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Article

Effects of oral citicoline in perimetric glaucoma defects

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Abstract: *Purpose*: to study the neuroprotective effect of oral citicoline (CT) in patients with primary open-angle glaucoma (POAG). *Methods*: this study recruits 110 patients with stage IV POAG and well-controlled intraocular pressure (IOP). Enrollees were randomly allocated in two groups: therapy group (TG) or control group (CG). Subjects in TG were treated with citicoline 500 mg / die for 4 months. The treatment period was followed by a wash-out phase of 2 months. At the end of the wash-out phase, subjects in TG resumed CT in the same fashion. Both groups were treated with pressure-lowering medications. Each subject was evaluated with standard automated perimetry (SAP) at baseline, and then again 12, 24, and 36 months after enrollment.
Results: TG showed a statistically significant improvement in MD values at 12 months (Δ = 21%) and T24 (Δ = 35%), and gradual improvements of the stage, up to the 3rd stage with localized defects after 36 months of therapy. Conversely, in CG, both the MD and PSD indices continued to deteriorate throughout the duration of the study.
Conclusion: long-term daily treatment with citicoline might have a neuroprotective effect. Patients treated with oral citicoline showed an improvement in perimetric indices. Additional studies with larger samples and longer follow-ups are needed to confirm these results.

Keywords: open-angle glaucoma, retinal ganglion cells, visual field, citicoline, neuroprotection

Introduction

Glaucoma is a chronic and degenerative optic neuropathy, characterized by progressive loss of retinal ganglion cells (RGC) with subsequent visual field alterations. It can lead to irreversible blindness, unless it is promptly diagnosed and treated. [1–5]
High intraocular pressure (IOP) is considered the principal risk factor for disease progression, but multiple other factors are involved. Medical literature and clinical experience indicate that a subset of patients continue to deteriorate despite adequate pressure control. In these patients, vascular or mechanical insults are likely responsible for disease progression. [6–13]
Treatments for POAG include pressure-lowering interventions and neuroprotective molecules, such as citicoline. [14–18] Citicoline, also known as CDP-choline, is a nucleotide and consists of ribose, cytosine, pyrophosphate and coline, that effect a crucial role in phospholipid synthesis. [19,20] It exerts its neuroprotective functions via several mechanisms: it is an intermediary in the synthesis of phosphatidylcholine, that is abundant in neural cells. [19] It has a trophic effect on cellular membranes, increases metabolism of cerebral structures, and inhibits phospholipid degradation [21,22]. In addition, it regulates bioavailability of neurotransmitters and neuromodulators, among these acetylcholine and dopamine, that are present in the retina and visual cortex. [21] Following oral intake, citicoline is hydrolyzed in the intestinal wall into coline and cytidine. The latter is converted into uridine. [23,24]. These compounds are absorbed and reach the central nervous system, where citicoline is reformed by the enzyme CTP-phosphocholine cytidylyltransferase [25–27].

The role and efficacy of neuroprotective chemicals in the treatment of glaucomatous patients have been subject of debate in the scientific community for a long-time. The purpose of this study is to evaluate a long-term treatment (3 years) with oral citicoline at the dosage of 500 mg/day. Enrollees were instructed to assume it daily for 4 months, then suspend it for 2 months. Thecycle was repeated 6 times total (3 years). All subjects maintained good intraocular pressure values (IOP ≤ 18 mmHg) throughout the study. Pressure control was achieved pharmacologically.

Materials and methods

This was a case-control study that included 110 patients with POAG. Patients were randomly assigned to two groups: therapy group (TG) or control group (CG). All patients showed mixed localization defects and stage IV disease upon enrollment. This study adheres to the tenets of the Helsinki declaration, and was approved by the University ethics board. All subjects signed written consent prior to enrollment. This clinical investigation was conducted according to good clinical practices. Glaucoma diagnosis and classification were based on the Glaucoma Staging System (GSS) [28,29].

