OTORHINOLARYNGOLOGY

Efficacy of Chotosan in Dizziness Induced by Head Rotation or Extension in the Standing Position: A Retrospective Study

Kazuhiro Hirasawa[1)], Koji Otsuka[1)], Koichiro Yoshino[1)], Yujin Chiba[1)], Kiyoaki Tsukahara[2)]

ABSTRACT

Objective: **We aimed to prove that chotosan, a Kampo medicine, is effective for dizziness induced by head rotation or extension in the standing position.**

Design: **Single-center, retrospective study registered in the UMIN Clinical Trials Registry (ID: 000045757).**

Materials and Methods: **Twenty-six patients (age range 37-89 years, 8 women) with dizziness who visited the Tokyo Medical University Ibaraki Medical Center and received chotosan from October 2016 to March 2021 were included in the study. They were classified into the effective (satisfied with the effect of chotosan) and ineffective groups (unsatisfied). The proportion of patients with dizziness induced by head rotation or extension in the standing position was compared between these two groups.**

Results: **Dizziness was induced by head rotation or extension in the standing position more frequently in the effective group (75 % vs. 10 %, p = 0.002). Compared to the patients who were given only chotosan, the rate was significantly higher in the effective group (80 % vs. 0 %, p = 0.024).**

Discussions/Conclusions: **Chotosan is useful for treating dizziness induced by head rotation or extension in the standing position. Presumably because of the effect of chotosan in improving the blood flow in the vertebrobasilar artery.**

KEY WORDS

dizziness, chotosan, Kampo medicine, vertebrobasilar insufficiency

INTRODUCTION

Dizziness or vertigo has been reported to occur in approximately 15% to over 20% of adults in one year[1)], although Bisdorff *et al.*[2)] reported a prevalence of over 30%. However, central vascular dizziness is uncommon (cerebrovascular disorders are reported in 3 % of patients with dizziness)[3)].

Regarding central vascular dizziness, it is often reported that maximal head rotation or extension in the standing position induces nystagmus, dizziness, and postural imbalance[4)]. This is thought to be due to transient ischemia of the vertebrobasilar artery due to mechanical compression of the vertebral artery[4)].

Chotosan, a traditional Kampo medicine, has a relaxing effect on the basilar arterial wall[5)]. Furthermore, 3α-Dihydrocadambine, which is contained in *Uncaria* hook, the main drug in chotosan, has a dilating effect on the vertebral arteries[6)]. Thus, chotosan may improve the blood flow in the vertebrobasilar artery. Ichimura[7)] has recommended the use of chotosan for dizziness due to vertebrobasilar insufficiency (VBI). Therefore, chotosan may be effective for treating central vascular dizziness. This retrospective study investigated whether chotosan is effective for dizziness induced by head rotation or extension in the standing position. The aim of this study was to add dizziness induced by head rotation or extension in the standing position as new indications for the use of chotosan.

MATERIALS AND METHODS

This retrospective study was conducted in compliance with the Declaration of Helsinki and ethical guidelines for medical research targeting humans, and received approval from the Tokyo Medical University Medical Ethics Review Board (approval number: T2021-0112). This study was registered in the UMIN Clinical Trials Registry (ID: 000045757). The need for informed consent was waived due to the retrospective nature of the study. From October 2016 to March 2021, 2040 patients with dizziness visited the Tokyo Medical University Ibaraki Medical Center. Of these, 30 patients were administered chotosan. Among them, 26 patients were included in this study after excluding two patients who could not be followed up and two patients who could not take chotosan. Only those patients whose progress could be tracked were included in the study. The exclusion criteria were discontinuation of chotosan due to adverse events, patients in whom the progress could not be tracked, and patients who refused to participate in this study. At every visit, the patients were asked whether they were satisfied with the therapeutic effect of chotosan. At the end of the administration period of chotosan, the patients who answered the question with "satisfied" were classified into the effective group, while the patients who answered "not satisfied" were classified into the ineffective group. In other words, all patients who were not satisfied even though there was some improvement were classified into the ineffective group.

