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Effect of *Ginkgo biloba* extracts in the prevention of posterior capsule opacification after cataract surgery: A randomized clinical trial

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Abstract:

PURPOSE: This study aims to explore the effect of *Ginkgo biloba* extracts (GbE) on the prevention of posterior capsule opacification (PCO).

STUDY DESIGN: This study was a double-blinded, placebo-controlled, single-center randomized clinical trial.

METHODS: Patients with senile cataracts randomly received GbE supplement capsules at a dose of 200 mg ($n = 74$) or an identical placebo ($n = 70$) daily for 6 months after cataract surgery. Patients' follow-ups were scheduled for up to 3 years after cataract surgery. PCO formation (Pearl/Fibrotic) was graded using slit-lamp examinations. The necessity of a Neodymium-doped yttrium aluminum garnet (Nd:YAG) laser capsulotomy was evaluated by patients' complaints of reduced visual acuity imputable to PCO.

RESULTS: A total of 144 patients with a mean age of 64.92 ± 7.77 years were studied. The mean Log MAR visual acuity in the placebo group started to decrease at 12 months ($P = 0.003$) and remained significantly lower than the GbE group throughout 36 months ($P = 0.005$). At 1-year postsurgery, a significant difference between the two groups of GbE and Placebo was observed regarding pearl PCO score, but obvious fibrotic PCO score differences occurred 3 years after surgery. The Nd:YAG capsulotomy was performed in six eyes (6.1%) for the GbE group and 18 eyes (20.4%) for the placebo group ($P = 0.004$) 3 years after the cataract surgery.

CONCLUSION: Six months of supplementation with GbE was well tolerated and may provide some marginal prevention in the PCO formation. Besides the effect of the GbE in the inhibition of PCO, we also observed a noticeable reduction in the need for Nd:YAG laser capsulotomy.

Keywords:

Capsule opacification, cataract, clinical trial, *Ginkgo biloba* extract

Introduction

Posterior capsular opacification (PCO) continues to exist as a common long-term complication of cataract surgery, which disrupts the visual function of up to 28% of patients. Laser capsulotomy is the most commonly used method to correct posterior capsular opacification (PCO) after cataract surgery.[1,2] Despite many efforts, the development of PCO remains the most common reason for the reduction of visual efficiency 1–3 years after cataract surgery.[3] Recent investigations have disclosed that the occurrence of PCO is pertinent to cell proliferation and migration, and transdifferentiation of epithelial–mesenchymal transition (EMT)

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by changing the extracellular matrix components in residual lens epithelial cells.[4] Transforming growth factor-beta 1 (TGF-β1) is a profibrotic cytokine extremely involved in PCO formation and EMT in the lens.[5]

Ginkgo biloba extract (GbE) is commonly prepared to contain either 24% of ginkgo-flavone glycosides and 6% terpene lactones (EGb-761) or 25% ginkgo-flavone glycosides and six percent terpenoids (LI 1370). GbE delivers some of its antifibrosis effects through a decrease in the TGF-β1 levels and connective tissue growth factor expression, leading to suppression in collagen production and extracellular matrix secretion.[6-8] Thus, it is believed to have protective potentials in cells and membranes against oxidative damage. Experimentally, GbE has been found to protect the lens against radiation-induced cataracts and diabetic cataract formation.[9-11] Clinically, GbE was associated with the improvement of disrupted visual function in patients with open-angle glaucoma.[12,13] Furthermore, its ability to protect the cell membrane from free radical damage may assist in halting the progression of age-related maculopathy.[14] This study aimed to assess the effect of GbE on the prevention of PCO occurrences in postenile-cataract surgery.

Methods

Study design

This double-blinded, placebo-controlled, single-center randomized clinical trial study was designed and conducted according to the declaration of Helsinki. After the approval by the Mazandaran University of Medical Sciences' ethics committee (reference ID 90-114), the patients' enrollment started February 2013 and ended in October 2018. This study was registered in the clinical trial registry at IRCT.ir (trial ID: IRCT20190912044755N1).

