Effect of *Ginkgo biloba* Extract on Visual Field Progression in Normal Tension Glaucoma

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Purpose: To evaluate the long-term effect of *Ginkgo biloba* extract (GBE) on progression of visual field (VF) defects in patients with normal tension glaucoma (NTG).

Methods: Forty-two eyes of 42 patients with treated NTG who received 80 mg GBE 2 times daily and who had at least 5 VF tests using the Humphrey Visual Field Analyzer for more than a 4-year period before and after GBE treatment were evaluated in this retrospective study. We evaluated the change of progression rate using mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI) after GBE treatment. The time course of mean total deviation in 10 zones corresponding to the glaucoma hemifield test was analyzed using a linear mixed effects model with unequal random effect variances.

Results: The mean follow-up period was 12.3 years. The post-therapeutic intraocular pressures before and after GBE treatment were not significantly different ($P = 0.509$ paired t test). Before GBE treatment, the regression coefficients (RCs) of MD, PSD, and VFI change were -0.619 dB/y, 0.626 dB/y, and -2.153%/y, respectively. After GBE treatment, the RCs of MD, PSD, and VFI change improved significantly to -0.379 dB/y, 0.342 dB/y, and -1.212%/y ($P < 0.001$), respectively. In zone 1, the RC of mean total deviation change was significantly increased after GBE administration ($P < 0.005$).

Conclusions: GBE administration slowed the progression of VF damage in patients with NTG, especially in zone 1 corresponding to the superior central field.

Key Words: normal tension glaucoma, *Ginkgo biloba* extract, change of progression rate, complementary therapy

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Glaucoma is defined as a progressive optic neuropathy characterized by specific patterns of optic nerve damage and visual field (VF) defect. Although the exact mechanisms of glaucoma are unknown, ophthalmologists have agreed on the 2 theories: a mechanical theory that increased intraocular pressure (IOP) causes stretching of the lamina cribrosa and damage to retinal ganglion cell axons, and a vascular theory positing damage caused by insufficient vascular supply, such as reduced blood flow to the optic nerve.[1,2] Normal tension glaucoma (NTG) is a type of chronic open angle glaucoma in which measurements of untreated and treated IOP remain within the normal range. For the pathogenesis of the NTG, a number of investigators have given weight to vascular theory more than mechanical theory, although they concur that IOP reduction is a beneficial treatment for NTG.[3] Many patients actually continue glaucoma progression despite IOP reduction.[4,5] Furthermore, in a previous randomized clinical trial, IOP was not significantly associated with progression in untreated eyes.[6] The fact that a reduction of ocular blood flow often precedes optic nerve damage[7] and that risk factors for NTG are low blood pressure, orthostatic hypotension, nocturnal hypotension, migraine, Raynaud phenomenon, and sleep apnea support an important role for hemodynamic alterations in NTG.[8–12]

Because leaf extracts of the *Ginkgo biloba* tree (GBE) were first introduced 5000 years ago for medicinal purposes in ancient China,[13] they have been used in alternative treatments for several vascular diseases. GBE treatment effects have been reported in cognitive impairment, cerebrovascular insufficiency, tinnitus, hypoxia, vestibular disorders, and aging.[14–18] Furthermore GBE has been reported to be neuroprotective for retinal ganglion cells in a rat model of chronic glaucoma.[19] In clinical studies, GBE increased ocular blood flow and ameliorated VF damage.[20–22]

Despite the favorable effects of GBE, there are a few clinical reports examining the use of GBE to treat glaucoma. We evaluated the long-term effects of GBE administration on VF progression in NTG patients.

METHODS

Patients

The records of all patients who were diagnosed with NTG at our glaucoma clinic at Samsung Medical Center from January 1, 1996 to January 1, 2011, and who received 80 mg GBE (Ginexin; SK Pharma, Korea) 2 times daily were reviewed for entry into this retrospective study. Patient information was extracted from medical records of our clinic, which included demographic information, ocular measurements, and systemic diseases. For the purpose of this study, patients who had at least 5 VF tests for more than 4-year period before and after GBE treatment were recruited. In cases of bilateral NTG, the included eye was randomly enrolled.

