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Few Changes Observed in Polysomnographic-Assessed Sleep Before and After Completion of Chemotherapy

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Abstract

Objective—Sleep disturbance is prevalent among patients undergoing chemotherapy and is strongly associated with cancer-related fatigue (CRF). However, little objective evidence has been gathered on the patterns of sleep before and following chemotherapy.

Methods—26 Patients scheduled to receive chemotherapy were recruited. Sleep parameters were assessed by in-lab polysomnography (PSG) for two consecutive nights prior to first chemotherapy, approximately three weeks following the patient's last chemotherapy, and three months following the last treatment. Fatigue was measured on the first night of each of the two-night PSG assessments. We focus on Slow-Wave Sleep (SWS) as we hypothesized that a decrease of this restorative phase of sleep might be implicated in CRF.

Results—Repeated-measures analyses examining changes from baseline to the later time points in the proportion of time asleep spent in each of the four sleep architecture stages (Stage 1, Stage 2, SWS, and REM sleep) were non-significant, all $P_s > 0.41$. Canonical correlation analysis showed that the proportion of time spent in SWS was not significantly correlated with any of the three CRF measures at any of the three assessment points, $P = 0.28$.

Conclusions—Sleep architecture is not affected by cancer treatment. No evidence of an association between CRF and SWS, or alterations in SWS, was found.

Keywords

Polysomnography; Chemotherapy; Sleep; Fatigue; Slow-Wave Sleep

Introduction

Nearly 30 years ago, descriptive studies of cancer patients indicated that sleep difficulties were a common problem experienced by as many as 45%.¹⁻³ A 2001 review supported these findings of a high prevalence of disrupted sleep in cancer patients; the majority of reviewed studies reported prevalence rates of approximately 50%.⁴ Other studies have shown a high prevalence of insomnia in patients receiving chemotherapy and that sleep difficulties begin prior to receipt of chemotherapy and may persist well beyond the active illness and/or ongoing treatment.⁵⁻¹²

Apart from its ubiquity, difficulties with sleep are strongly associated with CRF and are thought to be an important contributing factor and consequence of this problem. The majority of studies that have prospectively assessed the relationship between fatigue and sleep in patients with cancer or in cancer survivors reveal strong correlations between fatigue and various sleep parameters, including poor sleep quality, poor initiation and maintenance of sleep, lower perceived adequacy of sleep, insufficient sleep, sleep disturbance, night-time awakening, and restless sleep.¹⁰⁻¹⁹ In spite of the significant correlations observed many times between sleep difficulties and CRF, the true relationship between these two symptoms/syndromes is not fully understood.¹⁸ This may stem, in part, from difficulties in measuring and quantifying sleep in cancer patients, with researchers typically relying on self report measures and/or actigraphy for this purpose. Both types of measures have their weaknesses (see Krystal and Edinger²⁰ for a complete discussion of sleep assessment methods) and do not correlate well in cancer patients.⁵

One way to further elucidate the association between sleep disturbance and fatigue in cancer patients is with the use of PSG. This method, considered the gold standard for the assessment of sleep,²⁰ includes the use of electroencephalograms (EEGs) to provide direct and quantitative measures of cortical activity during sleep (in the form of brain waves). These measures are co-acquired with electrophysiologic measures of eye movement, muscle activity, respiratory flow and effort, oxygen saturation, and heart rate and rhythm. When assessed concomitantly, these signals allow for the full characterization of sleep in terms of sleep continuity, sleep architecture, and cardiac and respiratory function. The sleep continuity data derived from this technique include sleep latency (time taken to fall asleep), wake after sleep onset time, total sleep time, and sleep efficiency (SE). The sleep architecture information derived from this technique consists of the assessment of sleep in terms of its constituent component stages (i.e., percent Stage-1, Stage-2, SWS, and REM sleep). While the functions of these various stages are largely unknown, some evidence indicates that REM sleep is associated with mood and memory function and that SWS is linked to the duration of wakefulness^{21,22} and restorative processes.^{23,24}

