의학석사 학위논문

졸피뎀 사용과 악성 뇌종양에서 사망률의 연관성:

국민건강보험공단 청구자료를 이용한 후향적 코호트 연구

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Use of Zolpidem and Brain Cancer Survival:

A Retrospective Cohort Study based on the National Health Insurance Service Database

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이 논문을 의학석사 학위논문으로 제출함

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1. Introduction

Sleep is evolutionarily conserved across species, and it plays a critical role in sustaining homeostasis in brain and other organs. Sleep is an active restorative process rather than a dormant state. During the sleep synaptic homeostasis is restored and protein waste is vigorously removed from central nervous system.[1]

Deleterious effect of sleep disturbance on quality of life, cognition and emotional status is well-recognized.[2,3] Furthermore, there are several studies showing that sleep disturbance has negative impact on cancer survival and cancer progression.[4] In breast cancer, women who sleep longer had a higher risk of all-cause, breast cancer and non-breast cancer mortality.[5] In advanced hepatobiliary and pancreatic cancer, short and long sleep duration both were associated with increased mortality.[6] In 21,230 cancer patients from the Women' s Health Initiative (WHI) cohort, short pre-diagnostic sleep duration combined with frequent snoring was associated with poor cancer-specific survival.[7]

Among numerous types of cancers, brain cancer patients are vulnerable to sleep disorders especially because circadian oscillator that regulates sleep-wake cycle resides in the brain. In a thorough review of studies on sleep disturbances among brain cancer patients, prevalence of sleep disturbances were 17% to 54% of brain cancer patients.[8] Another systematic review found that 27 to 34% of brain cancer patients complained moderate to severe sleep disturbances.[9] Furthermore, insomnia was significantly related to disease progression in a prospective study with high-grade glioma patients.[10]

Though hypnotics for sleep disorders are common practice, adverse effects from unnecessary sedative-hypnotics are constantly reported. Common adverse effects include cognitive impairment, fatigue, traffic accident, fall, infection and even cancer development.[11] Furthermore, recent studies showed significantly increased mortality associated with sedative-hypnotics use.[11,12,13,14]

Among several hypnotics, benzodiazepines were associated with increased mortality in several studies.[12,14] But the effect of zolpidem on mortality have been controversial.[11,14,15]

Zolpidem, an imidazopyridine derivative, is one of the most common hypnotics prescribed for the treatment of insomnia worldwide. In the United States, 1.08% of community-dwelling adults were prescribed with zolpidem[16] and more than 23 million zolpidem pills were prescribed by the 2005.[17] In Taiwan, zolpidem was the most commonly prescribed Z-drug (86.7% in the year of 2010) among older people.[18] In a retrospective survey from a tertiary hospital in South Korea, zolpidem was prescribed in 8.7% of all older outpatients.[19] Although zolpidem is not a benzodiazepine, it is a gamma-aminobutyric acid A ($GABA_A$) receptor agonist acting much like benzodiazepines.[17] Zolpidem is classified as a Z-drug along with zaleplon, zopiclone and currently the only Z-drug available in Korea.

The association between zolpidem and mortality have been studied by many researchers. Also, several studies revealed that zolpidem is associated with increased risk of developing cancer. In a matched cohort study from Pennsylvania, USA, zolpidem was associated with increased mortality in a dose-dependent manner.[11] A Taiwanese cohort study revealed that cancer-specific mortality was higher in subjects with zolpidem exposure (adjusted HR = 1.65, 95% CI 1.57-1.74), although zolpidem exposure exhibited a lower risk of overall mortality (adjusted HR = 0.73, 95% CI 0.71-0.75).[15]

For patients with brain cancer, there was a study evaluating impact of hypnotics on cognitive function and sleep quality.[20] However, there has been no study investigating the association between hypnotics and mortality in brain cancer to the best of our knowledge.

We hypothesized that zolpidem is associated with increased brain cancer-specific mortality. To investigate the association between zolpidem and mortality in brain cancer patients, we performed a retrospective cohort study using the database from the National Health Insurance Service (NHIS) of the Republic of Korea.

The NHIS database provides a nation-wide, population-based information on all medical activities. Linked to national mortality data, the NHIS database also provides reliable data about deaths with a long follow-up period. Therefore, the NHIS database can be used as a tool for a retrospective cohort study.

