Combined Therapeutic Effect of Probucol and Cilostazol on Endothelial Function in Patients with Silent Cerebral Lacunar Infarcts and Hypercholesterolemia: A Preliminary Study

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Abstract

Objective: This study evaluated the efficacy of combined therapy with probucol and cilostazol on endothelial function in silent lacunar cerebral infarcts (SLCI) and mild hypercholesterolemia. ***Subjects and Methods:*** Flow-mediated vasodilatation (FMD) and nitroglycerin-induced vasodilatation (NMD) were measured before and after 4 weeks of combined therapy with probucol (500 mg/day) and cilostazol (200 mg/day) in 34 patients with a mean age of 72 ± 7 years (range 57–80 years) with SLCI, mild hypercholesterolemia (low-density lipoprotein cholesterol >100 mg/dl) and impaired endothelial function (FMD <6%). Patients were randomly allocated to one of the following two treatment groups: (1) aspirin (100 mg/day) with behavioral modifications, such as diet and/or exercise therapy (A group or control group, n = 17), and (2) probucol and cilostazol treatment (PC group, n = 17), also with behavioral modifications. ***Results:*** Although the baseline FMD was not different between the two treatment arms (2.7 ± 1.5 vs. 2.6 ± 1.5%, n.s.), the posttreatment FMD was significantly improved in the PC group (from 2.7 ± 1.5 to 3.5 ± 1.7%, p < 0.05) but not in the A group (from 2.6 ± 1.5 to 2.9 ± 1.4%, n.s.). No differences were observed between baseline and posttreatment NMD in either group. The effects of treatments on lipid profiles were more profound in the PC group. ***Conclusion:*** Combined treatment with probucol and cilostazol resulted in subacute improvement in FMD/endothelial function in patients with SLCI with mild hypercholesterolemia. This combination therapy has the potential to reduce the risk of cardiovascular events via improvements in endothelial function and lipid profiles.

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Introduction

Therapies that lower low-density lipoprotein cholesterol (LDL-C) are critical for the secondary prevention of acute coronary syndrome or other cardiovascular events, including stroke [1]. Silent lacunar cerebral infarcts (SLCI) complicated by hypercholesterolemia are associated with poor cardiovascular outcomes [2]. Among the therapies that lower LDL-C, there is strong evidence that statins are useful for the secondary prevention of acute

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coronary syndrome or ischemic cerebral infarction. However, statin therapy cannot be applied in all patients due to its side effects, such as liver dysfunction and myositis [1].

Probucol is a mild cholesterol-lowering agent that has antioxidant, anti-inflammatory and antiatherosclerotic properties [3]. Since probucol causes a significant reduction in high-density lipoprotein cholesterol (HDL-C) and prolongation of the QT interval, it has been withdrawn from the market in some countries [3]. However, studies suggest that probucol reduces atherosclerosis and prevents restenosis after percutaneous coronary intervention [3] and that it may produce a synergistic antiatherosclerotic effect when administered with cilostazol [4]. Cilostazol is an inhibitor of the type 3 phosphodiesterase that has antiplatelet and diverse antiatherogenic properties. Previous reports have shown that cilostazol improves endothelial function and attenuates antioxidant stress through an increase in nitric oxide production [5] and scavenging of free radicals [6], respectively. Cilostazol also inhibits foam cell formation [7] and smooth muscle cell proliferation [8].

Endothelial dysfunction is present in both the early and the advanced phase of atherosclerosis or the destabilized phase of atherosclerotic disorders [9]. Since endothelial function plays a central role in the pathogenesis of atherosclerotic progression, the synergistic effect of probucol and cilostazol on endothelial function is worth being evaluated in patients who are at high risk for atherosclerotic events, such as those with SLCI.

Endothelial function can be investigated through the assessment of brachial artery flow-mediated vasodilatation (FMD) or plethysmography with acetylcholine infusion in the forearm vessels. The FMD of the brachial artery combined with nitroglycerin-mediated vasodilatation (NMD) is frequently used to evaluate endothelial function [10].

