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Original Article

Effect of a 4–Week Treatment with Cilostazol in Patients with Chronic Tinnitus: A Randomized, Prospective, Placebo–controlled, Double–blind, Pilot Study

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OBJECTIVE: The aim of this prospective, double-blind, randomized, placebo-controlled study was to evaluate the efficacy of cilostazol, a selective phosphodiesterase 3 inhibitor, in patients with chronic tinnitus.

MATERIALS and METHODS: Adult patients of chronic tinnitus lasting more than 3 months were included. Fifty eligible patients were randomly assigned to either cilostazol or control (placebo) group. The study medication of oral 100-mg cilostazol and a matching placebo were used twice a day for 4 weeks. Subjective tinnitus severity was evaluated using the visual analog scale (VAS), tinnitus handicap inventory (THI), and Short-Form 36 health survey (SF-36) at baseline and at 2 and 4 weeks after study initiation. Changes in tinnitus pitch and loudness matching values were also analyzed.

RESULTS: The improvement range in the VAS score was significantly greater in the cilostazol group than in the placebo group after 4 weeks' administration of cilostazol. The SF-36 subscales also showed improvement in quality of life in the physical component summary subscale, the aggregate subscale of the physical category. There were no significant improvements in the cilostazol group compared to the placebo group in the THI subscales and tinnitus characteristics of pitch and loudness matching values. Various degrees of headaches were experienced by 68% of patients in the cilostazol group.

CONCLUSION: A 4-week administration of oral cilostazol in patients with chronic tinnitus may mitigate the severity of subjective tinnitus.

KEYWORDS: Tinnitus, phosphodiesterase inhibitors, vasodilators, drug effects, clinical trial

INTRODUCTION

Tinnitus is the perceived auditory sensation of sound in the absence of external acoustic stimulation [1]. It affects between 5% and 15% of the population, and severe tinnitus, which impairs quality of life, occurs in about 1% to 2% of people [2-4]. The degree of individual annoyance varies, but chronic persistent tinnitus may seriously affect daily activity, resulting in severe emotional problems such as anxiety, annoyance, and depression [4]. There is a wide variety of strategies for tinnitus management, such as cognitive–behavioral therapy [5], sound therapy [6], pharmacotherapy [7], and transcranial magnetic stimulation [8]. Although some patients may experience a certain degree of beneficial effect from these modalities, no standard treatment has been established or approved as a cure for tinnitus.

So far, the evidence for pharmacologic treatment is limited. No single drug has been approved by the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for the treatment of tinnitus [7]. According to recent systematic reviews, anticonvulsants, ginkgo biloba, and tricyclic antidepressants have failed to show significant beneficial effects on treating tinnitus.[1] Vasodilators have been used based on anecdotal evidence, although several studies have reported that ischemic conditions may play a role in chronic alteration of inner ear function and tinnitus pathogenesis [9, 10].

Cilostazol selectively inhibits phosphodiesterase type 3 (PDE3) and increases the amount of cyclic adenosine monophosphate (cAMP) by inhibiting its degradation. cAMP again suppresses the production of blood clots by increasing the active forms of protein kinases and increases blood flow by expanding blood vessels, which is comparable to the nitric oxide (NO) signaling pathway [11]. The anti-platelet and vasodilatation effects of cilostazol have been approved by FDA for treating intermittent claudication due

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to peripheral arterial disease [11]. Previous studies reported that the blood flow to stria vascularis and cochlear hair cells can be improved by increasing the activity of NO and protein kinases [12-14]. These studies suggest that cilostazol, which inhibits PDE3 and increases the levels of protein kinases, may improve tinnitus by increasing blood flow to peripheral cochlear cells. Thus, we hypothesized that cilostazol, which is widely used for enhancing peripheral blood flow, could improve tinnitus by increasing the peripheral blood flow to cochlea.

We conducted our randomized controlled study to validate these assumptions by determining whether the administration of cilostazol could improve subjective tinnitus in chronic tinnitus patients.

