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ORIGINAL ARTICLE

Polysomnography Analysis of Electroencephalography in Patients Expending Benzodiazepine Drugs

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Benzodiazepine 계열 약물 복용 환자의 수면다원검사에서 도출된 EEG유형 분석

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ABSTRACT

Benzodiazepines (BDZs) drugs act on the $GABA_A$ receptor, function as nerve suppressors, and are used to treat anxiety, insomnia, and panic disorder. We analyzed the data of 30 individuals to determine any differences in the sleep-electroencephalogram findings among individuals varying in age, benzodiazepine use, and duration of benzodiazepine use. Comparisons between users and non-users of benzodiazepines, short-term and long-term users, older and younger users, and older short-term and older long-term users, were achieved using electroencephalographic findings obtained through polysomnography. The parameters evaluated included sleep latency, sleep efficiency, sleep-stage percentages, number of sleep spindles, and average frequency of sleep-spindle. The difference between benzodiazepine users and non-users was significant with respect to sleep-stage percentages and average frequency of sleep-spindle. Older and younger users differed significantly with respect to sleep efficiency and sleep-stage percentages, whereas significant difference for sleep efficiency was obtained between long-term and short-term users. Taken together, our results indicate that BDZ consumption suppresses slow-wave sleep and increases the frequency of sleep spindles.

INTRODUCTION

Benzodiazepines (BDZs) are a group of drugs that act on the $GABA_A$ receptor, function as nerve suppressors, and are used to treat anxiety, insomnia, and panic disorder [1, 2]. This group of drugs includes diazepam, chlordiazepoxide, medazepam, oxazepam, potassium clorazepate, lorazepam, adinazolam, bromazepam, clobazam, ketazolam, prazepam, alprazolam, halazepam, pinazepam, camazepam, nordazepam, fludiazepam, ethyl loflazepate, etizolam, clotiazepam, cloxazolam, tofisopam, bentazepam, lorazepam, flurazepam, nitrazepam, flunitrazepam, estazolam, triazolam, lormetazepam, temazepam, midazolam, brotizolam, quazepam, loprazolam, oxazepam, and cinolazepam [3]. BDZs are widely used and have been used clinically since the

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1960s. Initially, it was believed that these drugs were not associated with significant dependence; however, the evidence regarding BDZ dependence has increased over time [4]. It was previously reported that in 2008, approximately 5.2% of adults in the United Stated aged 18~80 years used BDZs [5], and between 1996 and 2013, prescription rates increased by 67% [6]. Additionally, it has been reported that long-term BDZ use is associated with an increase in the incidence of dementia among people aged ≥65 years [7]. Despite the recommended short-term use of BDZs [8], the rate of prescription of BDZs to people aged ≥65 years for long-term use in the Republic of Korea reached 10.5% in 2018 [3].

Regarding the EEG of the polysomnography findings, it has been previously reported that BDZ users increase the amplitude and density of the sleep spindle and decrease delta waves compared to non-users, resulting in differences in sleep stage items [9-11], and several patients taking BDZs have undergone polysomnography for the diagnosis of sleep-related diseases. Due to the characteristics of polysomnography in which sleep stages are evaluated using EEGs [12], changes in EEG caused by BDZ cause confusion among sleep technologists with respect to the evaluation of sleep stages, which could negatively affect the quality of polysomnography. In this study, we analyzed the data on 30 individuals who underwent polysomnography between November 2016 and December 2020 at a medical institution in Bucheon, Korea to identify differences in EEG of the polysomnography findings among patients differing in terms of BDZ use, age, and duration of BDZ use. We analyzed the correlation between the polysomnography results according to the age and period of use of BDZ users, which has not been studied much, to provide a reference point for sleep technicians' sleep scoring and to help improve the accuracy of polysomnography tests for BDZ users.

MATERIALS AND METHODS

1. Patients

From November 2016 to December 2020, patients aged ≥19 years who underwent polysomnography at a medical institution in Bucheon, Korea, 30 patients who had taken benzodiazepines on the day they underwent polysomnography were recruited to this study (12 male, 18 female, mean age: 56.6 years, range: 31~83 years). These patients were included in a group of BDZ users.

