are unable to estimate their importance relative to stimulus control measures. It is possible that there was diffusion of bundled care by nursing staff into the SOC group, or that drift in intervention integrity by research staff occurred, which may have resulted in fewer group differences in sleep. Differences in other sleep disruptors, such as light and noise after bedtime, were not verified objectively (e.g. with light or sound meters). Finally, no record of the number or timing of negative treatment effects such as nausea, vomiting, diarrhea or pain was kept to estimate their role in sleep disruption.

There is scant published research testing interventions to improve sleep in hospitalized children, and fewer still in children with cancer undergoing intensive therapy. Although our intervention required coordination and planning beyond the time required for routine patient care, feasibility of this pilot study and preliminary efficacy in preserving sleep was demonstrated. Future studies should track sleep interruptions due to treatment and environmental disruptors to account for their effect on sleep duration and quality. This research should also be expanded to hospitals other than research institutions, additionally examining the feasibility of incorporating trained staff other than nurses, including child life specialists, nursing assistants or even volunteers, to carry out components of the intervention. While we did not evaluate costs of this intervention, in smaller hospitals with more constrained budgets and staffing, multidisciplinary involvement could make implementation of sleep interventions more practical.

In conclusion, bundled care and cognitive-behavioral strategies had a measurable, if modest, effect on preserving sleep in children with CNS cancers admitted for HDCT. Yet few other differences were found between groups, despite a rigorously implemented, evidence-based, multi-component sleep intervention. In order to further improve sleep in these children—an achievement that has potential to improve health outcomes, a better understanding of the causes of sleep disruption and development of innovative interventions addressing these mechanisms are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

aSCR	Autologous hematopoetic stem cell rescue
CNS	Central nervous system
HDCT	High dose chemotherapy
INT	Sleep intervention study arm

LMMs	Generalized linear mixed models
SOC	Standard of care study arm
St. Jude	St. Jude Children's Research Hospital

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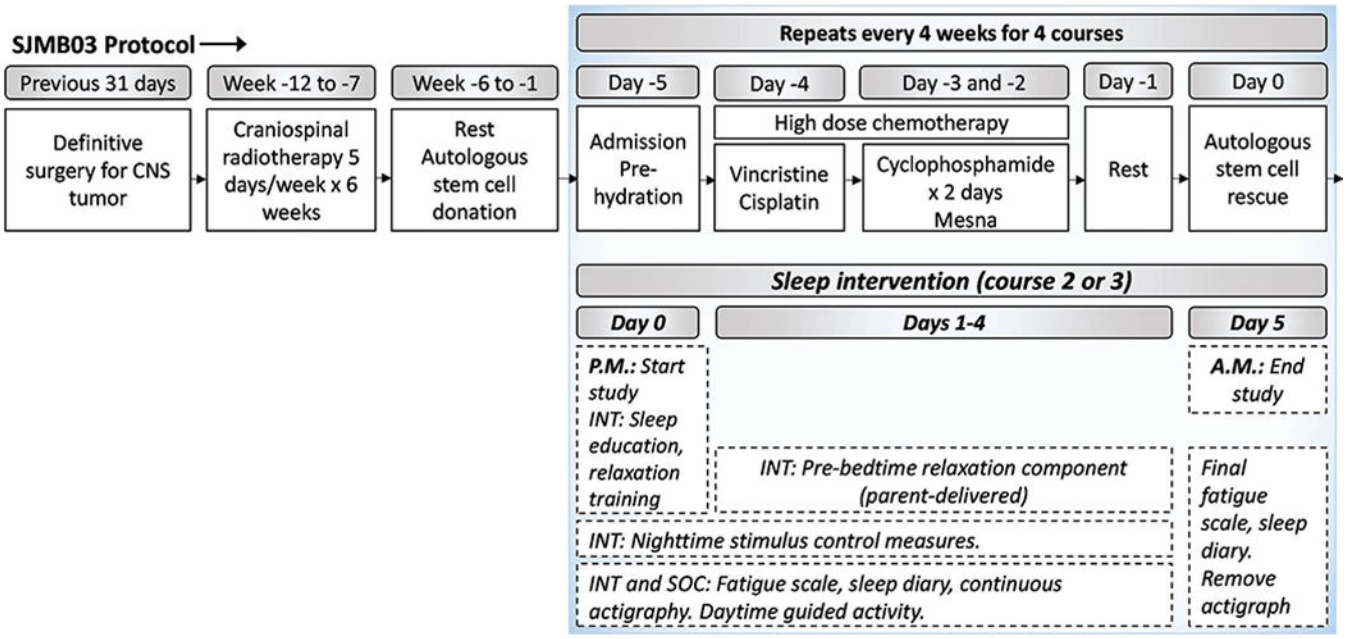

Figure 1.

