Sleep Measured by Polysomnography in Patients Receiving High-Dose Chemotherapy for Multiple Myeloma Prior to Stem Cell Transplantation

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Sleep-wake disturbances are common among patients with cancer (Berger, 2009; Berger et al., 2005; Davidson, Maclean, Brundage, & Schulze, 2002; Sateia & Lang, 2008; Savard, Ivers, Villa, Caplette-Gingras, & Morin, 2011), and are multifactorial in origin (Vena, Parker, Cunningham, Clark, & McMillan, 2004). Among cancer populations, sleep has been studied extensively among patients with breast or lung cancer either subjectively or in combination with actigraphy (ACTG). Although convenient, ACTG assesses only motion or its absence as a proxy of wakefulness or sleep (Tyron, 1991). The sleep of patients with all types of cancer has been studied less extensively using polysomnography (PSG). PSG is considered the gold standard of objective sleep measurement because it assesses and records electroencephalographic sleep changes (Dement, 2011). The current study is the first to describe sleep using PSG in patients with multiple myeloma (MM).

MM involves the development of abnormal plasma cells that collect in bone marrow and damage bone. Myeloma cells produce abnormal antibodies called plasma M proteins that accumulate in organs such as the kidneys, resulting in renal damage and failure. An estimated 21,000 new cases of MM, the most common type of plasma cell cancer, were diagnosed in the United States in 2012 (National Cancer Institute [NCI], 2012). MM usually develops in adults older than 65 years and is most common among African Americans and men (NCI, 2012).

Disease-related risk factors that may impair sleep in patients with MM include bone pain and peripheral neuropathy, which are among the most common neurologic symptoms of plasma cell cancer (Mangan, 2005). Opiates, often used to manage bone pain, are associated with drowsiness (Rome, 2010), which may contribute to daytime activity and excessive daytime napping, decreasing the homeostatic sleep drive and disrupting circadian rhythms.

Purpose/Objectives: To describe the objective sleep of patients receiving chemotherapy for multiple myeloma (MM) prior to stem cell transplantation.

Design: A descriptive study with repeated measures.

Setting: An international referral center in an urban area of the southern United States.

Sample: A convenience sample of a subset of 12 patients with MM, recruited from a randomized, controlled trial.

Methods: Objective sleep was assessed using two nights of polysomnography, one obtained before and one after a second cycle of high-dose chemotherapy prior to stem cell transplantation. Demographic and clinical data were obtained through a retrospective chart review.

Main Research Variables: Objective sleep including sleep characteristics, sleep-related respiratory events, and periodic limb movements (PLMs) of sleep.

Findings: Sleep was characterized by a relatively short sleep time, excessive time spent awake after the onset of sleep, and poor sleep efficiency (objective sleep quality). Patients spent more than the expected percent of time in non–rapid eye movement sleep and less in rapid eye movement sleep. Arterial oxyhemoglobin saturation nadirs reflected episodes of low arterial oxygen saturation. PLMs during sleep were in the mildly elevated range.

Conclusions: Findings suggest that patients had poor sleep efficiency (objective sleep quality) and were slightly better sleepers after receiving a second cycle of high-dose chemotherapy. A number of patients also demonstrated obstructive sleep apnea and frequent PLMs.

Implications for Nursing: Findings support the need for additional investigation of sleep in patients with MM, particularly poor sleep efficiency and PLMs. Improving sleep may improve quality of life by decreasing associated symptoms such as pain, fatigue, and depression.

Knowledge Translation: Oncology nurses should consider assessing patients with MM for insomnia symptoms, excessive daytime sleepiness, obstructive sleep apnea, and a history of jerking or kicking their legs when asleep. Those symptoms may suggest the need for additional investigation of a possible sleep disorder, which may negatively influence mood and function.