The group of BDZ users was divided Based on whether they had taken BDZs for ≥365 days or <365 days, the BDZ group were divided into long-term-use or short-term-use groups [3]; 13 patients were included in the long-term-use group (4 male, 9 female, mean age: 58.4 years, range: 31~80 years, average duration of BDZ use: 1983.8 days, range: 409~5523 days), and 17 patients were included in the short-term-use group (8 male, 9 female, mean age: 55.3 years, range: 31~83 years, average duration of BDZ use: 124.6 days, range: 1~341 days).

The group of BDZ users was divided based on age; patients aged ≥65 years were included in the older group and patients aged <65 years were included in the younger group [3]. Ultimately, nine patients were included in the older group (3 male, 6 female, mean age: 72.4 years, range: 66~83 years), and 21 patients were included in the younger group (9 male, 12 female, mean age: 49.8 years, range: 31~62 years).

In addition, only the older aged 65 or older were selected from the above long-term use group and the short-term use group, and the long-term use older group (1 male, 4 female, mean age: 72.4 years, range: 66~80 years, average duration of BDZ use: 2499.8 days, range: 569~5523 days) and the short-term use older group (2 male, 2 female, mean age: 72.5 years, range: 68~73 years, average duration of BDZ use: 79.5 days, range: 4~206 days) were compared.

Patients with severe sleep apnea (apnea-hypopnea index ≥30) and patients with underlying neurological diseases (such as epilepsy) that could affect poly-

somnography readings were excluded [13-15]. This study was approved by the Institutional Review Board of Dankook University and was performed in accordance with the principles stated in the Declaration of Helsinki (IRB number: DKU202103014).

2. Control group (non-users)

Thirty patients who underwent polysomnography but did not take any drugs on the day of the test were included in the group of non-users. Because age can affect sleep phases and cycles [16], patients were included in the non-users based on the average age of the patients in the BDZ-users group (male 22, female 8, mean age: 55.8 years, range: 45~77 years). None of the patients in the group of non-users had severe apnea or underlying neurological diseases and insomnia.

3. Polysomnography and scoring

In accordance with the standards described in the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (version 2.6), level 1 standard polysomnography was performed between 10:00 pm on one day and 6:00 am on the subsequent day. If a total sleep time of 360 min was achieved, the test was terminated. Polysomnography was performed in an independent examination room. In this room, to ensure that the patients' sleep was not disturbed, the patients themselves chose a comfortable temperature and humidity, which was maintained throughout, and we ensured that there was no noise or light. Additionally, the following six channels were projected in EEGs: F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2, and O2-M1, EOG is E1-M2, E2-M1, chin electromyography (EMG) is chinZ-chin1 was measured. Furthermore, oxygen saturation, respiration, respiratory effort, and leg EMG recordings were measured according to the AASM manual. The Embla® N7000 recording system and Embla® RemLogic™ software (V3.4.4.2413) (Natus Medical Incorporated, CA, USA) were used for the evaluation. During the examination, a skilled sleep technician continuously monitored the montage, and all scoring was carried out by a skilled technician according to the AASM scoring manual [12]. In addition, the following figure is referred to in the scoring of the sleep spindle (Figures 1, 2).

4. Comparative analysis

Based on the results of polysomnography associated with EEG findings, we evaluated the differences between the BDZ users and non-users, long-term-use and short-term-use groups, long-term-use and short-term-use groups, long-term-use older and short-term-use older groups.

The parameters considered were sleep latency (SL), sleep efficiency (SE), sleep-stage percentages, number of sleep spindles, and average sleep-spindle frequen-