Participants

The participants were recruited from the Bu Ali Sina Hospital eye clinic, Sari, Mazandaran, Iran. Patients of both sexes were included in the study if they met the following criteria: aged 50–85 years and impaired visual function defined as senile cataract which has surgically been treated. The exclusion criteria included: patients' unwillingness to continue participating in the study, history of diabetes mellitus; hypertension (defined as systolic blood pressure (BP) >159 mmHg or diastolic BP >99 mmHg); a history of renal and/or hepatic disease; history of cardiovascular, neurological diseases; bleeding disorders or increased bleeding tendency receiving treatment with anticoagulant and antiplatelet drugs; glucose-6-phosphate dehydrogenase deficiency; hypersensitivity reaction to GbE; patients currently taking any complementary supplements which would interfere with the study results; and any ophthalmologic diseases that would make impossible to obtain a postoperative visual acuity of better than 20/40; or history of ocular trauma or surgery. The participants provided us with written informed consent after being informed about the nature of the study.

To address the potential effect of the participants' dietary habits in this study, it is important to note that, even though monitoring the specific diet of the participants was not practically feasible, it is worth mentioning that given the even and unmixed ethnicity of the region from which the participants were enrolled, dietary habits did not play any major roles in the results of the study.

Sample size

Based on a previous report in which 20%–40% of patients suffered from decreased visual acuity induced by PCO,[15] while accounting for 95% confidence level, 80% power, and assuming the 20% difference in visual acuity resulted from supplementation with GbE between the two study groups, using the formula of:

$$n = \frac{2(z_{1-\alpha/2} + Z_{1-\beta})^2\, p(1-p)}{d^2}$$, a total of 156 cases were calculated to be enrolled.

Study groups, randomization, and blinding

The participants were divided into GbE and placebo (PLA) groups randomly. The randomization was conducted independently by an experienced health study counselor to ensure that all investigators and participants remained blinded. Randomization was performed on an individual level using four number blocks created in Excel software. Allocation concealment has been carried out by numbered containers using identical labels and packages for both groups with ascending drug numbers. Tablets containing active drugs and the related placebo tablets were indiscriminate in texture, color, shape, and size.

The participants' groups were coded. The list matching the drug codes with treatment groups was inaccessible to the personnel involved in conducting the study. Double-blinding was achieved using the two-dummies technique, with all patients receiving the same number of tablets, either GbE or GbE-like placebo. Thus, the patients, the surgeon, and the examiners, along with those administering the interventions and those assessing the PCO outcomes, were blinded to the study groups.

Cataract surgery

Surgery was carried out by one expert surgeon using a unified surgical technique to minimize the effect of the surgeon on PCO formation. A 3.2–3.8 mm temporal, limbo-corneal incision was made. The anterior chamber was filled with a hydroxyl propyl methylcellulose ophthalmic solution U. S. P (Viscolon P. F.). A round and

centered anterior continuous curvilinear Capsulorhexis was made using a bent needle. After phacoemulsification, intraocular lens (IOL) implantation into the capsule bag was done with an injector. The Viscolon was washed out from the anterior chamber by irrigation/aspiration. The TECNIS® IOL (Abbott Medical Optic Inc. Santa Ana. CA 92705 USA) is a one-piece aspheric posterior chamber biconvex acrylic IOL with an ultraviolet absorber, with an optic diameter of 6 mm, and an overall diameter of 13 mm. If a surgical intervention was needed for both eyes in one patient (n = 30), the time interval between surgeries of each eye varied between 1 and 4 months. Initial hematologic index evaluation, including complete blood count and coagulation status, was undertaken in any patient that underwent cataract surgery.

Postoperative care and intervention

Postoperative treatment for all patients in both groups included topical treatment with betamethasone 0.1% (Betasonate; Sina Darou, Iran) and chloramphenicol 0.5% (Chlobiotic; Sina Darou, Iran) ophthalmic drops, four times a day, for up to 3 weeks.