Treatment-related risk factors that may impair sleep include pain related to oral mucositis and peripheral neuropathy (Palumbo et al., 2008). Oral mucositis is a common side effect of chemotherapy, particularly with intensive treatment (Niscola et al., 2006). Chemotherapy-induced peripheral neuropathy has been well-established in relation to several agents used for MM therapy (such as thalidomide and bortezomib) (Chaudhry, Combiath, Polydefkis, Ferguson, & Borrello, 2008; Delforge et al., 2010; El-Cheikh et al., 2008), and associated sensory symptoms usually are worse at night (Snowden et al., 2011). Other treatment-related side effects include insomnia associated with adjunct corticosteroids (Faiman, Bilotti, Mangan, & Rogers, 2008) and daytime sleepiness and fatigue associated with thalidomide (Celgene Corporation, 2006). Those factors place patients with MM at higher risk for insomnia, noted as a common problem for patients with cancer (Savard et al., 2011).

Common complications with MM and its treatment may indirectly contribute to sleep disturbance. Anemia, renal failure, and peripheral neuropathy (Berenson, 2005) are related to iron deficiency, renal disease, and neuropathy, which are major risk factors for restless legs syndrome (RLS) and periodic limb movements (PLMs) (Allen & Earley, 2007; National Center on Sleep Disorders Research, n.d.). Anemia in MM is associated with inadequate erythropoietin production and responsiveness, decreased red blood cell lifespan, and incorrect release of iron from macrophages (normal to high iron stores with low serum iron) (Ludwig & Osterborg, 2010). Renal disease in MM is associated with the immunoglobulin products (M proteins) of monoclonal plasma cells in the bone marrow, which form kidney deposits typically progressing to renal tubular, glomerular, and vascular pathology and failure (Soloman, Weiss, & Herrera, 2010). Those disease-related factors may predispose patients with MM to develop secondary sleep disorders such as RLS and PLMs.

Psychosocial factors, such as anxiety, are theorized to be experienced by patients with cancer from the time of diagnosis through completion of induction therapy (Sherman, Simonton, Latif, Plante, & Anaissie, 2009) and may impact sleep. Depression highly correlates with sleep disturbance even before chemotherapy (Phillips, Jim, Donovan, Pinder-Schenck, & Jacobsen, 2012). In addition, depression and anxiety have been associated strongly with sleep problems in older patients with cancer during and following treatment (Sharma et al., 2011). Coleman et al. (2010) reported disturbed sleep and mood in patients with MM. Unpublished findings from that study suggested that total mood disturbance negatively correlated with sleep efficiency, a measure of how long patients slept while in bed attempting to sleep. Sleep efficiency also is considered an objective reflection of subjective sleep quality, the perception of sleep as

restorative for function (Van Cauter & Allostatic Working Group, 1997). Therefore, mood disturbance may contribute to the risk of sleep disturbance in patients with MM.

Sleep disturbance in patients with MM may result in alteration of normal sleep types, stages, and variables in the daily sleep-wake pattern. Non–rapid eye movement (NREM) sleep is characterized by progression to deep sleep with decreased responsiveness to stimuli and retained muscle tone. Stages 1 and 2 of NREM sleep often are referred to as light sleep, and stages 3 and 4 as deep or slow-wave sleep. Rapid eye movement (REM) sleep is characterized by dreaming, varied responsiveness to stimuli, paralysis of voluntary muscles, increased vital signs and cerebral blood flow, and decreased temperature regulation. A typical night of sleep is composed of four to six 90–110 minute cycles of NREM and REM sleep. Total sleep time is predominantly composed of 75%–80% NREM sleep and 20%–25% REM sleep (Carskadon & Dement, 2005).

The inability to attain adequate amounts of deep NREM or REM sleep may change the quality or restorative potential of sleep. Those changes also may be reflected through alterations in sleep variables such as sleep onset latency (time taken to fall asleep), wake time after sleep onset (time spent awake after initial onset of sleep), and sleep efficiency (amount of time spent asleep while attempting to sleep) in addition to the duration of total sleep time.

Despite the many risks for sleep disturbance, limited knowledge of sleep problems experienced by patients with MM exists. Coleman et al. (2010) found that sleep for patients with MM was characterized by decreased nocturnal sleep time for age, frequent wake episodes, and a low percentage of time asleep while in bed. However, the objective sleep of patients with MM assessed with PSG has not been described. Therefore, the primary purpose of the current study was to describe the sleep of patients with MM using PSG, before and after a second cycle of high-dose chemotherapy patients received prior to stem cell transplantation.

