A Systematic Review and Meta-analysis on the Effect of Citicoline on Visual Field Changes Among Patients with Primary Open Angle Glaucoma

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ABSTRACT

Background: Citicoline (cytidine diphosphate choline) is a neuroprotective agent that has been studied for its potential benefits in managing several neurodegenerative disorders, including primary open angle glaucoma (POAG). POAG is characterized as a chronic, gradually progressive optic neuropathy that leads to optic nerve deterioration and subsequent visual field loss. There are preliminary findings supporting the use of Citicoline as a supplementary treatment for glaucoma; however, there remains a significant gap in conclusive data regarding its impact on disease progression. While existing reviews have explored this topic, to the authors' knowledge, this is the first systematic review with a meta-analysis specifically evaluating the effect of Citicoline on visual field parameters in POAG patients.

Objective: To summarize the existing evidence regarding the effect of Citicoline on visual field changes in POAG patients, comparing different administration routes (intramuscular, topical, oral) and assessing overall treatment effects.

Methods: A literature search was conducted across PubMed, EBSCO, ProQuest, PLOS, and BMC, identifying 169 studies. After screening and removing duplicates, six studies published between 2005 and 2020 were included. The systematic review was conducted by comparing and tabulating the results of the included studies. The Newcastle- Ottawa Quality Assessment Form for Cohort Studies and the Revised Cochrane Risk of Bias Tool were utilized to assess the risk of bias. The meta-analysis was performed using data from two studies with comparable methodologies. Calculations were done using the Review Manager version 5.4 software.

Results: Six studies consisting of a total of 294 participants were included in this report. The weighted mean length of the follow-up was 28 ± 23 months. The weighted mean age of the patients was 57± 11 years. This review showed a trend of improvement or minimal change in mean deviation (MD) among participants receiving Citicoline, with statistically significant improvement noted in long-term studies of oral Citicoline. Secondary outcomes were intraocular pressure, side effects, retinal nerve fiber layer thickness, ganglion cell complex thickness, pattern electroretinogram and visual evoked potential parameters, visual acuity, and central corneal thickness. Meta-analysis revealed that oral Citicoline treatment produced a marginal significant effect in MD at 12 months (mean difference 1.95, 95% CI: - 1.10 to 4.01, p=0.06) and a significant improvement at 24 months (mean difference 3.49, 95% CI: 2.58 to 4.40, p<0.00001) compared to the control group.

Conclusion: Citicoline appears to offer a modest benefit in improving or stabilizing visual field parameters in POAG patients, particularly with longer treatment durations of oral Citicoline. Moreover, this review highlights the favorable safety profile of all forms of Citicoline. However, variability in study designs and methodologies highlights the need for standardized protocols and further research to confirm these findings and evaluate long- term efficacy. This study contributes to the growing body of evidence indicating that Citicoline can play a significant role in neuroprotection in glaucoma.

Key words: citicoline, cytidine diphosphate choline, visual field, glaucoma

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Globally, glaucoma is the leading cause of irreversible blindness, with an estimated prevalence of approximately 3.5% among adults aged 40 and older (Tham, et al, 2014). In Asia, primary open angle glaucoma (POAG) is the most prevalent kind of glaucoma, with a prevalence ranging from 0.5% to 3.9% (Tham, et al, 2014). According to the Third National Survey on Blindness in the Philippines, glaucoma is the third major cause of blindness with a prevalence reported to be 3% (Cubillan, 2005), reflecting a similar burden as seen in other parts of Asia. In the last few years, there has been growing interest in the promise of neuroprotective agents, such as Citicoline, as a supplement in the treatment of POAG. While existing systematic reviews address this topic, to our knowledge, this study is the first systematic review with a meta-analysis specifically assessing the effect of Citicoline on visual field metrics in patients with POAG.

Primary open angle glaucoma is often asymptomatic in its early stages, making regular screening crucial for early detection. Patients typically experience gradual peripheral vision loss, which may progress to severe constriction of the visual fields if left untreated. As the disease advances, central vision can also become compromised, leading to significant visual impairment (Weinreb & Khaw, 2004). The gold standard for diagnosing POAG includes a dilated fundus exam to visualize the optic nerve head and detect signs of glaucomatous damage. It also includes tonometry to measure intraocular pressure (IOP), gonioscopy to evaluate the drainage angles, standard automated perimetry (SAP) to assess visual field loss, and optical coherence tomography (OCT) to analyze the retinal nerve fiber layer and optic nerve head for early structural changes related to glaucoma (Kass, et al, 2002; American Academy of Ophthalmology, 2023).

Management primarily focuses on lowering IOP through pharmacological treatments, laser therapy or surgical interventions, to prevent further damage (Heijl, et al, 2002).