Thus, the purpose of the present study was to investigate the effect of combined therapy with probucol and cilostazol on endothelial function in patients with SLCI and hypercholesterolemia.

Subjects and Methods

Study Population

The study population consisted of 34 male patients (mean age 72 ± 7 years; range 57–80 years) with hypercholesterolemia and SLCI who were referred to our hospital. Patients were included in this study if their LDL-C was >100 mg/dl despite having already been prescribed lipid-lowering medication, including statins or other lipid-lowering agents. The SLCI was diagnosed by magnetic resonance imaging (MRI) with a Signa 1.5-T Cvi scanner (GE Medical Systems, Milwaukee, Wisc., USA) and a commercially available phased-array brain coil. Brain transverse proton density-weighted and T1-weighted and T2-weighted images were obtained, and SLCI was defined as focal T2 hyperintensities >3 mm with correlative T1 hypointensities [11].

Twenty-one of the study patients had coronary artery disease, and 17 were receiving statin therapy before entering this study. In these patients, statins were withdrawn for at least 5 half-lives of the respective statin before the initiation of probucol. In addition, aspirin had been prescribed to 24 of the patients. In these patients, aspirin was discontinued for at least 7 days before entry into this study. Exclusion criteria were: allergic reaction to probucol, cilostazol or aspirin; diabetic acidosis; advanced heart failure and arrhythmias; thyroid disease; severe disease of the liver and kidney; pregnancy, or any other acute disorder. In this study, the comorbid conditions were defined as follows: hypertension (either systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg); coronary artery disease (defined as in the text); diabetes mellitus (fasting blood sugar >126 mg/dl), and peripheral artery disease (ankle-brachial index <0.9 following the confirmation of luminal stenosis of the peripheral artery by conventional imaging modality). Written informed consent was obtained from each patient. The study protocol was approved by our Institutional Review Board.

Study Protocol

This was a prospective, open-label, single-blind, active control, randomized study, and FMD and NMD were measured before and after the treatments. Each eligible patient was randomly assigned to one of two 4-week treatment arms. Treatment was either combined probucol (500 mg/day) and cilostazol (200 mg/day) with additional behavioral modifications, such as diet and/or exercise therapy (PC group, n = 17, mean age 72 ± 15 years, range 64–80 years), or aspirin (100 mg/day) with the same behavioral modifications as those used in the PC group (A group or control group, n = 17, mean age 72 ± 8 years, range 57–78 years). After overnight fasting, venous blood sampling (for measurement of blood chemistries) and brachial artery endothelial function testing were done. Blood sample testing included routine blood chemistries with liver and renal function tests, lipid profile, fasting blood sugar and complete blood counts according to standard methods. All measurements were conducted before and after each treatment.

Ultrasound FMD and NMD Measurements in the Brachial Artery

All ultrasound studies were done in a temperature-controlled room (25°C) with the subject in a fasted, resting and supine state from approximately 14:00 h to 17:00 h. All studies were performed by the same technician, who was blinded to any other clinical information, including the study protocol. Heavy meals, including a high-fat diet and caffeine-containing beverages, were prohibited beginning on the night before the study. Patients were not allowed to have lunch on the day of the ultrasound study. Blood pressure and heart rate were recorded from the left arm every 3 min with an automatic sphygmomanometer (BP-203; Nihon Korin, Tokyo, Japan) during the ultrasound procedure. Vasodilatation responses of the brachial artery were determined via the ultrasound technique using a semiautomatic device (EF18G; UNEX, Nagoya, Ja-