The presence or absence of dizziness induced by head rotation or extension in the standing position was compared between the two groups and used as the primary endpoint. In addition, chotosan is conventionally used in middle-aged and older people who complain of chronic headache, stiff shoulders, and dizziness. Chotosan is often used for the treatment of hypertension in clinical practice. With reference to these conventional uses of chotosan, age and the presence or absence of headache, stiff shoulders, and hypertension were also compared in the

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1) Department of Otorhinolaryngology,
Tokyo Medical University Ibaraki Medical Center
3-20-1 Chuo, Ami-machi, Inashiki-gun, Ibaraki 300-0395, Japan

2) Department of Otorhinolaryngology, Head and Neck Surgery,
Tokyo Medical University
6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

Correspondence to: Kazuhiro Hirasawa
(e-mail: hirakazu@tokyo-med.ac.jp)

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A. Dizziness is induced by head rotation or extension in the standing position.
B. Dizziness is accompanied by visual impairment such as blurred vision, diplopia, and dimmed vision.
C. Nystagmus is induced by rotation or extension of the head, but is atypical for BPPV.
D. MRA reveals stenosis of the vertebrobasilar artery.
E. Doppler echocardiography shows pathological laterality of vertebral artery blood flow.

Those patients that satisfy criteria A and (B and/or C and/or D and/or E) were diagnosed as "transient VBI".

Figure 1: The diagnostic criteria for transient vertebrobasilar insufficiency used in this study
Abbreviations: BPPV: benign paroxysmal positional vertigo; MRA: magnetic resonance angiography; VBI: vertebrobasilar insufficiency

two groups, and used as the secondary endpoints. Regarding the patient background, the sex, period of administration of chotosan, and the concomitant use of other drugs, in addition to the age, were compared.

For statistical analyses, the D'Agostino-Pearson test was used to assess the normality of distribution of overall age as well as the overall administration period of chotosan, and the Mann-Whitney U test for comparing the difference in age and administration period of chotosan between the two groups. Fisher's exact test was used for the other parameters. A one-tailed p-value less than 0.05 was considered statistically significant. Post-hoc power analysis and multivariate regression analysis were also performed.

"Transient VBI" was diagnosed based on a review of the literature by Lima *et al*.[8]. All cases diagnosed with transient VBI in this study met the criteria (Figure 1).

RESULTS

Patient characteristics

The patient characteristics of the two groups are presented in Table 1. There were 16 patients in the effective group and 10 patients in the ineffective group. The overall age was 37-89 years (average age 67 years), and the p-value was 0.24 (normal distribution). The age distribution was 37 9 years (average age 69 years) in the effective group, and 51 6 years (average age 63 years) in the ineffective group. There were 11 men and 5 women in the effective group and 7 men and 3 women in the ineffective group.

The overall administration period of chotosan was 21-161 days (average, 73 days), with a p-value of 0.19 (normal distribution). The administration period of chotosan was 41-161 days (average, 85 days) in the effective group and 21-130 days (average, 54 days) in the ineffective group. The drugs used in combination with chotosan for the treatment of dizziness were adenosine triphosphate (ATP) 3 g/day in seven patients, ibudilast 30 mg/day in one patient, a combination of ATP 3 g/day and ibudilast 30 mg/day in three patients, and none in five patients in the effective group. In the ineffective group, five patients were administered ATP 3 g/day, and no drugs was administered to the remaining five patients.

There was no significant difference in the age, sex, and proportion of patients using chotosan alone (p = 0.20, 0.65, and 0.29, respectively) between the two groups. The administration period of chotosan was significantly longer in the effective group (p = 0.02).

The causes of dizziness were diagnosed as follows: 12 cases of transient VBI, three cases with an "unknown reason," and one case of orthostatic dysregulation in the effective group, and five cases of orthostatic dysregulation, three cases with an "unknown reason," one case of "after vestibular neuritis," and one case of benign paroxysmal positional vertigo (BPPV) in the ineffective group.