Conceptual Model

The current study is underpinned by, but does not attempt to validate, the Model of Impaired Sleep (Lee, 2003), which proposed that sleep impairment can be classified as either sleep deprivation or sleep disruption (fragmented sleep), is considered pathological, and often results from health problems. The pathology of MM and its treatment-related side effects present multiple risks for sleep impairment because they impact the complex mechanisms that regulate the sleep process. For example, sleep disruption because of frequent night awakenings may result in decreased sleep time and type, altering the homeostatic sleep drive. That

drive is theorized to regulate sleep and wake duration and promote sleep consolidation (Borbély, 1982). Sleep disruption may alter daily routines that impact the circadian process believed to maintain an approximate 24-hour sleep-wake cycle. Decreased environmental exposure to sunlight during periods of illness also may weaken circadian sleep patterns by inhibiting the formation of melatonin, a hormone that promotes initiation and maintenance of sleep (Scheer & Shea, 2009).

Methods

Design, Setting, and Sample

The design of this study was descriptive with repeated measures and was a preliminary investigation of sleep using PSG. The site of this study was an international referral center for patients with MM in an urban area of the southern United States. The PSG was conducted in the General Clinical Research Center. The study sample was composed of participants newly diagnosed with MM from a randomized, controlled trial of an individualized exercise therapy and whose sleep was assessed with PSG. All participants in the current study were on the Total Therapy 3 protocol. Cycles 1 and 2 of the Total Therapy 3 protocol consisted of bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide followed by interim thalidomide plus dexamethasone every 4 days for 21 days preceding the first and second PSG measures, respectively, prior to their first peripheral blood stem cell transplantation ($\bar{X}$ = 8.75 days prior). The small sample was composed of volunteers and did not reflect a random sample. Sample size was dependent on available voluntary participation in the preliminary study and was not justified based on design. Patients were initially informed about the study by clinic staff, and if they expressed interest, the study research assistant contacted them for additional discussion and informed consent. Patients were excluded if they were at high risk of pathological fractures or cord compression, unable to understand the study, diagnosed with a major psychiatric disorder, anemic, or hypertensive and poorly controlled (Coleman et al., 2010).

Variables and Measures

Demographic and clinical variables were obtained through retrospective chart reviews of participants' electronic medical records. Demographic variables included age, gender, and race and ethnicity. Clinical variables included type of MM, stage of disease, comorbid baseline diagnoses, sleep-impairing medications, body mass index, and laboratory findings (serum creatinine and hemoglobin). Those are summarized in Tables 1 and 2.

Sleep was measured objectively using portable PSG. In general, PSG refers to the simultaneous recording of multiple physiologic variables during sleep, including measures of brain activity, muscle activity, nasal airflow, chest and abdominal effort, oxyhemoglobin saturation, and limb movement. PSG is capable of measuring sleep stages and detecting sleep-related events such as brain arousals, awakenings, and apneic or hypopneic episodes (Collop, 2006). Apnea episodes, absence of airflow at the nose or mouth for 10 seconds or longer, can be classified by type, including obstructive sleep apnea (characterized by persistent pulmonary effort), central apnea (associated with the absence of respiratory effort), or mixed apnea. Frequency of hypopnea episodes, partial reductions in airflow for 10 seconds or more, also can be detected (Berry, 2012).

Two nights of portable PSG were obtained by a licensed practical nurse sleep technician trained and supervised by a registered PSG technologist using a **Grass Portable PSG Data Acquisition System**. The PSG recording began shortly before participants' usual bedtimes until the next morning at their final awakenings. The first PSG measure was conducted prior to the second chemotherapy cycle for mobilization of stem cells for collection, and the second PSG measure was conducted after the second chemotherapy cycle prior

Table 1. Sample Characteristics (N = 18)

Characteristic	Completed Study	Unable to Complete Study
Age (years)		
Younger than 65	8	6
Older than 65	4	–
Race		
Caucasian	10	5
African American	2	1
Gender		
Male	10	4
Female	2	2
Body mass index[a]		
Normal	2	1
Overweight	7	2
Obese	2	3
Baseline comorbidities[b]		
Gastrointestinal	6	1
Hypothyroidism	4	1
Cardiovascular	4	–
Musculoskeletal	2	4
Depression	2	2
Prostate cancer	2	1
Renal	2	1
Respiratory	2	–
Attention deficit hyperactivity disorder	1	–
Neuropathy	1	–
Benign prostatic hypertrophy	–	1
Restless legs syndrome	–	1

[a] Data are available for 11 participants who completed the study.
[b] Some participants reported multiple comorbidities.