The diagnostic method, IOP measurement, and routine treatment policy in our clinic were the following: The diagnosis of NTG required typical glaucomatous optic disc cupping and glaucomatous VF defects in eyes with an IOP of ≤ 21 mm Hg without treatment, open iridocorneal angles by gonioscopy, and the absence of any contributing ocular or specific systemic disorders. IOP was measured using a

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Goldmann applanation tonometer by a single glaucoma specialist, and the mean of 3 measurements was recorded for each eye. Baseline IOP was measured in the morning (09:00 AM to 12:00 PM) on one examination day and in the afternoon (01:00 to 05:00 PM) on another day with less than a 1-month interval between measurements, both after a 4-week washout period. After NTG diagnosis, patients were treated twice daily with betaxolol 5 mg/mL (Betoptic; Alcon Inc., Fort Worth, TX). During the follow-up, if IOP did not reach the target value, which is a 20% reduction in initial IOP, betaxolol was replaced by once a day latanoprost 50 μm/mL (Xalatan; Pfizer Inc., New York, NY). If latanoprost failed to achieve the desired effect, twice daily brimonidine 2 mg/mL (Alphagan P; Allergen Inc., Irvine, CA) was added. Patients did not receive systemic Ca^{2+} antagonists. The posttherapeutic IOP was calculated as the mean IOP at each hospital visit after the administration of a topical antiglaucoma agent.

Exclusion criteria included the following: (1) visual acuity of 20/40 or less, (2) lens opacities more severe than C2, N2, P2 according to lens opacities classification system III criteria,[23] (3) abnormal optic disc appearance such as high myopia and tilted disc that could affect VF test results, (4) previous ocular and systemic disorder that could affect optic disc appearance and VF test, and (5) history of cataract surgery during the follow-up period.

The methods applied in this study adhered to the tenets of the Declaration of Helsinki for the use of human subjects in biomedical research and it was approved by Institutional Review Board of Samsung Medical Center, Seoul, Korea.

VF Testing

VFs of NTG patients were performed with the 30-2 program of the Humphrey Visual Field analyzer (Model 750I; Humphrey Instruments Inc., San Leandro, CA) and were regarded as abnormal if 2 criteria were met on at least 2 consecutive VF examinations with acceptable reliability standards: (1) an abnormal glaucoma hemifield test (GHT) result (borderline findings were not regarded as abnormal), (2) at least 3 contiguous nonedge points (allowing 2 nasal step-edge points) by Humphrey 30-2 standard automated perimetry with $P < 0.5$ on the pattern SD plot and at least 1 point with $P < 0.01$. The location and pattern of the defect had to be consistent between the 2 consecutive VF examinations, and the glaucomatous optic disc damage had to be consistent with the VF abnormality.[24]

VF tests were routinely performed at diagnosis and 3 months later, and every 6 or 12 months thereafter. A reliable VF had to have a fixation loss of $<20\%$ and a false-positive and false-negative rate of $\leq 15\%$. VFs with mean deviations (MD) of ≤ -20 dB at baseline VF test were excluded because the progression of glaucoma would be difficult to evaluate in such eyes.

Progression Analysis and Statistics

To evaluate the change of progression rate using MD, pattern standard deviation (PSD), and visual field index (VFI) after GBE administration, we used a linear mixed effects model with unequal random effect variances, which estimates the regression coefficient (RC).[25] Covariates including age at diagnosis, baseline IOP, posttherapeutic IOP, and baseline MD, PSD, or VFI were used. The average values from 2 baseline fields were taken for baseline MD, PSD, and VFI. The posttherapeutic IOP was applied with division into 2 parts, before and after GBE treatment. The same analyses were performed using the mean of total deviations (mTD), which indicates deviation from the age-corrected normal reference threshold and is included in the STATpac software package of the Humphrey Visual Field Analyzer. The RCs of the time course of mTD were detected for 10 separate subfields, which were 10 zones corresponding to the GHT (Fig. 1).[26]

All statistical analyses were performed using SAS (version 9.1; SAS Institute Inc., Cary, NC). The $P \leq 0.025$ for the RC of MD, PSD, and VFI time course, and $P \leq 0.005$ for the RC of mTD in 10 zones were considered to be statistically significant.