MATERIALS and METHODS

Study Design and Patients

This randomized, prospective, placebo-controlled, double-blind, phase IIa clinical trial was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. The Institutional Review Board approved the study protocol and the informed consent form. Informed consent was obtained for all patients before their inclusion. Study participants were recruited from those patients with chronic tinnitus from October 2011 to May 2013. A total of 50 patients were enrolled by screening for eligibility. In this pilot study, a sample size of 25 patients per arm was established for a preliminary trial. Prior to determining eligibility, each patient was evaluated by detailed medical history, physical examination, visual analog scale (VAS) of tinnitus, pure tone audiometry, and speech audiometry. The inclusion criteria were as follows: (1) age older than 19 years; (2) unilateral or bilateral tinnitus; (3) chronic tinnitus lasting more than 3 months and less than 12 months; and (4) an initial VAS of tinnitus ≥4. The exclusion criteria included the following: (1) conductive hearing loss on pure tone audiometry; (2) any other associated inner ear disease such as Meniere's disease; (3) objective or pulsatile tinnitus; (4) contraindication to anti-platelet drugs; (5) any cardiac disease; (6) a bleeding tendency or history of major operation within 3 months; (7) breastfeeding; and (8) pregnancy.

Procedures

Fifty eligible patients who voluntarily signed an informed consent were randomly assigned to either a cilostazol (Korea Otsuka Pharmaceutical; Seoul, Korea) or control (placebo) group by means of a computer-generated random sequence. The random sequence was developed by a statistician at the clinical trial center. Study medications were manufactured according to the random sequence and sent to the clinical trial pharmacy at the clinical trial center. The assigned study medications of cilostazol or placebo, which were identical in appearance and labeled only with a case number, were both prescribed at baseline on day 0 (T0) for 2 weeks and at 2 weeks after enrollment (T1) for another 2 weeks. Oral 100-mg cilostazol tablets or matching placebo tablets were administered twice a day for a total of 4 weeks. The final evaluation was scheduled at 4 weeks after T0-that is, at the end point of the study (T2). Medical history taking, vital signs, routine blood analysis, and urine human chorionic gonadotropin (hCG) levels (from women only) were obtained at the day of random assignment. Participants were requested to consult investigators if any possible side effects occurred. Study patients and investigators remained blinded to the study drug allocation throughout the entire trial.

Assessment

The severity and characteristics of tinnitus were evaluated at each visit of the patients (T0, T1, and T2). To assess the subjective severity of tinnitus, a VAS of tinnitus severity and validated Korean versions of two established questionnaires, the tinnitus handicap inventory (THI), and the Short-Form 36 health survey (SF-36), were used at each visit [15, 16]. The VAS was a 10-cm long horizontal line on which patients indicated the tinnitus severity, beginning of the scale refers to no tinnitus (0 point) and the end to the most severe tinnitus they can imagine (10 points). The THI is a validated and widely used questionnaire for assessing the impact of tinnitus on daily life and for documenting the treatment outcomes of tinnitus [17]. It comprises 25 items, each with 0, 2, or 4 points, with three subscales: functional (12 items), emotional (8 items), and catastrophic (5 items). The total score ranges from 0 to 100, and a higher score represents a higher handicapped tinnitus. The SF-36 has been accepted as an established assessment tool for individuals complaining about tinnitus [18]. It consists of 36 items for the assessment of various aspects of the mental and physical health conditions of individuals through eight subscales. Higher scores represent a higher level of performance associated with quality of life. The SF-36 can also be divided into two aggregate summary measures: the physical component summary (PCS) and the mental component summary.

To evaluate tinnitus characteristics of each patient, tinnitus pitch and loudness were monitored at each visit. The pitch-match frequency and loudness-match dB sensation level (dB SL) were obtained with clinical audiometers. Tinnitus pitch was measured with pure tone sounds from 250 Hz to higher frequencies (up to 8kHz) until the matched frequency could be obtained. Narrow band noise was applied when necessary. After detection of the tinnitus pitch, the changing intensity of the stimulus was matched with tinnitus loudness with an increment of 1 dB in tinnitus pitch frequency.

Statistical Analysis

Efficacy analyses were primarily performed within the efficacy analysis population, which included all randomly assigned patients who took the allocated medication for at least 2 weeks with the available complete post-baseline data of T1. Statistical analyses were performed using linear mixed-effects models (LMM) with random intercept and compound symmetry for the correlation structure to compare changes in each variable from baseline to T1 or T2. The effect on the subjective severity, which was determined by the change in questionnaire scores, was the main outcome measure. The effect on tinnitus characteristics of pitch and loudness were evaluated by comparing the baseline data and the last available data using a Wilcoxon signed rank test and Mann–Whitney U test. Analyses were repeated within the per protocol population, which included all randomly assigned patients who completed the study as scheduled without major violations. Statistical analysis was conducted using SAS version 9.1 software (SAS Institute Inc.; Cary, NC, USA). Values of $p<0.05$ were considered to indicate statistical significance.