Table 2. Sleep Characteristics, Respiratory Events, Periodic Limb Movements of Sleep, and Serum Laboratory Findings (N = 12)

Sleep Variable	Expected	Prechemotherapy Cycle 2		Post-Chemotherapy Cycle 2	
		$\overline{X}$	SD	$\overline{X}$	SD
Sleep onset latency (minutes)	Less than 30	22.79	42.48	12.92	10.51
Time in bed (minutes) (n = 9)	–	495.13	32.71	502.38	34.76
Total sleep time (minutes)	420–540	360.04	89.78	395.58	41.44
Total wake time (minutes)	Less than 30	118.6	60.99	97.53	39.09
Sleep efficiency (%)	Greater than 85	74.2	15.12	80.19	7.1
NREM stage 1 sleep (minutes)	–	85.67	34.44	115.79	42.16
NREM stage 2 sleep (minutes)	210–324	199.5	77.69	204.92	40.58
NREM stage 3–4 sleep (minutes)	42–108	26.88	16.25	33.67	26.08
REM sleep (minutes)	84–135	48	19.82	41.21	32.23
Total awakening index[a]	Less than 6	4.78	4.65	4.96	2.14
Apnea hypopnea index[b]	–	9.94	14.15	10.29	10.6
Total SpO$_2$ nadir (%)	Greater than 95	85.5	5.6	84.75	4.56
PLMs total index[c]	–	8.01	11.68	16.01	17.11
Serum creatinine (mg/dl)	0.5–1.1	0.96	0.2	0.97	0.17
Serum hemoglobin (g/dl) (n = 11)	Male: 13.5–17.5 Female: 11.5–16	11.03	1.14	12.05	1.95

[a] Per hour of sleep
[b] Mild—less than 15; moderate—15–30; severe—greater than 30
[c] Normal—less than 5; mild—5–24; moderate—25–50; severe—greater than 50
NREM—non–rapid eye movement; REM—rapid eye movement; PLMs—period limb movements; SpO$_2$—hemoglobin oxygen concentration measured by pulse oximetry

to the first stem cell transplantation. PSG measure 1 and 2 were about five and a half weeks apart ($\overline{X}$ = 5.42 weeks, SD = 2.68, range = 3–13, median = 5). The PSG measures included electroencephalography (EEG), electromyography (EMG), electrooculography, electrocardiography, airflow, limb movement, respiratory excursion, and oxyhemoglobin saturation. The system software, Gamma, ran under Windows 98 and New Technology. The sleep technician used standard calibration and recording procedures. EEG electrodes were positioned using the International 10–20 system of measurement for conventional sleep recordings at central (C) lobe and occipital (O) scalp electroencephalogram electrodes (C3, C4, O1, O2), referenced to a contralateral mastoid electrode. Eye movements were monitored by electrodes attached to the outer canthus of each eye, and electrodes under the chin monitored EMG activity. Nasal and oral thermistors measured airflow, piezo elastic bands around the chest and abdomen measured respiratory excursion, and a finger probe measured oxyhemoglobin saturation. Two electrodes on the anterior tibialis muscle monitored limb movements.

All PSG recordings were analyzed by the registered sleep technologist using standardized scoring criteria to manually score the recordings (Rechtschaffen & Kales, 1968). All PSG recordings and scorings were reviewed by a PhD nurse with board certification through the American Academy of Sleep Medicine. Total frequencies of respiratory events and indices per hour of sleep were calculated. Arousals were scored based on EEG frequency shifts of 3 seconds or longer during REM sleep (American Sleep Disorders Association and Sleep Research Society Report, 1992). Awakenings were scored if the epoch met the criteria for awake after sleep onset and before sleep offset. Oxyhemoglobin saturation was measured using a built-in XPOD™ pulse oximetry with a Nonin 8000J flexible finger sensor. PLMs also were measured based on EMG activity lasting 0.5–5 seconds that repeated every 4–90 seconds with a minimum of four movements. The number of PLMs associated with awakenings and arousals per hour of sleep also was determined.

