



The Use of Citicoline in Ophthalmology: A systematic review

Erel Icel, Okan Akmaz

Department of Ophthalmology, Izmir City Hospital, Izmir, Türkiye

Abstract

Objectives: Citicoline is a chemical molecule, and it plays a crucial role in the biosynthesis of cell membranes and has many functions in the human body. This compound, which increases the amount of neurotransmitters, is used in the treatment of various diseases in ophthalmology, neurology, and psychiatry. Its use as a supplement to improve cognitive functions is also widespread. In this review, we aim to shed light on the neuroprotective effects of citicoline and its applications in the field of ophthalmology, based on data obtained from published studies.

Methods: In the literature, the effects of citicoline in various ophthalmological diseases have been mentioned; however, there is no clear consensus regarding its dosage, duration of use, or efficacy due to the limited number of published studies and designs of these studies. Upon reviewing the current studies, we found evidence suggesting that citicoline supplementation may be effective in amblyopia, glaucoma, and non-arteritic ischemic optic neuropathy.

Conclusion: This review aims to evaluate and summarize the current evidence on the neuroprotective effects of citicoline in ophthalmologic diseases. Findings from various clinical studies suggest that it may have a beneficial effect on the treatment of conditions including amblyopia, glaucoma, and non-arteritic ischemic optic neuropathy.

Keywords: Amblyopia, CDP-choline, citicoline, glaucoma, non-arteritic ischemic optic neuropathy

Introduction

Citicoline is a mononucleotide that comprises ribose, cytosine, pyrophosphate, and choline. It serves as a precursor to phosphatidylcholine, a key component of mitochondrial and neuronal membranes. Citicoline is a water-soluble compound with a bioavailability exceeding 90% (1).

The term citicoline refers to cytidine-5'-diphosphocholine (CDP-choline, CDPCho). This compound is a naturally occurring endogenous chemical. Citicoline is available in many countries as a dietary supplement and medication. When administered in oral or injectable form, citicoline undergoes hydrolysis and dephosphorylation, resulting in the breakdown into cytidine and choline. These components are then thought to act as substrates for the synthesis of

phosphatidylcholine and CDP-choline within neurons. The metabolism of citicoline's function has not yet been fully understood in all aspects (2).

Citicoline exhibits negligible toxicity. When the compound is taken, it is rapidly metabolized and converted into cholinergic and pyrimidinergetic metabolites. The resulting products can then be used for various biosynthetic pathways and are ultimately excreted as carbon dioxide. It has been repeatedly confirmed in previous studies that citicoline does not have any side effects in the acute and chronic phases (3).

Citicoline, which serves as a substrate for phosphatidylcholine formation, is also an inhibitor of phospholipase A2 (PLP-A2) and directly affects the membrane of damaged neurons that are still alive. With its neuromodulatory ef-

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Address for correspondence: Erel Icel, MD. Department of Ophthalmology, Izmir City Hospital, Izmir, Türkiye
Phone: +90 232 398 37 00 **E-mail:** dr_ereI@hotmail.com

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fect linked to the dopamine system, citicoline is effective in Parkinson's disease. Dopamine is a major neurotransmitter effective in the retinal and post-retinal areas (1). In addition to dopamine, this compound also affects the levels of acetylcholine and norepinephrine. It is currently used in the treatment of Alzheimer's disease and stroke due to its brain-stimulating effects (4).

Citicoline may help preserve sphingomyelin, a membrane component essential for neuronal signal transmission. CDP-choline enhances the concentration of dopamine, norepinephrine, and serotonin within the central nervous system. It has neuroprotective effects in hypoxia and ischemia. It also exhibits neuroprotective anti-aging effects on the brain. It has been demonstrated that CDP-choline restores mitochondrial ATPase and membrane Na/K ATPase activities in various experimental models, inhibits PLP-A2 activation, and accelerates the reabsorption of brain edema (5,6).

On the other hand, the neuroprotective effects of citicoline have been documented in dopaminergic mesencephalic neurons, neuroblastoma cells, and cultured retinal cells in *in vitro* models (7).

In conclusion, studies have determined that citicoline is effective in the regeneration of neurons and in the increase of various neurotransmitter levels. This study aims to evaluate the efficacy of citicoline treatment in improving visual function in ophthalmologic diseases compared to placebo or standard treatment.