A few studies have reported PSG assessments of sleep patterns in cancer patients. A study in 1985 assessed insomnia in patients receiving radiotherapy and found that patients' perceptions of how well they slept were significantly related to the amount of SWS they obtained.²⁵ The investigators considered this to be an unusual finding because perception of sleep quality in non-cancer patients is generally related to SE and not to specific stages of sleep. The authors suggested that SWS may be more critical for the cancer patient than for

normal individuals. This hypothesis is consistent with other research showing a relationship between SWS and biological recovery.²⁶ Two decades later, Savard and colleagues (2005) reported on fifty-seven breast cancer survivors an average of 30 months following completion of treatment who were randomly assigned to cognitive behavioral therapy for insomnia (CBT-I, n=27) or a wait-list control group (n=30).²⁷ PSG assessments were used to verify the effectiveness of the CBT-I intervention and showed that SE increased from ~70% to 85% in the treatment group compared with an increase from ~71% to 75% in the control group. A later report on that same study found that objective sleep improvements were correlated with reduced dysfunctional beliefs about sleep and less daytime napping.²⁸

A 2008 study evaluated sleep/wake cycles in patients with advanced cancer and found that patients had reduced quantity and quality of sleep when compared to normative data.²⁹ Sleep in the cancer patients was characterized by an average SE of only 77.2% and a relative absence of SWS. Patients also exhibited difficulty maintaining their current state of sleep or wakefulness. These findings suggest not only an inability to maintain sleep but also an inability to achieve “deep sleep.” Both findings may implicate abnormal sleep-wake homeostasis. Finally, a 2011 study by Budhiraja and colleagues compared polysomnographic sleep in a large community-based sample of 3282 participants with various medical disorders. The study found no significant differences in polysomnographic sleep in participants with and without cancer, although their cancer sample who underwent PSG was relatively small (N=30). In addition, it was not stated whether these participants were cancer patients (currently undergoing treatment) or survivors (finished with treatment). Interestingly, the study found lack of differences in PSG-measured sleep for most medical disorders assessed, suggesting that perhaps changes in polysomnography associated with insomnia and medical illness are rare.³⁰

To our knowledge, the study described herein is the first to conduct PSG both prior to and following chemotherapy in the same patients to assess changes brought about by treatment. While we report on eight different sleep parameters, we focus on SWS as we hypothesized that a decrease of this restorative phase of sleep might be implicated in CRF.²⁶

Methods

We assessed sleep architecture and sleep continuity via PSG at three time points in patients receiving chemotherapy. The first assessment was scheduled to occur prior to first chemotherapy, and the second assessment was scheduled to occur approximately three weeks following the last chemotherapy. The final assessment was scheduled to occur 12 weeks following the completion of all chemotherapy and radiation treatments.

Potential subjects were identified at their first medical oncology visit and were referred to study staff if they had a planned course of chemotherapy lasting between 9 and 33 weeks. Subjects were permitted to receive concurrent or sequential radiation therapy provided that all treatments were intended to be completed by 33 weeks. To be eligible, patients were required to have a stable sleep/wake schedule (no shift work) with a preferred sleep phase between 10:00 PM and 9:00 AM. Beta blockers or medications for depression or thyroid disorders were allowed provided the dosage was unchanged for at least one month prior to

study entry. Concurrent interferon treatment or a history of chemotherapy treatment in the past three years was prohibited. The study excluded subjects with current substance abuse or a history of post-traumatic stress or psychotic disorders. Additional exclusion criteria included taking any prescription medication for the control of anxiety, sleep, or fatigue or taking any over-the-counter medications known to affect sleep. All ancillary treatments, as appropriate for control of symptoms caused by the cancer or its treatment, were administered as clinically indicated. The protocol was approved by the Institutional Review Board of our Medical Center, and all patients provided written informed consent.

Procedures

The PSG data were collected exclusively in the University of Rochester Sleep Research Laboratory. Previously established and published procedures for conducting the PSG and scoring of the PSG data were followed.³¹ Enrolled subjects checked into the laboratory for two consecutive nights at baseline, approximately three weeks post-treatment, and approximately three months post-treatment. Subjects arrived at the sleep laboratory between 7:00 PM and 8:00 PM on each assessment night. After a brief orientation, the electrodes used for PSG assessment were affixed for 10 minutes so that a recording of quiet relaxed wakefulness could be collected. The 10-minute assessment ensured proper functioning of all equipment and provided an example EEG to compare time spent awake throughout the assessment. On the first night of each of the two-night PSG assessments, subjects completed three self-report measures of fatigue. Following the preliminary PSG recording, subjects were allowed to read or watch TV until normal bedtime. Subjects were encouraged to sleep ad libitum for an 8.0-hour interval; however, they were only required to stay in bed for a minimum of 7 hours with the exception of bathroom breaks. In the morning, electrodes were removed, and subjects left the sleep lab to resume their daily activities. Data from the two nights were averaged, and patients were compensated \$35.00 for each night of PSG assessment.

