

Effect of Ginkgo Biloba on Visual Field and Contrast Sensitivity in Chinese Patients With Normal Tension Glaucoma: A Randomized, Crossover Clinical Trial

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PURPOSE. We evaluated the effect of ginkgo biloba extract on visual field defect and contrast sensitivity in a Chinese cohort with normal tension glaucoma.

METHODS. In this prospective, randomized, placebo-controlled crossover study, patients newly diagnosed with normal tension glaucoma, either in a tertiary glaucoma clinic ($n = 5$) or in a cohort undergoing routine general physical examinations in a primary care clinic ($n = 30$), underwent two 4-week phases of treatment, separated by a washout period of 8 weeks. Randomization determined whether ginkgo biloba extract (40 mg, 3 times per day) or placebo (identical-appearing tablets) was received first. Primary outcomes were change in contrast sensitivity and mean deviation on 24-2 SITA standard visual field testing, while secondary outcomes included IOP and self-reported adverse events.

RESULTS. A total of 35 patients with mean age 63.7 (6.5) years were randomized to the ginkgo biloba extract-placebo ($n = 18$) or the placebo-ginkgo biloba extract ($n = 17$) sequence. A total of 28 patients (80.0%, 14 in each group) who completed testing did not differ at baseline in age, sex, visual field mean deviation, contrast sensitivity, IOP, or blood pressure. Changes in visual field and contrast sensitivity did not differ by treatment received or sequence ($P > 0.2$ for all). Power to have detected a difference in mean defect as large as previously reported was 80%.

CONCLUSIONS. In contrast to some previous reports, ginkgo biloba extract treatment had no effect on mean defect or contrast sensitivity in this group of normal tension glaucoma patients. (<http://www.chictr.org> number, ChiCTR-TRC-08000724)

Keywords: Ginkgo biloba, normal tension glaucoma, visual field, contrast sensitivity

Glaucoma is the second-leading cause of blindness in the world,¹ accounting for an estimated 11.2 million bilaterally blind persons by the year 2020.² Despite its high prevalence and the irreversible nature of the blindness it causes, glaucoma frequently remains undiagnosed and untreated in developing countries. While studies have shown glaucoma may be responsible for approximately 10% of blindness in Asia,^{3,4} only 10% of patients had been diagnosed and treated in a recent Indian study.^{5,6}

Extracts of Ginkgo biloba leaves have been suggested for many years to treat various conditions, including dementia,⁷ tinnitus,⁸ age-related macular degeneration,⁹ and circulatory problems.¹⁰ Recently, Ginkgo biloba has been studied for its potential neuroprotective and antioxidative effects,¹¹ possibly of benefit in the management of neurologic and vascular conditions, such as acute ischemic stroke,¹² Alzheimer's disease,¹³ and glaucoma.^{11,14,15}

Conflicting evidence for the effectiveness of Ginkgo biloba in the treatment of glaucoma has been reported in a number of recent trials.¹⁵⁻¹⁷ In a randomized, crossover trial, Quaranta et al.¹⁸ reported significant visual field improvement in patients with normal tension glaucoma (NTG) after oral

Ginkgo biloba administration for one month.¹⁸ A retrospective, noncontrolled study by Lee et al.¹⁹ suggested that Ginkgo biloba slowed visual field progression in NTG patients. On the other hand, population-based data from Khoury et al.²⁰ showed no effect of ginkgo on glaucoma. Though evidence for their efficacy is mixed, the widespread use of ginkgo and other complementary therapies for glaucoma²¹ underscores their importance and the need for more work in this area.

Many of the studies reporting an effect of ginkgo in treating glaucoma have focused on patients with NTG. Population-based studies in China have shown that >85% of patients with open angle glaucoma have IOP < 21 mm Hg at the time of screening, and that the 24-hour peak IOP is also <21 mm Hg in 83% of subjects.²²⁻²⁴ Given its ready availability, low cost, and good safety profile, Ginkgo biloba would be attractive as primary or adjunctive therapy in a Chinese setting, particularly in view of the paucity of available medications with neuroprotective potential.²⁵

We report now on the first randomized clinical trial of Ginkgo biloba on NTG in China of which we are aware,

