Research

Insomnia in patients undergoing Autologous Hematopoietic Stem Cell Transplantation

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Mayra Veronese[1], Federica Lacarbonara[1]

[1] RN, MSN, University of Padua, Italy
(email: veronese.mayra@gmail.com)

Abstract

Background: Insomnia has an elevated incidence in patients who receive autologous Hematopoietic Stem Cell Transplantation (HSCT), which can lead to psychic and physical dysfunctions and impair immunological and neuroendocrine processes, hence compromising the response to treatment. The aim of this study is to evaluate the incidence, severity, and changes in time of insomnia in patients following autologous HSCT. Identify the factors affecting the quality of sleep and, in the end, identify the number of nocturnal awakenings and night interruptions by healthcare personnel.

Methods: insomnia was detected through the Insomnia Severity Index (ISI) questionnaire. The questionnaire was handed out in three different periods: on the first day of hospitalization (T0), the day after the transplantation (T1), and at the discharge (T2). The questionnaire was given out at the hematology ward in two hospitals in Italy.

Results: The convenience sample consisted of 31 patients. 42% of patients (N=13) in the pre-hospitalization, 58% (N=18) the day of transplantation, and 65% (N=20) at discharge showed insomnia symptoms: a significant difference between the ISI score at T0 and the ISI score at T1 and T2. There was a relationship between the ISI score and the presence of adverse effects of chemotherapy.

Conclusion: Insomnia is already present in patients following autologous HSCT from pre-admission and worsens during hospitalization. In detecting the symptoms of insomnia, the nurse plays an important role. Multidisciplinary management, both medical and nursing, is essential.

Keywords: Hematopoietic Stem Cell Transplantation, Sleep Initiation and Maintenance Disorders, Sleep, Neoplasm, Sleep-Wake Disorders.

Introduction

Sleep is an essential component for maintaining and improving someone's health, representing one third of an individual's life[1]. Insomnia can contribute to the development of a series of physical and psychologic dysfunctions, including insomnia, depression, anxiety, stress, and immunological and neuroendocrine alterations[2-4].

Different biological systems regulate sleep patterns[5]. The neuronal system controls the cyclic alternation of the stages of sleep and vigil during the day. The functioning of the immune system is involved in the development of daytime drowsiness and delayed sleep times through the production of cytokines, which are essential extracellular chemical mediators, such as interleukin-1 (IL-1) and the Tumor Necrosis Factor-alpha (TNF – α). Cytokines promote the Non-Rapid Eyes Movement (NREM) phase of sleep; the Il-1, Il-6, and TNF – α promote the cytotoxic T-lymphocytes' growth, differentiation, and activation. The endocrine system contributes to the regulation of sleep mediated by cortisol and melatonin secretion[5,6].

The International Classification of Sleep Disorders- Third Edition (ICSD-3) defines insomnia as a condition characterized by "persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment"[7].

Insomnia causes clinically significant uneasiness and compromises the social functioning with a consequent decrease in quality of life, and other severe consequences, like delayed recovery from illness, immune dysfunction, and increased mortality risk[8,9]. In the population, generally, the prevalence of insomnia is between 6 to 20 percent[10]. Insomnia is defined as a subjective dissatisfaction consisting in a lack of rest caused by a sleep of low quality and quantity. Insomnia is identified by a subjective dissatisfaction to not drawing sufficient rest from sleep for the low quality and quantity of sleep [7]. People with insomnia have impaired daily activities since they have to live with asthenia, daytime hypersomnia, confusion, tension, easy fatigue and mood changes (depression and anxiety) caused by insomnia. On the other hand, insomnia involves physiological functions alterations such as an increase in cardiac, metabolic, hormonal, and hypothalamic activity, activation of the Sympathetic Nervous System (SNS), which can lead to the development of mental illnesses and substance use disorders[7,11].

Hematopoietic Stem Cell Transplantation (HSCT) is a curative therapeutic strategy for people with hematological diseases, in particular for people with acute lymphoid leukemia, acute myeloid leukemia, plasma cell diseases, multiple myeloma and autoimmune diseases. The number of HSTC performed each year is more than 50,000 per day and this is due to the increasing number of people with hematological diseases[12].

In patients undergoing Hematopoietic Stem Cell Transplantation, the immune and neuroendocrine systems functions are relevant for a good recovery after the treatment[11]. The literature on insomnia during HSCT is limited. In most cases, insomnia is only marginally discussed and valued through a single or few elements.