The herbal medicine intervention used by the GbE group in this trial was an extract of *Ginkgo biloba* L. (Ginkgoaceae; maidenhair tree). The extract was obtained from leaves of *Ginkgo biloba* L, which has 25% ginkgo-flavone glycosides and 6% terpenoids. The product used was LI 1370, an extract of *Ginkgo biloba* L. manufactured by Laboratories Vitarmonyl, France.

The GbE group received GbE supplements at a dose of 200 mg in the form of capsules (LI 1370), and the placebo group received identically appearing placebo capsules (pharmaceutical excipients containing the same color, shape, and size of capsules). The percentages of quantified chemical constituents per GbE capsule were as follows: 50 mg (25%) ginkgo-flavone glycosides, 12 mg (6%) ginkgolides. The placebo capsules were produced and supplied by an experienced pharmacist and were repacked, labeled, and stored at the Department of Pharmacy, Mazandaran University of Medical Sciences.

The oral supplementation with GbE or GbE-like placebo started from the first postoperative day and continued on a once-per-day dose until 6 months after surgery.

The presence of adverse clinical events were carefully evaluated and recorded through clinical observation of all symptoms, including gastrointestinal upset and skin reactions that could have been attributed to the study interventions.

Follow-up

At the first visit (V1), patients signed the informed consent form, were randomized to either the GbE or PLA, and received the postoperative medication relating to their group allocation. Posterior capsular analysis was performed during a diagnostic assessment at the first visit, which served as baseline values, after 1-week (V2), 1-month (V3), 6 months (V4), 12 months (V5), and within 3 years after surgery (V6). On-site visits for clinical assessment of PCO, compliance to study medication, changes in comorbidity and concomitant medication, and safety were performed. Between the clinical visits, monthly follow-up phone calls were performed to keep the investigators updated on comorbidity, commitment to medication, and safety.

The instrument of the study was the slit-lamp biomicroscopy, which was a part of the capsular variable assessment at each follow-up. Pupils were dilated using topical 1% tropicamide. The visual acuity tests were performed at a single seating by the same experienced, certified vision examiner in the same room with standardized low light conditions (approximately 10 cd/m^2) using the Snellen chart presented on a projector. The Snellen fraction was converted to LogMAR for statistical analysis without taking into account the differences in number of letters per line.[16] PCO formation was graded according to its appearance using the slit-lamp examination (score: 0–4).[17] The following scale was used in the assessment of PCO pearls: none visible at all (0); visible but none reaching to IOL edge (1); at IOL edge (2); well inside IOL edge but visual axis clear (3); and across visual axis (4). The fibrosis intensity of PCO was assessed using a Volk90D lens according to the degree of visualization of the optic nerve and macula, graded as follows: no fibrosis (0), foveal reflex not well visible as mild (1), optic nerve vessels not visible in detail as moderate (2), and poorly visualization of optic disc color and its margin as severe (3).[18] Eventually, the necessity of a Neodymium: yttrium-aluminum-garnet (Nd:YAG) laser capsulotomy was evaluated, as patient complaints of blurred vision and/or visual acuity of 20/25 or less imputable to PCO at the slit-lamp examination.

Statistical analyses

Statistical analyses were performed using PASW statistics software (version 24.0.0). The primary outcome was the change in the mean of the best corrected visual acuity from baseline in the operated eye (cataract surgery), secondary to PCO (study eye). Secondary outcomes included the prevalence of posterior capsule opacification, and the necessity for Nd:YAG capsulotomy in the study eye. Variables were analyzed using the Chi-square test for nominal data, independent samples t-test for continuous variables with normal distribution, and Mann–Whitney ordinal or continuous data without normal distribution. The participants' visit sessions, and interaction between treatment groups were considered as fixed factors in the model. Baseline assessment was used as a covariate.

Effect sizes for the difference in mean changes between the intervention and control groups were calculated using Cohen's *d*.[19] We assumed Cohen's *d* of <0.20, 0.20–0.49, 0.50–0.79, and ≥0.80 to consider trivial, small, moderate, and large effect sizes, respectively. Effect sizes that were at least moderate were explicated as proper changes. A $P < 0.05$ was considered statistically significant. All *P* values presented are two-sided and are to be interpreted in an exploratory sense.