Methods

The primary literature search was performed in PubMed (January 2025), and additional searches were conducted using open-access academic search engines, including Google Scholar and CrossRef to enhance the sensitivity of the search and reduce potential publication bias. Articles on the use of citicoline in the treatment of ophthalmological diseases were reviewed. The keywords "citicoline," "CDP-choline," "glaucoma," "amblyopia," "non-arteritic ischemic optic neuropathy," and "ophthalmology" were used to find the articles. The process of study identification, screening, and inclusion is illustrated in the preferred reporting items for Systematic Reviews and Meta-Analyses 2020 flow diagram (Fig. 1). Studies in which citicoline was combined with other neuroprotective agents, abstracts, reviews, comments, and letters were excluded from the study. Studies involving animals, biomechanics, computational models, *in vitro* research, and cadaveric studies were deemed ineligible. Two ophthalmologists conducted the analysis. Table 1 provides a summary of the inclusion and exclusion criteria. A three-stage analysis was conducted, including the title, abstract, and full text. The variables examined by the authors include study design, sample size, total number of participants, average age and gender of the study partici-

Table 1. Inclusion and exclusion criteria of the study

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Articles in English Clinical studies, multicenter studies, in humans. 	<ul style="list-style-type: none"> Publications written in languages other than English Reviews and case reports Studies conducted on subjects other than humans

pants, average duration of diagnosis, disease severity, outcome measures, citicoline dosage, and number of patients. Since this study did not involve direct human or animal participation, ethical approval was not required.

Results

A total of 2498 records were identified through PubMed, Google Scholar, and CrossRef searches. After removal of duplicates and title-abstract screening, 196 full-text articles were assessed for eligibility, and 30 studies met the inclusion criteria and were included in the qualitative synthesis.

Application of Citicoline in Amblyopia

The application of citicoline in amblyopia has attracted attention due to its potential to improve visual function and stimulate neural plasticity. Citicoline, a compound that enhances phospholipid synthesis and promotes neuronal repair, has been investigated as a potential adjunctive treatment in amblyopia. Citicoline may enhance retinal and post-retinal visual pathways by stimulating the dopaminergic system. It has been shown to improve contrast sensitivity, visual acuity (VA), visual evoked responses, and the effectiveness of part-time occlusion therapy (8). While the exact mechanisms and optimal dosages for citicoline in amblyopia remain subjects of ongoing research, preliminary findings have shown promise, particularly in conjunction with other therapies such as occlusion or vision training. However, further large-scale, controlled trials are needed to confirm its efficacy and establish definitive treatment protocols. Key clinical studies are summarized in Table 2. In their 1995 study, Campos *et al.* presented preliminary results from a trial investigating citicoline in amblyopia. The open-label study, initiated in 1991, included 50 patients with amblyopia treated with citicoline. In addition, a randomized and double-blind study was conducted involving 10 patients, who were allocated to either the treatment or placebo group and followed prospectively for 6 months. The double-blind study confirmed these findings, with no reported adverse effects throughout the observation period (9). In children, Campos *et al.* showed that oral CDP-choline, either alone or combined with part-time occlusion, produced significant VA improvement over 1 year, with the combined regimen providing the most stable long-term effect (10).