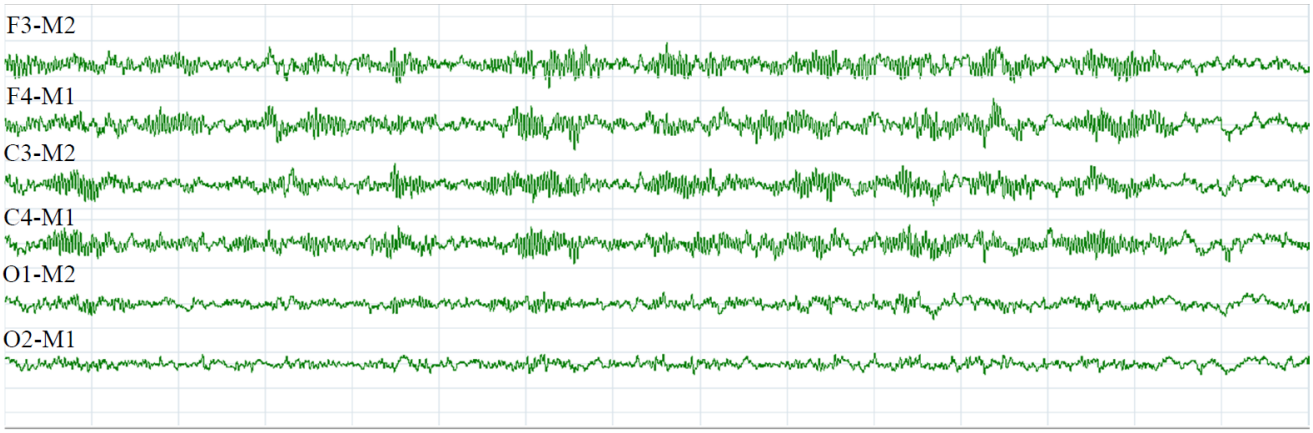

Figure 1. Beta wave of BDZ users. A wave of 14 to 30 Hz is continuously produced. Time base is 30 second (1 epoch). Amplitude is 70 μV/cm.

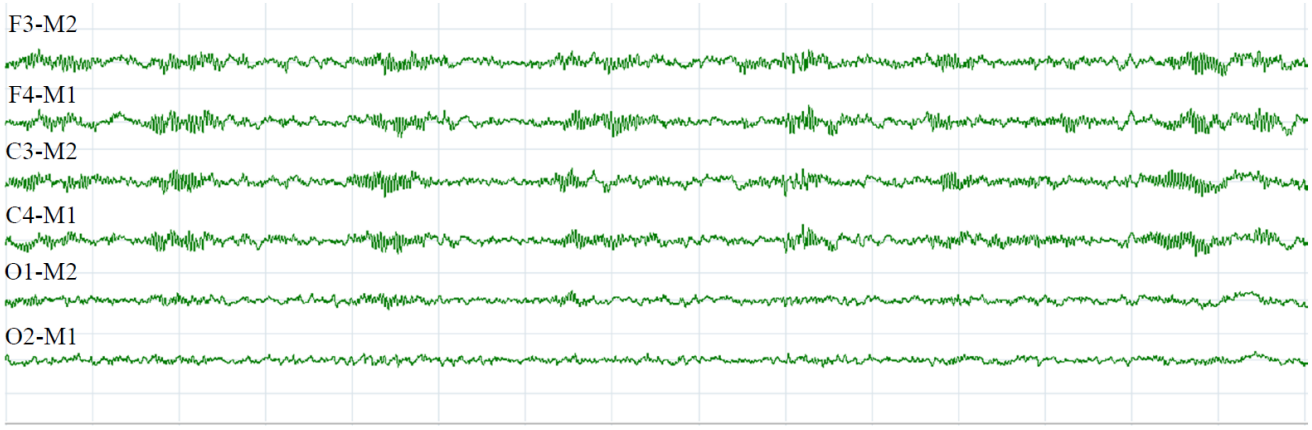

Figure 2. Sleep spindle of BDZ users. A sinusoidal wave of 11 to 16 Hz appears. Time base is 30 second (1 epoch). Amplitude is 70 μV/cm.

cies [17]. SL was defined as the time from when the point lights were turned off to sleep onset, and SE in each individual was calculated by dividing the total sleep time by the total recording time. Sleep spindles were counted by visually measuring consecutive distinct waveforms of 11~16 Hz with a duration emanating from C3 and C4 of more than 0.5 s, and the average frequency of sleep spindles was determined by calculating the average value of the frequencies of the sleep spindles emanating from C3 and C4.

