

The Effect of Hypnotics on Sleep Quality and Cognitive Function in Patients with Brain Tumors

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Objective : We investigated the effect of hypnotics on sleep quality, cognitive function, and depressive mood in patients with insomnia following brain tumor resection.

Methods : From patients who underwent brain tumor resection, we recruited 10 patients with insomnia who received hypnotics for more than 1 week during a 3-week follow-up period (insomnia group). We also recruited 12 control patients with brain tumors but without insomnia (control group). We evaluated sleep quality at baseline and 3 weeks later using the Insomnia Severity Index (ISI), the Pittsburgh Sleep Quality Index (PSQI), the Stanford Sleepiness Scale (SSS), and the Epworth Sleepiness Scale (ESS) and investigated cognitive function and depression using the Computerized Neuropsychological Test and the Beck Depression Inventory (BDI).

Results : At baseline, SSS, ISI, PSQI, and BDI scores were significantly higher and visual continuous performance test (VCPT) and auditory continuous performance test (ACPT) scores were significantly lower in the insomnia than in the control group. Three weeks later, the patients who had received hypnotics had significantly higher ISI, PSQI, ESS, VCPT, ACPT, visual span forward and backward, and visual recognition test scores, and significantly lower BDI scores.

Conclusion : Quality of sleep in patients with insomnia following brain tumor resection was initially poor but improved significantly after taking hypnotic medication. Further, the hypnotic medications appeared to contribute to the amelioration of cognitive impairments and depressive moods in patients who previously underwent brain tumor resection. We thus recommend the use of hypnotics for patients with brain tumors with insomnia.

Key Words : Hypnotics and sedatives · Sleep initiation and maintenance disorders · Cognition · Depression · Brain neoplasms.

INTRODUCTION

Although insomnia is one of the most common complaints in patients with brain lesions, little is known about insomnia in these patients²⁶. Lesions in the brain areas associated with

sleep, such as the hypothalamus, brainstem, and basal fore-brain, which are caused by the local effects of a brain tumor or by treatment procedures including surgery and irradiation, can lead to sleep disturbances³¹. Furthermore, sleep disturbances can persist in brain tumor survivors for many years af-

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ter diagnosis and completion of treatment, making it one of the most persistent problems experienced by patients with brain tumors¹². Previous studies have documented that although sleep disturbances are common in these patients, the problem has been neglected¹². Sleep disturbances are associated not only with reduced cognitive function but also with psychological and physical problems, which can interfere with recovery³³. Therefore, early treatment of insomnia is important to maintain active rehabilitation management of patients with brain tumors.

Several forms of treatment for insomnia have been developed, and hypnotic medications have been most frequently prescribed in inpatient rehabilitation units because of their rapid effect on sleep disturbances^{17,30}. Typically, hypnotics are divided into benzodiazepine and non-benzodiazepine drugs. All hypnotics induce and maintain sleep, thus improving the sleep quality of patients with insomnia. However, as an adverse effect, a decline in cognition has been reported in several studies in which members of the general population were administered hypnotics^{16,28}. Hypnotics may thus affect the cognitive function of patients with brain tumors, but the effect has not clearly been demonstrated to date.

In this study, we investigated changes in sleep patterns following administration of hypnotics. In addition, we attempted to determine whether the administration of hypnotics disturbs the cognitive recovery of patients with insomnia following brain tumor resection.

MATERIALS AND METHODS

Patients

The study protocol described here was approved by the Ethics Committee of Asan Medical Center, and written informed consent was obtained from each participant. We enrolled patients with a primary diagnosis of brain tumor who were transferred as inpatients to the Department of Rehabilitation Medicine at Asan Medical Center, following their brain tumor resection, between August 2011 and July 2012. A brain tumor was defined as a primary or metastatic lesion, as revealed by computed tomography or magnetic resonance imaging of the brain and confirmed by a pathological diagnosis of the biopsy following surgical resection. All benign and malignant tumors were included. To be enrolled, patients were required to be

able to follow simple commands, as determined by a score of 24 or higher on the Mini-Mental State Examination (MMSE). Patients were excluded if they were medically unstable, unable to read, or unable to answer questions because of severe aphasia, apraxia, blindness, deafness, cognitive impairment, or neglect. Patients taking hypnotics (prior to our study), neuroleptics, antipsychotics, anti-epileptics, H₂-blockers, or any other potentially sedating drug were also excluded.