Most severe insomnia symptoms appear within the first thirty days after transplantation. The same applies to the symptoms of fatigue, loss of appetite, and presence of pain. During the first hundred days after transplantation, the prevalence of insomnia and fatigue has been reported in 28-48% of cases. Even though there is a significant improvement in the quality of sleep, a group of patients continue to experience an elevated level of affliction and symptoms associated with a low quality of life[11,13-15].

Most studies show that the main reasons reported by patients for the interruption of night sleep are: bathroom use (85%), interruptions from the staff (80%), physical symptoms (41%), and anxiety (39%)[13,16,17]. Hacker et al.[16] also reported that the main reasons for the patient sleep interruption are related to the nursing activities. For the 40% of patients the reason was therapy administration, for the 21% was vital signs detection, and for the 11% was blood sampling[16]. Therefore, frequent vital signs detection and other nursing activities should be adequately planned and minimized during the night hours to ensure an adequate patients' sleep quality.

Multiple methods, such as polysomnography, sleep diaries, and self-reporting questionnaires, were used to assess sleep characteristics in the clinical setting. The gold standard for the assessment of sleep quality in hospitalized patients is the polysomnography[18].

Jim et colleagues[19] reported that insomnia symptoms are common in HSCT patients, and in addition to being distressing, they are also clinically meaningful. Research suggests that insomnia can negatively influence the immune and constitutional response, although no studies on this aspect of the HSCT treatment have yet been conducted. Chemotherapy is a potential inductor of inflammation, it sharply increases inflammation indicators, in particular:

the cytokine pro-inflammatory IL-6, which takes part in the regulation of sleep during the inflammatory and febrile processes; MIP-1 α (Macrophage Inflammatory Protein) that activates the neural process associated with the withdrawal and conservation of the energy to cause weariness, depression and insomnia; such modifications have also been found in patients who received Hematopoietic Stem Cell Transplantation. Moreover, the immune function is closely related to the neuroendocrine function and the circadian rhythm. As a result, the imbalance in these systems can also lead to insomnia. Vice-versa, the dysregulation of sleep can lead to altered immune profiles [6,11,14,20].

Although many studies have demonstrated that patients undergoing allogeneic transplantation have better sleep quality compared to those receiving autologous transplantation[9,13,21], up to three years after the transplantation[9] patients undergoing allogeneic transplantation exhibit a deterioration in sleep during the acute post-transplantation phase , due to the related adverse events, in particular Graft Versus Host Disease (GVHD)[9,13,21]. However, studies disagree on significant differences in sleep disturbances between patients undergone to autologous and allogeneic HSCT during profound neutropenia (NADIR)[22]. In patients undergoing the autologous HSCT treatment, insomnia is already present in pre-hospitalization among 32% of patients, increasing to 68 – 82% during the acute phase (between the transplant and engraftment), while 28% have symptoms of moderate insomnia, and three percent severe insomnia[14,19,21].

Therefore, the aims of this study were: to detect the occurrence, the severity, and the modifications of insomnia during the sleep, in patients receiving autologous stem cell transplantation; to identify possible correlations of insomnia symptoms with factors like conditioning therapy, drugs side effects, and comorbidities; to determine the number of nocturnal awakenings due to night interruptions by healthcare professionals, assessing the possibility to reduce them and to improve, in this way, the sleep quality.

Methods

Design and setting

An observational study was conducted at the hematology units of two hospitals in northern Italy: the University of Padua hospital and the Mestre hospital. In these hospitals, only autologous transplants have been performed. The study duration was four months.

Sample and setting

A convenience study sample was composed of hospitalized patients for the conditioning regimen and stem cell infusion.

The inclusion criteria were: patients scheduled to receive a hematopoietic stem cell transplantation, knowledge of the Italian language, and the consent to participate in the study.

The exclusion criteria were: deterioration of the cognitive state or lack of understanding of the Italian language.

Instruments

In this study, the Italian validated version of Insomnia Severity Index (ISI) [23] was used. Additional questions were added to evaluate the presence of daytime drowsiness, the presence of different habits before bedtime, the use of sedative-hypnotics medications at home, nocturnal awakenings, and if there have been night interruptions during hospitalization by healthcare staff. Other data collected from medical records were: the drug prescriptions, the presence of side effects (i.e. intestinal or oral mucositis, pain, evaluated with the Numeric Rating Scale NRS, and nausea or vomiting) and the presence of comorbidities.