Measures

The revised Brief Fatigue Inventory (BFI) is a 9-item, patient-report instrument with established reliability and validity that allows for the rapid assessment of fatigue level in cancer patients.³² Possible scores on this scale range from 0 - 10 with higher numbers indicating greater fatigue.

Fatigue was also assessed with the Fatigue Subscale of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT). The FACIT is a 28-item quality-of-life scale developed specifically for use in cancer clinical trials, along with a subscale of 13 additional questions directly related to the impact of fatigue on daily activities.³³ The basic measure has shown very good test/retest reliability as well as validity.^{34,35} The possible score range of the fatigue sub-scale, reported on herein, is 0 - 52 with a high score representing less fatigue.

The severity of fatigue at its worst over the prior seven days was assessed with a single question on an 11-point horizontal scale anchored by 0 = "Not Present" and 10 = "As Bad as You Can Imagine." The question was taken from a Symptom Inventory created at M.D.

Anderson Cancer Center.³⁶ Scores of 4 - 6 are considered moderate intensity, and scores of 7 - 10 are generally considered severe on this scale.³² The severity of pain at its worst was assessed in a similar fashion.

State Anxiety was measured using the Spielberger State/Trait Anxiety Inventory (STAI Form Y-1). This 20-item questionnaire is one of the most widely-used assessments of anxiety. Internal consistency coefficients > 0.90 have been shown, along with test/retest reliability coefficients > 0.70. Concurrent, construct, convergent and divergent validity have also been demonstrated.^{37,38}

Sleep architecture was assessed via PSG. In addition to the percentage of time spent in each stage of sleep, four sleep continuity measures were calculated and are defined as follows:

- Sleep latency (SL): time elapsed from “lights off” to the first sustained sleep, i.e., at least eight minutes duration
- Wake after sleep onset (WASO): number of minutes awake from sleep onset to “lights on”
- Total sleep time (TST): sum of all epochs, i.e., 30-second intervals, scored as any stage of sleep for the entire recording period
- Sleep Efficiency (SE): total sleep time over the duration of the total recording

Statistical Methods

Demographic data were tested with chi-square or t-tests as appropriate. Descriptive statistics (mean and standard deviation) were calculated for all the outcomes at each of the three time points. We used a log transformation for SWS because its distribution was highly skewed. In order to eliminate zeros for the later conversion of our findings to the geometric mean and SD, patients with no SWS were recoded as having one minute of SWS. Repeated-measures analyses were used to test differences in mean sleep and fatigue outcomes across the three time points. The analysis assumed an unstructured covariance matrix of the time (i.e. cycle) effects and tested the time effect with an F test using the Kenward-Roger degrees of freedom adjustment.³⁹ In addition to cycle, we also included tumor type (breast vs. non-breast), age, pain, anxiety (STAI), and the cycle*pain and cycle*anxiety interactions. Model terms (except Cycle) that were insignificant ($P > 0.10$) were dropped from the final models. Post hoc tests of the mean differences between the cycles were conducted using the Tukey-Kramer adjustment for multiple comparisons. The relationship of the three fatigue measures and log SWS was explored by first ruling out any available confounders (tumor type and age) associated with fatigue or log SWS. This was accomplished using doubly multivariate repeated-measures,⁴⁰ where all the fatigue and SWS outcomes were used as responses, structured into outcome type and cycle (“time”) factors, with tumor type and age as the independent variables. This was followed by a canonical correlation analysis⁴¹ to determine the correlation of log SWS at each of the three cycles with the fatigue measures (BFI, severity of fatigue and the FACIT fatigue subscale) and test for its statistical significance with a likelihood ratio test.