All patients were evaluated as follows:

- Slit lamp exam and intraocular pressure measurement with applanation tonometry
- Gonioscopy
- Measurement of central corneal thickness (CCT) with ACCUPACH V

- Standard automated perimetry (Humphrey 30 -2 HFA II and SITA strategy). Perimetric alterations were classified with the Glaucoma Staging System 2.
- RNFL and GCC thickness measure with OCT (RTVue, Optovue, Freemont, CA, USA).

Tonometry was always performed in the afternoon hours, between 2 and 4 P.M.

SAP was executed with the Humphrey Field Analyzer (HFAII, Carl Zeiss Meditec, Dublin, CA, USA), with a stimulus of grade III, SITA standard (Swedish Interactive Soglia), and model 30-2.
Each patient repeated SAP every six months. In addition, studies with poor reliability indices were excluded from analysis. Poor indices included 33% or more of fixation losses/false negatives or 15% or more of false positives.

Inclusion criteria:

- Diagnosis of primary open-angle glaucoma (POAG) (grade IV on the Shaffer classification)
- Adequate IOP control (18 mmHg or less) as measured with applanation tonometry
- Pachymetry within the normal range (> 520μm e <550μm)

A sample size calculation indicated that 55 patients per treatment arm would be sufficient to demonstrate a neuroprotective effect in patients, assuming a power of 80% and an alpha of 0.05.

Exclusion criteria:

- Inability to execute SAP
- BVCA worse than 20/40
- Significant opacities of the dioptric means
- Previous history of ocular surgery
- Presence of ocular or systemic disease that might affect SAP results
- Contraindications or intolerance to oral citicoline
- Secondary forms of open-angle glaucoma

Topical therapy included 0.5 mg timolol (11, 37%), travoprost 0,004% (10, 33%) and a fixed combination of 0,3 mg bimatoprost and 0,5 mg timolol (9, 30%). No IOP spikes were detected at follow-ups. Mean IOP increase was lower than 3 mmHg at each follow-up.
Patients of both groups received a comprehensive ocular exam, SAP and OCT exam every 6 months. In addition, subjects in the therapy group were questioned about therapy adherence or side effects at each visit.
At the beginning of the study, each group consisted of 55 patients. Some patients were excluded because they interrupted treatment with oral citicoline or were lost to follow up. The statistical analysis included data from patients who presented to all follow-up appointments and assumed oral citicoline as indicated.

A statistical analysis was conducted on the two groups of glaucomatous patients (therapy and control) through the calculation of the mean (± SD), median (IQR, max and min) and the comparison between the values of the parameters of study (linear correlations). For the comparison between the three independent groups medians, a paired Student's t-test or Wilcoxon-Mann-Whitney Test was

used, in case of non-parametric distribution. If the test shows a non-normal distribution and/or an inhomogeneous variance, the comparison is performed on the medians, using the Kruskal-Wallis test. Differences between groups with P<0,05 were considered significant. The values of the P were expressed in two queues.

Results

In the therapy group, mean MD value improved from a baseline value of -14 dB to -11 dB after 12 months, and improved further to -9 dB after 24 months ($p < 0.05$) (**Figure 1, Table I**). This change was statistically significant (p-value < 0.05) (**Table II**). No additional statistically-significant improvements were detected after 24 months. This likely results from minimal inter-patient variation. In the control group, mean MD value continued to deteriorate from a baseline value of -14 dB to -15 dB after 36 months.