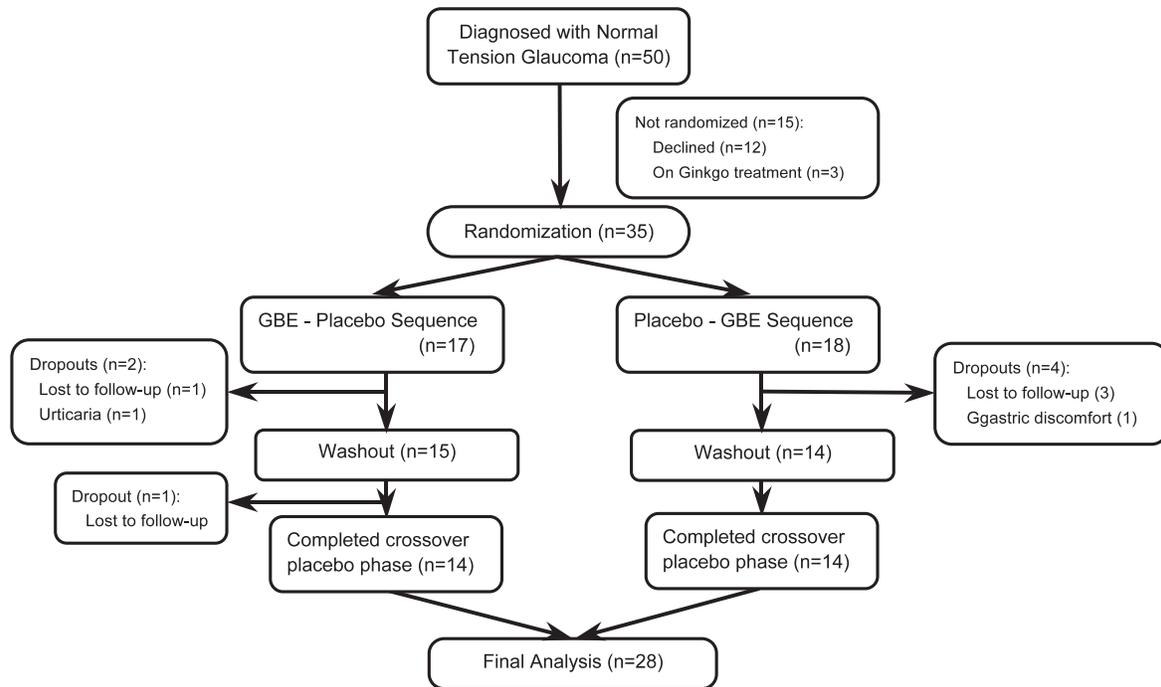


FIGURE 1. Flowchart detailing enrollment and follow-up of subjects in the study.

designed to assess impact on preexisting visual field defects and contrast sensitivity.

METHODS

Patients

From June 2010 to December 2011, a total of 50 consecutive patients with newly-diagnosed NTG were identified (Fig. 1) among potential subjects referred from a tertiary-care glaucoma clinic at the Zhongshan Ophthalmic Center ($n = 10$) and a cohort presenting for routine general physical examinations at a clinic in Lingtou, southern China ($n = 40$). Eligibility criteria included: age ≥ 30 years, visual field damage in at least one eye per Collaborative Initial Glaucoma Treatment Study criteria,²⁶ with consistent optic nerve changes in the opinion of a fellowship-trained glaucoma specialist (NC) based on slit-lamp biomicroscopy with a 90 diopter (D) lens through a pharmacologically-dilated pupil, maximum IOP ≤ 20 mm Hg in both eyes based on Goldmann applanation tonometry readings made every 2 hours from 8 AM to 4 PM during a single visit, open iridocorneal angles on 4-mirror gonioscopy as performed by a glaucoma specialist (NGC), and no clinical evidence of systemic neurologic disease or any ocular conditions that might explain the visual field defect. Exclusion criteria included: prior use of Ginkgo biloba extract (GBE), central corneal thickness < 500 μm in either eye, best corrected visual acuity $< 6/60$ in either eye, a history of IOP > 21 mm Hg in the patient record, inability to perform reliable visual field testing in both eyes, and inability to give informed consent to participate in the study. Among the initial series of 50 patients, 3 already were receiving Ginkgo biloba and 12 declined to participate. The remaining 35 were recruited and underwent randomization (see below).

Written informed consent was obtained from all subjects. The protocol of the study was approved in full by the Institutional Review Board of the Zhongshan Ophthalmic

Center, Guangzhou, China, and the tenets of the Declaration of Helsinki for the treatment of human subjects in biomedical research were followed throughout.