5. Statistical analysis

The normality test was confirmed using the Kolmogorov-Smirnov test. Significance was confirmed by a nonparametric method using the Mann-Whitney U test. *P*-value of <0.05 was considered statistically significant. correlation analysis was confirmed for all variables, and multicollinearity was confirmed with a Pearson correlation coefficient of 0.9 or less. All statistical analyses were performed using IBM® SPSS® Statistics 20.0 (IBM, Armonk, NY, USA).

RESULTS

1. Sleep-stage percentages among BDZ users and non-users

The Mann-Whitney U test was performed to determine whether there were differences between the BDZ users and non-users with respect to sleep-stage percentages. The following values were obtained: U (stage N2)=238; U (stage N3)=281, *P* (stage N2)=0.002; and *P*(stage N3)=0.002; the differences were statistically significant (*P*=0.01; Table 1). Therefore, with respect to sleep-stage percentages for stages N2 and N3 there were significant differences between BDZ users and non-users. Among the patients who took BDZs on the day they underwent polysomnography, the sleep-stage percentages were 15.03%, 56.23%, 0.47%, and 12.80% for stages N1, N2, N3, and R, respectively. Among the non-users, the sleep-stage percentages were 16.27%, 45.67%, 2.67%, and 14.17% for stages N1, N2, N3, and R, respectively.

2. Sleep spindles in BDZ users and non-users

The Mann-Whitney U test was performed to determine whether there were differences between BDZ users and non-users with respect to sleep spindles. The following values were obtained, U (number of sleep spindles per hour)=376.5; U (average frequency of sleep spindles)=182.5; *P* (number of sleep spindles per hour)=0.277; and *P* (average frequency of sleep spindles)=≤ 0.000. Since statistical significance was set at *P*<0.05 (Table 1), the difference between BDZ users and non-users with respect to the average frequency of sleep spindles was significant. The average number of sleep spindles per hour among BDZ users and non-users was 29.54 and 21.94, respectively. The mean

Table 1. Comparison of parameter values

Group	N	Sleep latency (min)			Sleep efficiency (%)			Stage N1 (%)			Stage N2 (%)			Stage N3 (%)			Stage R (%)			Number of sleep spindles/h			Average frequency of sleep spindles (Hz)		
		M	SD	U (*P*)	M	SD	U (*P*)	M	SD	U (*P*)	M	SD	U (*P*)	M	SD	U (*P*)	M	SD	U (*P*)	M	SD	U (*P*)	M	SD	U (*P*)
BDZ users	30	23.12	37.68	406.5 (0.520)	80.43	12.97	414 (0.594)	15.03	8.84	379.5 (0.296)	56.23	11.74	238** (0.002)	0.47	1.88	281** (0.002)	12.80	7.43	369.5 (0.233)	29.54	19.72	376.5 (0.277)	13.38	1.17	182.5*** (0.000)
Non-users	30	17.22	37.05		76.53	17.74		16.27	6.53		45.67	12.96		2.67	4.03		14.17	5.20		21.94	10.32		11.66	1.54	
Short-term use	17	15.12	24.08	63* (0.047)	82.88	14.56	69.5 (0.086)	14.88	7.42	103.5 (0.769)	57.29	12.65	96.5 (0.557)	0.82	2.48	91 (0.117)	12.18	7.06	100.5 (0.675)	26.20	15.62	94.5 (0.503)	13.39	1.26	109 (0.950)
Long-term use	13	33.57	49.49		77.38	10.29		15.23	10.74		54.85	10.76		0	0		13.62	8.09		33.91	24.03		13.37	1.11	
Older group	9	27.24	38.90	85.5 (0.684)	73.33	13.56	51* (0.049)	17.00	7.98	70 (0.267)	48.33	11.64	44.5* (0.023)	0	0	81 (0.241)	12	6.04	90.5 (0.856)	21.33	9.32	71.5 (0.293)	13.45	1.20324	89 (0.803)
Younger group	21	21.35	37.98		83.57	11.73		14.19	9.24		59.62	10.27		0.67	2.24		13.14	8.06		33.06	22.04		13.35	1.19523	
Older and short-term use	4	27.17	43.93	7 (0.462)	76.25	19.19	7 (0.462)	19.50	11.38	7 (1.0)	48.50	14.70	9 (0.806)	0	0	-	11.75	7.04	10 (1.0)	26.17	9.63	5 (0.221)	13.95	0.98	6 (0.319)
Older and long-term use	5	27.3	39.73		71.0	8.74		15.0	4.35		48.20	10.42		0	0		12.20	5.97		17.46	7.88		13.06	1.31	

