• Clinical Research •

Effect of oral citicoline therapy on retinal nerve fiber layer and ganglion cell-inner plexiform layer in patients with primary open angle glaucoma

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Abstract

● **AIM:** To evaluate the short-term effects of oral citicoline therapy on the retinal nerve fiber layer (RNFL) and the macular ganglion cell-inner plexiform layer (mGCIPL) in patients with primary open angle glaucoma (POAG).

● **METHODS:** Fifty-four eyes of 54 patients with POAG glaucoma included in the study. In addition to a topical hypotensive, 250-mg oral citicoline was administered to 27 patients, while 27 patients were assigned as the control group. RNFL and mGCIPL values were measured using optical coherence tomography (OCT) at 1d before treatment and 3mo after the initiation of treatment. At the third month visit, citicoline treatment was discontinued and drug-free control (wash-out) measurements were obtained at the fourth month in citicoline group.

● **RESULTS:** The average RNFL thickness was significantly higher at month 3 than the baseline (P=0.038) in citicoline group. However, this improvement partially regressed after a 1-month wash-out period. No statistically significant changes in RNFL were observed in the superior, nasal, temporal and inferior quadrants at months 3 and 4 (P>0.05). The change in the average and inferior quadrant RNFL thickness in the citicoline group at 3mo was significantly greater than the control group (P=0.006 and P=0.014, respectively). There were no significant differences between the groups according to the change in mGCIPL thickness and the superior, nasal and temporal quadrant RNFL thickness (P>0.05).

● **CONCLUSION:** With oral citicoline treatment, the loss in the average RNFL is prevented in POAG patients in the short-term. Study data show that citicoline may have a significant impact on slowing glaucoma progression, which could have a potential neuroprotective effect.

● **KEYWORDS:** glaucoma; citicoline; optical coherence tomography; retinal nerve fiber layer
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INTRODUCTION

Glaucoma is a progressive optic neuropathy characterized by thinning of the peripapillary retinal nerve fiber layer (RNFL) and loss of retinal ganglion cells (RGCs). It is one of the most common causes of irreversible vision loss throughout the world[1-3]. Findings such as thinning of the neuroretinal rim, cupping, and sectoral RNFL defects may occur. Glaucoma is generally classified as open or closed angle glaucoma and primary or secondary glaucoma based on the anterior chamber anatomy. The most common form is primary open angle glaucoma (POAG)[4-5].

Patients with both high and normal intraocular pressure (IOP) benefit from IOP lowering therapy and there is a decrease in the progression of glaucoma. Accordingly, it seems that some people's RGCs are more or less sensitive to changes in IOP. Different treatment strategies to reduce this sensitivity have been the subject of research. In addition, intolerance to multi-drug use and difficulty in compliance, inability to achieve the desired results with surgery, and continuation of glaucoma progression despite low IOP values have led to the investigation of different therapeutic goals. On the other hand, it has been shown that glaucoma does not only affect the optic nerve but also causes degenerative changes in the central visual pathways, lateral geniculate nucleus, and visual cortex. High IOP alone cannot explain this degeneration. It has been suggested that multiple factors, such as oxidative stress, ischaemia, neurotrophic growth factor deficiency, and axonal defects in the transport mechanism, play a role. For these reasons, interest in developing treatment strategies independent of neuroprotection and IOP has increased[1,6].

New treatment strategies are aimed at identifying agents that provide neuroprotection regardless of lowering the IOP and regenerating RGCs and axons and maintaining their functions. Citicoline (cytidine-5'-diphosphocholine) is an endogenous compound that acts as a mediator in the synthesis of membrane phospholipids, such as phosphatidylcholine. Experimental studies[7-8] have shown that oral citicoline increases brain metabolism by activating phospholipids of neuronal membranes and increasing the release of neurotransmitters, such as dopamine and norepinephrine. In addition, it plays an important role in neurodegenerative diseases by reducing the excitotoxicity of glutamate and oxidative stress, increasing neurotrophin levels, and regulating mitochondrial function. It has been demonstrated to be effective in treating cognitive and behavioural disorders in elderly patients and people with Alzheimer's disease, Parkinson's disease, and ischaemic and traumatic brain injury. Dopamine is an important intraretinal neurotransmitter that is also effective in retinal nerve conduction. It has been suggested that citicoline may have a neuron-enhancing effect, which may explain the improvement in glaucomatous perimetric conditions and reduction of the progression of visual field defects in glaucomatous eyes[8-12].