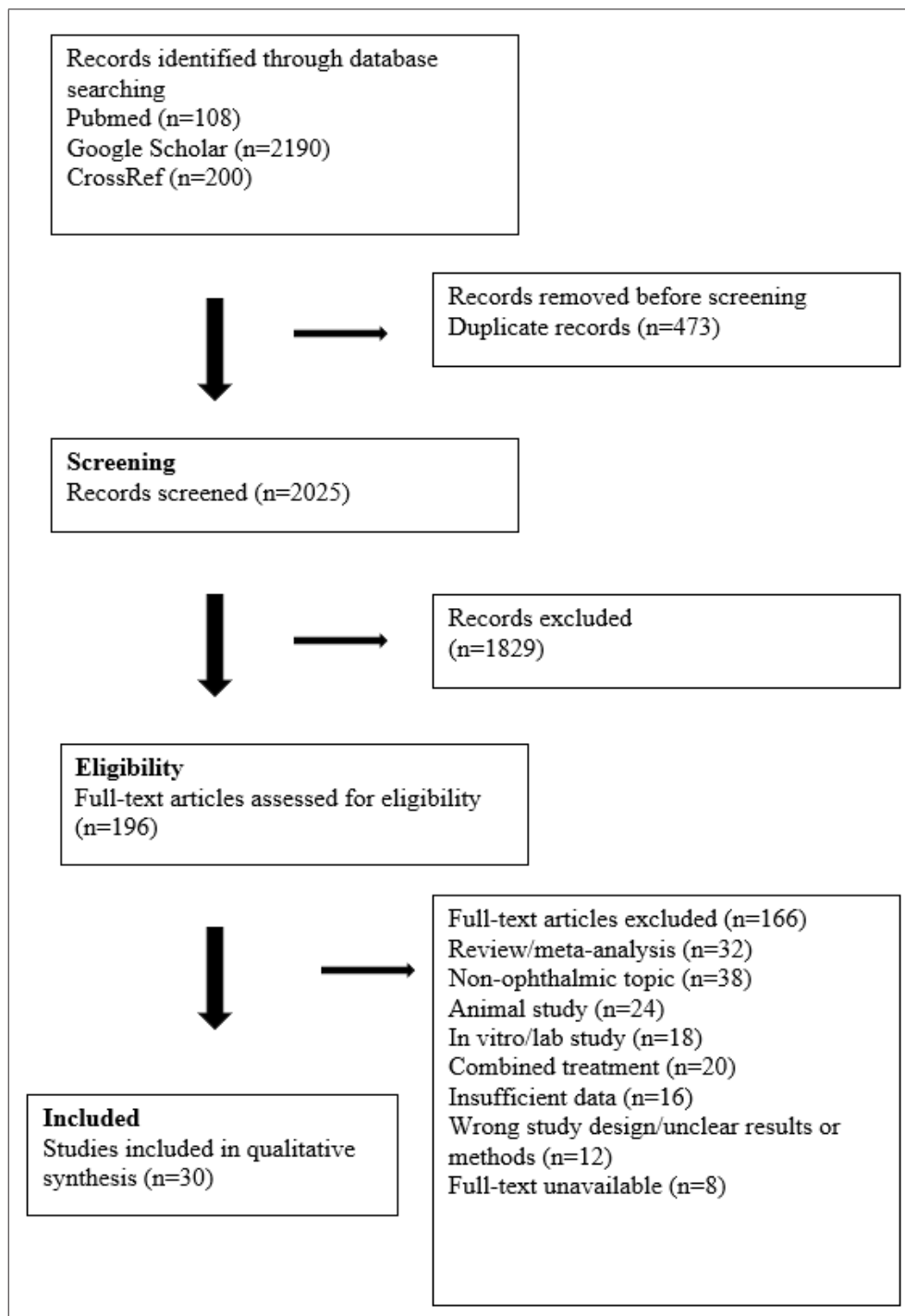


Figure 1. PRISMA 2020 flow diagram of the study selection process.

Porciatti *et al.* reported that intramuscular CDP-choline in adults improved VA, contrast sensitivity, and VEP parameters, supporting a functional neuroenhancing effect (11).

More recent pediatric data are heterogeneous. A retrospective series from Indonesia suggested that citicoline is particularly effective in mild to moderate refractive amblyopia, with treatment durations of 3–6 months (12).

Pawar *et al.* investigated the effectiveness of adding citicoline to patching therapy for amblyopia in children. During phase I, no notable disparity in the average VA was observed between the two groups until a plateau was reached. In phase 2, VA showed no considerable variation between the groups during the first 4 months. However, starting from the 5th month through the twelfth, a significant improvement was noted in Group I compared to Group II. This trend was con-

Table 2. Clinical studies evaluating citicoline in the treatment of amblyopia

First author (year)	Study design	Population	Citicoline regimen	Comparator/co-treatment	Follow-up	Main outcomes&key findings
Campos (9) (1995)	Open-label study+randomized double-blind placebo-controlled sub-study	50 patients with amblyopia, beyond critical period of visual development; additional 10 patients in RCT	1000 mg IM daily for 5 days	RCT: Citicoline vs. placebo	Up to 6 months	In the open-label cohort, VA improved significantly in both amblyopic and fellow eyes in 92% of patients, with effect maintained ≥ 4 months. The double-blind trial confirmed VA improvement without reported adverse events.
Campos (10) (1996-1997)	Prospective comparative study	45 children (5-9 years) with unilateral amblyopia	Group 1: CDP-choline 500 mg/day for 10 days every 6 months; Group 2: same regimen+ 1 h/day occlusion; Group 3: 1 h/day occlusion alone	Three arm comparison	12 months	All groups showed significant VA gains. Group 1 had initial improvement with partial regression by month 4 but further gain after retreatment. In Group 2, VA improvement occurred within 10 days and remained stable. Group 3 improved after 1 month and remained stable for 8 months.
Porciatti (11) (1998)	Prospective pre-post interventional study	10 adults with amblyopia	(CDP-choline) 1 g IM Daily for 15 days	None	Assessment pre-treatment and 1 day post-treatment	Mean VA gain of 1.4 to 1.5 lines in amblyopic eyes and 0.4 lines in fellow eyes. CS increased by ~ 3 dB in both eyes. VEP amplitude increased by $\sim 30\%$ with phase shift; overall improvement in VA, CS and VEP parameters. Citicoline was effective in mild-moderate amblyopia and treatment durations of 3 and 6 months.
Loebis (12) (2021)	Retrospective chart review	34 eyes; mainly 5-6 years old; mild (61.8%), moderate (20.6%); severe (5.9%) amblyopia	Various citicoline regimens; 3-8 months	No standardized control group	3-8 months	Citicoline was effective in mild-moderate amblyopia and treatment durations of 3 and 6 months.