No universal tool exists for the diagnosis of insomnia after a brain tumor. Insomnia was therefore diagnosed in patients who underwent brain tumor surgery if at least one of following criteria defined in previous reports of insomnia in the general populations was met^{7,23}. First, a total sleep time less than or equal to 360 minutes; second, a sleep latency greater than 30 minutes; or third, four or more awakenings from sleep during any one night. Patients diagnosed with insomnia were administered hypnotics, prescribed by individual physicians. In addition, individualized rehabilitation programs were provided. Every patient received 1-hour sessions of conventional physical and occupational therapy six times per week for 3 weeks. After 3 weeks, patients who required hypnotics for more than 1 week were classified into the Insomnia group. As controls, we recruited patients with brain tumors who did not have insomnia and were not taking any hypnotic medication.

Measurements

The Insomnia Severity Index (ISI)² and the Pittsburgh Sleep Quality Index (PSQI)⁵ were used to evaluate sleep disturbance and quality. The ISI is a brief self-reporting survey instrument measuring the patient's perception of insomnia. It targets the subjective symptoms and the consequences of insomnia, as well as the degree of concern or distress caused by those difficulties. The ISI comprises seven items assessing the severity of sleep onset and sleep maintenance difficulties (both nocturnal and early morning awakenings), satisfaction with the current sleep pattern, interference with daily functioning, noticeability of impairment attributed to sleep problems, and the degree of distress or concern caused by the sleep problems. Each item is rated on a 0–4 scale, with the total score ranging from 0 to 28. A higher score suggests more severe insomnia. The PSQI is a 19-item self-rated questionnaire for evaluating subjective sleep quality over the previous month. The 19 questions are combined into seven clinically-

derived component scores, each weighted equally, and scored from 0 to 3. The seven components are composed of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. These component scores are added to obtain a global score ranging from 0 to 21, with higher scores indicating worse sleep quality.

Daytime sleepiness was evaluated using the Stanford Sleepiness Scale (SSS)¹⁵ and the Epworth Sleepiness Scale (ESS)⁸. The SSS consists of a single seven-point scale. It ranges from 1 (feeling active and vital; alert; wide awake) to 7 (almost in reverie; sleep onset soon; lost struggle to remain awake). The ESS consists of eight self-rated items, each scored from 0–3, that measure a subject's habitual "likelihood of dozing or falling asleep" in common situations of daily living. Values of SSS ≥ 3 and values of ESS > 9 are considered to be indicative of significant daytime sleepiness.

The MMSE and the Computerized Neuropsychological Test (CNT; MaxMedica, Seoul, Korea) were used to assess cognitive function. The CNT was initially developed to evaluate cognitive function of Korean adults¹⁴. The reliability and validity of the CNT have been demonstrated previously¹⁴. The CNT contains the following six subtests : 1) a visual continuous performance test (VCPT); 2) an auditory continuous performance test (ACPT); 3) digit span forward and backward tests (DSFT and DSBT); 4) visual span forward and backward tests (VSFT and VSBT), for assessing attention; 5) an auditory verbal learning test (AVLT); and 6) a visual recognition test (VRT) for measuring memory function. All of the evaluations were performed both at baseline and after 3 weeks. Examiners were blinded to the identity and symptoms of each patient. The VCPT and ACPT were based on Conner's continuous performance test¹⁰. The DSFT and DSBT were derived from the Wechsler Adult Intelligence Scale-Neuropsychological Inventory^{6,20}, and the VSFT and VSBT were based on Corsi's block-tapping test^{4,21}. The AVLT was derived from Rey's AVLT²⁷. The VRT was similar to the AVLT, but figures were used instead of words.