Research Procedure

Human subject committee approval was obtained from the University of Arkansas for Medical Sciences Institutional Review Board, and the Winthrop P. Rockefeller Cancer Research Institute Protocol Review and Monitoring Committee, both in Little Rock, for the randomized, controlled trial in which the participants were enrolled (Coleman et al., 2010).

Data Analysis

The statistical package, Number Cruncher Statistical Systems, was used to analyze all aggregate data. Descriptive statistics including frequencies, mean measures of central tendency, and the SD measure of variability were used to describe demographic and clinical characteristics. The mean measure of central tendency also was used to describe sleep variables at measures one and two, including sleep characteristics, sleep stages, awakenings, and respiratory events.

Results

Sample

A convenience sample of 18 participants was included in a subset of patients being assessed by PSG. Findings

are based on the 12 participants who completed two nights of PSG testing. The mean age of the sample was 61 years (SD = 8.15, range = 48.3–72.2; median = 61.45), 83% were men, 83% were Caucasian, and 17% were African American. More participants had IgG kappa chain type of MM than any other type. The six participants who did not complete a second night of PSG had serious medical complications or procedures that prevented their participation. Those participants were younger and had fewer chronic comorbidities than the participants who completed the study.

Sleep Characteristics

At PSG measures 1 and 2, sleep onset latency ($\overline{X}$ = 22.8 minutes versus 12.9 minutes; normal < 30 minutes) remained in the expected limits. Wake time after sleep onset ($\overline{X}$ = 118.6 minutes versus 97.5 minutes; normal < 30 minutes), total sleep time ($\overline{X}$ = 360 minutes versus 395.6 minutes; normal 420–540 minutes), and sleep efficiency ($\overline{X}$ = 74% versus 80%; normal > 85%) all were less than expected for age.

Sleep Stages

NREM sleep stages 1 and 2 remained in the expected limits at measures 1 and 2. NREM sleep stages 3 and 4 (26.9 minutes versus 33.7 minutes) were less than the expected percent of total sleep time at both measures (8% versus 7%; normal 10%–20%). Combined, NREM sleep stages 1–4 exceeded the expected percent of total sleep time (87% versus 90%; normal 75%–80%). In contrast, REM sleep (48 minutes versus 41.2 minutes) was less than the expected percent of total sleep time (13% versus 8%; normal 20%–25%).

Respiratory Events

At PSG measures 1 and 2, the total apnea-hypopnea index (combined number of apneas and hypopneas per hour of sleep) was elevated (9.9 versus 10.3 per hour of sleep). Normal is less than 5–15 scoreable respiratory events per hour of sleep with no evidence of respiratory effort during all or a portion of each respiratory event. At those same measures, the combined total oxyhemoglobin saturation nadir (lowest point) during sleep was low (86% versus 85%; normal 95% or greater).

Periodic Limb Movements

The mean PLM index (number of PLMs per hour of sleep) was elevated at 8 (normal < 5 PLMs per hour, SD = 11.68 PLMs versus 16 PLMs, SD = 17.1 PLMs). The number of PLMs about doubled from PSG measure 1 to measure 2.

Discussion

The current study is the first of the researchers' knowledge to report objective sleep assessed with PSG in patients with MM. Because sleep disturbance is a common complaint for patients with cancer, and because the cancer and treatment-related symptoms that may impair sleep vary widely, overnight sleep studies using PSG in patients with MM are needed.

In the current sample, total wake time after onset of sleep, total sleep time, and sleep efficiency were less than expected for adults before and after the second cycle of high-dose chemotherapy cycle 2. Those findings reflect a relatively short duration of sleep and a prolonged time spent awake during the night despite spending more than eight hours in bed at night attempting to sleep.