Optical coherence tomography (OCT) is a non-invasive imaging method that obtains reproducible measurements in the diagnosis and follow-up of glaucoma as well as objective measurements of the optic nerve head and macula. Chronic degeneration of RGCs can be assessed by monitoring changes in the RNFL and the macular ganglion cell inner plexiform layer (mGCIPL) where the axons, dendrites, and soma of the RGCs are located[13-15].

The aim of this study was to evaluate the short-term effects of oral citicoline treatment in POAG patients by OCT parameters (RNFL and mGCIPL). In addition, we aimed to determine whether the potential effects of the study were due to citicoline treatment by leaving a wash-out period.

SUBJECTS AND METHODS

Ethical Approval This prospective study included 54 eyes of 54 patients who were followed up with a diagnosis of POAG in the Ordu University Training and Research Hospital Eye Clinic between March 2020 and August 2020. The study was conducted in accordance with the Helsinki Declaration and was approved by the Ordu University Training and Research Hospital Ethics Review Board (Number: 2020/24). Written informed consent was obtained from all participants.

Participants and Study Design POAG was defined as the presence of glaucomatous visual field defects corresponding to damage to the head of the optic nerve in at least one eye and an open irido-corneal drainage angle with gonioscopy. The inclusion criteria were as follows: patients aged 20-65y with a confirmed POAG diagnosis; patients with at least one year follow-up with at least two consecutive reliable visual fields within the previous year; and IOP<21 mm Hg with unchanged topical antiglaucomatous treatment in the last three months. The exclusion criteria were as follows: any anterior segment pathology (corneal opacities and intense cataracts that may interfere with OCT imaging); best corrected visual acuity (BCVA) worse than 20/40; previous history of glaucoma or retinal surgery; macular degeneration or retinal disorders; smoking; any systemic disease that may cause neurodegeneration (*e.g.*, multiple sclerosis, diabetes mellitus); use of any systemic drugs that may affect IOP values; optic neuritis; history of citicoline hypersensitivity; previous treatment involving lutein, zeaxanthin, citicoline, and coenzyme Q10; and pregnancy or lactation. All examinations of the patients were performed by the same researcher. If both eyes met the criteria, the eye with worse BCVA was included in the study.

A complete ophthalmological examination was performed to all patients, including BCVA (converted to logMAR for statistical analysis), slit-lamp examination, IOP measurement, central corneal thickness (CCT) measurement, and dilated fundus examination using the Snellen chart. IOP measurement was performed with Goldmann applanation tonometry and CCT was measured using ultrasonic pachymeter (Pac-Scan 300p, Sonomed Escalon, NY, USA). Following other ophthalmological examinations, mGCIPL and RNFL measurements were performed using an SD-OCT device (Cirrus HD-OCT 4000, Carl Zeiss Meditec, Dublin, CA, USA). Ophthalmological examinations and SD-OCT measurements were performed in the morning (between 8 *a.m.* and 10 *a.m.*).

Patients with glaucoma were under topical therapy with one or a combination of conventional antiglaucoma drugs, including beta blockers, prostaglandin analogues, carbonic anhydrase inhibitors, and alpha-adrenergic agonists. The patients were randomly assigned into two groups. Citicoline group: during the study, the patients received an oral dietary supplement (Cebrolux®NF, Bausch & Lomb) once daily in the form of granular soluble sachets containing 250 mg of citicoline as a neuroprotective co-adjuvant therapy. Control group, those who did not receive oral citicoline therapy. Measurements and OCT scans were performed one day before and three months after the initiation of oral citicoline. Citicoline treatment was discontinued at month 3 and drug-free control measurements were performed at month 4.