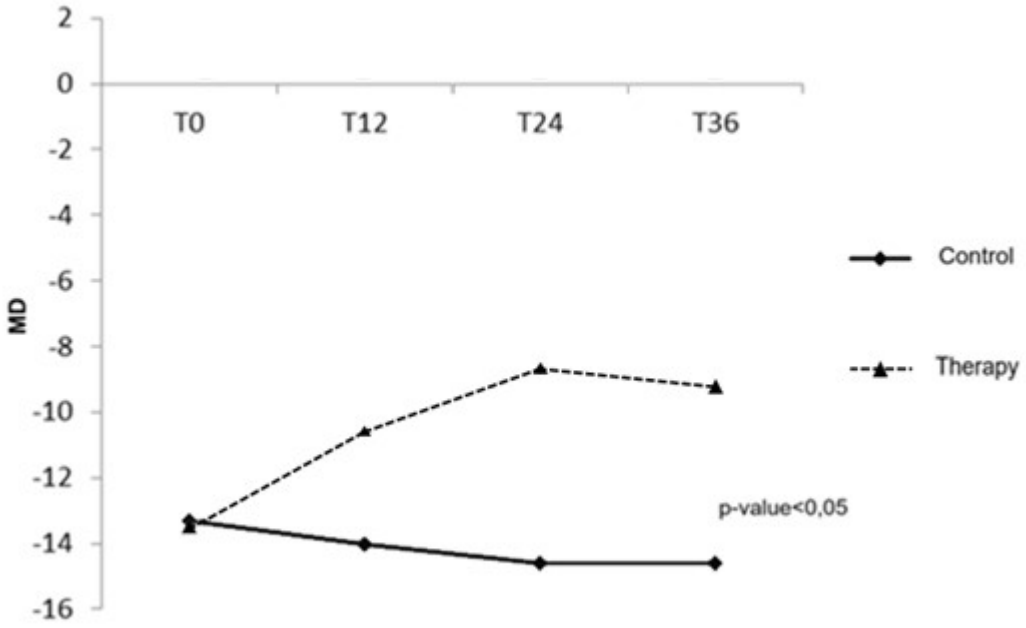

Figure 1: Mean Deviation (MD) trend as a function of time in both groups.

Parameter MD	T0 (mean ± SD)	T12 (mean ± SD)	T24 (mean ± SD)	T36 (mean ± SD)
Control	-14±6.1	-14±3.9	-15±4	-15±4
Therapy	-14±3.2	-11±2.4	-9±4	-8.8±3.8

Table I: Comparison of MD values between groups: CG, and TG. The table shows mean ± standard deviation (SD). Abbreviations: MD, mean deviation; SD, standard deviation.

Subjects in the therapy group also showed a decrease of mean PSD values over the entire follow-up period (**Figure 2**). Mean PSD value decreased from 13 dB to 11 dB after 36 months (**Table III**). This improvement was statistically significant (p value < 0.05) (**Table IV**). In the control group, mean PSD values continued to increase (deteriorate).