Multiple factors may have contributed to the impaired sleep the participants demonstrated. Some sleep impairment may have preceded cancer diagnosis and was never diagnosed. One participant had a documented diagnosis of insomnia at the initial medical oncology clinic visit, and three others at the time of PSG measure 1. Those findings are consistent with those of Savard et al. (2011), who reported rates of insomnia at 28% preceding surgical treatment in a large mixed sample of patients with cancer.

The sleep findings from the current article may be partly explained by the aging process, which is associated with increased light sleep, increased sleep fragmentation, and decreased total sleep time (Kryger, Monjan, Bliwise, & Ancoli-Israel, 2004). However, only four participants in the current study were aged 65 or older. Symptoms of common comorbidities also may have contributed (Kryger et al., 2004). In addition, many medications taken by older adults are associated with decreased REM sleep (Qureshi, 2008), insomnia, or daytime drowsiness (Kryger et al., 2004). Types of medications taken that are potentially associated with sleep impairment for the participants are summarized in Table 3.

Although mood disturbance has been associated with sleep disturbance, only one patient in the sample had an elevated total mood disturbance score at PSG measure 1 and none at PSG measure 2 ($\overline{X}$ t-score = 48.3, SD = 9.48, range = 38–69 versus $\overline{X}$ t-score = 47.8, SD = 7.15, range = 38–57). That suggests that mood disturbance did not play a major role in the sleep disturbance of the sample, consistent with the high variability of mood among individuals in the parent study (Coleman et al., 2010). Participants with less mood disturbance also may have been more inclined to volunteer for overnight sleep studies.

The apnea and hypopnea findings were primarily obstructive in nature and do not suggest a change in problems with breathing cessation or airflow following the second cycle of high-dose chemotherapy. The mean oxygen nadirs in NREM and REM sleep reflected episodes of low arterial oxygen saturation. Those findings may have reflected preexisting and undiagnosed

Table 3. Potential Sleep-Impairing Medications by Type

Medication	Potential Sleep Effects
Analgesic	
Opioid analgesics	Somnolence, insomnia, restlessness, myoclonus
Muscle relaxants	Insomnia, drowsiness
Cardiovascular	
Antihypertensives	Insomnia, decreased sleep continuity and rapid eye movement sleep, nightmares
Antilipidemic	Insomnia
Gastrointestinal	
Prokinetic agents	Restlessness, insomnia, drowsiness, fatigue
Endocrine	
Synthetic thyroxine	Insomnia, restless leg syndrome
Psychotropic	
Sedatives	Somnolence, daytime drowsiness
Benzodiazepines	Somnolence, insomnia
Antidepressants (selective serotonin reuptake inhibitors)	Insomnia, decreased rapid eye movement, restless leg syndrome
Antipsychotic (atypical)	Somnolence
Central nervous system stimulant	Insomnia, restlessness
Respiratory	
Antihistamines with or without decongestants	Somnolence, insomnia
Urologic	
Urinary antispasmodics	Somnolence, insomnia
Alpha-adrenergic blockers or alpha reductase inhibitors	Somnolence, insomnia, fatigue

Note. Based on information from Drug Information Online, 2012a, 2012b, 2012c, 2012d, 2012e; Hoque & Chesson, 2010; Kryger et al., 2004.

problems. Only one patient had documented obstructive sleep apnea syndrome (OSA) at the initial medical oncology clinic visit based on electronic medical records review. Apnea findings also may be partly explained by the predominance of men in the small sample, who have increased risk of OSA (Ancoli-Israel et al., 1991b; Bixler, Vgontzas, Ten Have, Tyson, & Kales, 1998; Punjabi, 2008). In addition, body weight may have contributed to problems with breathing cessation and airflow. One obese patient was diagnosed with severe OSA. Two obese participants, two overweight participants, and two of normal weight also were diagnosed with mild OSA. The relative stability of body mass index values before and after the second cycle of high-dose chemotherapy suggest that the OSA detected was unlikely related to changes in weight between PSG measures 1 and 2 (data not shown).