RESULTS

Patients and Baseline Characteristics

Of the 95 patients screened, 50 were finally enrolled in this study and randomized to the cilostazol group (n=25) or the placebo group

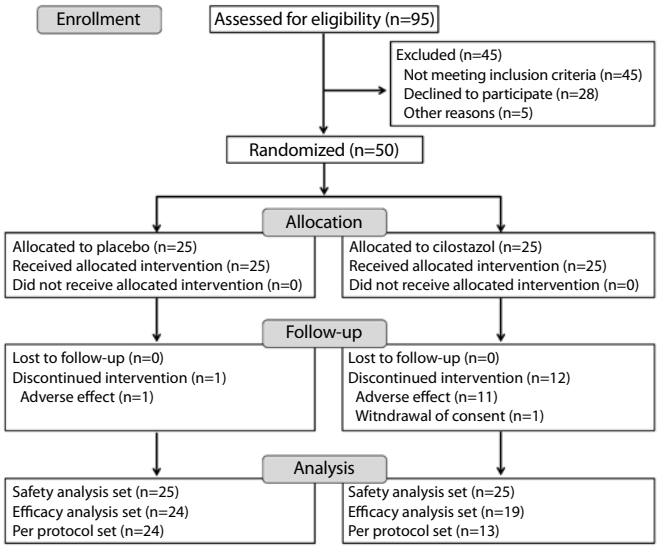

Figure 1. CONSORT flow diagram

Table 1. Baseline characteristics of the efficacy analysis population

Characteristics	All patients (n=43)	Placebo (n=24)	Cilostazol (n=19)	p
Sex				
Male	33 (77%)	20 (83%)	13 (68%)	0.295
Female	10 (23%)	4 (17%)	6 (32%)	
Age, years				
Mean±SD	46.6±12.6	46.5±11.9	46.6±13.7	0.941
Range	18 to 73	18 to 67	20 to 73	
Tinnitus laterality				
Unilateral	23 (53.5%)	15 (62.5%)	8 (42.1%)	0.294
Bilateral	20 (46.5%)	9 (37.5%)	11 (57.9%)	
Hearing level, dB HL[a]				
No. of ears	63	33	30	
Ears with tinnitus (mean±SD)	25.7±14.2	26.3±16.2	25.1±11.8	0.744
Ears without tinnitus (mean±SD)	16.9±9.9	18.7±11.5	13.4±6.7	0.821
Tinnitus description				
No. of ears	63	33	30	
Tonal	37 (58.7%)	17 (51.5%)	20 (66.7%)	0.306
Nontonal	26 (41.3%)	16 (48.5%)	10 (33.3%)	
Pitch match, kHz[b]				
No. of ears	49	21	28	
Mean±SD	5.8±2.6	5.7±2.7	5.8±2.6	0.994
Loudness match, dB SL				
No. of ears	49	21	28	
Mean±SD	8.1±6.8	7.9±6.4	8.3±7.2	0.817

dB HL: decibel hearing level; dB SL: decibel sensation level; SD: standard deviation

[a]Hearing level indicates pure tone threshold averages of 500, 1000, 2000, and 4000 kHz.

[b]The pitch of the tinnitus can be categorized in tonal tinnitus and cannot in nontonal (noisy) tinnitus.

(n=25) (Figure 1). After drug administration, 1 patient of the placebo group (prior to T1) and 11 patients of the cilostazol group (5 prior to T1 and 6 prior to T2) dropped out of the study due to persistent headaches. One patient of the cilostazol group withdrew consent after randomization at medication day 3. Thus, the efficacy analysis data set was comprised of 24 patients from the placebo group and 19 patients from the cilostazol group. In addition, 24 patients of the placebo group and 13 patients of the cilostazol group took all medications as scheduled and had complete post-baseline data and thus constituted the per protocol population.

