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Original Article

Non-benzodiazepine hypnotic drug is correlated with decreased risk of ischemic stroke

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Abstract: Background: It has been reported that insomnia was associated with an increased risk of cardiovascular and cerebrovascular events. Benzodiazepine (BDZ) and non-BDZ hypnotics may have opposite influences on the risk of coronary artery disease (CAD). However, the effects of BDZ_s and non-BDZ_s hypnotics on the risk of ischemic stroke event are still unclear. Methods: A hospital-based case-control study with 752 stroke patients and 760 controls was conducted to investigate the association between hypnotics use and ischemic stroke risk in Chinese Han population. Results: A significant decrease in ischemic stroke risk was observed for using non-BDZ (adjusted odds ratio, OR = 0.48; 95% confidence interval, CI = 0.32-0.72). BDZ_s use was not associated with ischemic stroke (adjusted OR = 1.25; 95% CI = 0.91-1.72). Adjusted ORs were 0.75 (95% CI = 0.39-1.46) for using non-BDZ_s 0 to 5 years, 0.44 (95% CI = 0.25-0.77) for 5 to 10 years, and 0.38 (95% CI = 0.16-0.90) for >10 years. The risk of ischemic stroke tended to decrease with an increase in duration of non-BDZ_s use (P<0.001 for trend). Conclusions: Non-BDZ is associated with reduced risk of ischemic stroke. The potential mechanisms need to be investigated further.

Keywords: Hypnotics, stroke, regression analysis

Introduction

Hypnotics are widely used in the general population. Overall population use of hypnotics is about 10% and increases to 20% among the elderly [1, 2]. Although generally prescribed for sleep problems, hypnotics are associated with many side effects and increased risk for fall and accidents [3, 4]. Recently, many studies reported that hypnotic use increased the mortality hazard caused by stroke and CAD [5]. However, more recently it was reported that use of non-BDZ hypnotics is associated with decreased risk of CAD, while BDZ_s may increase the risk of CAD [6]. For the similar risk factors of ischemic stroke and CAD, we designed a case-control study to investigate the potential association between non-BDZ_s use and ischemic stroke risk in Chinese Han population.

Material and methods

Study population

752 consecutive patients with ischemic stroke admitted to Jiangyin Hospital of Traditional Chinese Medicine. Ischemic stroke was defined as: sudden onset of focal neurological dysfunction that lasted ≥24 hours and subsequent confirmation of infarct in the brain by CT or MRI and no history of stroke. Therefore, only patients with first-ever ischemic stroke (thrombotic or embolic) were considered. For the ethical limitation, fatal cases due to stroke were not included. Control subjects were recruited from outpatient departments of Chinese medicine, Dermatology and Stomatology during the same period. Those controls have no history or clinical evidence that indicate previous stroke and the treatment for them at outpatient departments were not related to cardiovascular diseases, diabetes and malignant tumor. All subjects recruited in this study were of Han Chinese origin and residing in or near Jiangsu province. They did not have history of significant concomitant diseases including Alzheimer disease, bleeding disorders, renal failure, and malignant diseases. This study was approved by the Human Research Ethics Committees of Jiangyin Hospital of Traditional Chinese Medi-

Table 1. Baseline Characteristics of Participants

Variable	Ischemic stroke		P
	Yes (752)	No (760)	
Age, years	65.5±8.2	61.5±13.0	<0.001
Body mass index, kg/m^2	24.5±3.0	23.9±3.0	<0.001
Hypertension, n (%)	454 (60.4)	299 (39.3)	<0.001
Hyperlipidemia, n (%)	255 (33.9)	127 (16.7)	<0.001
Diabetes, n (%)	259 (34.4)	129 (17%)	<0.001
Alcohol drinker, n (%)	349 (46.4)	299 (39.3)	<0.001
Smoker, n (%)	509 (67.7)	398 (52.4)	<0.001
Physically active, n (%)	224 (29.8)	273 (35.9)	<0.001

Data are expressed as mean ± SD or frequencies (percentages).

Table 2. Association of BDZ_s and non-BDZ_s with Risk of Ischemic Stroke

Groups	Cases	Controls	Crude OR	Adjusted[a] OR
	n = 752	n = 760	(95% CI)	(95% CI)
Non-users[b]	558 (72.2)	561 (73.3)	1.00	1.00
BDZ_s-users	145 (19.3)	97 (12.8)	1.63 (1.23-2.2)	1.25 (0.91-1.72)
Non-BDZ_s-users	49 (6.5)	106 (13.9)	0.44 (0.31-0.63)	0.48 (0.32-0.72)

[a]Adjustment for age, gender, body mass index, hypertension, diabetes, hyperlipidemia, smoking, alcohol, and physical activity. [b]subjects who neither used BDZ_s nor non-BDZ_s.

cine and informed consent was obtained from each participant.

Data collection

A structured questionnaire was designed to solicit the participants' demography and life style characteristics including age, gender, weight, height, smoking habits (non-smoker, current/former smoker), and alcohol drinking status. Data including height and weight measurements and healthy conditions such as presence of hypertension, hyperlipidemia, and diabetes were confirmed with medical records. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Obesity was defined as a BMI ≥28 kg/m^2. Patients were regarded as physical activity involvement if they engaged in aerobic activities for >30 minutes (walking, bicycling, running, swimming, etc.) ≥3 times/week. The information about BDZ_s and non-BDZ_s use was obtained from medical record of each participant.