All OCT scans and measurements were obtained by the same experienced technician without pupil dilation. Minimum and average mGCIPL scanning was performed using a macular cube 512×128 scan protocol (128 consecutive line scans in a 6×6 mm^2 square grid). Peripapillary RNFL thickness was measured using the Optic Disc Cube 200×200 protocol

along a 1.73 mm radius circle aligned on the optical disc by the machine (Figure 1). For peripapillary RNFL thickness measurements, the average (360°) and quadrant (superior, nasal, inferior and temporal) values determined by the device software were recorded. Scans with signal strength >7/10 were used for analysis. Two consecutive scans were taken to exclude artifacts, and those with the best signal strength were analysed.

Statistical Analysis All analyses were performed with SPSS v21 (SPSS Inc., Chicago, IL, USA). As a normality check, the Shapiro-Wilk test was used. Data are given as the mean±standard deviation or median (minimum-maximum) according to distribution normality for continuous variables and as frequency (percentage) for categorical variables. Normally distributed variables were analysed with an independent *t*-test, and non-normally distributed variables were analysed with the Mann-Whitney *U* test. Categorical variables were analysed with the Chi-square test. The normally distributed repeated measurements were analysed with the paired *t*-test or repeated measures analysis of variance (ANOVA), depending on the count of measurements. With the Wilcoxon signed-rank test or Friedman's ANOVA by ranks, non-normally distributed repeated measurements were analysed. Pairwise comparisons were performed with Bonferroni's correction method (negative values represent a decrease in measurements, and positive values represent an increase in measurements). Between-group comparisons of the variables were performed by analyzing the differences between the measurements with the Mann-Whitney *U* test. *P* values <0.05 were accepted as statistically relevant findings.

RESULTS

We included 54 patients (23 males and 31 females) into our study; the mean age was 53.00±7.68y (range, 33-68y). Twenty-seven of the patients in this study were assigned as the citicoline group, whereas 27 patients belonged to the control group. The demographic characteristics of the patients are listed in Table 1. No substantial difference in gender distribution, age, visual acuity, spherical equivalent, IOP and CCT values (*P*>0.05) was observed between the groups. The IOP did not exceed 21 mm Hg in any of the patients during follow-up.

In citicoline group, there were no statistically significant differences between the baseline and the follow-up measurements regarding spherical equivalent, BCVA, IOP and CCT (*P*>0.05). Measurements at the third month of citicoline treatment and after 1mo of cessation (month 4) are shown in Table 2. The average RNFL thickness was significantly higher in the third month than the baseline (*P*=0.038). There were no notable differences between the baseline and the fourth month average RNFL thickness values (*P*=0.436) and between the third and fourth month values (*P*=0.895). No significant differences

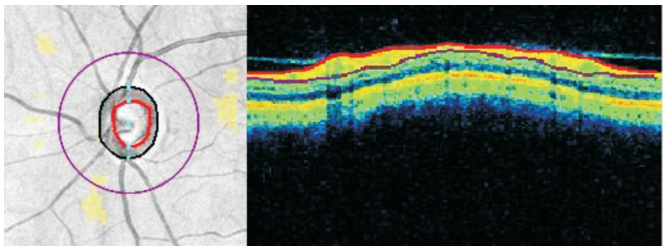

Figure 1 Optical coherence tomography image showing peripapillary retinal nerve fiber layer.