The ISI[24] has been developed to briefly assess and detect insomnia following the criteria of the DSM (Diagnostic and Statistical Manual of Mental Disorders) and ICSD (International Classification of Sleep Disorders). The scoring system consists of a five-points (0-4) Likert scale for each of the seven items; the total score is obtained by summing the score of the seven items. The ISI score can range from zero (lowest) to 28 (highest), allowing the stratification of the insomnia severity on four levels: 0-7 non-significant insomnia, 8-14 mild insomnia, 15-21 moderate insomnia, and 22-28 severe insomnia[25]. This instrument has been studied on cancer patients and turned out to be a valid and reliable tool for assessing the severity of insomnia. The factorial structure of the ISI indicates the presence of three different factors: identify the impact, the satisfaction, and the severity of the sleep disturbance[23,25]. The tool's sensitivity is 95%, specificity is 47%; positive predictive value is 68%, and the negative predictive value is 88%. The ISI is considered a first-line screening tool for identifying insomnia[25].

The ISI was administered during three different moments: at the admission, to assess insomnia in the previous four weeks at home (T0), on day +1 from the autologous HSCT to evaluate insomnia in the period from the day of hospitalization to T1 (during the chemotherapy cycle), and at last, on the day of discharge, to assess the quality of sleep in particular during the post-transplantation period, NADIR's phase (T2).

Data Analysis

The data were collected in Microsoft Excel and analyzed through the "SPSS PASW Statistics 18.0.1" software. The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables. A longitudinal linear mixed regression model was used to evaluate the trend of insomnia from baseline to T1 and T2; where applicable, Pearson's chi-square test was used for categorical variables.

Ethical issues

The protocol of the study was approved by the local Institutional Ethical Committee, and the participants gave their written informed consent to use data, according to the Declaration of Helsinki.

Results

Characteristics of participants.

The characteristics of participants are reported in Table 1. All 31 included participants completed the study. The mean age, at baseline, was 54.13 years (SD =13.73); 29 % (N=9) were female, and most of them (41.9%, N=13) were diagnosed with multiple myeloma, followed by Hodgkin's lymphoma and non-Hodgkin's lymphoma. Twenty participants did not present any comorbidity (64.5 %), while 11 participants presented at least one disease (Diabetes mellitus, high blood pressure, Neuropathy, psychiatric disorders).

Type of chemotherapy before the Autologous Hematopoietic Stem cell treatment is mainly represented by the Melphalan cycle (54,8 %, N= 17), followed by Fotemustine, Etoposide, cytosine Arabinoside and Melphalan (FEAM) (25,8 %, N=8), Bendamustine, Etoposide, cytosine Arabinoside and Melphalan (BEAN) (16,1 %, N=5), and Cytarabine (3,2 % N=1). The average hospital stay was 24.97 (SD 5.75) days.

Nine patients (29%) took home hypnotic medication; eight of them assumed Benzodiazepine, and one participant nonbenzodiazepine hypnotics (Z-drugs). Approximately half of the patients (45%) increased their intake of hypnotic medication during hospitalization.

Table 1. Sociodemographic characteristics of partecipants

Characteristic	n	%
AO Padua	23	74,2
AO Mestre	8	25,8
Gender		
Male	22	71
Female	9	29
Marital Status		
Never Married	7	22,6
Married	22	71
Divorced	1	3,2
Widower	1	3,2
Educational level		
Primary education	5	16,1
Secondary education	9	29
University	17	54,8
Comorbidity		
Yes	11	35,5
No	20	64,5
Diagnosis		
Hodgkin's lymphoma	8	25,8
Multiple myeloma	13	41,9
Non-hodgkin lymphoma	8	25,8
Leukemia	2	8
Chemioteraphy		
FEAM	8	25,8
Melphalan	17	54,7
BEAN	5	16,1
Cytarabine	1	3,2

**FEAM - Fotemustine, Etoposide, cytosine Arabinoside and Melphalan; BEAN - Bendamustine, Etoposide, cytosine Arabinoside and Melphalan*

Sleep quality of participants

Patients mean ISI score had a statistically significant increase from 7.45 at baseline (T0) to 9.90 at day +1 from the autologous HSCT (T1) and 9.52 at discharge (T2) (Table 2). Participants who had insomnia symptoms at baseline and an increase of the ISI score during hospitalization, ranged from 41.9 % (N=13) at the admission, to 58.1% (N=18) at T1, and 64.5% (N=20) before discharge (T2) (Table 3). The daytime drowsiness was significantly different at baseline (T0), at day +1 from the autologous HSCT (T1), and at discharge (T2) ($p < 0.001$) (see Table 4).