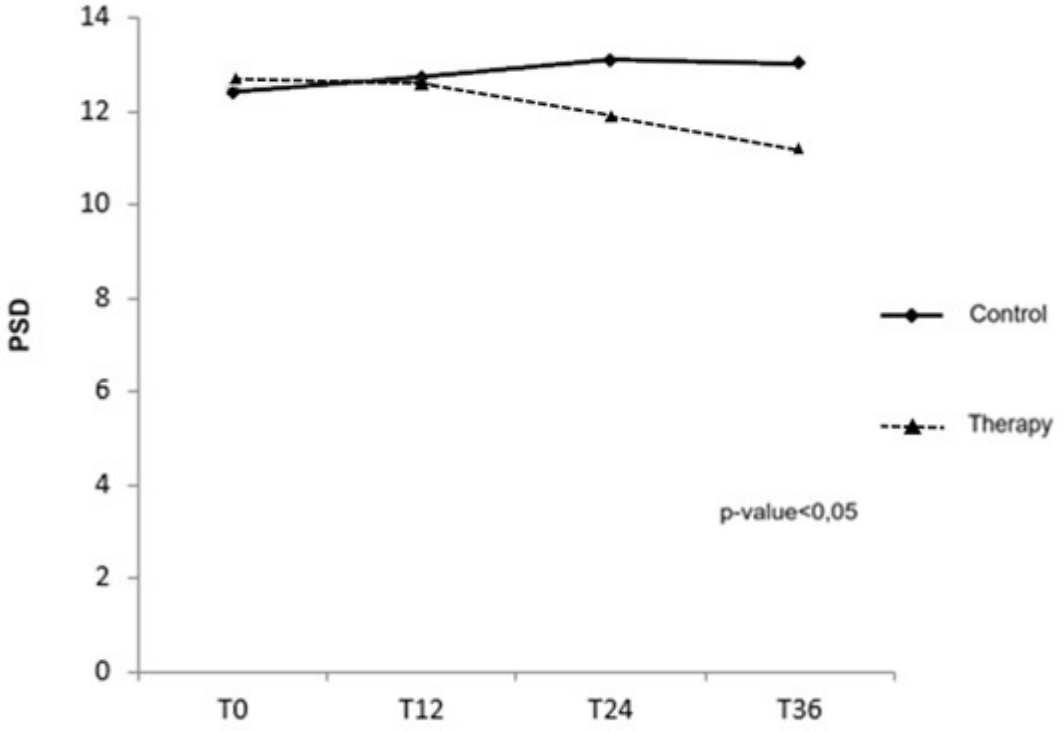

Figure 2: Pattern standard deviation (PSD) trend as a function of time in both groups

Parameter MD	T0-T12 (Δ)	p-value	T0-T24 (Δ)	p-value	T0-T36 (Δ)	p-value
Control	-7%	0.151	-6%	0.211	-7%	0.151
Therapy	21%	**0.001(*)**	35%	**0.001(*)**	35%	**0.001(*)**

Table II: Relative change in mean MD values. Student's t test application for paired samples. (*). A p value < 0.05 is statistically significant. Abbreviation: MD, mean deviation.

GSS2 stage was recalculated at each follow-up (**Figure 3**). All subjects were classified as 4th stage at baseline (**Table V**). Patients in the therapy group improved to III stage with mixed defects after 12 months. This improvement persisted after 24 months, when most subjects were still classified as stage III with mixed defects. At the end of the study period, the

same patients were reclassified as stage III with localized defects. This improvement was statistically significant (p-value < 0.05) (**Table VI**) and correlates with the improvements in MD and PSD values in patients of the therapy group. Patients in the control group continued to deteriorate throughout the follow-up period (Figure 3).