Citicoline, a neuroprotective agent, has gained attention for its potential role in managing glaucoma. Citicoline is a precursor of both phosphatidylcholine, contributing to the synthesis of structural phospholipids in cell plasma membranes, and acetylcholine, an important neurotransmitter in cell metabolism (Garcia-Lopez, et al, 2023). It is believed to exert its protective effects by supplying choline, which helps maintain the integrity of neuronal membranes and inhibits cell death during neurodegenerative events (Roberti, et al, 2014; Cavalu, et al, 2024). By preserving cellular integrity, Citicoline may serve as a valuable adjunctive treatment in POAG, potentially mitigating visual field loss and supporting overall visual function when used alongside traditional IOP-lowering therapies.

The role of neuroprotective agents in managing glaucoma has been a topic of ongoing debate. Despite various studies, there remains a lack of conclusive evidence regarding the impact of Citicoline on the progression of glaucoma. This systematic review and meta-analysis aims to evaluate the therapeutic potential of Citicoline by analyzing changes in visual field parameters among patients with POAG.

The objective of the study was to summarize the existing evidence regarding the effect of Citicoline on visual field changes among patients with POAG.

MATERIALS AND METHODS

Research Design

A systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study Population

The type of participants included were patients with primary open angle glaucoma who had adequately controlled intraocular pressures with topical IOP- lowering medications. The gender and race of the subjects were not consistently reported across the studies.

Eligibility Criteria

Studies were included in the systematic review if they met the following inclusion criteria: 1) studies looking at the effect of Citicoline as an adjunctive therapy to any IOP-lowering medications in patients with primary open angle glaucoma, 2) studies with participants comprised of males or females aged 18 years old or older, 3) studies published within the last 20 years, and lastly, 4) the selection process will only consider publications in English. Regarding publishing status, only papers that were in press or published were taken into consideration.

The criteria for exclusion of selected studies were as follows: 1) conference abstracts, case reports and case series, review articles, practice guidelines, commentaries, editorials or pre-print manuscripts that have yet to be reviewed with no available correspondence, 2) studies combining Citicoline with other neuroprotective substances were excluded, 3) studies with participants with secondary forms of open angle glaucoma were not accessed, and 4) studies involving animal subjects weren't included in the review.

Data Collection Process

A comprehensive literature search of PubMed, EBSCO/Medline, ProQuest, Directory of Open Access Journals, Public Library of Science (PLoS), and Biomed Central (BMC) databases was conducted from 2004 to 2024. However, the six studies that met the inclusion criteria were published between 2005 and 2020. Popular and often used phrases found in relevant literature were used in addition to Medical Subject Headings (MeSH) keywords to discover acceptable keywords. The search free text terms that were used through the advanced search strategy were "citicoline" or "cytidine diphosphate choline" and "visual field" and "glaucoma". The search plan was created and finished in PubMed first, and was applied to the other databases.

Selection Procedure

The initial screening of articles was carried out separately by two reviewers. Following their independent evaluation of the journal's titles and abstracts, they categorized the articles into three groups: relevant, irrelevant, and unclear. For the journals classified as unclear, the reviewers discussed their content to determine whether to categorize them as relevant or irrelevant. Journals deemed irrelevant by both reviewers were excluded from the analysis. After which, both reviewers examined the complete texts of the remaining papers and compiled a list of those to be included in the study. Finally, they compared their lists and explored any non-conformities.

Data Extraction

Two reviewers independently extracted data from the journals and recorded it in data sheets. If the necessary data were insufficient or unclear, questions were directed to the authors for clarification. The following information was extracted from each journal: authors, publication years, journal titles, inclusion and exclusion criteria, study designs, sample demographics, participant types, sample sizes, study protocols, instruments used, and the geographic and temporal scope of data collection.

Data Synthesis

The systematic review was conducted by comparing the results of the included studies. The reviewers examined and tabulated the homogeneity of the interventions based on treatment protocols, including study design, population characteristics, sample size, route of administration, dosage and duration.

For the meta-analysis, the continuous outcomes, mean deviation measure at baseline, and follow-ups (12 and 24 months after treatment) were considered. Effect of Citicoline on visual field changes to continuous outcomes were reported using weighted mean difference. Test for heterogeneity was carried out based on Cochran's Q and I^2. Cochran Q-value with p-value less than 0.05 was considered significant. As a guide, I^2 values of 25% may be considered low, 50% moderate, and 75% high. For cases with moderate to high heterogeneity, a random effects model was used to provide a conservative prevalence estimate otherwise fixed com effect model was preferred. Calculations were performed using Review Manager version 5.4 software. Publication bias was also evaluated using the same software. Discrepancies regarding the studies were discussed by the authors and resolution was done after considering the disagreements.

Study Risk of Bias Assessment

The methodological quality of each article was evaluated critically based on its suggested definition, with the use of a checklist that the authors have prepared. The quality of studies included in this systematic review was scored by two researchers. The Newcastle-Ottawa Quality Assessment Form for Cohort Studies (NOS) was used for non-randomized controlled trials (non-RCTs). The NOS consisted of three domains namely selection, comparability; and outcome. For randomized controlled trials (RCTs), the Revised Cochrane Risk of Bias Tool for Randomized Trials (Rob2 Tool) was utilized to evaluate the

overall risk of bias. Selection bias, performance bias, detection bias, attrition bias, reporting bias, and competing risk are the six domains of prejudice covered by the RoB2 Tool. Additionally, as previously noted, two researchers evaluated the entire texts independently.