Table 2. Baseline questionnaire scores (mean±SD) regarding the tinnitus severity of the efficacy analysis population

	All patients (n=43)	Placebo (n=24)	Cilostazol (n=19)	p
THI				
Total score	31.70±17.83	36.21±18.77	26.00±15.16	0.031*
Functional subscale	16.84±10.35	20.08±10.88	12.74±8.17	0.012*
Emotional subscale	9.09±5.89	10.21±6.53	7.68±4.77	0.133
Catastrophic subscale	5.76±4.03	5.92±3.93	5.58±4.25	0.892
VAS	6.47±1.97	6.58±2.10	6.32±1.83	0.765
SF-36				
Physical functioning	87.21±13.02	88.54±13.87	85.53±12.01	0.192
Role-physical	76.74±31.99	78.13±28.85	75.00±36.32	0.904
Bodily pain	74.69±24.15	74.83±25.13	74.53±23.53	1.000
General health	64.33±18.76	68.33±18.36	59.26±18.50	0.097
Vitality	57.79±17.54	58.54±19.25	56.84±15.56	0.825
Social functioning	47.67±9.15	48.83±9.52	50.00±8.33	0.177
Role-emotional	77.52±36.17	76.38±37.41	78.94±35.51	0.860
Mental health	67.26±19.79	68.50±18.55	65.68±21.68	0.768
Physical summary	50.18±5.99	51.02±5.93	49.12±6.07	0.334
Mental summary	42.74±8.26	42.55±8.11	42.98±8.67	0.760

*Statistical significance.
SD: standard deviation; THI: tinnitus handicap inventory; VAS: visual analogue scale; SF-36: the Short Form 36 health survey

The patient characteristics of the efficacy analysis population are presented in Table 1. There were no significant differences between the two groups in terms of sex, age, hearing levels, and tinnitus characteristics. Table 2 shows the baseline tinnitus severity of the efficacy analysis population. Hearing level and tinnitus laterality of all patients showed no interval change throughout the study. The total THI score and the functional subscale were not balanced between the placebo and cilostazol groups, with significantly higher scores in the placebo group. The VAS and all SF-36 subscale scores showed no significant differences among the two study groups.

Efficacy in Subjective Severity

The baseline total THI score and the functional subscale were not exactly balanced between study groups. Thus, additional statistical correction was implemented by adding interaction term of initial value and time. The influence of the initial value on the velocity of the change in the score was estimated for the analysis of all THI scores. If the velocity is different according to the baseline THI value, the significance of difference in score changes between study groups was finally determined considering the influence of the baseline value on the velocity.

Table 3. Statistical analysis of changes in tinnitus handicap inventory (THI) scores

Variables	Time span[a]	Placebo		Cilostazol		Intergroup difference[b]		
		Mean	SD	Mean	SD	LSMD	SE	p
Total THI score	ΔT1	–6.375	12.638	–0.947	11.262	1.687	3.243	0.605
	ΔT2	–10.083	15.160	1.538	8.452	7.093	3.589	0.052
THI subscales								
Functional	ΔT1	–4.500	6.653	–1.158	6.085	0.777	1.786	0.665
	ΔT2	–6.667	8.499	0.000	4.546	2.969	1.959	0.134
Emotional	ΔT1	–1.792	5.124	0.211	4.049	0.821	1.194	0.494
	ΔT2	–2.083	5.830	0.462	2.727	0.997	1.312	0.449
Catastrophic	ΔT1	–0.083	2.796	0.000	3.399	0.006	0.903	0.995
	ΔT2	–1.333	3.046	1.077	3.046	2.280	0.982	0.030*

*Statistical significance.

[a]T1 and T2 indicate 2 and 4 weeks after drug administration, respectively. Time span represents the change in values from T0 to T1 (ΔT1) and from T0 to T2 (ΔT2).

[b]Linear mixed effects models and additional statistical correction for baseline imbalances were used to compare the amount of change from baseline at each time point between the placebo and cilostazol groups.

THI: tinnitus handicap inventory; SD: standard deviation; LSMD: least squares mean difference; SE: standard error

Table 4. Statistical analysis of changes in tinnitus handicap inventory (THI) scores