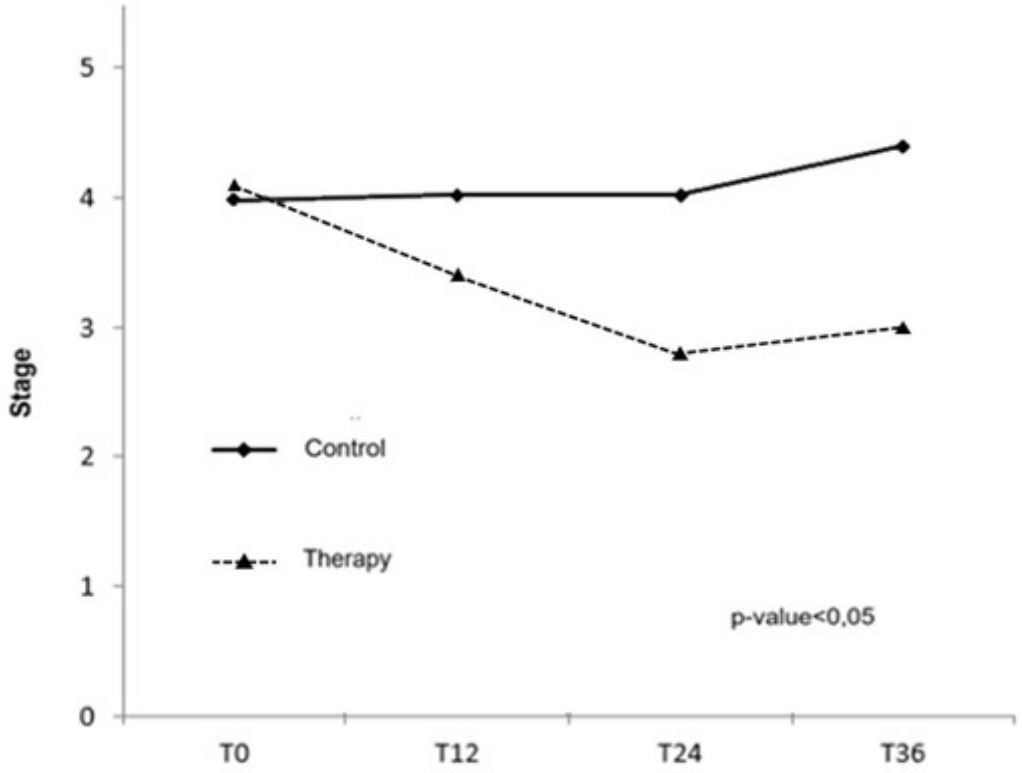

Figure 3: Stage trend as a function of time in both groups

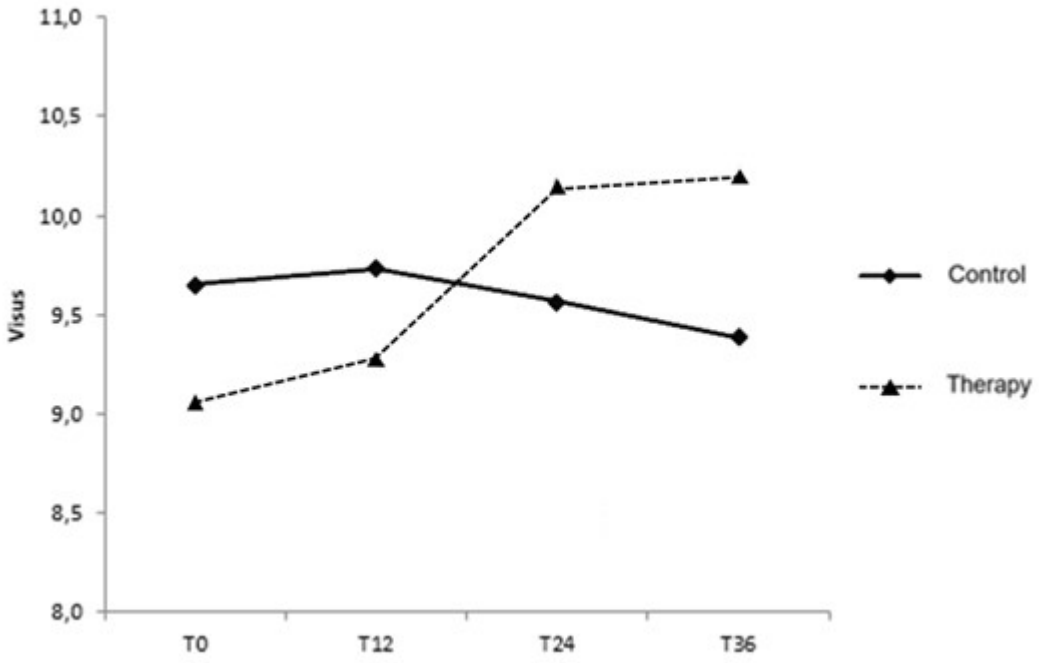

Figure 4: BVCA trend as a function of time in both groups

Parameter PSD	T0 (mean ± SD)	T12 (mean ± SD)	T24 (mean ± SD)	T36 (mean ± SD)
Control	13±3.9	13±4	13±2.8	13±3
Therapy	13±3.2	13±2.6	12±4.2	11±3

Table III: Comparison of mean PSD values between groups: GC and TG. The table shows mean ± standard deviation (SD). Abbreviations: PSD, pattern standard deviation; SD: standard deviation.