Randomization

After the diagnosis of NTG, a target IOP, calculated as a 30% reduction from baseline IOP (mean of 5 measurements on a single day as described above), was established and the patient initiated therapy with topical hypotensive agents as directed by the glaucoma specialist.

Patients were randomized to one of two treatment sequences as determined by a computer-generated random number in an envelope opened by an independent investigator: 4 weeks of oral GBE administration followed by a washout period of 8 weeks, then 4 weeks of placebo (Group A, GBE \rightarrow washout \rightarrow placebo); or 4 weeks of oral placebo followed by a washout period of 8 weeks, then 4 weeks of GBE (Group B, placebo \rightarrow washout \rightarrow GBE). Treatment consisted of GBE tablets (40 mg, Ginaton; Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany) or identical capsules prepared for the study, and filled with 40 mg fructose and starch, each administered three times daily. Patients were asked to swallow the capsules whole and to report any discomfort at the time of each visit. Patients and investigators were masked to the treatment.

Clinical Assessments

Each patient underwent 4 study visits in a clinical research setting at the Zhongshan Ophthalmic Center, scheduled at baseline (the day of enrollment), 4 weeks (completion of the first treatment phase), 12 weeks (completion of 8 weeks of washout), and 16 weeks (completion of the second treatment phase). At the baseline visit, demographic information, and medical and family history were recorded. Additionally, the following testing was carried out on each visit.

TABLE 1. Baseline Demographic and Clinical Characteristics of the Study Groups

Characteristics	Total	GBE → Placebo Sequence	Placebo → GBE Sequence
<i>N</i> patients	28	14	14
Age, y	63.7 (6.5)	62.3 (5.5)	65.1 (7.2)
Sex, <i>N</i> male/female	16/12	7/7	9/5
CCT, μm	530.3 (34.2)	532.7 (37.4)	528.2 (32.2)
Visual field MD, median dB (IQR)*	-5.85 (-9.73/-2.45)	-6.16 (-10.6/-2.90)	-3.77 (-9.02/-2.16)
Contrast sensitivity, logMAR			
1.5 cpd	1.60 (0.17)	1.59 (0.14)	1.61 (0.20)
3 cpd, median (IQR)*	1.68 (1.53/1.83)	1.68 (1.53/1.83)	1.68 (1.53/1.83)
6 cpd	1.53 (0.23)	1.49 (0.27)	1.57 (0.19)
12 cpd	1.19 (0.21)	1.24 (0.28)	1.15 (0.13)
18 cpd, median (IQR)*	0.75 (0.60/0.84)	0.78 (0.60/0.90)	0.69 (0.60/0.78)
IOP, mm Hg	15.7 (1.9)	15.7 (2.2)	15.8 (1.6)
Systolic blood pressure, mm Hg	129.5 (14.2)	129.7 (16.9)	129.3 (11.3)
Diastolic blood pressure, mm Hg	74.1 (12.1)	77.2 (11.0)	70.8 (12.9)
Heart rate, bpm	70.9 (8.4)	72.6 (8.3)	69.1 (8.6)

Data are expressed as mean (SD) unless otherwise noted. cpd, cycle per degree.

* Median (IQR) is given due to nonnormal distribution of the difference between the two groups.

Central corneal thickness (CCT) was measured in each eye (Lenstar LS 900; Haag-Streit USA, Mason, OH, USA) at baseline. Visual acuity (VA) and refraction were performed at baseline and the last visit. The VA was tested separately for each eye at 4 m using a retroilluminated logarithm of the minimum angle of resolution (logMAR) chart with tumbling-E optotypes (Precision Vision, La Salle, IL, USA). Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were recorded as the smallest line in which the correct orientation of at least four of the five letters could be identified. Refraction was performed using a desktop autorefractor (KR8800; Topcon Corp., Tokyo, Japan), with refinement by an optometrist.

The IOP was measured by Goldmann applanation tonometry every two hours from 8 AM to 4 PM, and the mean was calculated. Heart rate and systolic and diastolic blood pressure were measured in a seated position on the right arm using an automated digital sphygmomanometer (blood pressure monitor HEM-907; Omron, Kyoto, Japan).