Variables	Time span[a]	Placebo		Cilostazol		Intergroup difference[b]		
		Mean	SD	Mean	SD	LSMD	SE	p
VAS	ΔT1	–0.125	1.454	–0.026	0.920	0.099	0.607	0.871
	ΔT2	–0.500	1.978	–1.844	2.813	–1.344	0.659	0.045*
SF-36 subscales								
Physical functioning	ΔT1	–2.500	13.673	4.211	10.310	6.711	4.967	0.181
	ΔT2	–3.333	19.430	4.231	12.391	7.106	5.354	0.189
Role-physical	ΔT1	2.083	29.411	9.211	22.377	7.127	8.755	0.418
	ΔT2	–6.250	36.303	15.385	34.669	17.650	9.500	0.067
Bodily pain	ΔT1	–1.458	22.407	0.789	34.877	2.248	8.783	0.799
	ΔT2	–2.042	33.610	7.077	33.340	3.229	9.470	0.734
General health	ΔT1	–1.667	8.801	0.684	9.280	2.351	2.715	0.389
	ΔT2	–1.125	8.887	–0.154	6.914	1.033	2.961	0.728
Vitality	ΔT1	0.000	12.511	–3.684	12.785	–3.684	4.136	0.376
	ΔT2	–1.667	15.156	0.385	14.356	2.413	4.498	0.593
Social functioning	ΔT1	2.604	9.738	2.632	12.204	0.027	3.624	0.994
	ΔT2	3.125	12.901	2.885	12.659	–1.066	3.893	0.785
Role-emotional	ΔT1	0.004	35.454	0.000	22.225	–0.004	10.090	0.999
	ΔT2	5.558	44.695	7.700	24.172	–0.881	10.934	0.936
Mental health	ΔT1	3.000	17.265	0.632	14.561	–2.368	4.473	0.598
	ΔT2	3.667	14.634	0.615	7.974	–3.142	4.862	0.520
Physical summary	ΔT1	–1.025	3.837	1.795	5.619	2.820	1.907	0.143
	ΔT2	–2.479	8.989	2.792	6.188	4.172	2.066	0.047*
Mental summary	ΔT1	1.408	6.637	–0.721	4.985	–2.129	1.798	0.240
	ΔT2	2.596	7.519	0.300	4.076	–2.295	1.955	0.244

*Statistical significance.

[a]T1 and T2 indicate 2 and 4 weeks after drug administration, respectively. Time span represents the change in values from T0 to T1 (ΔT1) and from T0 to T2 (ΔT2).

[b]Linear mixed effects models and additional statistical correction for baseline imbalances were used to compare the amount of change from baseline at each time point between the placebo and cilostazol groups.

THI: tinnitus handicap inventory; SD: standard deviation; LSMD: least squares mean difference; SE: standard error

Regarding the total THI scores, the changes in scores from baseline to T1 and T2 were not significantly different among study groups (Table 3). In the analysis of subscales, the functional and emotional subscales also showed no significant differences in the change in scores at both T1 and T2 time spans from baseline. However, a greater score reduction at T2 was found in the catastrophic THI subscales in

Table 5. Changes in tinnitus pitch and loudness at the last follow-up

	Tinnitus pitch (kHz)			Tinnitus loudness (dB SL)		
	Baseline (mean±SD)	Last follow-up (mean±SD)	p[a]	Baseline (mean±SD)	Last follow-up (mean±SD)	p[a]
Placebo (n=21)	5.77±2.75	6.39±2.39	0.172	7.86±6.41	5.57±3.92	0.097
Cilostazol (n=27)	5.69±2.63	5.37±2.42	0.396	8.52±7.31	7.29±4.67	0.414
p[b]	0.849	0.917		0.126	0.19	

[a]Wilcoxon signed rank test was used.
[b]Mann-Whitney U test was used.
SD: standard deviation

the placebo group (p=0.030). With respect to the change in the VAS score, there were no differences in the change in values between the cilostazol and placebo groups at T1 (–0.026 vs–0.125), whereas significantly greater improvement in the cilostazol group versus the placebo group (–1.844 vs–0.500) was observed at T2 (p=0.045) (Table 4). For the SF-36, a significantly greater improvement was found in the cilostazol group for the PCS subscale at T2 (p=0.047) (Table 4). The changes in the other SF-36 subscales from baseline to T1 and T2 were not significantly different.

Efficacy in Tinnitus Pitch and Loudness

For the evaluation of changes in tinnitus characteristics, patients with unilateral and bilateral tinnitus were analyzed together. The tinnitus pitch changed from 5.77±2.75 kHz to 6.39±2.39 kHz in the placebo group and from 5.69±2.63 kHz to 5.37±2.42 kHz in the cilostazol group (Table 5). There were no significant within- and between-group changes with medication in both groups. Regarding tinnitus loudness, there was a nonsignificant tendency toward a decrease, from 7.86±6.41 dB SL to 5.57±3.92 dB SL in the placebo group and from 8.52±7.31 dB SL to 7.29±4.67 dB SL in the cilostazol group.