According to post-hoc power analysis, the statistical power was 0.45 (effect size 0.3 and significance level 0.05), indicating that the sample size was inadequate.

Presence or absence of dizziness induced by head rotation or extension in the standing position (primary endpoint)

The proportion of cases in which dizziness was induced by head rotation or extension in the standing position was 75% (12 cases) in the effective group and 10% (one case) in the ineffective group. Therefore, it was higher in the effective group (p = 0.002) (Figure 2). All 12 patients in the effective group were diagnosed with transient VBI. Conversely, one patient in the ineffective group was diagnosed with BPPV because dizziness was induced by head position conversion, although it was also induced by head extension in the standing position.

When comparing only the patients who were administered chotosan alone, the proportion of patients in whom dizziness was induced by head rotation or extension was 80% (four out of five patients) in the effective group and 0% (0 out of five patients) in the ineffective group. Therefore, it was also higher in the effective group (p = 0.024) (Figure 2).

Presence or absence of headache (secondary endpoint)

The proportion of patients with headache was 44% (seven patients) in the effective group and 10% (one patient) in the ineffective group (Figure 3). Patients in the effective group tended to have more headaches, although the difference was not significant (p = 0.08).

Table 1: Patient characteristics in the two groups

	Effective group (n = 16)		Ineffective group (n = 10)	
Age	37 9 years (average age 69 years)		51 6 years (average age 63 years)	
Gender	11 males, 5 females		7 males, 3 females	
Administration period	41-161 days (average 85 days)		21-130 days (average 54 days)	
Concomitant drugs	ATPa 3 g/day	7 cases	ATP[a] 3 g/day	5 cases
	Ibudilast 30 mg/day	1 case	None	5 cases
	ATP[a] 3 g + Ibudilast 30 mg/day	3 cases		
	None	5 cases		
Clinical diagnosis	Transient VBIc	12 cases	Orthostatic dysregulation	5 cases
	Unknown reason	3 cases	Unknown reason	3 cases
	Orthostatic dysregulation	1 case	After vestibular neuritis	1 case
			BPPV[b]	1 case

Abbreviations: [a]ATP: adenosine triphosphate; [b]BPPV: benign paroxysmal positional vertigo; [c]VBI: vertebrobasilar insufficiency

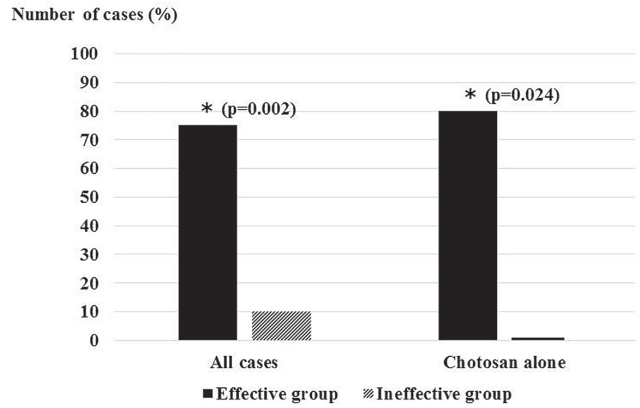

Figure 2: Primary endpoint: presence or absence of dizziness induced by head rotation or extension in the standing position
Abbreviations: ＊: significantly different

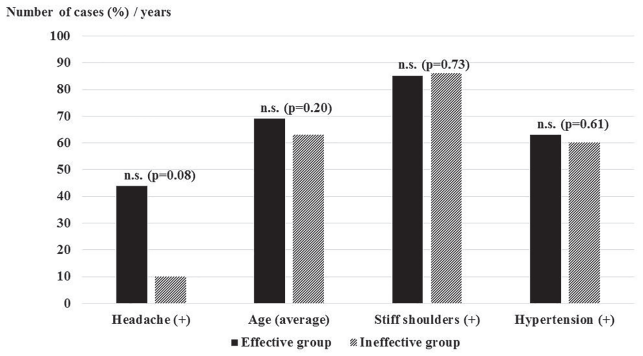

Figure 3: Secondary endpoints: age and the presence or absence of headache, stiff shoulders, and hypertension
Abbreviations: n.s.: not significant

Age (secondary endpoint)

There was no significant difference in age between the two groups (p = 0.20) (Figure 3). All patients in the ineffective group were over 50 years of age, however the effective group included one patient in their thirties and one in their forties.