Results

Sample Characteristics

The study population was 26 cancer patients with a mean age of 52.9 years. All participants were white and most were female (88%), had breast cancer (77%), were married (69%), and college educated (61%). All 26 patients had their initial PSG assessment prior to their first chemotherapy treatment with the average number of days prior being 10.8 (range = 1 to 37, SD = 9.6). One of these 26 patients had radiation therapy prior to her chemotherapy. Twenty-three of the 26 patients underwent the scheduled PSG following completion of all chemotherapy treatments with the average number of days following the last chemotherapy being 20.1 (range = 12 to 58, SD = 10.7). Seventeen of these 23 patients received doxorubicin-based therapy, and four received the FOLFOX regimen. One of the 23 patients had radiation therapy concurrent with chemotherapy, and one patient had a surgical procedure following the completion of chemotherapy and prior to the second PSG assessment. Twenty-two patients underwent the third PSG assessment that was scheduled to occur 12 weeks following the completion of all chemotherapy and radiation treatments. It took place an average of 165 days (range = 96 to 264, SD = 46.7) following their final chemotherapy. Fourteen of these 22 patients (64%) had intervening radiation therapy, and one had an intervening stem cell transplant.

Sleep Changes Over Time

Four repeated-measures analyses were conducted on the proportion of time asleep in each stage of sleep (stage 1, stage 2, SWS, and REM sleep) to test the statistical significance of changes across the three cycles. All four analyses were non-significant, with $P=0.411$ (stage 1), $P=0.981$ (stage 2), $P=0.691$ (log SWS), and $P=0.682$ (REM). Similarly, post hoc tests showed no significant pairwise differences between cycles (Table 2).

We also conducted four repeated-measures analyses examining changes over time in the four sleep continuity variables (SL, WASO, SE, and TST). The p-values for SL, WASO, SE and TST were 0.473, 0.234, 0.161, and 0.043, respectively. TST showed a significant increase of an average of 21 minutes per night from baseline to the first post-treatment assessment, $P=0.021$. There was no difference between the baseline and final assessments (Table 3).

Changes in Fatigue Over Time

The mean values and standard deviations for the three fatigue measures at the three assessment periods are provided in Table 4. Repeated-measures analyses showed significant changes in fatigue on the single-item measure of fatigue severity, $P=0.026$. There was a significant increase in fatigue from the initial assessment to the assessment following completion of chemotherapy, (time 2 vs time 1) $P=0.022$, followed by a decrease approximately 12 weeks after the last treatment (time 3 vs time 2), $P=0.114$. There was a significant change in the Additional Concerns subscale of the FACIT, $P<0.001$, with a pattern similar to that of the single-item measure, with increase in fatigue from time 1 to time 2, $P<0.001$, followed by a decrease from time 2 to time 3, $P<0.001$. Changes in BFI over the three times were not significant overall, $P=0.251$, but the post-hoc tests (after

adjustment for tumor type, age, pain and anxiety) showed statistically significant changes, with time 2 vs time 1 showing an increase, $P=0.005$, and a decrease from time 2 to time 3, $P=0.012$. There were no statistically significant increases in fatigue from the initial assessment to the final assessment in any of the fatigue measures, all $P>0.8$.

Correlation Between Fatigue and SWS

Using the doubly multivariate repeated-measures analysis (see the Statistical Methods section), there was no significant association of tumor type (breast vs. non breast, $P=0.5437$) or age ($P=0.2452$) with the time trends of log SWS and the three fatigue measures. The subsequent canonical correlation analysis showed no significant correlation between log SWS and the fatigue measures over the three cycles, $P=0.275$.

Post Hoc Power Analyses

Because SWS, our key variable of interest, showed no differences over time, we conducted post-hoc power calculations to determine the detectable differences for this variable using the sample sizes and observed standard deviations with $\alpha = 0.05$ and power = 0.80. For a paired t-test examining changes in the log-transformed values for SWS (see above) from baseline to approximately three weeks following the last chemotherapy, we had 80% power to detect a difference of 2.3 percentage points in the proportion of sleep time patients spent in SWS.