pan). Briefly, the diameter of the brachial artery was measured from B-mode ultrasound images using a 10-MHz linear array transducer. Then, a blood pressure cuff was inflated to 50 mm Hg above the systolic blood pressure over the proximal portion of the right forearm for 5 min. The diastolic diameter of the brachial artery was determined semiautomatically using an instrument equipped with software for monitoring the brachial artery diameter. The changes in diastolic diameter were continuously recorded. Then, FMD was determined as the maximum change in diameter after cuff release normalized to the baseline diameter (% of baseline diameter). After a 15-min interval to obviate any effect of reactive hyperemia, NMD was assessed. Baseline measurements of brachial artery diameter and flow velocity were again obtained, and 0.3 mg of sublingual nitroglycerin was then administered. Three minutes later, the brachial artery diameter was recorded. NMD was defined as the percent change of the brachial artery diameter relative to the baseline diameter. These measurements were obtained using the EF18G device. Calculation of these values by the EF18G device in our laboratory showed that the intra- and interobserver variabilities (coefficient of variation) for repeated measures of diameter before and after reactive hyperemia in the brachial artery were <3% [10, 12].

Statistical Analysis

Data are expressed as means ± SD. Student's t test was used to compare data before and after each treatment. Pearson's product-moment correlation was performed between the changes in FMD and those in LDL-C in response to each treatment. Differences or statistical values were considered significant at $p < 0.05$. Analyses were conducted using SPSS version 11 (SPSS Inc., Chicago, Ill., USA).

Results

Patient Profile

The clinical characteristics of the study population are given in table 1. The patients had a relatively high risk for atherosclerosis in addition to hypercholesterolemia and SLCI. Twenty-one (>60%) patients had coronary artery disease, 11 (30%) patients were hypertensive, and 17 (50%) patients were diabetic. Five (15%) patients had peripheral artery disease. Clinical characteristics were comparable between the two groups. Age, prevalence of comorbidities and combination treatments were similar in the two groups. The mean patient age in each group was 72 years (elderly population). Seventeen (50%) patients had already been prescribed statins. However, their LDL-C levels were ≥100 mg/dl, which met the inclusion criteria, so these patients were enrolled into this study. The average FMD was 2.6% in both groups, and the average NMD was 8% in both groups. None of the patients had FMD ≥6%, which is the normal cutoff value in our laboratory (table 2; fig. 1).

Table 1. Clinical characteristics of the study population

	PC group (n = 17)	A group (n = 17)
Age, years	72±7	72±8
Male/female ratio	17/0	17/0
Complications, n (%)		
Hypertension	6 (35)	5 (29)
Coronary artery disease	11 (65)	10 (59)
Diabetes mellitus	8 (47)	9 (53)
Peripheral artery disease	3 (18)	2 (12)
Combination treatment, n (%)		
ACE-I or ARB	14 (82)	13 (76)
β-Blocker	11 (65)	11 (65)
Calcium channel blockers	10 (59)	10 (59)
Nitrates	5 (29)	3 (18)
Antiplatelet agents	14 (82)	13 (76)
Oral antidiabetic agents	8 (47)	9 (47)

ACE-I = Angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; antiplatelet agents = antiplatelet agents other than cilostazol.

Changes in FMD and NMD

The effects of each treatment on hemodynamics, FMD and NMD are summarized in table 2. In contrast to the A group, the PC group showed a significantly increased heart rate after treatment. The PC group experienced a significant increase in FMD after treatment (table 2; fig. 1, 2) whereas the A group did not, despite no significant changes in baseline brachial artery diameter and NMD in either group. Seventeen (88%) patients in the PC group, and only 6 (35%) patients in the A group, experienced an increase in FMD after treatment.

Changes in Blood Chemistries

With the notable exception of lipid profiles, no changes were detectable in most parameters of blood chemistries in either treatment group (table 3). Combined treatment with probucol and cilostazol (PC group) resulted in a significant decrease in LDL-C of 31% (from 134 to 92 mg/dl). Further, serum levels of total cholesterol decreased and HDL-C significantly decreased in the PC group. Changes in triglycerides were not statistically significant (table 3).