Variable Description/Operational Definition

The independent variable was Citicoline as an adjunctive therapy to any IOP- lowering medications in patients with POAG.

The dependent variables were the various visual field indices of the Humphrey Field Analyzer (HFA) used across the included studies namely, mean deviation (MD), pattern standard deviation (PSD), mean sensitivity (MS), rate of progression (RoP), and mean progressive rate (MPR).

- Mean deviation (MD) is the overall deviation of a patient's visual field from age- matched normal values, reflecting the general extent of visual loss (American Academy of Ophthalmology, 2023).
- Pattern standard deviation (PSD) is the variability of the visual field compared to its normal patterns, reflecting localized visual field loss (American Academy of Ophthalmology, 2023).
- Mean sensitivity (MS) is the mean value of all test results, representing the overall sensitivity of the visual field across tested points (Yaqub, 2012).
- Rate of progression (RoP) measures how quickly a patient's visual field is deteriorating over time, with a smaller rate indicating slower deterioration and better disease management and a larger rate suggesting faster visual field loss (Parisi, et al, 2015).
- Mean progressive rate (MPR) indicates the average amount of change in visual field sensitivity over a period, but unlike RoP, it does not specify a particular time frame, providing a general sense of how visual field sensitivity is declining (Ottobelli, et al, 2013).

Ethical Considerations

This study was classified as exempt from ethical review by the FEU-NRMF Institutional Ethics Review Committee.

Conflict of Interest

There is no conflict of interest to be reported for this study. All costs for this study were shouldered by the primary investigator.

RESULTS

Study Selection

The literature search resulted in 169 records. Of them, 27 were excluded because of redundancy. Another 129 were removed based on the titles and abstracts of the records, 1 due to the lack of access to the full text, and 3 because the clinical trials are still in progress. A further 5 studies were screened but not included in the systematic review because they did not meet the eligibility criteria. No studies were excluded for not reporting quantitative data under the endpoints of interest. A total of 6 studies were included in the systematic review. Two of these were included in the meta-analysis. The literature search results are shown in Figure 1.

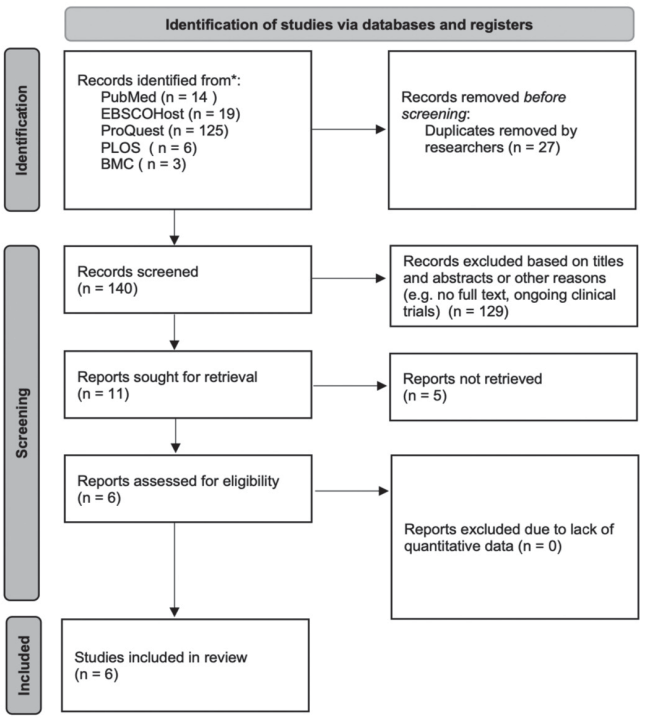

Figure 1. Flow chart of the literature search.

Study Characteristics

Two out of six studies included were ambispective in nature (Ottobelli, et al, 2013; Parisi, et al, 2019),

while the other 4 were randomized, prospective studies (Parisi, 2005; Parisi, et al, 2015; Lanza, et al, 2019; Arrico, et al, 2020). All of the studies, published from 2005 to 2020, were done internationally—5 in Italy and 1 in Turkey. Two studies were university-based, where one was a multicenter study (Ottobelli, et al, 2013) and the other was a single center study (Lanza, et al, 2019). The rest were not specified.

Data were collected from 333 participants at the time of inclusion. Information was gathered from both eyes; however, only the results from the worse eye were analyzed in all studies. Of the total participants, 39 from three studies (Parisi, et al, 2005; Parisi, et al, 2015; Lanza, et al, 2019) were classified as drop-out patients for various reasons: 18 due to an increase in IOP that necessitated changes in IOP- lowering treatment, 9 due to interruptions in Citicoline treatment, 7 were lost to follow- up, 4 because of lack of compliance, and 1 withdrew from the study. As a result, the total number of participants who completed each study was 294.