Visual field (VF) testing (Humphrey Visual Field Analyzer II Model 750; Humphrey Instruments, San Leandro, CA, USA) used the 24-2 Swedish Interactive Testing Algorithm (SITA) Standard program. All testing was performed on the same perimeter, with best correction for near vision provided for each patient. The VFs were regarded as reliable only when false responses and fixation losses were $\leq 33\%$.²⁷ To avoid learning effects in these newly-diagnosed patients, three reliable tests in each eye were required at baseline, and subsequently at least two tests were performed in each eye at each of the remaining 3 visits. At the baseline assessment, the first 2 VF tests were performed with an intervening 10-minute rest period, and a third VF test was carried out at least 4 hours later during the same day, or at another appointment within one week. The VF tests were spread between other evaluations during the follow-up visits, with a 10-minute break before each test. The final test at baseline for each eye and the best test for each eye at follow-up (defined as having the highest, or least negative, mean deviation value) were used for all analyses.

Contrast sensitivity (CS; distance Functional Acuity Contrast Test chart [FACT chart]; Vision Sciences Research Corporation, Lafayette, CA, USA) was tested before and after each treatment phase at a distance of 3 m under normal office illumination (luminance of 85 cd/m²). The FACT chart consists of 45 sine wave gratings arranged in five rows and nine columns, each

oriented vertically or diagonally to the right or left. The contrast step between each grating patch is 0.15 log units, indicating a 50% loss or 100% gain in contrast for any two-step change. Subjects were shown the various rows in a random sequence, and were tested three times in each eye. A final contrast sensitivity score was determined by the faintest contrast patch for which the patient was able to identify the orientation correctly two out of three times.

Ocular examinations were performed at every visit with fundus evaluation by the glaucoma specialist, and any ocular complications or patient-reported side effects with the study medication were recorded.

Statistical Methods

For patients with two eyes meeting study criteria, the right eye data were analyzed, and data from the affected eye were used for patients having only one affected eye. The principal study outcomes were change in mean deviation (MD) on VF testing and CS score before and after treatment. Secondary outcomes were IOP and self-reported adverse events. The study was designed to enroll 28 participants (14 in each group), resulting in 80% power at $\alpha = 0.05$ to detect a treatment effect on MD of 1.60 dB, as reported previously by Quaranta et al.¹⁸ with SD of 1.50 dB between sequences compared with placebo. This latter value was calculated²⁸ from raw data provided by Quaranta et al.¹⁸ based on their paper.

Results were presented as mean (SD) for data with normal distribution and median interquartile range (IQR) for data with nonnormal distribution. Demographic data, and baseline ocular and systemic characteristics were compared between the two treatment groups using the two-sample *t*-test for normally distributed continuous variables and the Wilcoxon-Mann-Whitney test for nonnormal data. Carryover effects were tested for using the Hills-Armitage approach.²⁹ For VF and CS outcomes, the paired differences between the results after each treatment phase and the corresponding baseline measurements in the two sequence groups were calculated separately. The data from both sequences were pooled for all outcomes to evaluate the treatment effects in all subjects by calculating the differences before and after treatment, and the difference between treatments. Paired *t*-tests were used for testing all paired differences. Due to the small sample size, the

TABLE 2. VF and CS Indices of the Groups After Each Phase of the Study

	GBE → Placebo Sequence, n = 14				Placebo → GBE Sequence, n = 14							
	Baseline	After GBE	Change, 95% CI*	After Washout	After Placebo	Change, 95% CI*	After Washout	After GBE	Change, 95% CI*			
Visual field indices, right eye												
MD, dB	-8.16 (7.22)	-8.20 (6.82)	-0.04 (-1.16, 1.00)	-7.20 (6.17)	-7.06 (6.53)	0.14 (-0.48, 0.80)	-5.27 (4.27)	-5.00 (4.28)	0.27 (-0.20, 0.71)	-4.82 (4.24)	-4.57 (4.44)	0.25 (-0.21, 0.97)
LogMAR contrast sensitivity, right eye												
1.5 cpd	1.59 (0.14)	1.57 (0.11)	-0.02 (-0.08, 0.03)	1.53 (0.17)	1.57 (0.17)	0.04 (-0.02, 0.12)	1.61 (0.20)	1.49 (0.20)	-0.12 (-0.26, 0.004)	1.47 (0.14)	1.54 (0.16)	0.07 (-0.001, 0.15)
3 cpd	1.63 (0.26)	1.70 (0.21)	0.07 (-0.002, 0.14)	1.68 (0.19)	1.71 (0.21)	0.03 (-0.06, 0.08)	1.65 (0.19)	1.62 (0.25)	-0.03 (-0.17, 0.07)	1.61 (0.11)	1.69 (0.12)	0.08 (-0.006, 0.15)
6 cpd	1.49 (0.27)	1.59 (0.23)	0.10 (0.003, 0.21)	1.63 (0.28)	1.64 (0.26)	0.01 (-0.08, 0.09)	1.57 (0.19)	1.51 (0.26)	-0.06 (-0.20, 0.05)	1.597 (0.18)	1.600 (0.19)	0.003 (-0.07, 0.08)
12 cpd	1.24 (0.28)	1.30 (0.27)	0.06 (-0.03, 0.17)	1.33 (0.26)	1.29 (0.20)	-0.04 (-0.13, 0.05)	1.15 (0.13)	1.14 (0.18)	-0.01 (-0.10, 0.07)	1.22 (0.20)	1.23 (0.17)	0.01 (-0.05, 0.11)
18 cpd	0.82 (0.23)	0.89 (0.24)	0.07 (-0.04, 0.25)	0.88 (0.26)	0.92 (0.25)	0.04 (-0.09, 0.19)	0.73 (0.17)	0.72 (0.20)	-0.01 (-0.12, 0.13)	0.87 (0.19)	0.86 (0.20)	-0.01 (-0.09, 0.08)