Adverse Events

Adverse effects were reported by 22 patients during the study: 19 headaches (17 in the cilostazol group and 2 in the placebo group) and 3 hyperglycemia occurrences (1 in the cilostazol group and 2 in the placebo group). Of the 25 cilostazol group patients of the safety population, 17 patients (68%) had headaches and 1 (4%) had hyperglycemia. All side effects of cilostazol were considered to be related to treatment (6 certain, 4 probable, and 8 possible cases). Among patients with headache, 11 in the cilostazol group and 1 in the placebo group discontinued study drug administration due to persistent headache, whereas the others with headache completed the study because their symptoms were mild enough to continue medication. All patients with hyperglycemia completed the drug administration since the elevated blood glucose level was not serious. No serious adverse event was reported in relation to medication.

DISCUSSION

The heterogeneity of etiology and the limited understanding of underlying pathogenesis prevent the development of a curative treatment for tinnitus. Pathologic changes in tinnitus can include any conditions along the entire auditory pathway from a primary cochlear lesion to an alteration of the central auditory pathway [1]. Impairment of blood supply from noise exposure, cardiovascular disease, hyperlipoproteinemia, diabetes mellitus, or excessive stress may result in long-term deterioration of microcirculation in the inner ear.

The cGMP and cAMP signaling pathways regulate a large number of physiologic processes, such as cell proliferation, gene expression, inflammation, apoptosis, and metabolism [19]. In the mammalian cochlea, cGMP is an essential second messenger of the NO system that regulates cochlear microcirculation [12, 20, 21]. cGMP formation activates protein kinases and subsequently increases cochlear blood flow [12]. Like cGMP-dependent protein kinase activation, cAMP-dependent vasodilation is possible through protein kinase activation, although its role in the cochlea is unknown [22]. Moreover, cAMP-dependent signaling is expected from animal studies to have neuroprotective effects in the cochlea [23, 24].

PDE, the enzyme that hydrolyzes cGMP and cAMP to their inactive forms, has been classified into 11 isoenzymes [25]. PDE3 has high affinity for both cGMP and cAMP, and cAMP hydrolysis by PDE3 is 10 times greater than cGMP hydrolysis in terms of amount [25]. Cilostazol is a selective PDE3 inhibitor and mainly increases the amount of cAMP by inhibiting cAMP degradation. Cilostazol induces cAMP-mediated vasodilation, platelet activation inhibition, and decreased vascular wall inflammation. Due to such properties of cilostazol, a substantial number of off-label clinical trials are currently underway for various vascular diseases such as heart failure, ischemic stroke, restenosis, and dementia [26]. From the vasodilation and neuroprotective effects of cAMP, we assumed that cilostazol, which blocks PDE3 and inhibits degradation of cAMP, would have beneficial effects on chronic tinnitus via an improvement in cochlear microcirculation.

In our present clinical trial, we found some positive effects of cilostazol in relieving subjective tinnitus severity, which were evident from changes in the VAS score. The improvement was significantly greater in the cilostazol group after 4 weeks' administration, possibly supporting the hypothesis that cilostazol could have a beneficial therapeutic influence on tinnitus treatment. Analysis of the SF-36 subscales also showed improved quality of life in the PCS subscale after 4 weeks' administration of cilostazol. The significant increase in the PCS seemed to reflect an overall improvement that resulted from a small amount of change in physical components. The mental components could have been influenced by the high incidence of side effects from cilostazol administration because two-thirds of the cilostazol group suffered headache. This may explain the lack of improvement in mental component measures.

On the other hand, analyses of the parameters of THI failed to show a significant drug effect of cilostazol. The total THI and subscale scores showed a tendency for a greater decrease in the placebo group at follow-up evaluation. This result seemed to be due to the higher baseline THI scores of the placebo group, so we attempted to statistically

correct the unmatched initial baseline THI scores. Unfortunately, the correction was thought to be insufficient due to the small number of study patients, making the analysis of the THI scores hard to interpret. The efficacy of medication for tinnitus can be measured audiologically through tinnitus loudness matching [27, 28]. In our present study, however, tinnitus characteristics of pitch and loudness did not show any significant within- and between-group improvements after medication.