RESULTS

Forty-two eyes of 42 patients who fulfilled the inclusion criteria were evaluated. Among 42 eyes, 20 eyes (47.6%) were treated with betaxolol alone. In 14 eyes (33.3%), betaxolol was replaced by latanoprost before GBE administration. Regardless of GBE administration, 8 eyes (19.0%) were treated with 1 or 2 drugs among betaxolol, latanoprost, and brimonidine throughout the follow-up period. Patient demographics and VF features are shown in Table 1. The follow-up periods before and after GBE administration were 75.0 ± 25.7 and 72.1 ± 16.4 months, totaling 148.1 ± 32.6 months. The average age at diagnosis was 47.1 ± 11.1 years. Four patients with diabetes mellitus and 4 patients with hypertension were included, and all subjects had a no other systemic diseases except diabetes mellitus and hypertension. Baseline IOP was 16.1 ± 2.3 mm Hg. The posttherapeutic IOPs before and after GBE administration were 14.4 ± 1.6 and 14.3 ± 1.3 mm Hg, and were not significantly different ($P = 0.509$ paired t test). Baseline MD, PSD, and VFI were -5.2 ± 3.4, 7.52 ± 4.1, and 84.7 ± 16.8 dB, respectively. The RCs of MD, PSD, and VFI changes using the linear mixed effects model with unequal random effect variances -0.619 ± 0.050 dB/y, 0.626 ± 0.056 dB/y, and $-2.153 \pm 0.142\%$/y before GBE administration, respectively. After GBE administration, the RCs of MD, PSD, and VFI change improved significantly to -0.379 ± 0.051 dB/y, 0.342 ± 0.053 dB/y, and $-1.212 \pm 0.166\%$/y ($P = 0.0008$, 0.0003, and <0.0001), although both values of MD and VFI were significantly negative and those of PSD were still positive (Table 2). The results of 10 zones corresponding to the GHT

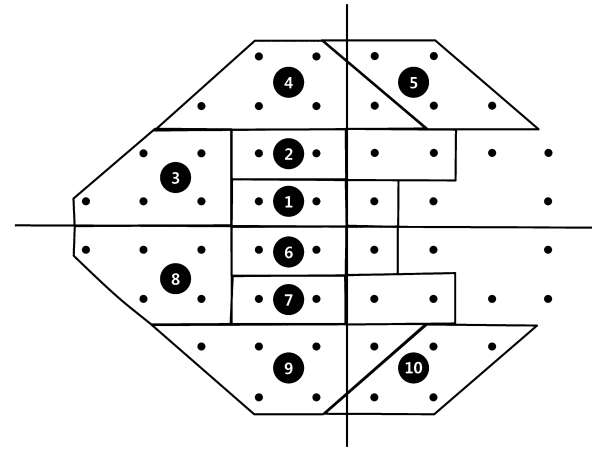

FIGURE 1. The 10 zones used in the glaucoma hemifield test.

TABLE 1. Demographics and Ocular Measurements

Variables	Value
Age (y)	47.1 ± 11.1
Sex	19 males, 23 females
Systemic disease	
Hypertension, n (%)	4 (9.5%)
Diabetes mellitus, n (%)	4 (9.5%)
Refraction (D)	−2.2 ± 3.6
IOP (mm Hg)	
Baseline IOP	16.1 ± 2.3
Posttherapeutic IOP before GBE treatment	14.4 ± 1.6
Posttherapeutic IOP after GBE treatment	14.3 ± 1.3
Visual field indices	
Baseline MD (dB)	−5.2 ± 3.4
Baseline PSD (dB)	7.52 ± 4.1
Baseline VFI (%)	84.7 ± 16.8

Data are presented as number and mean ± SD.
GBE indicates *Ginkgo biloba* extract; IOP, intraocular pressure; MD, mean deviation; n, number of eyes; PSD, pattern standard deviation; VFI, visual field index.

are summarized in Figure 2. In zone 1, the RC of time course of mTD was increased from −0.897 ± 0.105 to −0.176 ± 0.192 dB/y after GBE administration ($P = 0.0024$).