Data at baseline and after treatment are expressed as mean (SD) unless otherwise noted.

* The 95% bias-corrected bootstrap CIs were presented while the *P* values were not shown because no statistically significant difference was detected.

bootstrapped *P* value and 95% bias-corrected bootstrap confidence intervals (CIs) were calculated on 10,000 replications with seed 12345. Box and whisker plots were used to display the treatment effects on the changes in MD and logMAR CS. A sensitivity analysis then was performed by testing the significance of the treatment effect of GBE (posttreatment compared to baseline), and the difference between GBE and placebo treatments for patients who had dropped out, by assuming a posttreatment decrease in pre-GBE treatment MD over the range of 20% to 80%.

All analyses were conducted using Stata Statistical Software (Stata 10.0; Stata Corp., College Station, TX, USA) and a *P* value of < 0.05 was considered statistically significant throughout.

RESULTS

Patient Characteristics and Disposition

Among 35 patients undergoing randomization, 17 were assigned to receive GBE first then placebo, and 18 to placebo first then GBE. Among these, 3 patients (17.6%) from the GBE-placebo group and 4 (22.2%) from the placebo-GBE group experienced loss to follow-up or inability to tolerate medication. A total of 28 patients (80.0%) completed the study and were included for the final analysis, 14 patients in each group (Fig. 1). No statistically significant differences were observed at baseline between the two groups with regard to demographic or clinical characteristics (Table 1).

Effects of GBE on VF MD

The preliminary test for carryover effects was not significant ($P = 0.21$), so the data from both periods were analyzed. Patients in the GBE-placebo group had a nonsignificant decline in MD of -0.04 dB (95% CI -1.16, 1.00; $P = 0.952$) after GBE treatment, while those in the placebo-GBE group had a nonsignificant increase in MD from -4.82 to -4.57 dB (95% CI -0.21, 0.97; $P = 0.401$; Table 2). The changes in MD after placebo use for the GBE-placebo and placebo-GBE groups were +0.14 dB (95% CI -0.48, 0.80; $P = 0.662$) and +0.27 dB (95% CI -0.20, 0.71; $P = 0.236$), respectively.

The mean of the difference before and after treatment was -0.11 dB (95% CI -0.79, 0.60; $P = 0.777$) for GBE, pooling Phase 1 and Phase 2 data. The corresponding value was -0.21

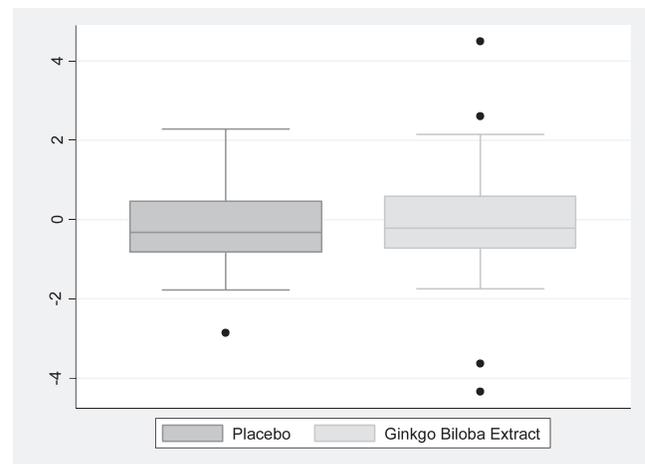


FIGURE 2. Effect of GBE versus placebo on pre- versus posttreatment change in VF MD, pooled across the two phases of treatment. Results shown are for the right eye of subjects with both eyes eligible for the trial, otherwise for the eligible eye.