Results

Out of 302 individuals screened for eligibility in this study, a total of 156 cases were enrolled, divided into two groups of GbE ($n = 80$) and placebo ($n = 76$). Twelve patients, six from each study group (four due to unwillingness to continue with their participation, and another eight due to inconsistency to the regimen) were lost during the follow-up period. A final dataset of $n = 144$, with a mean age of 64.92 ± 7.77, including 74 patients in the GbE group and 70 participants in the placebo group, was achieved for the PCO assessment and analysis.

Of the 144 participants, 186 eyes met the inclusion criteria for PCO assessment, including 98 eyes in the GbE group and 88 eyes in the PLA group.

Table 1 outlines the baseline demographics of the study groups. The mean surgery duration was 13.8 ± 5.1 and 14.1 ± 5.9 min in the GbE group and PLA group, respectively, ($P = 0.415$). No adverse events were observed during this study. Additionally, the IOL was preserved well within the center of the capsular bag and no tilt was observed in the position of IOL over time in all participants in both groups of our study.

Figure 1 demonstrates the lens capsule opacification patterns of pearl PCO and fibrosis PCO in two of our patients, respectively.

The mean LogMAR of the best-corrected visual acuity of PCO patients in the two study groups during the follow-up period is shown in Figure 2.

Mean LogMAR visual acuities in the placebo and GbE groups were virtually overlapped for the first 6 months after the primary cataract surgery ($P = 0.514$). A significant difference in LogMAR visual acuity between the PLA and GbE groups was observed at 12 months ($P = 0.003$), likely due to PCO formation, with the PLA group having worse visual acuity than the GbE group. This difference remained statistically significant throughout the 36 months postsurgery ($P = 0.007$). In the GbE group, mean LogMAR visual acuity was changed relatively insignificant, which indicates minimal PCO development over time. Table 2 demonstrates the ocular parameters of the patients enrolled in the GbE study at 3 years postsurgery.

Posterior capsule opacification was emerging over time in the lenses of both placebo and GbE patients. At 6 months postoperatively, both groups displayed little evidence of fibrosis ($P = 0.626$) or pearl ($P = 0.64$) PCO formation without any statistically significant difference. By 12 months, the PLA group had developed a pearl opacification on the posterior lens capsule, of which the score was significantly higher than that of the GbE group ($P < 0.001$). In contrast, there was no statistically significant difference in fibrotic opacification scores between the two groups at 12 months (P=0.278). At 12 months, 75 of 98 lenses (76.5%) in the GbE group were free from dirt; meanwhile, 51 of 88 lenses (58%) in the PLA group remained clear ($P = 0.008$). Mean pearl PCO scores at 12 months were 0.28 ± 0.61 and 0.79 ± 1.04 in the GbE group and PLA group, respectively, and mean fibrosis PCO scores at 12 months were 0.20 ± 0.54 and 0.29 ± 0.60 in GbE group and PLA group, respectively.

Table 1: Baseline values of the study groups

Parameters	GbE (patient *n*=74)	PLA (patient *n*=70)	*P*
Age at surgery (years)	65.44±7.62	64.37±7.94	0.409
Sex (male/female)	35/39	32/38	0.491
Eye surgery	98	88	0.663
BMI (kg/m^2)	26.82±3.62	26.24±2.99	0.297
Follow-up (years)	3.69±0.42	3.63±0.38	0.385

Data are demonstrated in mean±SD or numbers. BMI: Body mass index, GbE: *Ginkgo biloba* extract, SD: Standard deviation, PLA: Placebo

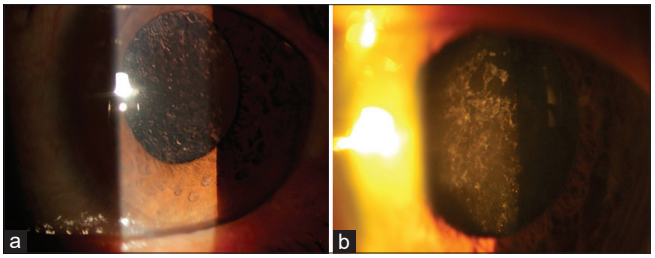

Figure 1: Cluster of Elschnig pearls (a), and patchy fibrosis (b) behind the surface of a cataract intraocular lens implant. Images are magnified x15.