*$P<0.05$, **$P<0.01$, ***$P<0.001$.
Abbreviations: BDZ, benzodiazepine; M, mean; SD, standard deviation; U, Mann-Whitney U.

frequency of sleep spindles among BDZ users and non-users was 13.38 Hz and 11.66 Hz, respectively.

3. Sleep latency and sleep efficiency among long-term and short-term benzodiazepine users

The Mann-Whitney U test was performed to determine whether there were statistically significant differences between long-term BDZ users and short-term BDZ users with respect to SL and SE. The following values were obtained: U (SL)=63; U (SE)=69.5; P (SL)=0.047, and P (SE)=0.086. Since statistical significance was set at $P<0.05$ (Table 1), the difference between long-term and short-term users with respect to the Sleep latency was significant. The Sleep latency among long-term and short-term users was 33.57 and 15.12, respectively.

4. Sleep latency and sleep efficiency among older and younger BDZ users

The Mann-Whitney U test was performed to determine whether there were significant differences between older and younger BDZ users with respect to SL and SE. The following values were obtained: U (SL)=85.5; U (SE)=51; P (SL)=0.684, and P (SE)=0.049. Since statistical significance was set at $P<0.05$ (Table 1), with respect to SE, the difference between older and younger BDZ users was significant. The average SE among older and younger BDZ users was 73.33% and 83.57%, respectively.

5. Sleep-stage percentages among older and younger BDZ users

The Mann-Whitney U test was performed to determine whether there were differences between the BDZ users and non-users with respect to sleep-stage percentages. The following values were obtained: U (stage N2)=44.5, P (stage N2)=0.023. the differences were statistically significant (P=0.05; Table 1). Therefore, with respect to sleep-stage percentages for stage N2 there were significant differences between older and younger BDZ users. Among the patients older group, the sleep-stage percentages were 17%, 48.33%, 0%, and 12% for stages N1, N2, N3, and R, respectively. Among the younger group, the sleep-stage percentages were 14.19%, 59.62%, 0.67%, and 13.14% for stages N1, N2, N3, and R, respectively.

DISCUSSION

The purpose of this study was to determine whether there were any significant differences in EEG of the polysomnography findings among individuals who differ with respect to age, BDZ use, and duration of BDZ use; several statistically significant differences were identified.

1. Differences between benzodiazepine users and non-users

With respect to the sleep-stage percentages among BDZ users and non-users, as in previous studies [9, 10], we found that the sleep-stage percentage for stage N2 among BDZ users was significantly higher than that among non-users, and the sleep-stage percentage for stage N3 among non-users was significantly higher than that among BDZ users. Although there was no significant difference between BDZ users and non-users with respect to sleep-spindle frequency (which, along with K-complexes, is an important indicator of stage N2 readings), it was interpreted that the relatively higher sleep-stage-N2 percentage among BDZ users was caused by the relatively higher sleep-spindle frequency among BDZ users. Furthermore, through the present study, we were able to confirm the findings of previous studies that showed that BDZs cause a decrease in the frequency of slow waves [10, 18-20]. Studies have shown that the loss of slow waves is related to brain contraction and damage [21, 22]. In addition, previous studies have shown that BDZs cause cognitive decline [23]. In this study, it was observed that BDZ administration caused a significant decrease in slow-wave sleep, which suggests that taking BDZs accelerates brain contraction, brain damage, and cognitive

decline. This information should be considered to ensure the careful administration of BDZs. Additionally, it was confirmed that the average frequency of sleep spindles in BDZ users was significantly higher than that among non-users. In a previous study, an increase in the frequency and frequency of sleep spindles was reported when taking BDZ [11], and we can confirm this result again.