Table 2. Clinical studies evaluating citicoline in the treatment of amblyopia

First author (year)	Study design	Population	Citicoline regimen	Comparator/co-treatment	Follow-up	Main outcomes&key findings
Pawar (4) (2014)	Randomized controlled trial	4-13 years with amblyopia	Phase 2: Group I received citicoline 250 mg/day(<5 years) or 500 mg/day (≥5 years) plus patching	Group II: patching alone	Phase I: until VA plateau; Phase 2: 12 months	During phase I VA improvement was similar between groups. In phase 2, starting from the fifth month through the twelfth, a significant improvement was noted in Group I compared to Group II.
Fresina (13) (2008)	Randomized comparative study	61 children (5-10 years) with anisometropic or strabismic amblyopia	Group A: 800-1200 mg oral citicoline + 2h/day patching for 30 days	Group B: 2h/day patching only	30 day treatment-60 day follow-up	Short-term VA improvement was similar between groups. However at 90 days, VA gains were better maintained in the citicoline group, whereas BCVA tended to regress towards baseline in controls.
Sabetti (14) (2017)	Prospective comparative study	39 patients with amblyopiatreated with Bangerter filters	Oral citicoline once daily, 5 days/week, combined with Bangerter filter in one group.	Bangerter filter alone	12 months	VA improved in both groups. Filter only group: VA from 0.27 to 0.09 logMar. Filter+citicoline group: from 0.35 to 0.01 logMar.

RCT: Randomized controlled trial, IM: intramuscular.

sistent across both younger (<7 years) and older (>7 years) patients (4).

Fresina *et al.* (13) compared the combination of patching and oral CDP-choline with patching on its own. The vision improvements in the control and citicoline groups were similar. However, integrating CDP-choline with conventional amblyopia therapy led to a more pronounced medium-term effect, as evidenced by enhanced visual function stabilization at 90 days. Notably, in those receiving CDP-choline, the visual improvements obtained with patching were maintained over the next 2 months. In contrast, the control group (CG)

exhibited a tendency for BCVA to decrease, gradually approaching pre-treatment values.

Sabetti *et al.* examined the effect of choline supplementation in combination with the Bangerter filter as a treatment for amblyopia. Neither group exhibited any notable alterations in the angle of deviation throughout the study. Both therapies led to improvements in VA; however, the combination of the Bangerter filter with choline demonstrated notably greater efficacy, particularly in cases of severe amblyopia (14).

Based on the above analysis, the efficacy of citicoline in improving the clinical condition of individuals with amblyo-

Table 3. Clinical studies evaluating im citicoline as an adjunctive therapy in glaucoma

First author (year)	Study design	Population	Citicoline regimen	Comparator/co-treatment	Main outcomes&key findings
Pecori Giraldi (15) (1989)	Prospective interventional study	POAG	IM 1 g/day for 15 days, repeated every 6 months	No citicoline	Smaller VF loss in citicoline treated eyes
Virno (16) (2000)	Long-term follow up	POAG; 11 treated vs 12 untreated	IM 1 g/day for 15 days, repeated every 6 months; 11 year follow-up	No citicoline	VF area remained more stable in the citicoline group ≥ 500 mm ² VF loss occurred in 2/11 vs 5/12 controls
Parisi (17) (1999)	Randomized double blind placebo controlled trial	OAG, n=40	IM 1 g/day for 60 days; repeated after wash out in a subgroup	Placebo injections	Significant improvement in PERG and VEP parameters in the citicoline group
Parisi (18) (2005)	Prospective electrophysiologic follow-up	OAG, long-term follow up	IM 1 g/day for 60 days; repeated after wash out in a subgroup	No citicoline	Sustained electrophysiologic benefit over 8 years with periodic treatment.
Parisi ^[20] (2008)	Prospective comparative study	OAG	IM 1 g/day vs oral citicoline 1.6 g/day for 60 days	Route comparison	Both routes produced similar improvements in PERG and VEP; benefits decreased within 4 months after discontinuation but increased again with retreatment.

POAG: Primary open angle glaucoma, IM: intramuscular, OAG: open angle glaucoma.

pia remains inconclusive. Although most studies suggest that citicoline has a substantial positive impact on clinical outcomes, definitive conclusions remain uncertain. Prospective studies with a larger number of participants are required to obtain more definitive results.

Application of Citicoline in Glaucoma

The earliest clinical experience with citicoline in primary open-angle glaucoma (POAG) dates back more than two decades and was based on repeated intramuscular cycles. In an initial series and its long-term extension, patients receiving 1 g/day intramuscular citicoline for 15 days every 6 months showed a slower loss of visual field (VF) sensitivity than untreated controls over follow-up periods of up to 10 years (15,16).