No ocular or systemic side effects were described in any patients during follow-up in this retrospective study cohort.

DISCUSSION

GBE contains more than 60 known bioactive compounds.[27] A number of explanations for its mechanism of action have been offered. First, GBE may increase blood flow by changes in blood viscosity and potent inhibition of platelet-activating factor, which causes platelet aggregation, neutrophil degranulation, and oxygen radical production, and may potentiate glutamate excitotoxicity in brain injury.[28–31] Second, GBE may play an antagonistic role in oxidative stress. It has been reported to prevent glutamate neurotoxicity in a murine model[32] and protect against lipid peroxidation in various tissue and experimental systems.[32–34] It can also scavenge free radicals.[34–36] Experimental studies indicate that GBE has neuroprotective properties in conditions such as hypoxia, seizure, cerebral edema, and peripheral nerve damage.[37] Furthermore, effects have been reported in peripheral arterial occlusive disease, protecting the myocardium against hypoxia and ischemia reperfusion injury, and for functional improvement in dementia patients.[38–40] GBE has been examined for ocular effects. In normal eyes, GBE increased blood flow in the ophthalmic artery, but did not have an effect on blood pressure, heart rate, or IOP.[20] An intravitreal injection of GBE blunted the development of induced vitreoretinal proliferation, possibly through free radical scavenging in a rabbit eye model.[41] GBE has also been reported to be neuroprotective for retinal ganglion cells in a rat model of chronic glaucoma and was reported to inhibit the apoptosis of retinal ganglion cells in animals after optic nerve injury.[19,42,43]

The results of this study, in which the RCs of VF improved after GBE administration, demonstrate that GBE administration can slow the progression of VF in patients with NTG. The precise explanation of this favorable effect is not clear. Theoretically, GBE should be beneficial for treating glaucoma, because it may have favorable effects on abnormalities of ocular blood flow and risk factors such as orthostatic hypotension, migraine, and Raynaud phenomenon in patients with glaucoma. In addition, the neuroprotective effect of GBE, demonstrated in several animal studies, may be helpful in patients who continue to show progression despite low IOP. We hypothesize that these mechanisms affected our results.

To investigate the change of progression rate after GBE treatment, we evaluated the RCs of MD, PSD, and VFI, using the linear mixed effects model with unequal random effect variances. This linear mixed effects model compares the average RCs as fixed effects after controlling for interindividual variability as random effects.[25,44] The RCs of MD and PSD significantly improved ($P = 0.0008$ and 0.0003) after GBE administration. Although MD and PSD are widely used measures to quantify the severity of VF and we excluded eyes with clinically significant media opacity, we also evaluated VFI that was independent of cataracts and other causes of generalized depression of visual function in addition to glaucoma.[45] For VFIs that more accurately reflect the relative importance of the central and more peripheral VFs to patient visual function,[45] the RC of that change also significantly increased after GBE treatment ($P < 0.0001$). Previously, Quaranta et al[22] reported that VF improved in patients with NTG 4 weeks after GBE administration. In contrast, our RCs of VF remained negative after GBE treatment. We suggest that the explanation for this disagreement is the difference in follow-up period. In our study, patients were followed up for at least 4 years after GBE administration. In the present study, it is reasonable to assume that GBE administration has value as an effective complementary therapy for glaucoma, but does not stop VF progression.