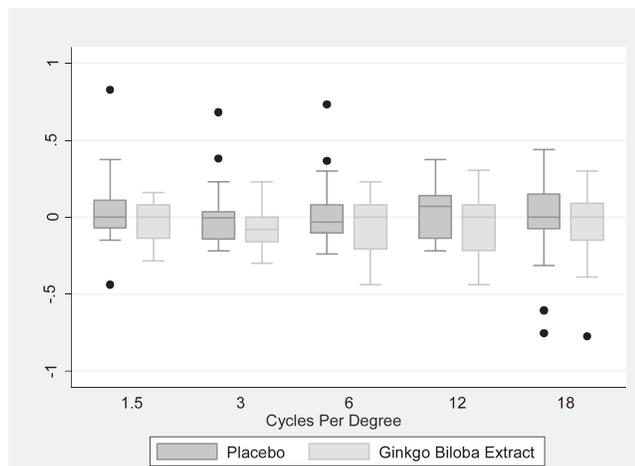


FIGURE 3. Effect of GBE versus placebo on pre- versus posttreatment change in CS, pooled across the two phases of treatment. Results shown are for the right eye of subjects with both eyes eligible for the trial, otherwise for the eligible eye.

dB (95% CI $-0.59, 0.19$; $P = 0.297$) for placebo. The treatment difference was -0.10 dB (95% CI $-0.72, 0.51$; $P = 0.730$) and, thus, the overall effect of GBE treatment on MD in this trial was a nonsignificantly smaller decrease in MD when compared to placebo (Fig. 2).

Effect of GBE on CS

Results of each CS test, incorporating scores for 5 different spatial frequencies, were converted to logMAR CS. No significant differences in the change of CS at the 5 spatial frequencies over time in either sequence were observed, whether considering the effect separately by phase (Table 2), or pooling Phase 1 and Phase 2 together (Fig. 3).

Effects of GBE on IOP and Blood Pressure, Adverse Events

No significant effects were seen of GBE treatment on heart rate (mean [SD] value before and after GBE treatment, 74.5 [10.6] and 73.4 [10.4] beats per minute [bpm], respectively; mean difference 1.11 bpm [95% CI $-2.16, 4.89$; $P = 0.543$]), blood pressure (mean [SD] systolic blood pressure before and after treatment, 129.7 [16.0] and 127.0 [13.2] mm Hg, respectively; mean difference 1.79 mm Hg [95% CI $-2.95, 6.74$; $P = 0.467$]; mean [SD] diastolic blood pressure before and after treatment, 75.6 [9.6] and 75.2 [8.9] mm Hg, respectively; mean difference 0.42 mm Hg [95% CI $-2.47, 3.21$; $P = 0.774$]), or IOP (mean [SD] value before and after treatment, 15.1 [2.6] and 14.8 [3.3] mm Hg, respectively; mean difference 0.28 mm Hg [95% CI $-0.99, 1.49$; $P = 0.657$]).

Among the 35 patients undergoing randomization, two reported adverse events associated with their medication during the placebo phase of treatment and withdrew from the study. One subject complained of gastric discomfort and another presented with urticaria. No adverse events were reported during GBE treatment.

Sensitivity Analysis

Even a posttreatment decrease of 80% in pretreatment MD scores among all participants who failed to complete testing still would not have resulted in a statistically significant improvement with GBE treatment, either comparing pre- versus posttreatment values, or comparing GBE and placebo.

DISCUSSION

We found no evidence for a significant impact of GBE therapy on either VF MD or logMAR CS in this study of newly-diagnosed patients with NTG.

The power of our study was 80% to have detected an effect on MD as large as that reported previously by Quaranta et al.,¹⁸ calculated using raw data provided by those investigators.