Subsequent randomized placebo-controlled work by Parisi *et al.* confirmed that similar cyclic intramuscular regimens improved pattern electroretinogram (PERG) and VEP recordings in open-angle glaucoma (OAG) with functional

gains diminishing after wash-out but reappearing when treatment was restarted, suggesting a reversible neuroenhancing effect rather than a permanent cure (17,18).

Due to the impracticality of injections for managing chronic ophthalmic conditions, a pilot study was conducted to evaluate the effects of two biweekly courses of orally administered citicoline (1 g/day), separated by a 2-week interval, on VEPs in POAG patients. Despite the small sample size (21 eyes from 11 patients), the study demonstrated a statistically significant shortening of VEP P100 latency and a notable, albeit less pronounced, increase in VEP amplitude. The prolonged latency and diminished amplitude of VEP, frequently seen in ocular hypertension and OAG, suggest a delay in neural conduction within the visual pathways. Previous investigations have shown enhanced VEP latency and amplitude after the intramuscular delivery of citicoline, known for its neuroprotective properties. This study aimed

to determine whether oral administration of citicoline could achieve similar effects. In 21 glaucomatous eyes, VEP latency and amplitude were evaluated before and after two bi-weekly regimens of oral citicoline, administered at a dose of 1 g/day. The treatment regimens were spaced 2 weeks apart, and VEP measurements were performed 2 weeks after the completion of the second regimen. In 62% of the eyes, treatment resulted in a positive response, marked by a reduction of 11.6 ms in VEP latency ($123.5 \text{ ms} \pm 3.9$ standard error of the mean (SEM) to $111.9 \text{ ms} \pm 1.9$ SEM) ($p=0.0008$) and an increase of $1.32 \mu\text{V}$ in VEP amplitude ($6.56 \mu\text{V} \pm 1.39$ SEM to $7.88 \mu\text{V} \pm 1.16$ SEM) ($p=0.04$). According to these findings, oral citicoline appears to enhance visual evoked potentials in a subset of patients with glaucoma (19).

Later studies comparing intramuscular versus high-dose oral citicoline found comparable electrophysiologic benefits, again with a tendency for the effect to decline a few months after discontinuation and to improve with retreatment (20). An overview of the studies using intramuscular citicoline in glaucoma is presented in Table 3.

Further support for the sustained benefits of oral citicoline was provided by research conducted in three university clinics in Italy. A total of 41 patients with advancing POAG, despite adequate control of intraocular pressure (IOP), were included in this study. Participants received oral citicoline solution at a dose of 500 mg daily for 4 months, with treatment cycles interspersed by 2-month no-treatment intervals. Although not randomized, this study began with a retrospective analysis of disease progression before treatment, utilizing Humphrey perimetry, before transitioning into its prospective phase. The rate of VF progression significantly improved, decreasing from -1.1 dB/year before treatment to -0.15 dB/year during citicoline therapy. Participants were selected based on a documented progression of disease at a rate of no < -1 dB/year in mean deviation (MD) over the prior 3 years, even though IOP had been effectively controlled. Patients underwent four VF tests annually during the study period.

Despite maintaining IOP consistently under 18 mm Hg for a minimum of 3 years, the mean rate of VF decline at baseline still measured -1.1 (± 0.7) dB annually. At study initiation, the average IOP was calculated as 15.5 (± 2.6) mm Hg, while the most affected eye exhibited a MD of -9.2 (± 6.7) dB. After citicoline therapy commenced, the average rate of VF decline exhibited a marked reduction, reaching -0.15 (± 0.3) dB annually by study completion ($p=0.01$). The results imply that adding citicoline to the treatment regimen might play a substantial role in slowing down glaucomatous deterioration (21).

Lanza et al. (22) enrolled one eye per subject from a total of 60 individuals diagnosed with POAG, subsequently allo-

ating them randomly into two equal groups, labeled A and B. Computed tomography (CT) therapy was administered exclusively to Group A, with both groups being comparable in terms of age, sex, and duration of disease. Although IOP remained within controlled limits, all participants exhibited gradual disease progression over the preceding 3 years, as determined through standard automated white-on-white perimetry (SAP). Comprehensive ophthalmic evaluations – including IOP assessment, SAP, and OCT-derived measurements of RNFL and GCC thickness – were performed on all patients before CT initiation and at 6, 12, 18, and 24-month follow-ups.

By the 18-month mark, Group A demonstrated a significantly less negative mean MD value of -7.25 dB compared to -8.64 dB in Group B ($p=0.039$). In Group A, MD values remained relatively unchanged, whereas Group B exhibited a continued and statistically significant decline, reaching -9.28 dB over time ($p<0.001$). Following 12 months of CT treatment, Group A exhibited significantly greater mean RNFL and GCC thicknesses – $70.39 \mu\text{m}$ and $71.19 \mu\text{m}$, respectively – than those measured in Group B, which averaged $64.91 \mu\text{m}$ and $65.60 \mu\text{m}$ ($p<0.01$). These thicknesses remained stable in group A during subsequent visits, while they significantly thinned ($p<0.001$) in group B (22).