Discussion

Despite the mounting evidence that changes in sleep may somehow contribute to CRF, our findings suggest that few changes occur in the architecture or continuity of sleep of cancer patients over the course of treatment. The only significant change we observed in our cancer patients' PSG data was an increase of about 20 minutes in the total time asleep between the pre-chemotherapy assessment and the assessment following the conclusion of chemotherapy. As expected, we observed a significant increase in fatigue from prior to the first chemotherapy to following the last one. This finding is in line with data from multiple studies which indicate that 70% or more of patients receiving chemotherapy experience fatigue.⁴²⁻⁴⁴

One of our objectives was to examine the role of SWS in the development of chemotherapy-induced fatigue as a potential target for interventions to reduce fatigue. Because significant changes in SWS were not seen over time, our hypothesis that changes in SWS activity are a significant factor in etiology of CRF was not supported. This is further evidenced by the lack of significant correlations between SWS and fatigue measures at any of the assessments and by the lack of significant correlations between changes over time in SWS and changes over time in the fatigue measures.

One possibility for extended sleep following chemotherapy compared to baseline is that increased stress prior to chemotherapy may contribute to poor sleep and insomnia-like extended wake time (both minutes to fall asleep and minutes awake after sleep onset were higher following chemotherapy). The other possibility is that post chemotherapy sleep occurs in the context of elevated fatigue, which may contribute to or be a marker of

sleepiness and the ability to sleep more. Of course, either (or neither) of these possibilities may be accurate explanations for this finding. Given the relative weakness of this sole PSG finding and the fact that TST returns to near-baseline levels at the 12-week post-chemotherapy assessment, any further speculations seem unwarranted.

The lack of any significant changes over time in the PSG assessments of sleep, other than the small increase in total sleep time, is surprising considering the large number of studies which have reported on sleep difficulties in patients receiving chemotherapy (see our earlier citations). The lack of a difference on the PSG parameters between the initial assessment and the assessment following the completion of chemotherapy is particularly surprising considering that fatigue levels significantly increased during this period, and changes in fatigue in cancer patients are strongly related to both self-reported changes in sleep⁴⁵⁻⁵⁰ and also to an objective measure of sleep continuity, i.e., actigraphy.⁵¹⁻⁵⁴ While it is possible that the relatively small sample size accounts for our failure to detect significant changes over time in SWS, we think that unlikely because our post hoc power analyses showed we had 80% power to detect a difference as small as 2.3 percentage points in the proportion of sleep time patients spent in SWS between the first and second assessments. We note that we did not do post hoc power analyses on the other PSG variables other than SWS, as they were not our primary outcome, and that the analyses we conducted on other PSG variables may have been underpowered.

Limitations of the study include the heterogeneity of our sample with three different cancer diagnoses and diverse chemotherapy/radiation regimens. Our patient sample was also not representative of cancer patients in general. We had strict ineligibility criteria regarding prescription and over-the-counter medications that might affect sleep in order to ensure the integrity of the PSG assessments, and this, combined with the necessity of undergoing the overnight PSG assessments, greatly affected our recruitment. Fewer than one patient in five whom we approached agreed to the study. Our eligibility criteria may have eliminated those patients who were prone to sleep problems or who had already developed sleep problems associated with diagnosis and surgery for cancer and left only those who are least likely to develop sleep problems.

We conducted this study with the belief that the utilization of PSG would be a promising avenue for understanding the complex relationship between CRF and sleep because it offered the ability to quantify various objective indicators of sleep. Our findings show that sleep architecture and sleep continuity in cancer patients were not affected by cancer treatment. This finding, while encouraging in that it shows the resilience of patients in maintaining a stable sleep architecture during the stress of cancer and its treatment, also points to our overall lack of understanding of the root cause(s) of cancer-related fatigue and the intricate balance among the psychological and physiological components of the human restorative process.

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Table 1

Demographic and treatment details for the 26 participants undergoing PSG

Age:	Mean (SD)	52.9 (7.3)
	Range	37 -67
Sex:	Male	3
	Female	23
Ethnicity:	Non-Hispanic	25
	Hispanic	1
Race:	White	26
	Black	0
	Other	0
Education:		
	Attended college	16
	High School Graduate	9
	Non High School Graduate	1
Diagnosis:		
	Breast	20
	Colo-rectal	5
	Lymphoma	1
Chemotherapy Regimen: ¹		
	CA ² with a taxane	9
	CA without a taxane	3
	FOLFOX ³	4
	Taxol without doxorubicin	4
	Other	3

¹ Provided only for the 23 patients completing the post chemotherapy assessment;² doxorubicin and cyclophosphamide;³ leucovorin, 5-fluorouracil and oxaliplatin.