Half of the participants (n = 6) had no PLMs at PSG measure 1; however, all but two had PLMs at PSG measure 2 (8 mild, 1 moderate, 1 severe). That increase in PLMs, with associated arousals and awakenings, may suggest a clinically significant impact on sleep through increased fragmentation of sleep. None of the participants had a documented diagnosis of PLM disorder or RLS prior to this study, but they were not screened for those disorders.

The increased PLMs in the sample may be partly because of changes associated with increasing age, although eight of the participants were younger than 65 years. PLMs also are more common in older women than in men (Ancoli-Israel et al., 1991a; Hornyak & Trenkwalder, 2004), and the current sample predominantly was male. Although PLMs appear to increase with advancing age and may occur without sleep disturbance (Youngstedt, Kripke, Klauber, Sepulveda, & Mason, 1998), a PLM index exceeding five per hour of sleep has been associated with sleep disturbance in older adults (Ancoli-Israel et al., 1991a). All but two of the current participants exceeded this cutoff at PSG measure 2, suggesting the potential for sleep disruption. An approximate doubling of the PLM index in six participants in a time span of approximately five weeks ($\overline{X} = 35.7$ days; range = 17–64) suggests an acute change unlikely related to age and gender.

The PLMs findings may have been related to comorbid disorders; PLMS was reported in association with inattention and hyperactivity (Chervin et al., 2002), upper airway resistance (Exar & Collop, 2001), and insomnia (Karadeniz, Ondze, Besset, & Billiard, 2000). The one participant in the current study who developed PLMs in the severe range had a documented diagnosis of attention deficit hyperactivity disorder, which is not commonly anticipated in an older population. As previously noted, four of the participants were diagnosed with insomnia and seven with OSA, which could have contributed to the PLMs detected in the participants.

Pharmacologic-induced PLMs have been associated with particular medications (Hoque & Chesson, 2010). However, based on an electronic medical record review, none of the participants were receiving medications recognized as inducing PLMs. Pharmacologic-induced RLS, often associated with PLMs (Hoque & Chesson, 2010), also had been reported. Five of the participants were receiving medications recognized as inducing symptoms of RLS (escitalopram, 2 participants; L-thyroxine,

3 participants). Peripheral neuropathy commonly is associated with the cumulative dose of chemotherapy. Peripheral neuropathy has been suggested as a secondary cause of RLS (Gemignani et al., 2006), and pharmacologic-induced RLS has been associated with PLMs (Hoque & Chesson, 2010). Although the relationship of RLS to PLMs remains unclear, peripheral neuropathy may potentially contribute to the development of PLMs. However, a search of the chemotherapy agents included in the regimen taken by those participants did not note an increase in PLMs among the side effects. In addition, peripheral neuropathy was documented in only one patient during this period, suggesting that the length of chemotherapy treatment in the current study was inadequate for clinical symptoms of peripheral neuropathy to emerge. Consequently, it was not clear whether the increase in PLMs among the current sample was associated with medications.

The current PLM findings may have been related to impaired renal function, a common complication of MM (Dimopoulos, Kastritis, Rosinol, Blade, & Ludwig, 2008); increased PLMs have been associated with impaired renal function for some time (Bliwise, Petta, Seidel, & Dement 1985; Trenkwalder, Walters, & Hening, 1996). Serum creatinine, one measure of renal function, was elevated in two of the participants at PSG measure 1 and in an additional participant at PSG measure 2 (1.2 mg/dl for those with elevated levels). Although this level does not appear excessively high, the poor sensitivity of serum creatinine for detecting renal failure in ambulatory older adults has been noted (Swedko, Clark, Paramsothy, & Akbari, 2012). However, neither of the participants with moderate or severe PLMs at PSG measure 2 had an elevated serum creatinine, suggesting that renal function was not the issue.