Researchers carried out a study to investigate how liposomal citicoline (CLF) eye drops influence retinal performance and neural signal transmission through the visual pathway in individuals diagnosed with OAG. The cohort consisted of 12 individuals diagnosed with OAG, averaging 52.58 ± 11.39 years in age, all exhibiting controlled IOP (< 18 mmHg) through topical agents and a Humphrey MD value of -4.49 ± 2.46 dB. CLF eye drops (OMKI-LF[®], Omikron Italia) were administered to a single eye per participant at a dosage of three drops daily over a 4-month treatment period. Evaluations of retinal activity and neural signal transmission were conducted through PERG, VEP, and VF testing both before treatment initiation and following the 4-month intervention period. Treated eyes demonstrated notable functional enhancements, evidenced by elevated PERG P50-N95 amplitudes and shortened VEP P100 implicit times. Moreover, a significant correlation was found between the reduction in VEP P100 implicit time and the enhancement in PERG P50-N95 amplitude. This pilot study suggests that CLF eye drops enhance retinal bioelectrical responses (evidenced by increased PERG amplitude), leading to improved bioelectrical activity in the visual cortex (23).

The study conducted by Sahin et al. (24) focused on assessing early structural changes in RNFL and mGCIPL following a short duration of oral citicoline therapy in POAG patients. The study included 54 eyes of 54 patients, divided into two groups: 27 patients received 250 mg of oral citi-

coline in addition to topical hypotensive therapy, while the other 27 served as a CG. RNFL and mGCIPL thickness were measured using OCT 1 day before treatment, 3 months after starting treatment, and 1 month after discontinuing citicoline (washout period). In the citicoline group, the average RNFL thickness was significantly higher at the 3-month mark compared to baseline ($p=0.038$), although this improvement partially diminished after the washout period. RNFL measurements in the superior, nasal, temporal, and inferior sectors showed no meaningful variation at the 3- and 4-month timepoints ($p>0.05$). Nevertheless, at the 3-month mark, the citicoline group exhibited a significantly greater increase in both average RNFL thickness and inferior quadrant measurements compared to controls ($p=0.006$ and $p=0.014$, respectively). There were no statistically significant intergroup differences in mGCIPL thickness or in RNFL measurements across the superior, nasal, and temporal quadrants ($p>0.05$). The findings suggest that oral citicoline therapy may help preserve average RNFL thickness in the short term for POAG patients, potentially slowing glaucoma progression.

Another study explored the controversial role of nutraceuticals in glaucoma treatment, aiming to assess the effects of Vitamin C, citicoline, and docosahexaenoic acid (DHA) on glaucoma patients. This study included 73 participants who were divided into four groups: One receiving Vitamin C, another DHA, a third citicoline, and a fourth DHA and citicoline, all treated for 3 months. Participants underwent monthly comprehensive eye evaluations and VF testing, with subsequent analysis and comparison of VFI values and their progression slopes across the study groups. Patients receiving a combination of citicoline and DHA exhibited a marked enhancement in VF parameters, with MD improving from -9.52 ± 4.36 to -7.85 ± 4.36 dB ($p=0.001$), alongside a significant rise in mean VFI ($p=0.001$) over the course of the study. Among all groups, only the DHA and citicoline group demonstrated a statistically significant shift in MD slope, improving from -0.1041 ± 0.2471 to 0.1383 ± 0.2544 dB/month ($p=0.006$), along with a corresponding enhancement in the VFI slope (25).

Parisi et al. (26) studied 56 patients with OAG receiving topical β -blocker monotherapy and maintaining IOP below 18 mmHg. Forty-seven eyes completed follow-up. Of these, 24 eyes were assigned to receive topical citicoline (OMKI[®], Omikron Italia), 3 times daily for 4 months, followed by a 2-month washout (GC group), while 23 eyes continued β -blocker monotherapy alone (GP group). At baseline, PERG and VEP parameters did not differ between groups. After 4 months, the GC group showed clear functional improvement with increased VEP N75-P100 and PERG P50-N95 amplitudes and a significant shortening of P100 implicit time ($p<0.01$). The reduction in P100 implicit time correlated

with the increase in PERG P50-N95 amplitude. Following the washout period, electrophysiological values in the GC group returned to levels comparable to baseline, with no significant intergroup differences, whereas the GP group demonstrated stable PERG and VEP findings throughout the study.