2. Differences between long-term and short-term users of benzodiazepines

The difference between these two groups regarding SL was statistically significant as the average SL of long-term users was 33.57 minutes and the average SL of short-term users was 15.12 minutes. Based on this result, it may be hypothesized that there is a positive correlation between the duration of BDZ use and SL, and we believe that in-depth research is needed to further study this association.

3. Differences between older and younger benzodiazepine users

Among BDZ users, the SE in younger users was better than that in older users; this finding is consistent with that of other studies in which it was found that SE decreases with increasing age [16, 24]. In this study, it was found that the number of sleep spindles was rather high among younger BDZ users, and a previous study showed that the number of sleep spindles decreases with age [17].

4. Differences between older and short-term use and older and long-term use benzodiazepine users

No statistically significant variables were found in these two groups. It has been reported that sleep spindles are related to cognitive abilities and memory processing in mammals, including humans [25, 26]. Several studies regarding cognition and memory following long-term use of BDZs have been conducted previously [2]; however, to the best of our knowledge, the effect of short-term BDZ use on cognitive ability and memory processing has not been evaluated in previous studies. In the present study, with respect to the number and frequency of sleep spindles, no significant differences between long-term and short-term BDZ users were found; consequently, data obtained in this study could be used as reference data for the evaluation of the differences in memory processing among long-term and short-term BDZ users.

Overall, based on the results of this study, we can conclude that the use of BDZs suppresses slow-wave sleep and increases the frequency of sleep spindles. Furthermore, as humans age, there is a decrease in their SE and slow-wave activity. In addition, prolonged BDZ use can cause increased SL; however, there is no difference between long-term and short-term BDZ users with respect to sleep spindles.

The present study has certain limitations. With respect to subjective readings based on information observed by sleep technicians, there may be differences in readings among different laboratories. Additionally, since only BDZ users were included in the older and younger groups, the findings associated with differences in EEG of the polysomnography results among the two groups may not be generalizable to individuals who do not use BDZs.

In several previous studies, the results and characteristics of polysomnography among BDZ users and non-users have been analyzed; however, to the best of our knowledge, differences in polysomnography results among individuals who differ with respect to their age and the duration of BDZ use have not been analyzed in any previous studies. In this study, differences in polysomnography results among older and younger BDZ users and long-term and short-term BDZ users were observed; The data obtained in this study can be used to evaluate sleep in patients taking BDZ. Furthermore, none of the similar past studies regarding BDZs and sleep had a predominance of Korean individuals in their study populations. It is known that there are some differences among individuals of

different races with respect to their sleep architecture; in this regard, in the present study, we were able to evaluate the effect of BDZ use on sleep architecture in Korean people [27-29].

요 약

벤조디아제핀은 $GABA_A$ 수용체에 작용하고 신경 억제제로 작용하며 불안, 불면증 및 공황 장애를 치료하는 데 사용되는 약물 그룹이다. 우리는 연령, 벤조디아제핀 사용 여부 및 사용 기간에 따라 수면 중 뇌파 소견에 차이가 있는지 관찰하기 위해 30명의 개인의 데이터를 분석했다. 수면다원검사를 통해 얻은 뇌파 소견을 이용하여 벤조디아제핀 복용군과 비복용군, 단기 및 장기복용, 노인과 비 노인군, 고령 단기복용 및 고령 장기복용군을 비교했다. 평가된 항목은 수면 잠복기, 수면 효율, 수면 단계별 백분율, sleep spindle의 개수 및 평균 주파수로 설정하였다. 복용군과 비복용군의 비교에서 sleep stage와 sleep spindle의 평균 주파수 항목에서 유의미하였다. 장기복용과 단기복용군의 비교에서 sleep efficiency 항목에서 유의미하였다. 노인군과 비 노인군과의 비교에서 sleep efficiency, sleep stage 항목에서 유의미하였다. 전반적으로 이 연구 결과를 바탕으로 벤조디아제핀의 사용은 느린 주파수 수면을 억제하고 수면 방추파의 주파수와 빈도를 증가시킨다는 결론을 내릴 수 있다.

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Conflict of interest: None

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