Given our present results, the effect of cilostazol on chronic tinnitus is possibly significant; however, it remains unclear. It is possible that the protocol could be modified with respect to the treatment duration or target to evaluate the therapeutic effect of cilostazol on tinnitus. First, the 4-week overall duration of medication could be insufficient. In previous clinical trials for intermittent claudication, atherosclerosis, and secondary stroke prevention, the duration of drug administration was 12–24 weeks [29, 30]. Considering the chronic feature of the tinnitus in our current study patients, the period of drug treatment may have to be longer than 12 weeks to affect tinnitus. Second, considering the etiological heterogeneity of acute hearing loss and tinnitus, administration of cilostazol for acute vascular insufficiency may have a role in the treatment of acute tinnitus. Indeed, clinical trials of cilostazol have shown beneficial effects on treatment for acute cardiovascular disease, acute renal dysfunction, and acute ischemic stroke [31, 32].

Headaches and migraines are very common side effects of cilostazol. In two large prospective clinical studies of cilostazol, the incidences of headache development were reported to be 24% and 50.6% [29, 31]. According to recent studies, cilostazol induced migraine-like headache in most of the participants without any history of migraine, and this phenomenon is believed to be due to intracellular cAMP accumulation [33, 34]. In our current study, about two-thirds of the patients experienced various degrees of headache and a substantial number of the cilostazol group dropped out of the study due to headache. The high incidence of headache due to cilostazol may be an important obstacle to the use of cilostazol for tinnitus patients, who can be susceptible to emotional stress.

In this first off-label clinical trial of a PDE3 inhibitor for tinnitus, we found a positive effect of cilostazol in relieving subjective tinnitus severity. Frequent development of headache due to cilostazol seemed to adversely impact continuous drug use in patients with tinnitus. Extension of the administration duration in chronic tinnitus or a clinical trial for acute tinnitus may be considered in order to confirm the beneficial effects of cilostazol on tinnitus.

Ethics Committee Approval: Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Asan Medical Center, Seoul, Korea.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

1. Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes and clinical management. Lancet Neurol 2013; 12: 920-30. [CrossRef]
2. Heller AJ. Classification and epidemiology of tinnitus. Otolaryngol Clin North Am 2003; 36: 239-48. [CrossRef]
3. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. Am J Med 2010; 123: 711-8. [CrossRef]
4. Axelsson A, Ringdahl A. Tinnitus--a study of its prevalence and characteristics. Br J Audiol 1989; 23: 53-62. [CrossRef]
5. Hesser H, Weise C, Westin VZ, Andersson G. A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress. Clin Psychol Rev 2011; 31: 545-53. [CrossRef]
6. Hobson J, Chisholm E, El Refaie A. Sound therapy (masking) in the management of tinnitus in adults. Cochrane Database Syst Rev 2012; 11: CD006371. [CrossRef]
7. Langguth B, Elgoyhen AB. Current pharmacological treatments for tinnitus. Expert Opin Pharmacother 2012; 132495-509. [CrossRef]
8. Meng Z, Liu S, Zheng Y, Phillips JS. Repetitive transcranial magnetic stimulation for tinnitus. Cochrane Database Syst Rev 2011: CD007946. [CrossRef]
9. Mazurek B, Haupt H, Georgiewa P, Klapp BF, Reisshauer A. A model of peripherally developing hearing loss and tinnitus based on the role of hypoxia and ischemia. Med Hypotheses 2006; 67: 892-9. [CrossRef]
10. Lamm K, Arnold W. Noise-induced cochlear hypoxia is intensity dependent, correlates with hearing loss and precedes reduction of cochlear blood flow. Audiol Neurotol 1996; 1: 148-60. [CrossRef]
11. Dawson DL, Cutler BS, Meissner MH, Strandness DE Jr. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. Circulation 1998; 98: 678-86. [CrossRef]
12. Hoshijima H, Makimoto K, Noi O, Ohinata Y, Takenaka H. Effects of nitric oxide synthase inhibitor on cochlear blood flow. Hear Res 2002; 171: 32-42. [CrossRef]
13. Pall ML, Bedient SA. The NO/ONOO- cycle as the etiological mechanism of tinnitus. The international tinnitus journal 2007; 13: 99-104.
14. Mazurek B, Haupt H, Gross J. [Pharmacotherapy in acute tinnitis. The special role of hypoxia and ischemia in the pathogenesis of tinnitis]. HNO 2006; 54: 9-15. [CrossRef]
15. Kim JH, Lee SY, Kim CH, Lim SL, Shin JN, Chung WH, et al. Reliability and validity of a Korean adaptation of the Tinnitus Handicap Inventory. Korean J Otolaryngol-Head Neck Surg 2002; 45: 328-34.
16. Han CW, Lee EJ, Iwaya T, Kataoka H, Kohzuki M. Development of the Korean version of Short-Form 36-Item Health Survey: health related QOL of healthy elderly people and elderly patients in Korea. Tohoku J Exp Med 2004; 203: 189-94. [CrossRef]
17. Zeman F, Koller M, Figueiredo R, Aazevedo A, Rates M, Coelho C, et al. Tinnitus handicap inventory for evaluating treatment effects: which changes are clinically relevant? Otolaryngol Head Neck Surg 2011; 145: 282-7. [CrossRef]
18. Refaie AE, Davis A, Kayan A, Baskill J, Lovell E, Owen V. A questionnaire study of the quality of life and quality of family life of individuals complaining of tinnitus pre-and postattendance at a tinnitus clinic. Int J Audiol 2004; 43: 410-6. [CrossRef]
19. Francis SH, Blount MA, Corbin JD. Mammalian cyclic nucleotide phosphodiesterases: molecular mechanisms and physiological functions. Physiol Rev 2011; 91: 651-90. [CrossRef]
20. Nakashima T, Naganawa S, Sone M, Tominaga M, Hayashi H, Yamamoto H, et al. Disorders of cochlear blood flow. Brain Res Brain Res Rev 2003; 43: 17-28. [CrossRef]