No significant relationship was found between the effect of combined treatment with probucol and cilostazol on FMD and that on LDL-C (delta FMD by treatment in the PC group vs. delta LDH-C by treatment in the PC group, r = –0.13, n = 17, n.s.).
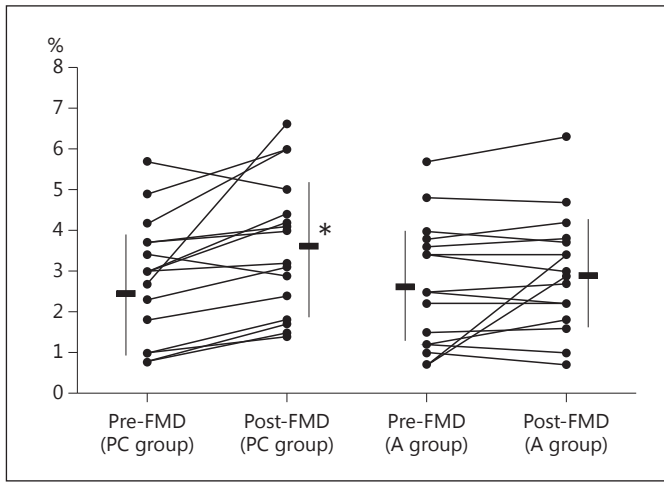
Fig. 1. Effect of each treatment on FMD. * p < 0.05 vs. Pre-FMD (PC group). Data are presented as means ± SD.
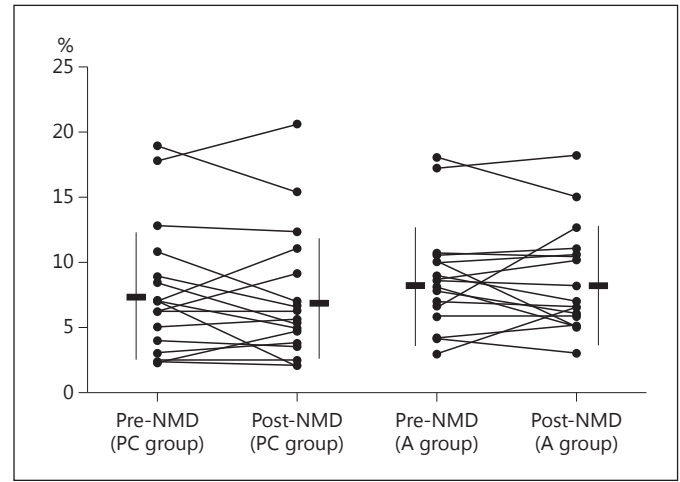
Fig. 2. Effect of each treatment on NMD. Data are presented as means ± SD.

Table 2. Summary of ultrasound measurements for FMD and NMD in the brachial artery and the effect of each treatment

	PC group (n = 17)		A group (n = 17)	
	pretreatment	posttreatment	pretreatment	posttreatment
Systolic BP, mm Hg	133±23	130±16	132±25	131±17
Diastolic BP, mm Hg	71±9	72±9	72±10	71±9
Heart rate, beats/min	60±11	66±11*	61±10	60±12
Brachial artery diameter at baseline, mm	4.67±0.56	4.78±0.40	4.52±0.57	4.52±0.61
FMD, %	2.69±1.51	3.53±1.69*	2.63±1.48	2.92±1.39
NMD, %	7.68±4.98	7.22±5.06	8.78±4.06	8.61±4.02

BP = Blood pressure. * p < 0.05 vs. pretreatment.