While the results appeared comparable to those achieved with oral citicoline, the concept of topical citicoline delivery is less favorable. Due to its water solubility, citicoline demonstrates poor corneal penetration. Nonetheless, the authors propose – based on preclinical evidence – that citicoline may penetrate into the vitreous chamber when formulated with high molecular weight hyaluronic acid and benzalkonium chloride serving as absorption enhancers. Oral citicoline, which is typically devoid of significant side effects, presents a considerably more favorable alternative.

In their investigation, Rosetti et al. (27) focused on individuals diagnosed with mild to moderate OAG, all of whom demonstrated a VF deterioration exceeding -0.5 dB annually over the past 2 years, even though their IOP remained within controlled limits. In this trial, participants were randomly assigned to administer either citicoline ophthalmic solution or a placebo, with dosing scheduled 3 times/day over a period of 3 years. The evaluation parameters comprised alterations in the progression rates of VF loss – quantified via MD values from both 24-2 to 10-2 testing algorithms – as well as changes in RNFL thickness. The study cohort comprised 80 patients. Following 3 years of treatment, the citicoline group exhibited a mean 24-2 MD decline of -1.03 dB (± 2.14), while the placebo group showed a greater deterioration at -1.92 dB (± 2.23), with the difference approaching statistical significance ($p=0.07$). For 10-2 MD, the progression rate was significantly slower in the citicoline group (-0.41 dB ± 3.45) compared to the placebo group (-2.22 dB ± 3.63 , $p=0.02$). In addition, the citicoline group experienced less RNFL thinning, with an average loss of 1.86 μ m over 3 years, compared to 2.99 μ m in the placebo group ($p=0.02$).

Carnevale et al. (28) recently showed that citicoline eye drops, when applied topically, achieve high concentrations in the vitreous of the human eye.

In a study exploring parallels between glaucoma and senile dementia, the authors proposed that neuroenhancement could be pursued in both conditions using agents like citicoline (18).

In the study conducted by Rosetti et al., (29) participants were randomized into two treatment sequences: One group received 500 mg/day of oral citicoline before switching to placebo, while the other group followed the reverse sequence. After 3 months, the treatments were switched, and patients were monitored for an additional 6 months. The main endpoint was the average change from baseline in VFQ-25 composite scores at 6 months, comparing citicoline

oral solution to placebo within the same patients. This multicenter study, carried out in five European ophthalmology centers, enrolled OAG patients with bilateral field defects, a better-eye MD ranging from -5 to -13 dB, and stable IOP. The predefined primary analysis revealed a significant benefit favoring citicoline ($p=0.0413$), with the most notable improvement observed in patients initially assigned to placebo followed by citicoline ($p=0.0096$, 0.0007 , and 0.0006). Citicoline's impact was particularly evident in those with poorer baseline vision-related quality of life.

Arrico et al. (30) evaluate the neuroprotective effects of oral citicoline in patients with POAG. A total of 110 patients with Stage IV POAG and well-controlled IOP were included. The participants were randomly divided into two groups: The therapy group (TG), which received 500 mg of citicoline daily for 4 months, followed by a 2-month wash-out period before resuming the same treatment; and the CG, which continued their standard glaucoma therapy without citicoline. Both groups were also treated with pressure-lowering medications. The results showed that the TG experienced a statistically significant improvement in MD values at 12 months ($\Delta=21\%$) and in PSD at 24 months ($\Delta=35\%$). In addition, there was a gradual improvement in the glaucoma staging system (GSS2) stage, reaching the 3rd stage with localized defects after 36 months of therapy. In contrast, the CG continued to experience deterioration in both MD and PSD indices throughout the study (30).

A study involving 22 patients with glaucoma and progressive visual dysfunction assessed the effects of oral citicoline. VEP analysis revealed fluctuations in P100 wave amplitude, with a notable increase at 6 months. P2 wave amplitude exhibited minimal variation, while a statistically significant increase in P2 latency was observed at the 6-month mark. Negative correlations emerged between RGC layer thickness and P100 latency, as well as between the amplitude and latency of the P100 wave. Conversely, at 6 months, a positive correlation between RGC layer thickness and P100 amplitude was detected. Furthermore, RNFL thickness at the optic disc demonstrated a statistically significant increase at 6 months, accompanied by a slight rise in RGC layer thickness. However, these findings may reflect measurement artifacts rather than true clinical improvement. Notably, RNFL thickness correlated positively with the amplitudes of P100 and P2 waves (31).

Glaucoma is increasingly recognized as a neurological disorder, and evidence pointing to the limitations of exclusively relying on IOP-lowering therapies highlights the potential role of neuroprotection as an alternative or complementary approach in its management. However, current evidence is insufficient to confirm that citicoline effectively slows the progression of glaucoma.