The weighted mean length of the follow-up was 28 ± 23 months. The weighted mean age of the patients was 57± 11 years. All of the studies included patients diagnosed with POAG who had well-controlled IOP. Across the six studies, well- controlled IOP was set as less than 18 to 21 mmHg. The generalities and patients' characteristics of the included studies are shown in Table 1.

Table 1. Generalities of the included studies.

Author, Year, Country	Study Design	Population Characteristics	Intervention	Protocol	Total of Patients at Inclusion	Total of Patients Who Completed Study	Follow-up (months)
Parisi, 2005, Italy	RCT	-Mean age: 45.6 -Open angle glaucoma (OAG) patients -IOP <21mmHg with topical monotherapy with beta-blockers, which remained stable throughout the study (mean 17.5±1.3 mmHg). -Glaucomatous optic nerve head cupping (cup/disc ratio >0.5) -Glaucomatous visual field defects HFA with MD between -3 and -6 dB) -Best corrected visual acuity (BCVA) of 20/20 or better -CCT within 500-600 um	Citicoline	1st period 1000mg Citicoline/IM daily for 2 months + washout for 4 months + IOP-lowering medication (topical beta blocker) 2nd period 1000mg Citicoline IM daily for 2 months + washout for 4 months + IOP-lowering medication (topical beta blocker)	15	12	96
			Control	1st period Placebo daily for 2 months + washout for 4 months + IOP-lowering medication (topical beta blocker) 2nd period Placebo daily for 2 months + washout for 6 months + IOP-lowering medication (topical beta blocker)	15	12	
Parisi, et al., 2015, Italy	RCT	-Mean age: 52.1 -OAG patients -IOP values <18 mmHg on beta- blocker monotherapy, which was maintained during the 8 months preceding the first electrophysiological evaluation and during the whole study -HFA 24-2 MD >-10 dB; pattern standard deviation (PSD) <10 dB; fixation losses, false positive rate, and false negative rate each less than 20% -Presence of a localized loss of neuroretinal rim (notch), thinning of the neuroretinal rim, generalized loss of optic rim tissue, optic disc excavation, vertical or horizontal cup/disc ratio greater than 0.5, cup-disc asymmetry between the two eyes >0.2, peripapillary splinter hemorrhages -BCVA ranging from 0.0 to 0.1 logMAR	Citicoline	200mg Citicoline Eye drops 3x/day for 4 months + washout for 2 months + IOP-lowering medications (topical beta blocker)	28	24	6
			Control	Placebo 3x/day for 4 months + washout for 2 months + IOP-lowering medications (topical beta blocker)	28	23	
Parisi, et al., 2019, Italy	Ambi-spective	-Mean age: 52.6 -OAG defined as a repeatable HFA 24-2 SITA standard visual field defect compatible with glaucoma; an MD between -2 and – 6 dB; typical glaucomatous optic nerve head damage -IOP<18 mmHg under topical hypotensive treatment -BCVA ≥5/10 Snellen	Citicoline	200mg Citicoline Eye drops 3x/day for 4 months + washout for 2 months + IOP-lowering medications (not specified)	12	12	4
Ottobelli, et al., 2013, Italy	Ambi-spective	-Mean age: 72.5 -Patients with unilateral or bilateral POAG -Progressing disease in the last 3 years (MD at least -1 dB/year) -IOP always <18 mm Hg in the last 3 years with any type of treatments and all patients were under topical therapy -At least 2 reliable visual fields per year in the last 3 years	Citicoline	500mg Citicoline per orem daily for 4 months + washout for 2 months + IOP-lowering medications (not specified)	41	41	24
Lanza, et al., 2019, Italy	RCT	-POAG diagnosis based on Glaucoma Staging System (GSS 2) -MD reduction ranging between -1 and 1.5 db/year during the previous 2 years, although IOP had apparently stablilized with therapy (≤18 mmHg measured with Goldmann applanation tonometry or GAT) -BVCA better than 20/40	Citicoline	500mg Citicoline per orem daily for 4 months + washout for 2 months + IOP-lowering medications (topical timolol, travoprost, and fixed combination of bimatoprost + timolol)	42	30	24
			Control	Placebo daily for 4 months + washout for 2 months + IOP-lowering medications (topical timolol, travoprost, and fixed combination of bimatoprost + timolol)	42	30	
Arrico, et al., 2020, Turkey	RCT	-Diagnosis of primary open-angle glaucoma (POAG) (grade IV on the Shaffer classification) -Adequate IOP control (≤18 mmHg) as measured with GAT -BVCA better than 20/40 -CCT within > 520µm to <550µm	Citicoline	500mg Citicoline per orem daily for 4 months + washout for 2 months + IOP-lowering medications (topical timolol, travoprost, and fixed combination of bimatoprost + timolol)	55	55	36
			Control	Placebo daily for 4 months + washout for 2 months + IOP-lowering medications (topical timolol, travoprost, and fixed combination of bimatoprost + timolol)	55	55	

In this review, Citicoline was evaluated via different administration routes: intramuscularly in 1 study (Parisi, 2005), topically as eye drops in 2 studies (Parisi, et al, 2015; Parisi, et al, 2019), and orally in 3 studies (Ottobelli, et al, 2013; Lanza, et al, 2019; Arrico et al., 2020). The study on the intramuscular route employed a 2-month washout period. The eye drop groups received Citicoline with the same dosage and duration, but Parisi, et al (2015) included a 2-month washout period, while Parisi, et al (2019) did not. For oral administration, the dosage, frequency, and washout period were consistent across studies, with the primary difference being the duration of the studies: Arrico, et al (2020) conducted follow-ups for up to 36 months, while Ottobelli, et al (2013) and Lanza, et al (2019) had follow-up durations of 24 months each.