Table 3. Effect of each treatment on lipid profiles and blood chemistry

	PC group (n = 17)		A group (n = 17)	
	pretreatment	posttreatment	pretreatment	posttreatment
Total cholesterol, mg/dl	215±30	166±23*	217±31	202±34
LDL-C, mg/dl	134±27	92±21*	136±30	125±21
HDL-C, mg/dl	56±14	52±11*	55±16	58±15
Triglycerides, mg/dl	145±34	143±56	149±73	139±61
s-ALT, IU/l	27±8	33±16	26±9	26±10
s-AST, IU/l	35±36	34±19	36±42	32±18
BUN, mg/dl	15±3	16±3	15±4	15±4
Cr, mg/dl	0.83±0.11	0.83±0.10	0.97±0.13	0.88±0.33
FBS, mg/dl	130±42	126±44	136±50	120±48
CPK, IU/l	101±39	103±45	93±35	101±42

s-ALT = Serum alanine aminotransferase; s-AST = serum aspartate aminotransferase; BUN = blood urea nitrogen; Cr = serum creatinine; FBS = fasting blood sugar; CPK = creatine phosphokinase. * p < 0.05 vs. pretreatment.

Discussion

The present study demonstrated that combined therapy with probucol and cilostazol resulted in subacute improvement in endothelial function and a decrease in LDL-C. Four weeks of treatment with probucol and cilostazol significantly improved the FMD without changing the NMD, suggesting that this therapy resulted in an improvement in brachial artery endothelial function. Changes in FMD in response to probucol and cilostazol did not correlate with changes in LDL-C. Thus, the effect of probucol and cilostazol on endothelial function is likely independent of that on LDL-C levels.

This is the first report to show a favorable effect of combined therapy with probucol and cilostazol on brachial artery FMD in patients with SLCI, hypercholesterolemia and other atherosclerotic risk factors (table 1). Since previous reports have shown that brachial artery FMD correlates with coronary endothelial function [10, 13] and that improvements in FMD play an important role in preventing the progression of atherosclerosis and the destabilization of atherosclerotic plaque [9, 14], the therapeutic effect of a 4-week course of combined therapy with probucol and cilostazol is relevant to daily clinical practice. Endothelial dysfunction combined with plaque destabilization is a risk factor for cardiovascular events, such as acute coronary syndrome. The relatively quick action of combined therapy with probucol and cilostazol is another beneficial feature of this regimen.

Since the risk of developing overt stroke, dementia, depression and aspiration pneumonia is closely associated with SLCI [15], ameliorating the atherosclerotic burden in patients with multiple atherosclerotic risk factors is a clinically important goal. In this study population, more than 60% of patients suffered from coronary artery disease, 50% had diabetes and approximately 20% had peripheral artery disease. Since SLCI complicated with hypercholesterolemia has been reported to be associated with poor cardiovascular outcomes, and the impaired endothelial function reflected by decreased FMD values correlates with this increased risk, the salutary effect of probucol and cilostazol combined therapy on FMD can be considered to provide useful information to clinicians who treat SLCI patients with hypercholesterolemia. With the general aging of the population and the more widespread use of MRI, the prevalence of a diagnosis of SLCI is likely to increase.

Because of the prognostic role of SLCI [16] and the fact that endothelial function is a common pathway connecting atherosclerotic risk factors with the progression of atheromatous plaques and lesions, the effective treatment for endothelial function as shown in this study, that is combination therapy of probucol and cilostazol, is expected to improve the untoward outcome in patients with lacunar infarction. Lacunar infarction has been reported to be mainly caused by occlusion of a single penetrating artery, and pathophysiological studies revealed that this occlusion is brought about by either microatheromatosis or lipohyalinosis. In general, lacunar infarction shows a favorable prognosis in the short term, whereas it increases the risk of death, stroke recurrence and dementia in the mid and long term.

Since statin treatment has already been reported to improve endothelial function, combined therapy of probucol and cilostazol could be a potential alternative treatment to statins in patients with lacunar infarction. The role of statin treatment for either primary or secondary prevention of ischemic cardiovascular events including ischemic stroke has been widely accepted [17]. In addition, pretreatment with statins improves the early outcome in patients with first-ever ischemic stroke [18], and a recent meta-analysis on statin treatment and functional outcome after ischemic stroke [19] showed that statin therapy is associated with improved early and late outcomes in stroke [20, 21].