2. Methods

2.1. Data source and study population

We conducted a retrospective cohort study using the NHIS database of the Republic of Korea. International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes were utilized to identify diagnoses of each subject. For deceased subjects during study period, cause of death for each individual was obtained from the Statistics Korea (KOSTAT).

Study population included adults (age of 18 or older) diagnosed as malignant neoplasm of cerebral meninges (ICD-10 code: C70.0) or brain (ICD-10 code: C71) from January 2003 to December 2017. To include only incident cases from 2003 to 2017, subjects with a diagnosis of malignant neoplasm of cerebral meninges or brain in 2002 were excluded. Subjects diagnosed as malignant neoplasm of other origins than central nervous system (ICD-10 code: C00 ~ C69, C70.1 ~ C70.9, or C72 ~ C97) from 2002 to 2017 were excluded to minimize potential influence of other cancers on survival.

2.2. Variables

Onset of brain cancer diagnosis was defined as the first day with an ICD-10 code for brain cancer (C70.0, or C71.0 ~ 71.9). Age at brain cancer diagnosis and sex were obtained. For every death during the study period, cause of death was reviewed from the KOSTAT database to determine if it was due to brain cancer. Survival duration was defined as number of days from brain cancer diagnosis to death.

Comorbid diseases and prescribed medications were also obtained from the NHIS database. Subjects with a diagnosis of nonorganic sleep disorders (ICD-10 code: F51.x) or sleep disorders (ICD-10 code: G47.x) were classified to have sleep disorders. Likewise, subjects with a diagnosis of depressive episode (ICD-10 code: F32.x) or recurrent depressive disorder (ICD-10 code: F33.x) were considered to have depression. Zolpidem exposure was defined as prescription of any forms of zolpidem (regular and continuous-releasing forms). Exposure to any antidepressants available in Korea were identified.

2.3. Statistical Analysis

Characteristics of the study population were compared between zolpidem exposure and non-exposure groups using *t*-test for continuous variables and chi-square test for categorical variables. The mortality risk of zolpidem was analyzed using Cox regression model for multivariate analysis to calculate hazard ratio (HR) and 95% confidence interval (CI) after adjusting for the possible confounding factors (age at brain cancer diagnosis, sex, sleep disorder, depression and antidepressant). For further analysis, subjects were divided into two groups according to age at brain cancer diagnosis - young adults (18-64 years old) and older adults (65 years old or older). Hazard ratio for each group was computed. For primary analysis, deaths attributable to brain cancer were used for survival analysis. Deaths due to other causes than brain cancer was considered as censored data. Subjects who was alive at the end of the study period (31 December 2017) was also considered as censored data. Cause of death acquired from the KOSTAT is based mainly on death certificates. Considering possible errors in death certificates, secondary analysis evaluating the mortality risk of zolpidem on all-cause deaths was performed. Statistical analysis was performed using R (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.).

3. Results

We identified 38,037 incident cases of adult brain cancer from 2003 to 2017. There were 16,791 (44.1%) males and 21,246 (55.9%) females. Mean age at brain cancer diagnosis was 53.32 years old with a standard deviation of 17.88 years. Mean overall survival was 2,478 days (or 6.79 years) with a standard deviation of 1,939 days (or 5.31 years). Overall, 14,521 (38.1%) subjects died during the follow-up period and 8,839 (23.2%) subjects died of brain cancer.

3.1. Comparison of characteristics according to exposure to zolpidem

11,823 (31.1%) subjects were exposed to zolpidem from 2003 to 2017 (Table 1). The exposure group was older at brain cancer diagnosis (57.1 vs. 51.6, p-value < 0.001) with higher all-cause mortality (41.4% vs. 36.7%, p-value < 0.001) and brain cancer-specific mortality (23.9% vs. 22.9%, p-value = 0.038) than the non-exposure group. Sleep disorders (91.8% vs. 26.2%, p-value < 0.001), depression (63.4% vs. 32.6%, p-value < 0.001) and antidepressant use (69.8% vs. 39.4%, p-value < 0.001) were more prevalent in the exposure group than in the non-exposure group.

3.2. Univariate analysis for brain cancer-specific mortality

Table 2 shows the HR of covariables on mortality. Sex type showed the greatest risk of mortality (unadjusted HR = 1.50 for males). Age at brain cancer diagnosis was also associated with increased mortality (unadjusted HR = 1.04). Diagnosis of sleep disorder (unadjusted HR = 0.92), depression (unadjusted HR = 0.83) or antidepressant use (unadjusted HR = 0.71) were associated with decreased mortality. Zolpidem use was not significantly associated with mortality in univariate analysis.