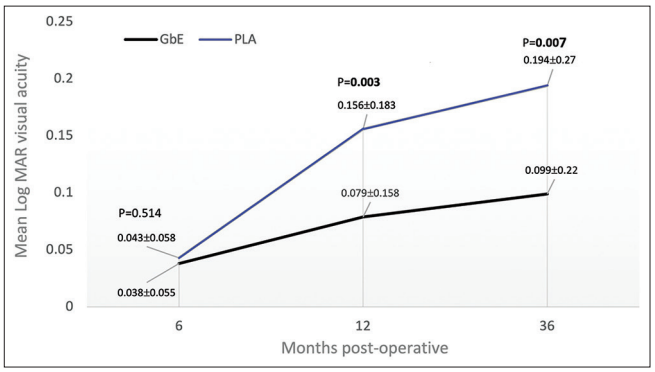

Figure 2: The mean LogMAR visual acuity of posterior capsular opacity patients in the placebo (gray color) and *Ginkgo biloba* extract (black color) groups

Table 2: Ocular parameters of the study groups at 36 months postsurgery

Parameter	GbE (eye *n*=98)	PLA (eye *n*=88)	*P*
VA (logMAR)	0.099±0.215	0.194±0.245	0.005
IOP (mmHg)	15.26±0.99	15.21±0.95	0.762
PCO pearls			
None visible	79 (80.61)	48 (54.54)	<0.001
Visible not reaching the IOL edge	7 (7.14)	9 (10.22)	
At IOL edge	10 (10.2)	11 (12.5)	
Inside IOL edge, clear visual axis	2 (2.04)	18 (20.45)	
Across visual axis	0	2 (2.27)	
PCO fibrosis			
No	67 (68.36)	27 (30.68)	<0.001
Mild	21 (21.42)	37 (42.04)	
Moderate	4 (4.08)	13 (14.77)	
Severe	6 (6.12)	11 (12.5)	
Nd:YAG	6 (6.12)	18 (20.45)	0.004

Data are demonstrated in mean±SD or *n* (%). GbE: *Ginkgo biloba* extract, IOL: Intraocular lens, IOP: Intraocular pressure, Nd:YAG: Neodymium-doped yttrium aluminum garnet, PCO: Posterior capsular opacity, PLA: Placebo, VA: Visual acuity, SD: Standard deviation

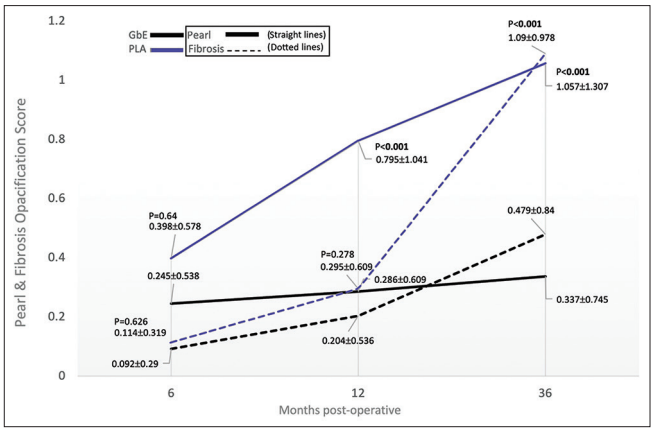

Figure 3: Pearl (continuous line) and fibrosis (dashed line) posterior capsular opacity scores comparison the placebo (gray color) and *Ginkgo biloba* extract (black color) study groups

At 36 months postoperatively, we observed a significant difference regarding both pearl ($P < 0.001$) and fibrosis ($P < 0.001$) PCO development in our study groups. After 3 years postoperatively, however, 65 of 98 lenses (66.32%) in the GbE group remained clear and 26 out of 88 lenses (29.54%) stayed without any signs of PCO formation ($P < 0.001$). Figure 3 demonstrates the pPCO and fPCO scores between the study groups over time in detail, using the data described above. These graphs display quantitatively what is observed on the lens capsule scales. The PCO progression during the time in the placebo group is much greater than that in the GbE.