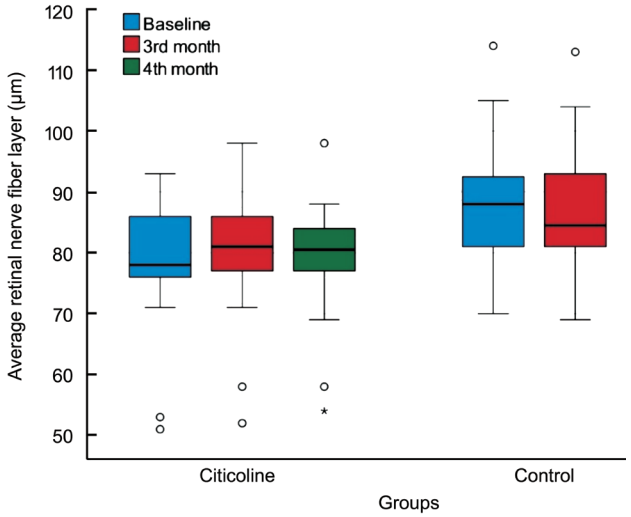

Figure 2 Average retinal nerve fiber layer with regard to groups and times The box represents 50% of the sample. Single line inside the box represents median. Small circles and asterisk represent the outliers at nerve fiber layer thickness.

in the RNFL thicknesses of the superior, nasal, temporal and inferior quadrants were observed between the baseline and the third and fourth month measurements (*P*=0.617, 0.397, 0.877, and 0.092, respectively). The differences between the minimum mGCIPL and the average mGCIPL were not statistically significant in months 3 and 4 (*P*=0.207 and 0.925, respectively).

Table 3 shows the mGCIPL and RNFL measurements of the control group. In the control group, a significant decrease in the minimum mGCIPL at 3mo was noted, but no significant change in the average mGCIPL was observed (*P*=0.025 and 0.246, respectively). In addition, the temporal RNFL was significantly decreased in the 3rd month (*P*=0.047). There were no significant changes in the RNFL thicknesses of the average, superior, nasal and inferior quadrants between the baseline and the third month measurements (*P*=0.067, 0.372, 0.482, and 0.154, respectively).

Table 4 shows the mean difference in measurements between both groups. When we assessed changes in the measurements between groups, the change in the average RNFL thickness in the citicoline group at 3mo was significantly greater than the control group (*P*=0.006; Figure 2). Furthermore, the average

Table 1 Demographic and clinical characteristics of participants

Parameters	Groups		*P*
	Citicoline (*n*=27)	Control (*n*=27)	
Age (y)	52.23±7.52	53.71±7.89	0.483[a]
Gender			0.248[b]
Male	10 (37.04%)	13 (48.15%)	
Female	17 (62.96%)	14 (51.85%)	
Topical hypotensive drug			1.000[b]
Single	10 (38.46%)	11 (39.29%)	
Multiple	16 (61.54%)	17 (60.71%)	
Side			0.441[b]
Right	16 (59.26%)	14 (51.85%)	
Left	11 (40.74%)	13 (48.15%)	
SE (D)	0.05±1.48	0.01±0.92	0.919[a]
BCVA (logMAR)	0.06 (0.3, 0.0)	0.03 (0.2, 0.0)	0.278[c]
IOP (mm Hg)	15.13±2.44	15.54±2.48	0.541[a]
CCT (μm)	556.5 (515, 582)	555 (510, 609)	0.876[c]

Data are given as mean±standard deviation or median (minimum, maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. SE: Spherical equivalent; D: Diopter, BCVA: Best corrected visual acuity; IOP: Intraocular pressure; CCT: Central corneal thickness. [a]Independent samples *t*-test; [b]Chi-square test; [c]Mann-Whitney *U* test.

Table 2 Summary of measurements observed in POAG patients treated with citicoline

Parameters	Time			*P*
	Baseline	3rd month	4th month	
mGCIPL (μm)				
Minimum	74.46±7.26	75.92±7.15	76.12±7.07	0.207[a]
Average	80.00±6.75	80.08±5.99	80.12±6.40	0.925[a]
RNFL (μm)				
Average	78 (51, 93)[a]	81 (52, 98)[b]	80.5 (54, 98)[a,b]	0.026[b]
Superior	97.81±19.02	99.19±18.19	98.81±17.11	0.617[a]
Nasal	63.73±11.93	63.15±10.89	62.42±11.11	0.397[a]
Temporal	56.58±6.09	56.81±6.24	56.46±4.88	0.877[a]
Inferior	102.5 (52, 123)	103 (57, 124)	103.5 (53, 122)	0.092[b]

Data are given as mean±standard deviation or median (minimum, maximum) according to normality of distribution. Same letters denote the lack of statistically significant differences between repeated measurements. POAG: Primary open angle glaucoma; mGCIPL: Macular ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer. [a]Repeated measures analysis of variance; [b]Friedman's analysis of variance by ranks. 3rd month: Citicoline treatment; 4th month: Citicoline treatment stopped-the washout period.