3.3. Multivariate analysis for brain cancer-specific mortality for zolpidem

Zolpidem exposure was associated with increased mortality after adjustment for potential confounders (adjusted HR = 1.14, p-value < 0.001, Table 3). While the risk of mortality was significantly increased in young adults (18-64 years old, adjusted HR = 1.37, p-value < 0.001), there was no significant association between zolpidem exposure and mortality in older adults (65 years old or older, adjusted HR = 0.94, p-value = 0.131).

Mortality risk of zolpidem exposure was significantly increased in males (adjusted HR = 1.20, p-value < 0.001), but it was not significantly associated with mortality in females (adjusted HR = 1.08, p-value = 0.057). Among young adults, however, there was significant increase of mortality in females (adjusted HR 1.32, p-value < 0.001) as well as males (adjusted HR = 1.41, p-value < 0.001).

3.4. Mortality risk of zolpidem on all-cause mortality

Regarding the association between zolpidem and all-cause mortality, zolpidem exposure was associated with increased mortality for all adults (18 years old or older, adjusted HR = 1.10, p-value < 0.001, Table 4). As in the case of brain cancer-specific mortality, mortality risk was significantly increased in young adults (adjusted HR = 1.35, p-value < 0.001) but no significant association between zolpidem and mortality was observed in older adults (adjusted HR = 0.95, p-value = 0.11).

4. Discussion

In this study, 38,037 incident brain cancer cases for a period of 15 years were identified using the NHIS database, which is a nation-wide, comprehensive database comprising all medical activities including prescriptions, diagnoses and demographic information.

Zolpidem exposure was not associated with brain cancer-specific mortality before adjustment. However, subjects for whom zolpidem was prescribed had significantly higher risk of mortality (adjusted HR = 1.14, 95% CI 1.08-1.21) after adjustment for several potential confounding factors including age at brain cancer diagnosis, sex, comorbid sleep disorder, depression and antidepressant exposure. Compared to cancer-specific mortality (adjusted HR = 1.65) from the aforementioned Taiwanese cohort study,[15] our result suggests less increased risk of mortality associated with zolpidem in brain cancer patients.

Interestingly, association between zolpidem exposure and mortality showed different patterns between age groups. In young adults (18-64 years old), zolpidem exposure was robustly associated with increased mortality after adjustment (HR 1.37, 95% CI 1.27-1.49). In older adults (65 years old or older), however, zolpidem exposure was not significantly associated with mortality after adjustment (HR 0.94, 95% CI 0.86-1.02). Concerning sex differences, risk of mortality in adult males was significantly increased (adjusted HR = 1.20, 95% CI 1.11-1.30), but there was no significant association between zolpidem exposure and mortality in adult females (adjusted HR = 1.08, 95% CI 1.00-1.18, p-value = 0.57). Nevertheless, in young adults, mortality risk was significantly increased in females (adjusted HR = 1.32, 95% CI 1.17-1.50) as well as males (adjusted HR = 1.41, 95% CI 1.27-1.57). For older subjects, there was no significant association between zolpidem exposure and mortality regardless of sex (p-value > 0.1). With regard to zolpidem-related mortality, increased risks of traffic accidents and hip fractures from falls have been reported repeatedly. Prescription of zolpidem in the previous day was associated with increased risk for fatal motor vehicle collision (odds ratio = 1.48, 95% CI 1.06-2.07).[21] The risk was further increased in subjects with a high Charlson Comorbidity Index, in younger subjects, and in new zolpidem users.[21] There was significant association between Z-drugs and increased risk of hip fracture (relative risk = 1.90, 95% CI 1.68-2.13).[22] These

conditions might contribute to increased mortality in subjects on zolpidem.

On the other hand, little is known about increased cancer-specific mortality associated with zolpidem use. In this study, we excluded all subjects who were diagnosed as cancer of other origin than brain, and all subjects had brain cancer already. Thus, putative carcinogenic effect of zolpidem cannot explain increased mortality in this population. Furthermore, increased brain cancer-specific mortality as well as all-cause mortality cannot be explained by traffic accidents or falls. This suggests that specific biological effect of zolpidem on mortality would more plausibly explain the increased brain cancer-specific mortality in this study population.