These results among Chinese patients are in contrast with some previous reports. Lee et al.¹⁹ reported that GBE slowed the worsening of MD over a follow-up period of 4 years, though no control group was included in this retrospective study, and the duration of GBE administration was not specified. In another retrospective study conducted by Shim et al.,³⁰ oral administration of GBE for an average of 24 months improved VF indices (MD and PSD) in patients with NTG, although the study was not randomized, patients in the treatment group were younger than those in the control group, and selection bias was not excluded. The only previous randomized trial, reported by Quaranta et al.,¹⁸ concluded that 4 weeks of oral GBE treatment was associated with significant improvement in MD among Italian subjects with NTG. Our study was designed to follow the methods of Quaranta et al.¹⁸ closely. Besides being Italian rather than Chinese, patients in their study had significantly worse MD (-11.76 dB) than subjects in the current report (-5.85 dB), which might explain in part the contradictory results. Our study enrolled newly-diagnosed NTG patients, but the study of Quaranta et al.¹⁸ does not indicate whether or not this was the case in their study.

The last VF test at baseline and the best VF test during follow-up were used in the analysis of MD. This choice was based on the fact that visual field outcomes of newly-diagnosed glaucoma patients are more variable and likely to be affected by learning, while over time such effects decline.³¹ We also sought to avoid regression to the mean by avoiding using the best baseline MD result. At baseline, the mean within-individual SD for the 3 VF tests was 1.16 dB. This value declined to 0.83 dB at visit 2, 0.89 dB at visit 3, and 0.77 dB at the last visit. This decline in variability is consistent with previous studies in newly diagnosed glaucoma patients.³¹

The IOP was recorded as a potential confounder in the study, and a target for reduction of 30% set to assure that patients received the standard of care. However, no statistically significant change was observed in IOP over the course of this brief trial (Table 2), consistent with previous studies²⁵ showing that achieving a 30% IOP reduction requires many months of trial and error. In view of this and studies showing IOP reductions as much as 4 mm Hg are unassociated with significant short term changes in VF parameters,³² it is unlikely that IOP changes could have masked significant effects of GBE on MD in the current study and change, thus, could be eliminated in this study.

To the best of our knowledge, no previous study has evaluated the impact of GBE treatment on CS in glaucoma patients. Abnormal CS has been reported in early glaucoma,^{33,34} and functional acuity contrast testing such as we used has been advocated for the diagnosis of glaucoma.³⁵ Our study found no significant change in CS at any of the 5 spatial frequencies with administration of GBE over 4 weeks.

Several explanations have been offered for the potential benefits of systemic GBE treatment on glaucoma. The GBE has been reported to increase ocular blood flow,^{16,17} which may be beneficial in reversing the underlying disease process in NTG. However, Wimpfissinger et al.³⁶ have reported no impact on ocular blood flow from a single oral dose of GBE. Also, GBE has been suggested to have neuroprotective effects in NTG patients.¹¹ Others have argued that GBE use leads to cognitive improvements, which, in turn, result in better functional

outcomes on vision testing.^{18,37} However, a recent Cochrane review casts some doubt on the efficacy of GBE in treating dementia.⁷

There are at least three possible explanations for the negative findings in our current study. It may be that GBE does not affect visual functioning in patients with glaucoma. Another possibility is that the effect size was too small to be detected by our relatively small trial, although our power was sufficient to detect effects as large as those reported in a previous trial of similar design. On the other hand, the MD changes observed in the previous trial were prominent; to detect a smaller, while still clinically significant, change would require a much larger sample size. Finally, the treatment period of 4 weeks might not have been sufficient to reveal a clinical benefit, though Quaranta et al.¹⁸ reported significant improvements in MD with 4 weeks of oral treatment, identical to the time frame we used.

Strengths of this study include the randomized controlled design, selection of a relevant population (Chinese, who have a high prevalence of NTG and wide access to GBE), and assessment of two clinically meaningful visual outcomes in glaucoma. Limitations of the study included the relatively small sample size and limited treatment period of only 4 weeks. Further, it has been suggested³⁸ that the procedure in testing for crossover effects used in this study²⁹ may increase Type I error (likelihood of obtaining a false-positive result). This is of less concern given the negative result of the current trial.

Results from studies to date are contradictory. Recent reports²¹ document widespread use of GBE and other complementary therapies for glaucoma in the developed world, and there is a need for safe, inexpensive, and widely-available treatments for the very large number of people in Asia affected with NTG. For all of these reasons, larger trials of GBE in the treatment of glaucoma are justified.

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