Parameter PSD	T0- T12 (Δ)	p-value	T0- T24 (Δ)	p-value	T0- T36 (Δ)	p-value
Control	<1%	0.654	<1%	0.222	<1%	0.151
Therapy	<1%	0.234	-7%	0.752	-16%	**0.001(*)**

Table IV: Relative changes in mean PSD values. Student's t test application for paired samples. (*). A p value < 0.05 is statistically significant. Abbreviation: PSD, pattern standard deviation.

Best-corrected visual acuity (BVCA) was remeasured at each visit. Patients in the therapy group reported an increase in BVCA, more marked after 12 months since initiation of therapy. BVCA improved from a mean baseline value of 0.9 up to a value exceeding 1 at the end of the observation (**Figure 4**). Conversely, mean BVCA of patients in the control group continued to deteriorate during the observation period (Figure 4).

Mean intraocular pressure remained relatively stable for both groups throughout the follow-up period. (**Figure 5**). Changes were not statistically significant.

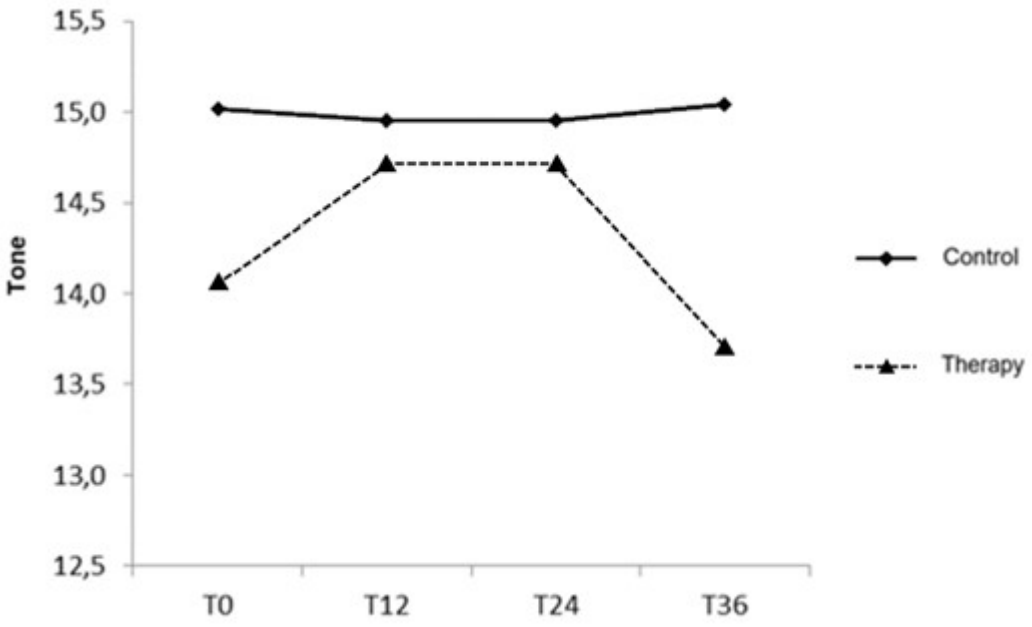

Figure 5: IOP trend as a function of time in both groups

Parameter Stage	T0 (mean ± SD)	T12 (mean ± SD)	T24 (mean ± SD)	T36 (mean ± SD)
Control	4±1.5	4±1.6	4±1.1	4.2±1.6
Therapy	4.1±1.4	3.4±1.3	2.7±1.2	3±1.3

Table V: Comparison of staging between groups: Control and Therapy. The table shows the mean ± standard deviation (SD). Abbreviations: SD, standard deviation.

Parameter Stage	T0- T12 (Δ)	p-value	T0- T24 (Δ)	p-value	T0- T36 (Δ)	p-value
Control	<1%	0.255	<1%	0.512	+2%	0.413
Therapy	-12.8%	0.068	-30%	**0.001(*)**	-35%	**0.001(*)**

Table VI: Relative change between groups. Student's t test application for paired samples. (*). A p value < 0.05 is statistically significant.