RNFL difference between the fourth month and the baseline was significantly higher in the citicoline group than the difference at the third month in the control group (*P*=0.040). Changes in mGCIPL thickness, superior, nasal and temporal quadrant RNFL thickness did not indicate major differences between the groups (*P*>0.05).

Table 3 Summary of optical coherence tomography measurements in the control group

Parameters	Time		*P*
	Baseline	3rd month	
mGCIPL			
Minimum	76.14±5.82	74.96±7.01	0.025[a]
Average	79.89±5.96	79.54±6.65	0.246[a]
RNFL			
Average	88 (70, 114)	84.5 (69, 113)	0.067[b]
Superior	108.57±14.97	107.43±12.85	0.372[a]
Nasal	67.36±9.42	67.89±9.04	0.482[a]
Temporal	63.93±12.21	60.71±13.3	0.047[a]
Inferior	109 (85, 149)	107.5 (80, 151)	0.154[b]

Data are given as mean±standard deviation or median (minimum, maximum) for continuous variables according to normality of distribution. [a]Paired *t*-test; [b]Wilcoxon signed ranks test. mGCIPL: Macular ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer.

Table 4 Changes in repeated measurements with regard to groups (3rd month *vs* baseline)

Parameters	Groups		*P*[a]
	Citicoline (*n*=27)	Control (*n*=27)	
mGCIPL			
Minimum	0 (-4, 12)	-1 (-9, 2)	0.052
Average	0 (-9, 4)	0 (-3, 3)	0.315
RNFL			
Average	2 (-11, 8)	-1 (-19, 4)	0.006
Superior	1 (-18, 20)	-2 (-16, 13)	0.196
Nasal	1 (-27, 11)	0.5 (-7, 12)	0.896
Temporal	1 (-7, 15)	-2.5 (-28, 11)	0.075
Inferior	2.5 (-7, 11)	-1 (-54, 22)	0.014

Data are given as median (minimum, maximum) for continuous variables according to normality of distribution. Negative values represent a decrease in measurements, and positive values represent an increase in measurements. mGCIPL: Macular ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer. [a]Mann-Whitney *U* test.

DISCUSSION

Although treatments for lowering IOP are neuroprotective in glaucoma, additional different treatments have been investigated with the purpose of sustaining regeneration in the RGCs and to reduce loss in functional vision[16-18]. It has been reported that pro-apoptotic effects and synaptic loss in neural tissues decrease with citicoline[19]. It is thought that this damage can be prevented by increasing the plasma citicoline level in neurodegenerative diseases. Citicoline has been investigated as a potential neuroprotective therapeutic agent for amblyopia, nonarteritic ischaemic optic neuropathy, corneal oxidative damage and glaucoma[7,20-23]. Citicoline administration may become a potential treatment for the prevention of cellular death in glaucoma with neurodegeneration.

The neuroprotective effect of citicoline in glaucoma has been demonstrated. Parisi *et al*[24] showed that oral and intramuscular

(IM) citicoline significantly improved retinal and cortical responses in patients with glaucoma. In this study, which evaluated treatment responses using visual evoked potentials (VEPs) and pattern electroretinograms (PERGs), oral (1600 mg/d) and IM (1000 mg/d) citicoline were compared, and no difference was found between the two methods of use. In addition, it has been reported that VEP and PERG values decreased to pre-treatment levels after a 2-month wash-out period. Another study showed that topically administered citicoline improved retinal function and neural conduction along the visual pathway. Following topical citicoline treatment, an increase in PERG amplitudes and a shortening in VEP latency values were observed[25]. In a study that showed long-term efficacy of oral citicoline by Lanza *et al*[26], perimetry measurements were obtained from patients with POAG who were followed up for two years with oral 500 mg citicoline therapy and wash-out periods, and RNFL and RGC thickness analysis with OCT was performed. The group that received citicoline had morphological and functional improvements compared to the control group. During the 2-year follow-up period, RNFL and RGC complex thicknesses were reported to be higher and more stable in patients who received citicoline.