Presence or absence of stiff shoulders (secondary endpoint)

There were three patients each in the effective and ineffective groups, in whom the presence or absence of stiff shoulders was unknown based on the medical record; therefore, they were excluded from the analysis. The proportion of patients with stiff shoulders was 85% (11 out of 13 patients) in the effective group and 86% (6 out of 7 patients) in the ineffective group. There was no significant difference between the two groups (p = 0.73) (Figure 3).

Presence or absence of hypertension (secondary endpoint)

The proportion of patients with hypertension was 63% (10 patients) in the effective group and 60% (6 patients) in the ineffective group (Figure 3). There was no significant difference between the two groups (p = 0.61).

Multivariate regression analysis

Multivariate regression was performed using the parameters of presence or absence of dizziness induced by head rotation or extension in the standing position, presence or absence of headache, age, presence or absence of hypertension, but not the presence or absence of stiff shoulders, as there were unknown cases. The hazard ratios were as follows (in descending order): presence or absence of dizziness induced by head rotation or extension in the standing position (10.6), presence or absence of headache (1.54), presence or absence of hypertension (1.27), and age (0.02).

DISCUSSION

Chotosan is effective for treating dizziness induced by head rotation or extension in the standing position

This study focused on the induction of dizziness by head rotation or extension in the standing position as an example of suspected VBI. The results indicated that the proportion of cases in which dizziness was induced by head rotation or extension in the standing position was significantly higher in the effective group. Accordingly, it was proven that chotosan was effective for treating dizziness induced by head rotation or extension in the standing position.

The chotosan administration period was significantly longer in the effective group. In cases where chotosan was ineffective, it is probable that the administration period was shortened because chotosan was considered to be ineffective and its administration was terminated early. Strictly speaking, the administration period should be the same in both groups. This is a limitation of the study owing to its retrospective nature.

Since this study was retrospective, there were some patients in whom ATP and ibudilast were used in combination with chotosan. ATP increases cerebral blood flow[9] and peripheral vasodilation in the inner ear[10]. Ibudilast improves cerebral blood flow by enhancing prostacyclin secretion[11] and cerebral vasodilation[12]. Therefore, these combination drugs may also contribute to the improvement of dizziness. However, even after selecting the cases in which chotosan was administered alone, the number of cases of dizziness induced by head rotation or extension in the standing position was significantly higher in the effective group. Therefore, it can be concluded that chotosan alone has a sufficient therapeutic effect.

In one patient in the ineffective group, dizziness was induced by head extension in the standing position. However, dizziness was also induced by head conversion, and the patient was diagnosed with BPPV. Even in the presence of dizziness induced by head rotation or extension in the standing position, chotosan may not have an effect if the dizziness is not due to VBI (e.g., neurovascular cross-compression of the 8th cranial nerve[4], other than BPPV). Therefore, it cannot be said that chotosan is uniformly effective for dizziness induced by head rotation or extension in the standing position. However, it is certain that dizziness induced by head rotation or extension in the standing position is an important indication for the administration of chotosan.

Pharmacological action of chotosan: improvement of vertebrobasilar artery circulation and cerebral microcirculation

Chotosan is composed of 11 crude drugs, including *Uncaria* hook, the main drug. Various pharmacological actions of chotosan have been elucidated, including the relaxing effect on the basilar arterial wall[5]. In addition, 3α-Dihydrocadambine, an alkaloid found in *Uncaria* hook, has a dilating effect on the vertebral arteries[6]. Therefore, chotosan can be expected to improve the blood flow in the vertebrobasilar artery. There is also a case report of a chotosan-suppressed transient ischemic attack, which was resistant to treatment by Western drugs[13]. Therefore, the effectiveness of chotosan in clinical practice has been demonstrated.