The efficacy of probucol or cilostazol in endothelial function is consistent with that described in previous reports [22, 23]. In many reports on experimental materials [30] and clinical populations [4], probucol or cilostazol improved endothelial function through decreases in oxidant stress [24] or upregulated endothelial nitric oxide synthase (eNOS) activity [25], respectively. In addition, previous reports have demonstrated that combined therapy with probucol and cilostazol reduced restenosis after percutaneous coronary intervention more effectively than either cilostazol or probucol alone. In addition, recent reports demonstrated the potential synergistic effects of cilostazol and probucol when they were used in combination for the prevention of atherosclerosis [27, 28]. In one recent study [27], the combined administration of cilostazol and probucol resulted in a greater decrease in the atherosclerotic lesion than when either drug was administered separately in LDL receptor-deficient mice.

It might be important to measure the plasma level of apolipoprotein-E when the effect of probucol on atherosclerotic lesions in patients with hyperlipidemia is studied, especially if type III hyperlipidemia is suspected in the study population. The reason apolipoprotein-E measurement is necessary is that probucol has been reported

to have a strong proatherogenic effect in apolipoprotein-E-deficient mice despite a reduction in the total plasma cholesterol levels [29], even though the results are still conflicting. Apolipoprotein combines with lipids to form lipoprotein particles. Thus, apolipoproteins are carrier proteins, and several classes of lipoproteins exist. Among these different lipoproteins, apolipoprotein-E is important when the antiatherosclerotic effect of probucol is studied, as shown above. Three different isoforms of apolipoprotein-E have been reported. These isoforms include apo-E2, apo-E3 and apo-E4. Especially apo-E2 is connected with type III hyperlipidemia where the blood levels of both LDL-C and triglyceride increase. In the present study, the plasma level of apo-E was not measured because none of the patients in this study showed the feature of type III hyperlipidemia, as shown in table 3. In this study population, LDL-C was abnormally high whereas the levels of triglycerides were not robustly high enough for type III hyperlipidemia to be diagnosed.

This study has several limitations. First, the number of patients was small, and all patients were men. In addition, the study was conducted in only two medical centers, including one academic medical school hospital. Thus, this study should be duplicated with a randomized, multicenter clinical trial design. Second, the mechanisms of the effect of the combined therapy of probucol and cilostazol were not investigated in the present study. However, as mentioned above, many previous experimental and clinical studies [26] have suggested possible mechanisms for the therapeutic benefit of these drugs. Third, the combined therapeutic effect of probucol and cilostazol on cognitive impairment was not evaluated in the present study. In addition, the effect of this therapy on the relationship between endothelial function and mild cognitive impairment was not evaluated. Since the pathological and morphological features on MRI subcortical hyperintensities have been reported to correlate with mild cognitive impairment of the vascular type in patients with lacunar infarction [30], the improvement of endothelial function with this therapy could possibly prevent the progression of subcortical hyperintensities and could subsequently preclude the cognitive aggravation in patients with lacunar infarction. Also, neuopsychological evaluations were not carried out in this study. These parameters should be investigated in future studies. Lastly, only the subacute effect of combined therapy with probucol and cilostazol was investigated. Therefore, the long-term effect of this regimen would benefit from further study. Indeed, the SECURE trials have already been started [4], and additional information regarding combined therapy with probucol and cilostazol should be available in the near future.

Conclusion

Combined therapy with probucol and cilostazol resulted in improved endothelial function in patients with SLCI, hypercholesterolemia and many other atherosclerotic risk factors. These results suggest that combined therapy with probucol and cilostazol might be a powerful antiatherosclerotic regimen and may improve long-term outcomes. Large-scale, randomized clinical trials are needed to confirm this conclusion.

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