21. Brechtelsbauer PB, Nuttall AL, Miller JM. Basal nitric oxide production in regulation of cochlear blood flow. Hear Res 1994; 77: 38-42. [CrossRef]
22. White RE, Kryman JP, El-Mowafy AM, Han G, Carrier GO. cAMP-dependent vasodilators cross-activate the cGMP-dependent protein kinase to stimulate BKCa channel activity in coronary artery smooth muscle cells. Circ Res 2000; 86: 897-905. [CrossRef]
23. Navaratnam DS, Su HS, Scott S-P, Oberholtzer JC. Proliferation in the auditory receptor epithelium mediated by a cyclic AMP–dependent signaling pathway. Nat Med 1996; 2: 1136-9. [CrossRef]
24. Nakagawa T. Roles of prostaglandin E2 in the cochlea. Hear Res 2011; 276: 27-33. [CrossRef]
25. Kanlop N, Chattipakorn S, Chattipakorn N. Effects of cilostazol in the heart. Journal of cardiovascular medicine 2011; 12: 88-95. [CrossRef]
26. Maurice DH, Ke H, Ahmad F, Wang Y, Chung J, Manganiello VC. Advances in targeting cyclic nucleotide phosphodiesterases. Nat Rev Drug Discov 2014; 13: 290-314. [CrossRef]
27. van de Heyning P, Muehlmeier G, Cox T, Lisowska G, Maier H, Morawski K, et al. Efficacy and safety of AM-101 in the treatment of acute inner ear tinnitus--a double-blind, randomized, placebo-controlled phase II study. Otol Neurotol 2014; 35: 589-97. [CrossRef]
28. Arda HN, Tuncel U, Akdogan O, Ozluoglu LN. The role of zinc in the treatment of tinnitus. Otol Neurotol 2003; 24: 86-9. [CrossRef]
29. Kwon SU, Cho YJ, Koo JS, Bae HJ, Lee YS, Hong KS, et al. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. Stroke 2005; 36: 782-6. [CrossRef]
30. Geng DF, Deng J, Jin DM, Wu W, Wang JF. Effect of cilostazol on the progression of carotid intima-media thickness: a meta-analysis of randomized controlled trials. Atherosclerosis 2012; 220: 177-83. [CrossRef]
31. Lee YS, Bae HJ, Kang DW, Lee SH, Yu K, Park JM, et al. Cilostazol in Acute Ischemic Stroke Treatment (CAIST Trial): a randomized double-blind non-inferiority trial. Cerebrovasc Dis 2011; 32: 65-71. [CrossRef]
32. Choi YH, Suh SH, Choi JS, Kim CS, Sim DS, Bae EH, et al. Triple vs. dual antiplatelet therapy in patients with acute myocardial infarction and renal dysfunction. Circ J 2012; 76: 2405-11. [CrossRef]
33. Guo S, Olesen J, Ashina M. Phosphodiesterase 3 inhibitor cilostazol induces migraine-like attacks via cyclic AMP increase. Brain 2014. [CrossRef]
34. Birk S, Kruuse C, Petersen KA, Tfelt-Hansen P, Olesen J. The headache-inducing effect of cilostazol in human volunteers. Cephalalgia 2006; 26: 1304-9. [CrossRef]