Results of Individual Studies

For the primary outcomes, which were the changes in visual field indices, all 6 studies reported the MD values, 3 documented PSD values (Parisi, et al, 2015; Parisi, et al, 2019; Arrico, et al, 2020), 1 took note of the MS values (Parisi, et al, 2019), 1 recorded the MPR (Parisi, et al, 2015), and 1 focused on the the RoP (Ottobelli, et al, 2013) (Table 2).

For the secondary outcomes, all 6 studies took note of any changes in IOP and side effects, 3 studies focused on the electrophysiological parameters (Parisi, 2005; Parisi, et al, 2015; Parisi, et al, 2019), 3 took note of the visual acuity (Parisi, et al, 2015; Parisi, et al, 2019; Arrico, et al, 2020), while only 1 reviewed the retinal nerve fiber layer (RNFL) thickness, ganglion cell complex (GCC) thickness,

Table 2. Visual field parameter changes.

Author/s, Year, Country	Mean Deviation (dB)				Pattern Standard Deviation (dB)				Mean Sensitivity (dB)			Mean Progressive Rate (MPR) (dB)			Rate of Progression (RoP) (dB/year)	Standard Automated Perimetry Program
Intramuscular																
Parisi, 2005, Italy		Treatment Group	Control Group													HFA 24-2
	Month 96	MD increased compared to baseline	MD decreased compared to baseline													
Topical																
Parisi, et al., 2015, Italy		Treatment Group	Control Group			Treatment Group	Control Group						Treatment Group	Control Group		HFA 24-2
	Month 4	17/24 MD increased >1.0 dB compared to baseline	23/23 MD change <1.0 dB compared to baseline		Month 4	17/24 PSD reduction >1.0 dB compared to baseline	23/23 PSD change <1.0 dB compared to baseline					Month 4	0.56	-0.24		
	Month 6 (Washout)	22/24 MD change <1.0 dB compared to baseline	23/23 MD change <1.0 dB compared to baseline		Month 6 (Washout)	22/24 PSD change <1.0 dB compared to baseline	23/23 PSD change <1.0 dB compared to baseline					Month 6 (Washout)	0.18	-0.34		
Parisi, et al., 2019, Italy		Treatment Group	P value			Treatment Group	P value			Treatment Group	P value					HFA 24-2
	Baseline	-4.49 ± 2.46	p = 0.58		Baseline	6.05 ± 3.36	P = 0.43		Baseline	25.33 ± 2.05	P = 0.53					
	Month 4	-4.36 ± 2.24			Month 4	5.78 ± 3.68			4 months	25.51 ± 1.82						
Ottobelli, et al., 2013, Italy		Treatment Group	Change from baseline	P value									Treatment Group	P value		HFA 24-2
	Baseline	-9.2										2 years before study inclusion	- 1.1 dB/year (SD 0.7)	p = 0.01		
	Month 4	-8.8	0.4	p = 0.2												
	Month 6 (Washout)	-9.4	0.2	p = 0.7												
	Month 10	-8.6	0.6	p = 0.1												
	Month 12 (Washout)	-9.1	0.1	p = 0.7								Month 24	0.15 dB/year (SD 0.3)			
	Month 16	-9.0	0.2	p = 0.5												
	Month 18 (Washout)	-9.3	0	-												
	Month 22	-8.3	0.9	p = 0.1												
	Month 24 (Washout)	-9.5	0.3	p = 0.3												
Lanza, et al., 2019, Italy		Treatment Group	Control Group	P value												HFA 30-2
	Baseline	-6.5	-6.4													
	Month 6	-7.0	-7.1													
	Month 12	-7.1	-8.0													
	Month 18	-7.3	-8.6	p<0.039												
	Month 24	-7.3	-9.3	p<0.006												
Arrico, et al., 2020, Turkey		Treatment Group	Control group	P value		Treatment group	Control group	P value								HFA 30-2
	Baseline	-14	-14		Baseline	13	13									
	Month 12	-11	-14		Month 12	13	13									
	Month 24	-9	-15	p<0.05	Month 24	12	13									
	Month 36	-8	-15		Month 36	11	13	p<0.05								

and central corneal thickness (CCT) (Lanza, et al, 2019) (Table 3).

All these studies were included in the qualitative synthesis regarding the generalities of the included studies (Table 1), visual field parameter changes (Table 2), and secondary outcomes measures (Tables 3-10).