There was no significant association between history of zolpidem use and mortality in older subjects (65 years old or older) in the current study. Similar result was observed in a 12-year prospective study with subjects aged 65 years or older. Benzodiazepines (adjusted HR 1.11, 95% CI 0.94-1.30) and Z-drugs including zolpidem (adjusted HR 0.92, 95% CI 0.71-1.20) were not associated with increased mortality after adjusting for confounding factors.[23] More prevalent comorbidities and shorter life expectancy in older population than in young population might explain minimal effect of zolpidem on mortality in older adults.

On the contrary to previous studies, diagnosis of sleep disorder was associated with significantly decreased mortality before and after adjusting for confounding factors in the current study. One of possible explanations is underestimation of sleep disorders in brain cancer patients. Sleep disturbance in cancer patient is frequently overlooked and underestimated by physicians.[24] In this population-based retrospective study, sleep disorders were identified only by physician's diagnosis. Objective sleep characteristics in subjects such as sleep duration, sleep quality or daytime sleepiness were not evaluated, leaving the possibility of undiagnosed sleep problems in the subjects. In addition, subjects who were diagnosed as sleep disorders are assumed to be patients to whom physicians pay more attention.

Thus, cancer progression and other medical problems could be detected more frequently and earlier, ultimately resulting in better outcome.

This study has several limitations. 1) All information about comorbidity, prescription and cause of death was collected based on the database originally used for medical claims. There can be discrepancy between actual and registered diagnosis. Quantitative and objective assessment of sleep or mood cannot be achieved. 2) Zolpidem prescription over the entire study period was included. Thus, exposure to zolpidem was not confined to the period after brain cancer diagnosis. 3) Data related to zolpidem dose were not available because of regulatory authority protecting the confidentiality of prescription dose. However, previous study reported increased mortality even with low dose of zolpidem (5–130 mg/year).[11] 4) Heterogeneous disease status (including pathologic classification, stage, disease extent of brain cancer, concurrent treatment and other medical conditions) was not controlled in this retrospective cohort study.

Despite these limitations, this study included all incident brain cancer patients for a period of 15 years comprising more than 38,000 subjects. The study subjects are literally representative of brain cancer patients in Korea. Long follow-up period with few follow-up losses is another strength of this study, which provides completeness of this study. We also performed a sensitivity analysis with all-cause mortality to minimize misleading cause of death. The association between zolpidem exposure and all-cause mortality was similar to the results of primary analysis.

5. Conclusions

Zolpidem exposure in brain cancer patients was associated with brain cancer-specific and all-cause mortality in adults aged 18–64 years old regardless of sex. On the other hand, zolpidem was not associated with brain cancer-specific or all-cause mortality in older population aged 65 years old or older. However,

data on dose of zolpidem prescription and detailed evaluation about sleep status were not available in this study. Further prospective studies, designed for detailed evaluation on sleep characteristics, are warranted to understand the mechanism behind the effect of zolpidem on mortality in brain cancer patients.

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Table 1. Characteristics of the study population according to exposure to zolpidem

	Zolpidem	No zolpidem	*p*-value
No. of subjects (%)	11,823 (31.1%)	26,214 (68.9%)	
Age at brain cancer diagnosis (mean ± SD)	57.1 ± 16.4	51.6 ± 18.3	< 0.001
Sex			
Male (%)	4,468 (37.8%)	12,323 (47.0%)	< 0.001
Female (%)	7,355 (62.2%)	13,891 (53.0%)	
Sleep disorder (%)	10,855 (91.8%)	6,859 (26.2%)	< 0.001
Depression (%)	7,496 (63.4%)	8,534 (32.6%)	< 0.001
Antidepressant use (%)	8,250 (69.8%)	10,323 (39.4%)	< 0.001
Overall deaths (%)	4,896 (41.4%)	9,625 (36.7%)	< 0.001
Brain cancer-specific deaths (%)	2,827 (23.9%)	6,012 (22.9%)	0.038