Citicoline in Non-arteritic Ischemic Optic Neuropathy

Non-arteritic anterior ischemic optic neuropathy (NAION) is a sudden, typically painless ischemic event affecting the intraocular optic nerve. It results in irreversible damage, leading to a reduction in VA and VF. Multiple pharmacological strategies have been investigated in an effort to preserve or enhance visual function in individuals affected by NAION, among them systemic corticosteroids, diphenylhydantoin, anticoagulant therapies, and hyperbaric oxygen treatment. However, none have demonstrated proven efficacy. In 2008, Parisi et al. (32) assessed visual function in patients with NAION before and after treatment with citicoline. 26 patients, at least 6 months post-NAION onset, were randomly assigned to two age-matched groups. 14 patients received citicoline (Cebrolux-Tubilux, Italy) for 60 days, followed by a 120-day washout period (days 60–180) (T-NAION group). The remaining 12 patients received no treatment during the same period (NT-NAION group). In the T-NAION group, a second treatment phase was administered from days 181 to 240, followed by another washout period from days 241 to 360. Normative data were obtained from 14 age-matched healthy controls. PERG, VEPs, and VA were measured in all patients at baseline, day 60, and day 180. Additional measurements were conducted in the T-NAION group at days 240 and 360. Initial assessments revealed that patients with both NT-NAION and T-NAION had impaired PERG and VEP readings, as well as diminished VA, relative to healthy subjects. Following treatment (at days 60 and 240), the T-NAION group showed statistically significant gains ($p<0.01$) across all three measures compared to baseline. These functional improvements persisted even after the washout period, while no changes were observed in the NT-NAION group (32).

Parisi et al. (33) investigated the effects of a 6-month treatment with citicoline oral solution (500 mg/day) in 36 patients diagnosed with NAION. They evaluated various parameters, including VA, RNFL thickness, VEP, and Humphrey 24-2 VF, pERG results. The study revealed significant improvements across all measured parameters in the citicoline-treated group. Notably, these benefits persisted even after a 3-month washout period, reinforcing the neuroprotective role of citicoline in managing this condition (33).

Although the limited studies on the use of citicoline in NAION have reported beneficial findings, further research with a larger number of participants is necessary to establish definitive conclusions.

Application of Citicoline after Laser *in situ* Keratomileusis (LASIK)

There is only one study that meets the inclusion criteria for this topic. Çınar et al. (34) investigated the effect of topical citicoline drops on macular microcirculation in 45 patients after LASIK. They found no significant difference between

the CG and the treatment group in measurements of the superficial retinal vessel density, foveal avascular zone and deep retinal vessel density at pre-operative, 1-month post-operative, and 3-month post-operative evaluations ($p>0.05$) (34).

Strengths and Limitations

This article is a comprehensive evaluation of citicoline use in ophthalmology, incorporating studies on its application across various ophthalmic conditions. A broad range of articles from different years was reviewed.

However, several limitations should be acknowledged. Due to institutional access restrictions, the literature search was conducted using PubMed, Google Scholar, and CrossRef which together provide a broad coverage of clinical research articles, and only articles published in English were included. This language restriction may have led to omission of relevant data and introduces a potential selection bias. In addition, the available studies are heterogeneous with respect to patient characteristics (age, disease stage, and etiology), ophthalmic indication (amblyopia, glaucoma, NAION), and outcome measures (VA, contrast sensitivity, VF indices, electrophysiology, and OCT parameters), which makes direct comparison difficult. One of the key weaknesses of the current literature is the absence of a standardized citicoline regimen. Across published studies, dosing schemes vary considerably, from 250 to 500 mg/day in pediatric amblyopia to 1.0–1.6 g/day in adult glaucoma. Citicoline has been administered as short im cycles of 10–15 days, as intermittent oral courses lasting several months, and as long-term topical 2% eye drops. The duration of therapy likewise ranges from a few weeks to follow-up periods extending over several years, and treatment schedules are largely empirical rather than evidence-based. Moreover, few trials were specifically designed to compare different doses, routes of administration, or treatment intervals, so a reliable dose-response profile is still lacking. Consequently, an optimal citicoline regimen for ophthalmic indications cannot yet be defined, and its use should currently be considered an adjunctive, investigational neuroprotective option until more standardized randomized controlled studies become available. This lack of standardization in dosing, treatment schedules, and routes of administration has also been underscored in recent comprehensive reviews and systematic analyses of citicoline use in ophthalmology and glaucoma (35,36).

Conclusion

This systematic review highlights the broad spectrum of applications for citicoline in ophthalmologic conditions. Although its use as a supplement in glaucoma treatment is increasingly common today, larger, long-term, and more comprehensive studies are needed. Depending on its use, citicoline can be regarded both as a pharmaceutical agent and a dietary sup-

plement. Further studies are needed to explore its potential benefits in both ophthalmic and non-ophthalmic diseases.

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