Table 3. Summary of secondary outcome measures.

Author/s, Year, Country	IOP	SE	RNFL	GCC	PERG	VEP	BCVA	CCT
Parisi, 2005, Italy	√	√			√	√		
Parisi, et al, 2015, Italy	√	√			√	√	√	
Parisi, et al, 2019, Italy	√	√			√	√	√	
Ottobelli, et al, 2013, Italy	√	√						
Lanza, et al, 2019, Italy	√	√	√	√				√
Arrico, et al, 2020, Turkey	√	√					√	

. – Significant . – Insufficient data

Table 4. Intraocular pressure (IOP).

Author/s, Year, Country	
Intramuscular	
Parisi, 2005, Italy	No significant changes in IOP
Topical	
Parisi, et al, 2015, Italy	No significant changes in IOP
Parisi, et al, 2019, Italy	No significant changes in IOP
Oral	
Ottobelli, et al, 2013, Italy	IOP significantly lower compared to baseline (average reduction of approximately 1 mmHg) (p=0.02)
Lanza, et al, 2019, Italy	No significant changes in IOP
Arrico, et al, 2020, Turkey	No significant changes in IOP

Only Ottobelli, et al (2013) found statistically significant changes in IOP. The authors noted that the IOP was approximately 1 mmHg lower during the study follow-up as comparted to baseline.

Table 5. Side effects of citicoline.

Author/s, Year, Country	
Intramuscular	
Parisi, 2005, Italy	No ocular side effects
Topical	
Parisi, et al, 2015, Italy	No ocular side effects
Parisi, et al, 2019, Italy	No ocular side effects No significant changes in blood systolic pressure
Oral	
Ottobelli, et al, 2013, Italy	No ocular side effects
Lanza, et al, 2019, Italy	No ocular side effects
Arrico, et al, 2020, Turkey	No ocular side effects

No side effects were observed across the six studies.

Table 6. Retinal nerve fiber layer (RNFL) thickness.

Author/s, Year, Country	
Oral	
Lanza, et al, 2019, Italy	Overall RNFL thickness values in the treatment group were statistically higher than those in the control group at 12 ($p<0.007$), 18 ($p<0.0001$), and 24 months ($p<0.0001$) of follow-ups

Overall RNFL thickness (superior, inferior, temporal, nasal) changes indicated that the overall thinning was significantly lower in the treatment group (oral Citicoline) than in the control group (oral placebo) and appeared to be stable in the succeeding months.

Table 7. Ganglion cell complex (GCC) thickness.

Author/s, Year, Country	
Oral	
Lanza, et al, 2019, Italy	Both superior and inferior thickness showed significantly higher values in the treatment group than the control group at 12 ($p<0.003$), 18 ($p<0.0001$), and 24 months ($p<0.0001$) of follow-ups

Overall GCC thickness (superior and inferior) showed significantly higher values at 12, 18 and 24 months of follow-ups.

Table 8. Electrophysiological parameters.

Author/s, Year, Country		
Intramuscular		
Parisi, 2005, Italy	Treatment Group	1st Treatment Period - Significant ($p<0.01$) shortening in VEP P100 and PERG P50 times- to-peak - Significant reduction of RCT - Significant increase in VEP N75-P100 and PERG P50-N95 amplitudes 1st Washout Period - Worsening trend, but the electrophysiological improvement with respect to baseline conditions was maintained
		2nd Treatment Period - Further ($p<0.01$) improvement of VEP and PERG parameters 2nd Washout Period - VEP P100 and PERG P50 times-to-peak and RCTs were still significantly reduced with respect to baseline values - VEP N75-P100 amplitudes still significantly increased when compared to baseline
		- PERG P50-N95 amplitudes were similar to baseline conditions
	Control Group	1st & 2nd Periods - Control patients displayed similar VEP and PERG parameters in all examinations

Topical		
Parisi, et al, 2015, Italy	Treatment group	Treatment Period - The mean values of PERG P50-N95 and VEP N75-P100 amplitudes and VEP P100 implicit times were significantly ($p < 0.01$) increased and reduced, respectively, when compared with those observed at baseline Washout Period - PERG and VEP values were similar to baseline ones
	Control group	- Non-significant changes in mean values of PERG and VEP parameters
Parisi, et al, 2019, Italy	Treatment group	- Increase of PERG P50–N95 amplitudes (83.33%) - Shortening of VEP implicit times (91.66%) - Improved VEP N75–P100 amplitudes (58.33%)

All 3 studies that analyzed the effect of Citicoline on electrophysiological parameters observed an improvement in retinal function (increase in Pattern Electroretinogram (PERG) amplitude) and improvement in neural conduction along the visual pathway (increase in Visual Evoked Potential (VEP) amplitude and reduction of VEP P100 implicit time).

Table 9. Best corrected visual acuity (BCVA).