Table 2

Changes over time sleep architecture

	Time 1	Time 2	Time 3
	Baseline: prior to chemotherapy (N = 26)	Approximately 3 weeks following last chemotherapy ¹ (N = 23)	Approximately 12 weeks following last treatment ² (N = 22)
Stage 1 (SD) P=0.411 [#]	5.9% (5.1)	5.2% (3.8)	6.1% (4.1)
Stage 2 (SD) P=0.981 [#]	67.3% (7.4)	67.1% (6.4)	67.5% (6.1)
SWS (SD) ³ P=0.691 [#]	2.2% (5.0)	2.2% (5.1)	2.4% (4.0)
REM sleep (SD) P=0.682 [#]	21.5% (6.4)	22.4% (5.1)	21.7% (5.7)

Notes: SWS = slow-wave sleep.

¹ One of the 23 patients had radiation therapy concurrent with chemotherapy and one patient had a surgical procedure following the completion of chemotherapy and prior to the second PSG assessment.

² Following last chemotherapy or last radiation treatment if radiation therapy followed the conclusion of chemotherapy.

³ Values for SWS represent a geometric mean (see text).

[#] Significance of the time effect using repeated-measures.

Table 3

Changes over time sleep continuity

	Time 1	Time 2	Time 3
	Baseline: prior to chemotherapy (N = 26)	Approximately 3 weeks following last chemotherapy ¹ (N = 23)	Approximately 12 weeks following last treatment ² (N = 22)
Sleep latency in minutes (SD) P=0.473 [#]	13.6 (11.9)	12.2 (9.7)	14.2 (13.6)
Wake-time after sleep onset in minutes (SD) P=0.234 [#]	62.2 (41.7)	52.8 (22.5)	64.5 (38.5)
Total sleep time in minutes (SD) P=0.043 [#]	396.7 (48.1)	418.4 ^a (26.6)	401.1 (44.6)
Sleep efficiency (SD) P=0.161 [#]	84.1% (9.5)	86.6% (4.6)	83.6% (9.0)

Notes:

¹ One of the 23 patients had radiation therapy concurrent with chemotherapy and one patient had a surgical procedure following the completion of chemotherapy and prior to the second PSG assessment.

² Following last chemotherapy or last radiation treatment if radiation therapy followed the conclusion of chemotherapy.

[#] Significance of the time effect using repeated-measures.

^a Significantly different from Baseline at P=0.021.

Table 4

Changes over time in fatigue

	Time 1	Time 2	Time 3
	Baseline: prior to chemotherapy (N = 26)	Approximately 3 weeks following last chemotherapy ¹ (N = 23)	Approximately 12 weeks following last treatment ² (N = 22)
Brief Fatigue Inventory (SD) P=0.252 [#]	2.9 (1.8)	3.5 ^a (2.4)	2.7 ^b (2.5)
Additional Concerns subscale of FACIT ³ (SD) P<0.001 [#]	36.1 (11.1)	30.2 ^c (13.5)	38.1 ^d (12.7)
Single-item measure of fatigue severity (SD) P=0.026 [#]	3.6 (2.8)	5.0 ^e (3.4)	3.8 (3.4)

Notes: Higher scores on the Additional Concerns subscale of FACIT represent less fatigue and higher scores on the other two measures indicate greater fatigue.

¹ One of the 23 patients had radiation therapy concurrent with chemotherapy, and one patient had a surgical procedure following the completion of chemotherapy and prior to the second PSG assessment.

² Following last chemotherapy or last radiation treatment if radiation therapy followed the conclusion of chemotherapy.

³ Functional Assessment of Chronic Illness Therapy-Fatigue.

[#] Significance of the time effect using repeated-measures.

^a Significantly different from Baseline at P=0.005.

^b Significantly different from Time 2, P=0.012.

^c Significantly different from Baseline at P<0.001.

^d Significantly different from Time 2, P<0.001.

^e Significantly different from Baseline, P=0.022.