Most participants (97%, N=30) had at least one nocturnal awakening during hospitalization and the number of nocturnal awakenings increased from T0 to T2 (2.03 vs 3.03, p=0.004) (Table 5).

Even though the majority of patients reported nocturnal awakenings (96.8 %, N=30) at T1 and T2, only 41.8 % (N=13) at T1 and 45.2 % (N=14) at T2 declared that their sleep was disturbed by health providers: the main reason for the interruptions are the therapy administration and the vital signs detection or therapy administration by the nurse (25 %, N= 8), followed by noises (10 %, N=3), and at last, a small part was disturbed by both (10%, N=3) (see Table 5).

Table 2. Descriptive statistics of ISI and comparison in three time

	Mean ± SD	Difference at T1 (Δ)	p	Difference at T2 (Δ)	p
ISI T0	7.45 ± 6.33	2.12	0.034*	2.46	0.014*
ISI T1	9.90 ± 6.76	0		0.024	0.981
ISI T2	9.52 ± 5.53	0.024	0.981	0	

Note. Wilcoxon test was used to test ISI value in three time.

Table 3. Assessing the severity of insomnia at T0, T1 and T2

	T0 n (%)	T1 n (%)	T2 n (%)
Non-significant insomnia	18 (58.1)	13 (41.9)	11 (35.5)
Mild insomnia	8 (25.8)	13 (41.9)	16 (51.6)
Moderate insomnia	4 (12.9)	2 (6.5)	3 (9.7)
Severe insomnia	1 (3.2)	3 (9.7)	1 (3.2)

Table 4. Comparison of adverse events at T1 and T2 and relation with ISI score.

	T1 n (%)	ISI_T1 mean (SD)	T2 n (%)	ISI_T2 mean (SD)
Intestinal mucositis				
Yes	8 (26%)	16.75 (8,41)	5 (16%)	14.8 (7,32)
No	23 (74%)	7.52 (4. 11)	2.6 (84%)	8.5 (4,64)
Sign.		0.006*		0.071
Oral mucositis				
Yes	8 (26%)	1487 (9.22)	7 (23%)	13,37 (8,03)
No	23 (74%)	8.17 (4.82)	24 (77%)	8.38 (4,14)
Sign.		0.081		0.104
Diarrhea				
Yes	8 (26%)	13,75 (9.56)	9 (29%)	11,33 (8,14)
No	23 (74%)	8.56 (5.11)	22 (71%)	8.77 (4,07)
Sign.		0.212		0.507
Pain				
Yes	4 (4%)	16.75 (8,42)	3 (10%)	14 (4.58)
No	27 (87%)	8.89 (6,02)	28 (90%)	9.03 (5. 48)
Sign.		0.054		0.122
Nausea/vomiting				
Yes	11(35)	12.27 (8.58)	9 (29%)	13 (6,32)
no	20 (65%)	8.6 (5.33)	22 (71%)	8.09 (4,6)
Sign.		0.290		0.046*

Adverse events and insomnia symptoms

The participants developed mainly nausea and vomiting at day +1 from the autologous HSCT (T1), and diarrhea before discharge (T2).

ISI score was associated to the presence of intestinal mucositis at T1 (ISI value 16.75 vs. 7.42, p=0.006) and to the presence of nausea and vomiting at T2 (ISI score 13 vs. 8.09; p=0.0,46). Pain association with insomnia symptoms is not statistically significant (ISI value 16.75 vs. 8.89, p=.054) at T1 (Table 4) .

Table 5. Nocturnal awakenings and interruption sleep

	T0	T1	T2
Nocturnal awakenings	*N (%)* *Mean (SD)*	*N (%)* *Mean (SD)*	*N (%)* *Mean (SD)*
Yes	26 (83.87) 2.03 (1.44)	30 (96.8) 2.74 (1.36)	30 (96.8) 3.03 (1.47)
No	5 (16.13)	1 (3.2)	1(3.2)
Daytimes drowsiness	*n (%)*	*n (%)*	*n (%)*
No	8 (25.8)	1 (3.2)	4 (12.9)
mild	19 (61.3)	15 (48.4)	20 (64.5)
Moderate	3 (9.7)	12 (38.7)	6 (19.4)
severe	1 (3.2)	3 (9.7)	1 (3.2)
Interruption sleep		*n (%)*	*n (%)*
Yes		13 (41)	14 (45)
Nurse		7 (22,6)	8 (25)
Noise		5 (16)	3 (10)
Nurse and noise		1 (3)	3 (10)
No		18 (59)	17(55)