For evaluating depressive symptoms, the Beck Depression Inventory (BDI), a self-report questionnaire containing 21 items, was used. BDI scores range from 0 to 63, with higher BDI scores indicating more depression¹³.

Statistical analysis

SPSS version 22.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Mann-Whitney U test was used to compare the Insomnia and Control groups in terms of general patient characteristics and regarding the results of the following tests : ISI, PSQI, SSS, ESS, MMSE, CNT, and BDI. The Wilcoxon signed rank test was used to compare baseline and follow-up data for the Control and Insomnia groups. Any association with a *p* value less than 0.05 was considered to be statistically significant.

RESULTS

Demographic and disease-related characteristics of the patients

Of 25 patients who were confirmed to have a brain tumor, 22 patients were enrolled in this study, and 10 were diagnosed with insomnia. Three patients were excluded because they took hypnotics for less than 1 week. Therefore, 10 patients were assigned to the insomnia group, and 12 patients were assigned to the control group. None of the included patients had a history of seizures. The demographic characteristics of the patients in both groups are shown in Table 1. There were no significant differences in sex, age, time since operation, history of radiation therapy, or Motricity Index¹⁹ between the Control and Insomnia groups (Mann-Whitney U test, $p > 0.05$). The following hypnotics were administered for more than 1 week to patients in the insomnia group during the 3-week follow-up course of the study : seven patients received 10 mg of zolpidem and three patients received 25 mg of trazodone. Patients in the control group were administered no hypnotic medications.

Sleepiness and quality of sleep

Baseline mean scores for the ISI, PSQI, and SSS were significantly higher in the Insomnia group than in the control group (Mann-Whitney U test, $p < 0.05$) (Table 2). The ISI, PSQI, and ESS scores in the insomnia group were significantly improved after hypnotic medication, compared with baseline scores (Wilcoxon signed rank test, $p < 0.05$) (Table 2).

Cognitive function

There was no significant difference in MMSE scores be-

tween the insomnia and control groups, either at baseline or at the 3-week follow-up (Mann-Whitney U test, $p>0.05$). Significant improvement in MMSE scores was observed between baseline and the follow-up in both groups (Wilcoxon signed rank test, $p<0.05$) (Table 3).

During the baseline CNT assessment, the mean scores for VCPT and ACPT in the Insomnia group were significantly

lower than the Control group scores (Mann-Whitney U test, $p<0.001$). However, there were no differences in the mean scores of the other tests between the two groups at baseline (Mann-Whitney U test, $p>0.05$). After 3 weeks, in the Insomnia group, the mean scores on the VCPT, ACPT, and VSFT were significantly higher, with more figures being recalled during the first and fifth VRT trials (Wilcoxon signed rank

Table 1. Demographic characteristics of all subjects

	Insomnia group	Control group	p-value
Sex (M : F)	4 : 6	3 : 9	
Age (years)	55.6±12.3	53.3±12.6	0.862
Duration after operation (days)	15.7±10.2	13.8±11.3	0.643
Corticosteroid use	3	5	0.674
Radiation treatment	5	5	0.696
Motricity index	72.6±7.8	72.8±8.6	0.792
Diagnosis			
Meningioma	1	5	
Low grade glioma	1	1	
Ependymoma	1	0	
Glioblastoma	3	2	
CNS lymphoma	1	0	
Metastatic tumor	2	2	
Craniopharyngioma	0	1	
Choroid plexus papilloma	1	0	
Neuroma	0	1	
Site of lesion (right : left : both)	5 : 2 : 3	7 : 3 : 2	
Hypnotics			
Zolpidem 10 mg	7		
Trazodone 25 mg	3		

Values are presented as mean±standard deviation or number unless otherwise indicated. M : male, F : female, CNS : central nervous system

Table 2. Comparison of sleep status

	Insomnia group				Control group
	Before medication		After medication		
	Score	p-value*	Score	p-value†	
ISI	12.1±4.1	<0.001‡	8.8±2.8	0.022‡	3.1±2.2
PSQI	10.4±2.8	<0.001‡	7.1±2.8	0.010‡	3.3±1.7
SSS	4.0±1.5	0.002‡	3.3±0.8	0.227	2.1±1.4
ESS	7.4±4.6	0.070	4.4±2.8	0.004‡	3.7±2.3