Uncaria hook contains many other alkaloids such as hirsutine, rhynchophylline, and geissoschizine methyl ether[14]. They have several pharmacological actions, such as peripheral vasodilatory action[15], antihypertensive action[16], protective effect on brain cells[17], and preventive action against cerebral ischemia[14]. Based on these effects, chotosan improves microcirculation in the brain[18,19] and has a neuroprotective effect on brain cells[20,21]. Because of these effects, chotosan is effective in patients with cerebrovascular dementia[20,22,23]. These effects are also considered advantageous for dizziness.

Secondary endpoints: There was no significant difference in the age and presence or absence of headache, stiff shoulders, and hypertension

Regarding the proportion of patients with headaches, it was not sig-

nificantly different between the two groups, but tended to be higher in the effective group ($p = 0.08$). This may be due to the small number of cases, and could be examined further by evaluating additional cases. In addition, there is a saying that most of the headaches that chotosan works for are "morning headaches." Kimura *et al*.[24] showed that chotosan is highly effective for "morning headaches." In the present study, patients were asked about the presence or absence of headaches. However, they were not asked whether the headache was stronger in the morning. In the future, the number of cases can be increased, and the study can focus not only on the presence or absence of headache, but also on whether the headache was stronger in the morning.

There was no significant difference in age, presence or absence of stiff shoulders, and presence or absence of hypertension between the two groups. Therefore, based on the results of this study, age, presence or absence of stiff shoulders, and presence or absence of hypertension cannot be considered influencing factors when considering the application of chotosan for dizziness. Regarding age, one patient in their thirties and one in their forties were included in the effective group. Although chotosan is said to be effective in the older, there are a few cases in which chotosan was effective even in young people.

Consequently, when considering chotosan for dizziness, the presence or absence of headache, age, presence or absence of stiff shoulders, and presence or absence of hypertension, which have been conventionally referred to, are not necessarily helpful (regarding headache, it is necessary to evaluate more cases). On the other hand, it has been shown that chotosan is useful for dizziness induced by head rotation or extension in the standing position. This is not mentioned in "Fusai honjihou," the original text referring to chotosan. Dizziness induced by head rotation or extension in the standing position can be added as the new indication for the use of chotosan.

This study had some limitations, which were as follows: (1) small sample size, (2) inability to generalize the findings to different populations, and (3) potential for selection bias due to the enrollment of subjects from only one institution.

CONCLUSION

The study results showed that chotosan was useful for dizziness induced by head rotation or extension in the standing position. This is presumed to be based on the effect of chotosan in improving the blood flow in the vertebrobasilar artery. Dizziness induced by head rotation or extension in the standing position can be considered a new indication for the use of chotosan.

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ETHICAL STATEMENT

This retrospective study was conducted in compliance with the Declaration of Helsinki and ethical guidelines for medical research targeting humans, and received approval from the Tokyo Medical University Medical Ethics Review Board (approval number: T2021-0112).

INFORMED CONSENT

The need for informed consent was waived due to the retrospective nature of the study.

CONFLICTS OF INTEREST

The authors have no conflicts of interest or financial relationships to disclose.

SUPPORTING INFORMATION

The chotosan used in this study was an extract preparation from Tsumura & Co., Ltd., and the composition of 7.5 g of this drug is as follows: *Uncaria* hook 3.0 g, Chrysanthemum flower 2.0 g, Gypsum 5.0 g, Citrus unshiu peel 3.0 g, *Pinellia tuber* 3.0 g, *Ophiopogon* root 3.0 g, *Poria* sclerotium 3.0 g, Ginseng 2.0 g, *Saposhnikovia* root 2.0 g, Licorice root 1.0 g, Ginger 1.0 g.

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