Author/s, Year, Country	
Topical	
Parisi, et al, 2015, Italy	No significant changes in visual acuity
Parisi, et al, 2019, Italy	No significant changes in visual acuity
Oral	
Arrico, et al, 2020, Turkey	Mean BVCA increased in the treatment group and deteriorated in the control group

Arrico, et al. (2020) found that the mean BCVA increased in the therapy group receiving oral Citicoline, whereas the mean BCVA in the control group receiving oral placebo continued to decline at each visit. However, it was not specified whether this difference was statistically significant

Table 10. Central corneal thickness (CCT).

Author/s, Year, Country	
Oral	
Lanza, et al, 2019, Italy	No significant changes in CCT value

CCT was observed in one study on oral supplementation with Citicoline. No significant changes were reported.

Risk of Bias (ROB) in Studies

The two authors' judgment of each risk of bias item for the studies included is displayed in Table 11 NOS for non-randomized controlled trials and in Table 12 Rob2 Tool for randomized controlled trials.

Two studies had an ambispective study design. The quality assessment for the non-randomized

studies using the NOS revealed one study with fair ROB, while the other study had good ROB. Since both studies utilized a retrospective chart review and prospective interventional design, the outcome information of all included patients in the studies were based on records from databases and independent blind assessment, respectively.

Among the included studies, the four RCTs were evaluated using the Rob2 Tool. None had high risk of bias. Three studies had unclear allocation concealment bias while one study had unclear performance and detection of bias. The weighted risk of bias is presented as a plot in Figure 2.

Results of Syntheses

Only two studies met the criteria for inclusion in the meta-analysis due to their methodological similarities. Specifically, these studies were both RCTs and utilized the same visual field testing settings, namely the Humphrey Field Analyzer 30-2 (HFA 30- 2), which allowed for consistency in evaluating outcomes. Additionally, both studies included MD as one of their primary outcome measures. The use of MD in the meta- analysis was valid because it provided a clear and quantifiable measure of visual field changes by reflecting the overall deviation of a patient's visual field from age-matched normal values, making it a reliable indicator for tracking disease progression and assessing treatment efficacy.

Baseline MD showed no heterogeneity between the studies (p-value of Q = 0.88 and I^2 = 0%), thus fixed effects model was used for calculating the summary or pooled effect. Baseline MD of treatment and control groups were not significantly different for the two studies (pooled mean Difference = -0.02; 95% CI: -0.32 to 0.28; Z = 0.02, p-value = 0.91).

For the 12-month and 24-month follow-ups, high heterogeneity was observed between the trials (I^2 = 0.82 and p-value = 0.02, I^2 = 0.94 and p-value < 0.001, respectively), thus, random effects model was used for calculating the summary or pooled effect. To assess Citicoline effect on MD during follow-ups, pooled mean difference estimates for 12-month and 24-month follow-ups were analyzed. For the 12- month follow-up, a marginal significant effect of Citicoline showed 1.95 pooled mean difference (95% CI: -0.10 to 4.01; Z = 1.86, p-value = 0.06) in the Citicoline-treated group with respect to the control group.

Regarding the 24-month follow-up, a statistical improvement by a mean difference of 3.49 (95% CI: 2.58 to 4.40; Z = 7.50, p-value < 0.00001) was detected in favor of the group treated with Citicoline compared to the control group.

Table 11. Summary of NOS scale for risk of bias for non-randomized studies.

Author/s, Year	Study design	A				B	C			Risk of bias
		1	2	3	4	1	1	2	3	
Parisi, et al, 2019, Italy	Ambispective	c	c	*	*	c	*	*	*	Fair
Ottobelli, et al, 2013, Italy	Ambispective	*	c	*	*	c	*	*	*	Good

A: selection, B: comparability, C: exposure/outcome
Note: small letters denote the appropriate assessment per item based on the NOS scale.

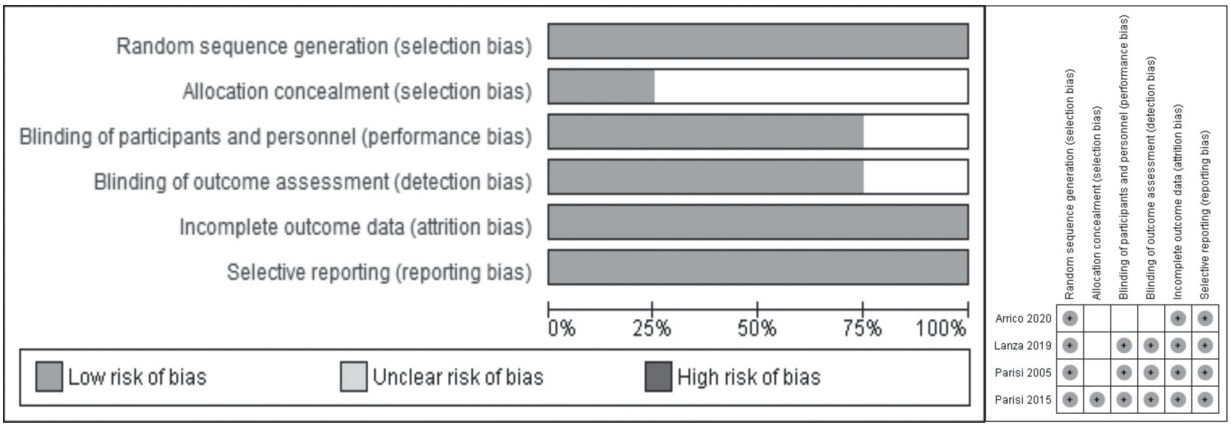

Figure 2. Cochrane collaboration's tool for risk of bias (Higgins and Altman) graph and summary for randomized studies.