Values are presented as mean±standard deviation. *Comparison of data from the Insomnia group and baseline data from the Control group, using the Mann-Whitney U test. †Comparison of data before and after hypnotic medication treatment in the Insomnia group, using the Wilcoxon signed rank test. ‡ $p<0.05$. ISI : Insomnia Severity Index, PSQI : Pittsburg Sleep Quality Index, SSS : Stanford Sleepiness Scale, ESS : Epworth Sleepiness Scale

test, $p < 0.05$) (Table 3). In contrast, in the control group, only the scores on the first VRT trial were improved after 3 weeks (Wilcoxon signed rank test, $p < 0.05$), while other scores were not changed (Wilcoxon signed rank test, $p > 0.05$) (Table 3).

Depression

At baseline, BDI scores in the Insomnia group were significantly higher than those in the control group (Mann-Whitney U test, $p < 0.001$). When the severity of depression was compared between baseline and follow-up, patients in the insomnia group showed significant improvements after the follow-up (Wilcoxon signed rank test, $p < 0.05$), but the control group patients did not ($p > 0.05$) (Table 3).

DISCUSSION

In this study, we examined the effects of hypnotics on sleep

quality and cognition in patients who had undergone surgery for brain tumor resection. Additionally, we evaluated changes in the patients' depressive mood after taking hypnotics.

Sleep disturbances, especially insomnia, are frequently observed in healthy individuals. The prevalence of insomnia has been reported to range between 20% and 35% in the general population and between 10% and 52% in the elderly^{11,18}. A high prevalence of insomnia has also been observed in patients with neurological diseases. In previous studies, 68% of patients with stroke and approximately 50% of brain tumor survivors presented with insomnia^{22,24}. This reported prevalence (50%) of insomnia in patients with brain tumors is similar to our study, in which 10 of 25 screened patients (40%) were diagnosed with insomnia. After administration of hypnotics to the patients with insomnia, at the 3-week follow-up, ISI, PSQI, and ESS scores of the patients with insomnia were significantly improved. ISI and PSQI scores are related to sleep disturbances and quality of sleep, and the ESS score is associ-

Table 3. Comparison of depressive mood and cognitive function

	Insomnia group			Control group		
	Baseline	Follow-up	<i>p</i> -value*	Baseline	Follow-up	<i>p</i> -value [†]
MMSE (30)	24.7±1.8	26.9±1.7	0.011 [‡]	25.9±2.1	27.3±1.8	0.006 [‡]
Attention						
VCPT (135)	103.6±28.7	126.4±24.6	0.014 [‡]	132.8±5.6	133.4±2.9	0.902
ACPT (135)	113.0±21.2	127.6±17.6	0.012 [‡]	128.2±9.5	130.6±4.6	0.345
DSFT (8)	4.1±1.3	4.9±1.5	0.202	5.2±1.2	4.6±1.4	0.144
DSBT (8)	2.6±0.6	3.2±1.3	0.128	3.5±1.2	3.1±0.7	0.524
VSFT (8)	3.6±1.2	5.2±1.2	0.047 [‡]	4.1±1.7	3.9±1.1	0.462
VSBT (8)	3.4±1.7	3.1±1.1	0.344	3.1±1.4	3.2±0.8	0.465
Memory						
AVLT (15)						
1st trial	4.0±2.1	4.6±2.3	0.161	3.2±2.1	5.0±2.8	0.197
5th trial	7.1±2.2	6.9±4.0	0.902	8.1±4.1	9.2±3.7	0.104
Delay trial	2.9±3.6	4.5±3.3	0.493	4.4±3.2	4.4±5.2	0.285
VRT (15)						
1st trial	6.7±2.3	8.8±2.3	0.033 [‡]	6.3±3.7	9.2±1.5	0.021 [‡]
5th trial	7.6±2.5	8.9±2.8	0.047 [‡]	9.5±3.7	9.6±1.5	0.705
Delay trial	7.3±4.1	8.1±4.6	0.528	6.8±5.9	9.8±2.8	0.080
BDI (63)	24.4±13.3	18.9±11.1	0.008 [‡]	6.4±8.5	6.9±8.9	0.552