Discussion

Results of this study indicate that oral citicoline seems to improve both MD and PSD values in patients with stage-IV POAG. This effect is sustained throughout the duration of the study.
In patients of TG, mean MD value has improved from an initial value of -14 dB to a value of -8.8 dB after 36 months. This corresponds to a relative improvement of 35%. Accordingly, mean PSD decreased by 16% as compared to baseline, from an initial value of 13 dB to a value of 11 dB after 36 months. On the other hand, subjects in the CG continued to deteriorate (mean MD continued to decrease, and mean PSD continued to increase).
There is no doubt that IOP lowering is the mainstay of glaucoma therapy. However, a subset of POAG patients continue to deteriorate, despite adequate IOP control. For this reason, IOP management is only part of the picture. These patients should also be supplemented with neuroprotective agents, such as citicoline.

Previous studies have shown the benefits of oral citicoline in improving retinal sensitivity, reducing scotomas, halting the progression of perimetry alteration, and improving the electrophysiological parameters of PERG and PEV [8,9,30,31]. Experimental studies illustrate the possibility of protecting RGCs from degeneration with oral citicoline [32,33]. These studies corroborate the validity of supplementing POAG patients with oral citicoline, as an adjunct of standard pressure-lowering therapy. [21,27,30]

Conclusions

As found in this study, oral citicoline 500mg/day shows a neuroprotective effect in patients with POAG. Oral supplementation has been chosen over topical therapy for two reasons: higher bioavailability and better patient's compliance. Subjects with advanced POAG are generally elderly. For some of these, applying eye drops might be challenging. For this reason, the oral route is likely a better choice in the elderly population. In terms of clinical efficacy, it is difficult to determine whether topical or oral citicoline is superior. Data on this topic are lacking. This might be the purpose of a new prospective study.

The efficacy of this drug becomes apparent as early as one year after treatment initiation. Visual field function continues to improve for three years after treatment initiation. In the therapy group, mean MD improved throughout the three year period. Longer follow-up studies are needed to explore whether additional perimetric improvements might occur. No subjects reported any side effects from oral citicoline supplementation. This indicates an excellent benefit-to-risk ratio. The improvement in retinal sensitivity is likely not due to increased local bioavailability of neurotransmitters and neuromodulators. In fact, if this was the case, subjects in TG would show regression of MD and PSD parameters back to baseline values following the 2-month wash-out period.

According to the data present in the literature, glaucoma represents a degenerative disease of the fibers of the optic nerve similar to age-related changes. [28,33] Treatment with oral citicoline in POAG patients has been found to improve retinal sensitivity. Parisi et al. (2008) showed that one-year

treatment with oral citicoline improves retinal function, optic neuropathy, as well as neural conduction along the visual pathway, as shown with visual evoked potentials. [27]
As mentioned, the mainstay of treatment in POAG patients is pressure control [7,26]. Oral citicoline supplementation might be a valid adjunct to standard glaucoma therapy, as shown by this study. Oral citicoline might in fact help to avoid or delay RGCs degeneration.

Contributors

AR, CS, PF, BD, BC, TP, MM, PE made substantial contributions to conception and design. AR, PE, PF, BD, BC made substantial contributions to developing the protocol. AR, CS, BD, BC, MM, made substantial contributions to the acquisition of data, analysis, and interpretation of data. All authors have been involved in drafting the manuscript or revising it critically for important intellectual content; given final approval of the version to be published.

Ethical approval

Complete details of ethical procedure and methods are reported in the companion paper. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Financial support

None

Conflict of interest

The authors declare no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Abbreviations in this article:

RGCs: Retinal Ganglion Cells
IOP: Intraocular Pressure
MD: Mean Deviation
PSD: Pattern Standard Deviation
GSS2: Glaucoma Staging System 2
TG: Therapy Group
CG: Control Group

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