Alignment of timing of the StJude SJMB03 CNS cancer treatment protocolflow depicted across the top of the figureand the pilot sleep interventionflow depicted below SJMB03 protocol days-5 through 0

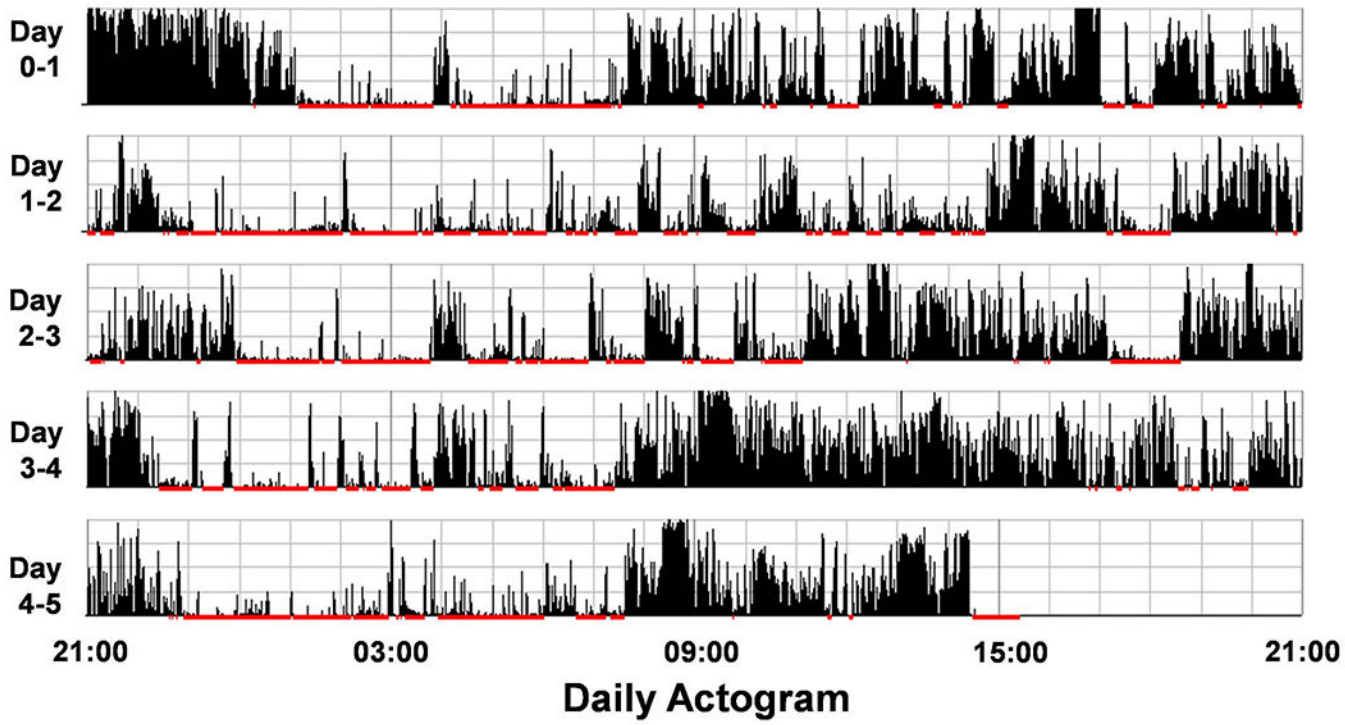

Figure 2.

Actogram of child undergoing high dose chemotherapyEach row depicts one dayfrom 9 PM21 00to 9 PM the following dayBlack vertical lines indicate frequency and vigor of activity across time broken red

TABLE 1

Definition of actigraphy variables

Variable	Definition
Total sleep time (min)	Number of minutes scored as sleep across each 24-hour period.
Percent sleep (%)	Percent of minutes scored as sleep ([# minutes scored as sleep / duration of period, in minutes] * 100) during a period of interest (e.g. daytime, nighttime or 24-hour periods). Higher during nighttime, lower during daytime, is better.
Mean duration sleep episodes (min)	Mean duration of all sleep episodes lasting ≥5 minutes, in minutes. Longer during nighttime is better.
Sleep episodes (#)	Number of sleep episodes lasting ≥5 minutes. Fewer episodes (that are longer during nighttime, shorter during daytime) indicate better consolidation of sleep and wake.
Longest sleep episode (min)	Duration of the longest sleep episode, in minutes. Longer during nighttime is better.
Mean duration wake episodes (min)	Mean duration of all wake episodes lasting ≥5 minutes, in minutes. Shorter during nighttime and longer during daytime are better.
Wake episodes (#)	Number of wake episodes lasting ≥5 minutes. Fewer episodes (that are shorter during nighttime, longer during daytime) indicate better consolidation of sleep and wake.
Longest wake episode (min)	Duration of the longest wake episode, in minutes. Longer during daytime and shorter during the nighttime is better.
Activity score	Mean number of activity counts per epoch (minute) for the time period being scored. Higher during daytime and lower during nighttime are better.