Values are presented as mean±standard deviation. *Comparison between baseline and follow-up in the Insomnia group. [†]Comparison between baseline and follow-up in the Control group. [‡] $p < 0.05$, Wilcoxon signed rank test. MMSE : mini-mental status examination, VCPT : visual continuous performance test, ACPT : auditory continuous performance test, DSFT : digit span forward test, DSBT : digit span backward test, VSFT : visual span forward test, VSBT : visual span backward test, AVLT : auditory verbal learning test, VRT : visual recognition test, BDI : beck depression inventory

ated with daytime sleepiness. Our results therefore indicate that hypnotics can improve quality of sleep and also reduce sleep disturbance and daytime sleepiness in patients with insomnia after brain tumor resection.

At baseline, sleep-deprived patients' VCPT and ACPT mean scores were lower than those of controls. At the follow-up in our study, the scores for the VCPT, ACPT, VSFT, and VRT (1st and 5th trials) were improved. The VCPT, ACPT, and VSFT are tests that measure attention abilities, and the VRT reflects memory function¹⁵. No decline was detected in any of the tests for evaluating cognitive functions. Considering these results, the lower VCPT and ACPT baseline scores for patients with insomnia indicate that these patients had a lower capacity for attention than patients without insomnia. In addition, the increase in some of the cognitive function test scores (with no simultaneous declines in other scores) indicates that the use of hypnotics for managing insomnia does not disturb cognitive function in patients with brain tumors, and our results demonstrate in fact the possibility of a positive effect of hypnotics on cognitive function in patients with brain tumors, especially attention and memory functions. The different baseline results in the two groups and the positive effect on cognitive function in the insomnia group are consistent with the findings of previous studies indicating that sleep deprivation causes impairments in attention and memory functions and that the management of insomnia improves those functions^{1,9,25}.

We also observed that patients with insomnia had higher BDI scores than controls, with a mean value at baseline of 6.4 in the control group and 24.4 for the patients with insomnia. A higher BDI score is indicative of more severe depression, suggesting that the patients with insomnia experienced more severe depressive moods. Several studies have reported a close correlation between insomnia and depression^{3,32}. Likewise, in our study, the depressive symptoms in the insomnia group seemed to stem from the insomnia itself, as treatment with hypnotics reduced the symptoms of insomnia, which in turn relieved the depressive mood. Regarding the benefits of pharmacological treatment of depression, Rooney and Grant²⁹ conducted a meta-analysis, and reported that the effects of medication cannot be determined yet, because there are no high-quality studies that have examined the value of pharmacological treatment of depression in patients with brain tumors. Additional well-designed studies are needed to address this issue.

CONCLUSION

In this study, the quality of sleep of patients after brain tumor resection who experienced insomnia was initially poor but significantly improved after administering hypnotic medication. In addition, our results suggest that hypnotics attribute, at least in part, to the improvement of cognitive impairments and depressive moods in patients after surgery for brain tumor resection. The appropriate use of hypnotics is therefore recommended for patients experiencing insomnia after brain tumor operations. To the best of our knowledge, this is the first study that evaluates the effectiveness of hypnotics in patients with brain tumors with insomnia. However, several limitations of this study should be considered. First, we did not control for sub-type and location of the brain tumor. Second, we did not investigate any potential long-term effects of hypnotics. Third, the number of patients recruited was small. Fourth, our study was conducted without a placebo control group (i.e., a group of patients with insomnia receiving placebo medication). Lastly, we did not consider preoperative comorbid conditions. Therefore, further studies addressing these limitations are necessary to confirm the findings of the current study.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in this study.

AUTHOR CONTRIBUTIONS

Conceptualization : MHC

Data curation : MHC

Formal analysis : MCC, MHC

Funding acquisition : MHC

Methodology : MHC

Project administration : MHC

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