Statistical analysis

Participant characteristics were summarized with descriptive statistics. Age and BMI data were defined as continuous variables. Sex, diabetes, hypertension dyslipidemia, smoking, drinking and physical activity were treated as categorical variables. Besides the use of hypnotics, age, gender, education level, BMI, physically activity involvement, smoking, alcohol drinking, hypertension, diabetes, hyperlipidemia were included in the multiple logistic regression models as independent variables. Odds ratio (OR) and 95% confidence interval (CI) were calculated to indicate the relation between non-BDZ_s and BDZ_S use and ischemic stroke risk. *P* value <0.05 was defined statistically significant. Statistical analyses were undertaken with SPSS 16.0 (SPSS, nc., Chicago, IL).

Results

Table 1 profiles the characteristics of our study subjects. Patients with ischemic stroke were much older, smoked more cigarettes, drank more wine, had higher BMI and less physical activity, and were more likely to be hypertensive, diabetic and hyperlipidemic than the control subjects.

Results of univariate and multivariate logistic regression analysis for BDZ_s or non-BDZ_s use are shown in **Table 2**. BDZ_s use was associated with an increased risk of ischemic stroke (adjusted OR, 1.25; 95% CI, 0.91-1.72), while non-BDZ_s use was associated with decreased risk of ischemic stroke (adjusted OR = 0.48, 95% CI = 0.32-0.72).

Table 3 presents the relationship between duration of non-BDZ_s use and risk of ischemic stroke. Inverse association with ischemic stroke risk was observed for the duration of non-BDZ_s use, especially subjects who had been administrating non-BDZ_s for more than 10 years (adjusted OR, 0.38; 95% CI, 0.16 to 0.90). Adjusted ORs were 0.75 (95% CI = 0.39-0.46) for using non-BDZ_s 0 to 5 years, 0.44 (95% CI = 0.25-0.77) for 5 to 10 years.

The comparison of non-BDZ_s Users and non-Users in Terms of ischemic stroke Risk Factors

Table 3. Risk of Ischemic Stroke for non-BDZ_s Duration

Non-BDZ_s use Duration, years	Cases n = 752	Controls n = 760	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
0	703 (93.5)	658 (86.1)	1.00	1.00
0-5	19 (2.5)	30 (3.9)	0.63 (0.35-1.13)	0.75 (0.39-1.46)
5-10	22 (2.9)	48 (6.3)	0.45 (0.27-0.75)	0.44 (0.25-0.77)
>10	8 (1.1)	28 (3.7)	0.28 (0.13-0.62)	0.38 (0.16-0.90)
P for trend			P<0.001	P<0.001

[a]Adjustment for age, gender, body mass index, hypertension, diabetes, hyperlipidemia, smoking, alcohol, and physical activity.

Table 4. Comparison of non-BDZ_s users and the other subjects in terms of ischemic risk factors

Ischemic stroke risk factors	Non-BDZ users		P
	Yes (150)	No (1362)	
Age	62.3±10.4	63.6±11.2	NS
Body mass index, kg/m^2	24.1±3.2	24.2±3.0	NS
Hypertension	62 (43.0)	691 (50.7)	NS
Hyperlipidemia	39 (26.0)	358 (26.3)	NS
Diabetes	39 (26.0)	387 (28.4)	NS
Smoking	103 (68.7)	804 (59)	NS
Alcohol drinking	55 (36.7)	433 (31.8)	NS
Physical active	64 (42.7)	593 (43.5)	NS

NS: not significant.

in terms of ischemic stroke is shown in **Table 4**. No significant differences were observed in ischemic stroke risk factors between users and non-users.

Discussion

Stroke is the second leading cause of death and the most important cause of acquired adult disability in many countries [7]. Sleep duration has been evidenced to be a significant risk for cardiovascular events including cardiovascular disease and stroke [8]. However, BDZ_s and non-BDZ_s exert contrast effects in cardiovascular disease [6, 9]. To date, there have not been any studies evaluating the relation between ischemic stroke and non-BDZ_s. Therefore, we conducted a hospital based case control study with 752 ischemic stroke patients and 760 controls to investigate the association between non-BDZ_s use and ischemic stroke risk in China. All stroke patients included in this study were image-confirmed first-ever ischemic stroke cases, and all potential control subjects were screened for stroke symptoms by experienced neurologists in order to minimize the likelihood of misclassification of the case-control status.

The present study demonstrated that BDZ_s use was associated with an increased risk of ischemic stroke, while non-BDZ_s decreased the stroke risk, which is in accordance with the effects of hypnotics on coronary heart disease [6, 9]. Zolpidem and zaleplon were the most commonly prescribed non-BDZ_s among the study subjects. The risk of ischemic stroke predisposed to be decreased with longer time non-BDZ_s exposure, which suggests that non-BDZ_s may have some protective effects on the cerebral vascular system.

Previous studies have reported that lack of sleep was an independent risk for adult stroke [8]. Also, there are growing evidences that anxiety is associated with an increased risk of stroke [10]. Therefore, the protective effect of non-BDZ_s is possible due to relief of insomnia and anxiety. However, it is difficult to explain the increased risk of ischemic stroke caused by BDZ use, which may be due to its increased overall risk of adverse effects [11]. Nevertheless, further studies are necessary to investigate the potential mechanism of the protective effect of non-BDZ_s.

Although our study demonstrates that non-BDZ_s use is associated with a decreased risk of ischemic stroke, the results of this case-control study could potentially be affected by some bias. First, the relatively small sample size of this study may limit the statistical power. Second, although we recruited controls from individuals with no history of stroke, no symptoms or signs of other atherosclerotic vascular diseases, we could not ruled out recall bias completely without specific examination. Therefore, further replications are recommended before generalizing the findings to other populations.

Conclusions

Non-BDZ use is associated with reduced risk of ischemic stroke. The potential mechanisms need to be further investigated.

Disclosure of conflict of interest

None.

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