Because glaucomatous VF loss tends to occur in local zones and at different rates in the upper and lower hemifields, cluster analysis such as that used in GHT has been suggested.[26,46] In accordance with this suggestion, the same analyses were performed on mTD in 10 zones corresponding to the GHT and the RCs of mTD change were significantly improved in zone 1 ($P = 0.0024$). Multiple studies have reported that VF defects in NTG occurred closer to fixation

TABLE 2. Regression Coefficients for the Linear Mixed Effect Model With Unequal Random Effect Variances Regarding Changes in MD, PSD, and VFI

Visual Field	Before GBE Administration	After GBE Administration	*P**
MD	−0.619 ± 0.050	−0.379 ± 0.051	0.0008
PSD	0.626 ± 0.056	0.342 ± 0.053	0.0003
VFI	−2.153 ± 0.142	−1.212 ± 0.166	< 0.0001

All data presented are mean ± 2 SD.
**P* value for the differences between regression coefficients before and after GBE treatment.
GBE indicates *Ginkgo biloba* extract; MD, mean deviation; PSD, pattern standard deviation; VFI, visual field index.

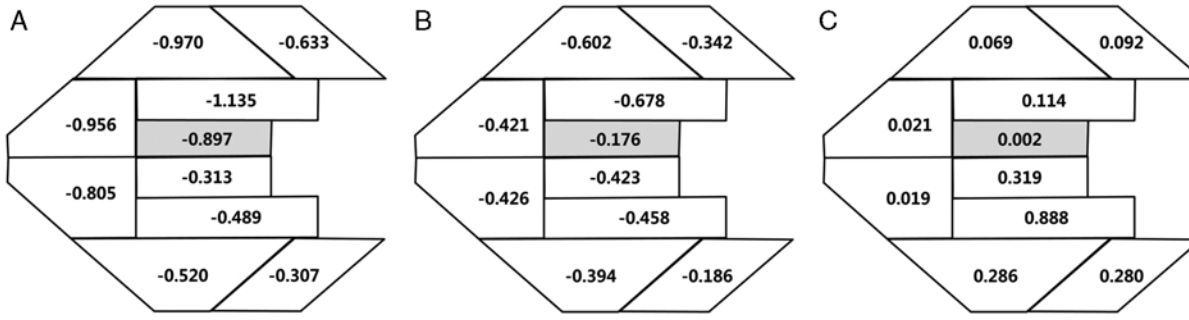

FIGURE 2. The regression coefficients of 10 zones before (A) and after (B) *Ginkgo biloba* extract treatment. *P* value (C) is evaluated using a linear mixed effects model with unequal random effect variances, in which covariates were age at diagnosis, baseline intraocular pressure (IOP), posttherapeutic (IOP), and baseline mean of total deviations. Data are presented as means (dB/y).

and more often just above the horizontal meridian.[47–51] Ahrlich et al[52] and Membrey et al[53] found that NTG eyes progressed more often in central VF. Considering that NTG eyes have more VF defects in the superior hemifield and that eyes with superior defects in baseline VF comprised 33 of 42 eyes in this study,[49,54–56] the improvement of zone 1 corresponding to a superior central field may support the beneficial effects of GBE for glaucoma treatment.

Among the patients in this study, no one has ocular or systemic adverse events related to the use of GBE. This result seems to be in agreement with those of a previous placebo-controlled, double-blind, randomized clinical trial.[40]

The main strength of this study is that it included a cohort of patients who received long-term follow-up after GBE administration. Furthermore, we compared VF progression in the same patients with NTG before and after GBE administration. To our knowledge, the present study is unique in these respects. The possible limitations of this study are biases because of its retrospective nature and small sample size. We included only eyes that had undergone at least 5 VF tests and more than 4-year follow-up before and after GBE administration and excluded advanced glaucomatous damage in baseline VF test for the benefit of reliability on VF and statistical evaluation. Moreover, because the study was conducted in a tertiary medical care institution, rather than in new patients, many patients had been referred from primary and secondary medical institutions with continuous progression, despite having been treated. This might have affected the accuracy of statistical evaluation and limited our ability to extrapolate the conclusions.

In conclusion, GBE administration decelerated progression of VF damage in patients with NTG. In particular, there appeared to be an effect in zone 1 corresponding to the superior central field, which is the main location of VF defect in NTG eyes. Therefore, GBE seems to be a favorable complementary treatment for glaucoma.

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