The necessity for Nd:YAG capsulotomy among the two groups was evaluated using the opacification findings. The number of patients within the two studied groups who underwent Nd:YAG capsulotomy at 36 months postoperatively is disclosed in Table 2. Three years following cataract surgery, Nd:YAG capsulotomy was carried out on 18 eyes (20.4%) of the placebo patients; however, only six eyes (6.1%) of the GbE patients were planned to undergo an Nd:YAG capsulotomy. The difference in Nd:YAG capsulotomy requirement in the PLA and GbE groups was statistically significant ($P = 0.004$).

Discussion

Utilization of the factors that can hinder PCO, besides the improvement in IOL designs, surgical techniques, and IOL material, will provide us with the chance to retain a fine level of vision following cataract surgery.[20-24] Our results indicate that the systemic administration of GbE at a dose of 200 mg per day was well tolerated and prevents visual impairment after cataract surgery in individuals with PCO for up to 36 months.

Reports on the effects of GbE on visual function speculated that the GbE function attributes to ocular blood circulation and antioxidant properties, which improve visual acuity in patients with normal-tension glaucoma.[25]

Recently, investigators showed a significant adjusting relation between aldose reductase (AR) and TGF-β1 signaling. They proposed that AR impediment could be a possible therapeutic plan to prevent PCO development.[26,27] In another animal-based study, it was suggested that GbE can attenuate selenite-induced cataract through the reduction of the intracellular malondialdehyde content in the lens, and an obvious increase in the reduced glutathione levels, and thereby protect the cells from oxidative damage and putting cataract formation on hold.[28] Therefore, the anti-cataract potential of GbE can be attributed to the presence of high phenolics and flavonoid components.

To the best of our knowledge, limited clinical studies evaluating the effect of GbE on the prevention of PCO after cataract surgery are found. However, in an animal study, Lu *et al*. found that GbE can potentially halt diabetic cataract formation through inhibition of oxidative stress and the polyol pathway.[28] In another experimental study, Ertekin *et al*. showed oral *Ginkgo biloba* supplementation can protect rats' lenses from radiation-induced cataracts.[10] In the current study, the PCO grades and the need for Nd:YAG capsulotomy were significantly greater in the PLA group than in the GbE group after 36 months.

Although Nd:YAG capsulotomy is commonly considered safe, it is associated with undesirable outcomes, such as IOL damage, cystoid macular edema, secondary

glaucoma, and retinal detachment. Besides, an extra economic burden on healthcare systems is substantial.[29] Thus, inhibition of PCO formation to restrict the need for additional laser therapy can affect patients' sight emphatically.

Our work presents with a few limitations. The PCO severity was assessed using biomicroscopic photographs on sectorial images of the anterior segment exerting on the haziness area. However, the fact that manual image grading may not represent the accurate opacification morphology cannot be denied. Therefore, further studies using more comprehensive methods could be suggested.

Moreover, although the per-participant analysis of the clinical significance of GbE intervention did not provide dissimilar findings as that of per-eye analysis, it can be suggested that a unilateral study design may provide a preferable manner to evaluate the efficacy and safety of supplementary medicinal products in PCO.

Conclusion

To summarize, we demonstrated the pivotal role of GbE in the prevention of PCO after cataract surgery. The ability of this compound to hold PCO progression may relate to its potential in restraining the activation of TGF-β2, decreasing the AR activity, and ameliorating oxidative stress response through increasing glutathione activity. This research was the first human-based clinical-trial study to hinder PCO using GbE supplements, which is consistent with the reports on a dietary supplement useful for controlling systemic diseases other than cataract formation. In addition to the effect of the GbE in the inhibition of late-onset PCO, we also reported noticeable results on the reduction of the projected need for Nd:YAG laser capsulotomy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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