Table 2. Hazard ratios of brain cancer-specific mortality for all variables

	Numbers	Number of brain cancer-specific deaths	Unadjusted HR (95% CI)	*p*-value
Age at brain cancer diagnosis (mean ± SD)	53.33 ± 17.88		1.04 (1.03-1.04)	< 0.001
Sex				
Male (%)	16,791 (44.14%)	4,671 (52.85%)	1.50 (1.44-1.56)	< 0.001
Female (%)	21,246 (55.86%)	4,168 (47.15%)	1.00 (reference)	
Sleep disorder (%)	17,714 (46.57%)	3,995 (45.20%)	0.92 (0.88-0.95)	< 0.001
Zolpidem	11,823 (31.1%)	2,827 (31.98%)	1.01 (0.97-1.06)	0.564
Depression (%)	16,030 (42.14%)	3,456 (39.10%)	0.83 (0.79-0.86)	< 0.001
Antidepressant use (%)	18.573 (48.83%)	3,721 (42.10%)	0.71 (0.68-0.74)	< 0.001

Table 3. Hazard ratios of brain cancer-specific mortality for zolpidem according to age groups

	Number of subjects with zolpidem use (%)	Number of brain cancer-specific deaths	Univariate analysis		Multivariate analysis	
			Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
All adults (18 or older, n=38,037)	11,823 (31.1%)	8,839	1.01 (0.97-1.06)	0.564	1.14 (1.08-1.21)	< 0.001
Young adults (18-64, n=26,563)	7,548 (28.4%)	4,900	1.17 (1.11-1.25)	< 0.001	1.37 (1.27-1.49)	< 0.001
Older adults (65 or older, n=11,474)	4,275 (37.3%)	3,939	0.67 (0.63-0.72)	< 0.001	0.94 (0.86-1.02)	0.131

Table 4. Hazard ratios of all-cause mortality for zolpidem according to age groups

	Number of all-cause deaths	Univariate analysis		Multivariate analysis	
		Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
All adults (18 or older, n=38,037)	14,521	1.10 (1.06-1.14)	< 0.001	1.10 (1.05-1.15)	< 0.001
Young adults (18-64, n=26,563)	6,724	1.22 (1.16-1.28)	< 0.001	1.35 (1.26-1.44)	< 0.001
Older adults (65 or older, n=11,474)	7,797	0.73 (0.69-0.76)	< 0.001	0.95 (0.90-1.01)	0.11

초 록

연구 목표: 수면제 사용과 사망률 증가가 연관되어 있다는 것을 시사하는 연구 결과들이 다수 보고되었다. 또한 최근의 후향적 코호트 연구에서는 흔히 사용되는 수면제 중 하나인 졸피뎀이 암으로 인한 사망률 증가와 연관되어 있다는 결과가 발표되었다. 본 연구에서는 졸피뎀과 사망률의 상관관계를 조사하기 위해 악성 뇌종양 환자를 대상으로 한 후향적 코호트 연구를 수행하였다.

방법: 국민건강보험공단 데이터베이스에서 2003년부터 2017년까지 15년간 발생한 신규 악성 뇌종양 환자의 정보를 추출하였다. 악성 뇌종양 진단 당시 18세 이상의 성인이 대상자로 포함되었다. 졸피뎀 노출력과 악성 뇌종양 사망률 사이의 상관관계를 분석하기 위해 진단시 나이, 성별, 수면장애, 우울증, 항우울제 사용력을 고려한 다변량 콕스 회귀분석을 수행하였다.

결과: 38,037례의 신규 성인 악성 뇌종양 사례가 확인되었으며, 전체 대상자 중 11,823명 (31.1%)가 졸피뎀을 처방받았다. 다변량 콕스 회귀 모델에서 졸피뎀을 처방받은 대상자들은 졸피뎀을 처방받지 않은 대상자에 비해 유의하게 높은 사망률을 보였다. (조정 위험 비율 1.14, 95% 신뢰구간 1.08−1.21, p−값 < 0.001) 18−64세의 젊은 성인에서는 졸피뎀 노출력이 높은 사망률과 유의한 상관관계를 보였다. (조정 위험 비율 1.37, 95% 신뢰 구간 1.27−1.49) 하지만 65세 이상의 노인에서는 졸피뎀 노출력과 사망률 간에 유의한 상관관계는 확인되지 않았다. (조정 위험 비율 0.94, 95% 신뢰 구간 0.86−1.02)

결론: 졸피뎀 노출력은 18−64세의 악성 뇌종양 환자들에서 높은 사망률과 유의한 상관관계를 보인다. 졸피뎀이 악성 뇌종양 환자의 사망률에 미치는 영향의 기전을 밝히기 위해 추가적인 연구가 필요하다.

주요어: 악성 뇌종양, 졸피뎀, 사망률
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