Discussion

Sleep constitutes a vital biophysical process although it is a somewhat neglected aspect within clinical care settings among hospitalized. The present findings, indicate that patients undergoing hematopoietic cell transplantation while hospitalized are experiencing insufficient sleep during their hospital stay. In the present study, the minimum ISI score of eight, the cut-off to define the presence of insomnia symptoms, was reached by 42% (N =13) of the subjects at hospitalization, by 58% (N=18) at day +1 from the HSCT, and by 65% (N=20) at discharge. These results align with literature, highlighting the presence of insomnia in people undergoing autologous HSCT with the same characteristics of the population of this study, during the pre-hospitalization with an incidence of 38 %, against 68 % to 82 % during hospitalization[14,19,21]. However, it is difficult to compare the results because in these different studies, as reported in the articles, were used different instruments to evaluate the quality of sleep (Pittsburgh Sleep Quality Inventory[13,14], European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30[8] and polysomnography[18]).

A statistically significant association between the intestinal mucositis at T1 and greater severity of insomnia symptoms at the same time was observed. This may be associated with an increase in the severity of intestinal mucositis after five days from the start of chemotherapy treatment, improving progressively[9]. At time T2, there is a statistically significant association between the presence of nausea and vomiting and a higher score on the Insomnia Severity Index. As far as the other side effects (diarrhea, pain, and oral mucositis), there is no statistically significant relationships with the ISI score. Daytime drowsiness tends to increase during hospitalization, especially at time T1, with a median of 1.55, corresponding to mild-moderate somnolence. However, daytime drowsiness decreases slightly during the post-transplant period. This may be related to chemotherapy and its related fatigue.

The administration of hypnotic medications increased from 29 % (N=9) to 45% (N=14) during hospitalization, and the benzodiazepine was the more prescribed. Although some patients were given hypnotic therapy, no significant difference in the Insomnia Severity Index score was found compared to those who did not take medications.

Between 10:00 p.m. and 7:00 a.m., patients reported an average of two awakenings per night at both T0 and T1. However, this number increased to an average of three awakenings per night at T2. This rise in awakenings during hospitalization is noteworthy, particularly when compared to the commonly reported figure in the literature, which suggests an average of ten awakenings per night[16].

The most frequently documented nighttime care activities included medication administration and vital sign measurements, followed by instances of noise. Importantly, all patients experienced interruptions during the night, half of these disruptions were caused by healthcare providers. The findings of this study emphasize a significant need for the

development of care protocols and interventions aimed at addressing sleep disturbances among hospitalized patients undergoing hematopoietic cell transplantation (HCT).

Limitations

Although the current study provides crucial objective documentation on sleep in hospitalized patients undergoing autologous HSCT, limitations exist. The firsts one were the small sample size and the impossibility to compare the quality of sleep in autologous and allogenic HSCT by analyzing the association between type of chemotherapy and severity of insomnia symptoms. The current study included a predominance of males and patients hospitalized at the Padua hospital and this plays against the homogeneity between the enrolled patients in the two different centers. Some patients encountered difficulties in completing the questionnaires, particularly on day +1 from the Hematopoietic stem cell transplant, due to the consequence of chemotherapy.

Conclusions

Sleep has a vital role in human life, especially in healing process, since it can alter the immune and neuroendocrine systems, as evidenced by the literature. Mitigating sleep disturbances in hospitalized patients presents an ongoing challenge necessitating a holistic and multifaceted strategy.

This observational study allowed to assess the sleep quality, in particular insomnia symptoms, in patients who received Autologous Hematopoietic Stem Cell Transplant in two hospitals in Italy, comparing the ISI score, the daytime drowsiness level, and the nocturnal awakenings at home, at day +1 from the HSCT and at the discharge from the hospital.

The study's primary outcome was the occurrence, severity, and modifications of insomnia in the three times point of the study, focusing on insomnia symptoms in patients receiving autologous stem cell transplantation.

In HSCT patients, sleep deprivation during hospitalization may negatively affect the post-transplant recovery, lengthening the NADIR phase and worsening their clinical condition [1]. Exclusive use of patient self-reported tools may not be representative of the full extent of the problem.

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