Anemia may have contributed to the current PLMs findings. Low levels of serum ferritin (< 50 mg/l) have been associated with PLMs (Allen, Barker, Wehrl, Song, & Earley, 2001). However, only two of the participants had documented baseline levels lower than 50 mg/l, with PLMs in the mild range only. Serum hemoglobin levels were low in all 12 participants at PSG measure 1, and in 8 participants at measure 2 ($\overline{X}$ = 11.04, SD = 1.14 versus $\overline{X}$ = 12.05, SD = 1.95; normal 13.5–17.5 g/dl). However, the participant with severe PLMs at PSG measure 2 had serum hemoglobin in normal limits. In addition, six participants had anemia with no PLMs at PSG measure 1, and four of them experienced increased PLMs at PSG measure 2 despite improved hemoglobin levels. The findings do not suggest a relationship between serum ferritin or hemoglobin with PLMs in the current sample, but because decreased brain iron stores are theorized as the underlying pathology associated with RLS and PLMs (Allen et al., 2001), serum laboratory values may have been inadequate.

Overall, the number of PLMs in the small sample was not suggested to be related to age, gender, known medications, renal function, or anemia. The presence, but not increase, of PLMs may have been related to comorbidities of insomnia, OSA, and attention deficit-hyperactivity disorder. The current sample's size was not sufficient for additional investigation, but the findings suggest the need for it.

The current findings differed somewhat from one previously published study of 187 patients with MM that described baseline sleep (before chemotherapy) measured by ACTG (Coleman et al., 2010). Sleep onset latency measured by PSG was shorter in the current sample ($\overline{X}$ = 23 minutes and 13 minutes versus 29 minutes), as was total sleep time ($\overline{X}$ = 495 minutes and 502 minutes versus 512 minutes). Sleep efficiency was lower at PSG measure 1 and similar at PSG measure 2 (74% and 80% versus 80%). Total night wake episodes were much higher detected by PSG than by ACTG (25 times and 32 times versus 12 times per night); although, those measures are not interchangeable. The findings suggest that sleep-onset latency, total sleep time, and sleep efficiency using PSG and ACTG are fairly consistent. Variations were likely because of differences in treatment status and symptom severity. Overall, PSG and ACTG reflected short sleep duration, poor sleep efficiency, and frequent night awakenings in patients receiving high-dose chemotherapy for MM prior to stem cell transplantation.

Even in the current study's small sample, the presence of previously undiagnosed insomnia, OSA, and excessive PLMs in adult patients with MM was concerning. Sleep may deteriorate substantially before patients develop adequate awareness to bring sleep problems or worsening daytime symptoms, such as excessive sleepiness, to the attention of their healthcare provider. That may be true more of older adults who are experiencing multiple adverse symptoms including fatigue because of cancer and its treatment. Inadequate duration and quality of sleep during cancer treatment has ramifications for immune status, stamina to endure treatment, pain perception, and mood.

Limitations

Limitations include a small sample size, a short time frame for comparing changes in sleep related to treatment, and laboratory findings near, but not at, the precise time of sleep measurement. However, because of the severity of MM and of its treatment with high-dose chemotherapy prior to stem cell transplantation, as well as the expense incurred with PSG, the current study offers a preliminary examination of findings that may direct future research. The current study included a predominance of male, Caucasian participants, and although representative of the setting in which the

study took place, the findings may not be generalized to all patients with MM, which has a greater prevalence in African Americans. The mean age of the current sample (61 years) also was younger than the peak age of MM diagnosis (65–70 years), although younger adults are now diagnosed with MM either through improved identification or to increased incidence in younger age groups.

However, strengths of the current study included the measurement of sleep using a trained sleep technologist, evaluation of sleep findings by a PhD nurse who was board certified by the American Academy of Sleep Medicine, two nights of PSG to avoid a potential first-night effect, and very specific points in treatment for sleep measurement while patients were receiving high-dose chemotherapy.

Implications for Nursing

The current study is a first attempt to characterize the unique sleep and sleep problems of patients with MM using PSG. Increased knowledge of poor objective sleep quality in those patients will improve the promotion of restorative sleep at a time when it is most needed. Symptoms, such as pain, and how they interact with sleep and mood may suggest related management strategies. Possible underlying sleep disorders, such as PLM disorder, OSA, or RLS, could be unidentified sources of sleep disturbance. The potential presence of RLS is of particular research interest because of its association with PLMs and its frequency among people with renal failure and anemia. The current study has provided new information to help support the future investigation of sleep issues in patients with MM, which may impact the quality of life, function, and immune status of patients who live with MM.

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