The objective of this study was to determine the short-term efficacy of oral citicoline supplementation in patients with POAG whose IOP was under control with topical anti-glaucomatous therapy. In our study, a lower dose of citicoline was used compared to the systemic dose of citicoline reported in previous studies. There was a statistically significant increase in the mean RNFL thickness values in the third month of citicoline use. Although this effect did not return to the pretreatment level in the fourth month following the 1-month wash-out period, a decrease was observed. Furthermore, although there was an increase in RNFL thickness in the superior and inferior quadrants at month 3, it was not statistically significant. The role of IOP in neurodegeneration in glaucoma is important. No significant change in IOP values during follow-up was noted, and no sudden increase in IOP requiring treatment modification was observed. Succeeding scans with better image quality were evaluated to exclude the effect of artifacts on OCT scans. Thus, the effect of this parameter could be excluded while evaluating the OCT results. In the control group, there was an insignificant decrease in the average RNFL values at the third month control. In the citicoline group, after the citicoline treatment, no significant loss in the average RNFL thickness values at the visits was reported, and the average RNFL was more preserved than the control group.

The patients with POAG were not classified according to the antiglaucomatous drugs they used in our study. Systemic use of citicoline was reported to slow down the rate of glaucoma progression in patients using beta blockers alone, or beta blockers combined with prostaglandin analogues. However, the occurrence of these effects took longer time[26]. Chițu *et al*[27], in their study evaluating heterogeneous glaucoma patients using VEP and OCT, indicated that oral citicoline therapy had positive effects after 6mo in patients with POAG. The antioxidant and neuroprotective effects of alpha-adrenergic agonists were reported to occur when IOP was high and used for longer than 3mo[28]. Consequently, we believe that antiglaucomatous eye drops would not have a significant effect, in our study evaluating the short-term effects of oral citicoline therapy.

RGC axons are rich in myelin and are important structures that are affected in glaucoma. Therefore, damage to RGCs is one of the primary indicators of glaucomatous damage. It has been reported that citicoline has a protective effect on damaged RGCs in tissue culture of the retina[29]. In their study, van der Merwe *et al*[30] created an experimental glaucoma model and showed that oral citicoline improved neurodegenerative changes and decreased visual function due to IOP elevation. In the evaluation of the minimum mGCIPL thickness in our study, there was an increase in the third month after the initiation of citicoline treatment. When citicoline treatment was discontinued, this increase did not return to previous levels, but these changes were not statistically significant. There was no significant change in the average mGCIPL with citicoline treatment and when the treatment was discontinued. Changes in mGCIPL thickness did not indicate major differences between the groups.

There were some limitations in our study. First, in the treatment preparation that was used, in addition to citicoline, there were also antioxidants, such as low-dose vitamin C and vitamin B12, and components known to have a positive effect on nerve tissue. We believe that the effect on the results was primarily due to citicoline, since these substances were used at very low doses compared to the treatment doses. Second, it may not be possible to measure neuroprotective effects with OCT in the short follow-up period. Furthermore, our sample size was limited. In addition, glaucoma stages were heterogeneous in the patients who were included in the study. This could be considered a sample profile that is more consistent with the routine glaucoma patient profile, which may contribute to a more realistic evaluation of the results.

In conclusion, oral citicoline treatment prevents reduction of the average RNFL in patients with POAG, and this effect occurred in the short period of three months. Since the effect is reversible when drug therapy is discontinued, extending the duration of the treatment may be considered to maintain the effect. Considering the limited sample size, these results should be supported by further studies with larger patient groups and

longer follow-up periods. The study data suggested that oral citicoline supplementation may have a significant effect in slowing glaucoma progression.

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