TABLE 2

Sleep in hospitalized children with CNS cancers undergoing high dose chemotherapy and comparison to age-group recommendations

	Full sample, N=33	Preschoolers, n=7	School-age, n=20	Teens/young adults, n=6
[a]Total sleep time (min)	537.5 ± 130.9	508.3 ± 128.7	545.7 ± 129.3	544.3 ± 157.1
[a]Total sleep time (h)	8.96 ± 2.2	8.5 ± 2.1	9.1 ± 2.2	9.1 ± 2.6
Recommended minimum 24-h sleep[28]	N/A	10 h (600 min)	9 h (540 min)	8 h (480 min) teens, 7 h (420 min) young adults
[b]Sleep difference (min)	2.46 ± 139.3	91.7 ± 128.7	−5.7 ± 129.3	−74.3 ± 149.1
Achieved minimum sleep recommendation (%)	48.5	14.3	55.0	66.7

Note:

[a]Mean ± SD of 24-h total sleep time averaged across the study, measured by actigraphy;

[b]Recommended sleep minus achieved sleep (positive value indicates sleep deficit). Age-groups are defined in the National Sleep Foundation recommendations[28]: preschoolers, 3-5 years; school-age children, 6-13 years; teens, 14-17 years; young adults, 18-25 years.

TABLE 3

Actigraphy-derived sleep and wake of children with CNS cancers admitted for high dose chemotherapy, N=33

	Daytime (9 AM to 9 PM)			Nighttime (9 PM to 9 AM)		
	INT	**SOC**	**Cohen's d**	**INT**	**SOC**	**Cohen's d**
Percent sleep (%)	17.3 ± 10.3	18.5 ± 10.7	0.114	56.6 ± 10.5	58.3 ± 12.4	0.157
Mean duration sleep episodes (min)	16.1 ± 5.9	16.9 ± 6.2	0.132	23.1 ± 8.5	26.3 ± 14.5	0.269
Sleep episodes (#)	4.6 ± 2.7	5.5 ± 3.8	0.273	12.3 ± 2.2	12.5 ± 3.0	0.076
Longest sleep episode (min)	41.8 ± 14.8	45.5 ± 16.3	0.238	87.6 ± 32.0	92.9 ± 26.0	0.182
Mean duration wake episodes (min)	167.2 ± 115.1	159.2 ± 126.8	0.066	17.1 ± 5.4	17.9 ± 9.4	0.104
Wake episodes (#)	5.8 ± 2.4	7.2 ± 3.9	0.432	10.7 ± 2.4	10.9 ± 2.6	0.080
Longest wake episode (min)	361.1 ± 124.6	342.1 ± 139.6	0.144	104.8 ± 26.8	112.0 ± 60.0	0.155
Activity score	155.9 ± 45.4	146.1 ± 45.2	0.216	62.9 ± 19.6	59.5 ± 23.0	0.159

Note:

INT, intervention group; SOC, standard of care group. All numbers presented as mean ± standard deviation of all available actigraphy periods. There were no significant differences between groups for any daytime or nighttime sleep/wake variable by t-test. Classical Cohen's d ($d = \frac{\left|m_1^2 - m_2^2\right|}{\frac{\sqrt{s_1^2 + s_2^2}}{2}}$, where m_1 or m_2=mean of group 1 or group 2, s_1 or s_2=standard deviation of group 1 or group 2), was used to calculate effect sizes, all of which were small based on Cohen's[35] proposed interpretation (0.2=small; 0.5=medium; 0.8=large).

TABLE 4

Effects of nighttime sleep on next day fatigue in linear mixed models (n=33)

Predictive variables	Outcome variables					
	Parent report fatigue		Adolescent report fatigue		Child report fatigue	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Percent sleep (%)	−0.003 (−0.13, 0.12)	0.966	**−0.22 (−0.35, −0.09)**	**0.001**	0.07 (−0.06, 0.19)	0.299
Mean duration sleep episodes (min)	0.03 (−0.05, 0.11)	0.530	0.01 (−0.06, 0.08)	0.741	0.04 (−0.12, 0.19)	0.629
Sleep episodes (#)	0.05 (−0.34, 0.44)	0.798	0.12 (−0.29, 0.54)	0.561	−0.23 (−0.74, 0.27)	0.366
Longest sleep episode (min)	0.004 (−0.03, 0.04)	0.844	−0.02 (−0.06, 0.02)	0.258	**0.05 (0.01, 0.10)**	**0.015**
Mean duration wake episodes (min)	0.07 (−0.05, 0.19)	0.270	0.07 (−0.03, 0.16)	0.156	−0.01 (−0.21, 0.19)	0.920
Wake episodes (#)	0.001 (−0.41, 0.41)	0.998	0.05 (−0.42, 0.53)	0.831	−0.35 (−0.83, 0.12)	0.147
Longest wake episode (min)	−0.02 (−0.04, 0.01)	0.262	0.02 (−0.01, 0.05)	0.201	−0.01 (−0.04, 0.01)	0.321
Activity score	−0.02 (−0.09, 0.04)	0.479	**0.09 (0.02, 0.16)**	**0.014**	−0.01 (−0.08, 0.05)	0.741

Note. All models controlled for baseline (day 0) fatigue and age group.

Significant models are denoted in bold font.