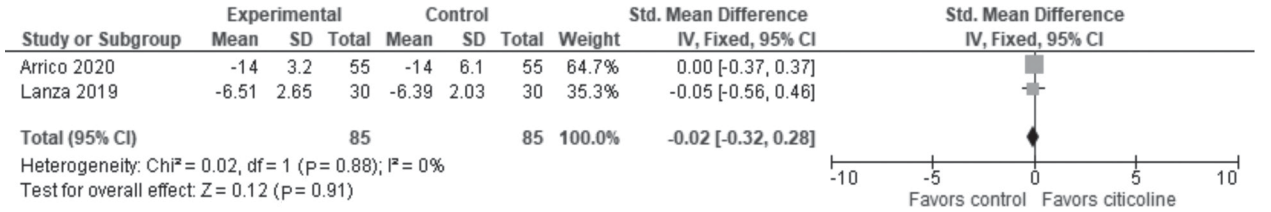

Figure 3. Baseline.

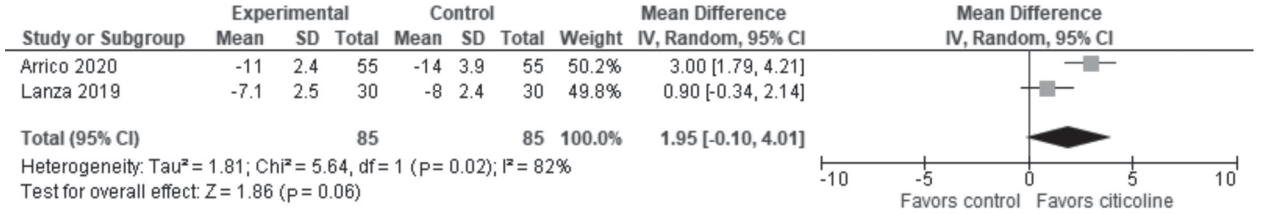

Figure 4. 12-month post-treatment.

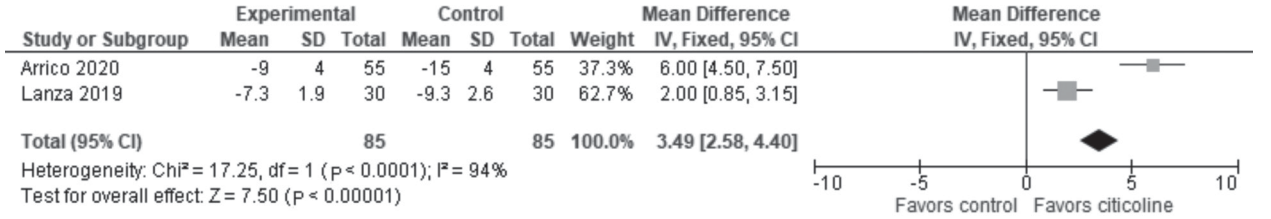

Figure 5. 24-month post-treatment.

DISCUSSION

The purpose of this systematic review and meta-analysis was to evaluate the effect of Citicoline on visual field parameters and other secondary outcomes in patients with POAG. Detailed analysis of six studies revealed a consistent trend of improvement in MD among participants receiving Citicoline, with significant enhancements noted in long-term studies of oral Citicoline, particularly by Lanza, et al (2019) and Arrico, et al (2020). These results are consistent with prior research, which suggests that neuroprotective agents, such as Citicoline, may help mitigate functional decline in glaucoma patients. For instance, studies have shown that citicoline can enhance retinal function and neural conduction, as indicated by improvements in electrophysiological parameters (Redjak, et al, 2003; Parisi, et al, 2008; Rossi, et al, 2022). Gandolfi, et al (2020) further confirmed Citicoline's neuroprotective effects, noting its role in stabilizing visual fields and retinal ganglion cell function by supporting phospholipid metabolism.

Although the immediate impact of adding Citicoline to glaucoma treatment regimens may seem modest, it's important to recognize that glaucoma is a progressive, lifelong disease. Even small improvements in slowing visual field progression can translate into substantial long-term benefits. From a public health perspective, these results suggest that oral Citicoline has the potential to serve as a cost-effective option for adjunctive therapy for POAG. The strength of this review lies in its inclusion of studies with comparable methodologies, allowing for a meta-analysis that provided valuable insights into Citicoline's role in managing glaucoma. Importantly, none of the randomized controlled trials included in this review exhibited a high risk of bias, which strengthens the reliability of the findings, while the non-randomized studies demonstrated fair to good risk of bias.

Trend of Improvement or Minimal Change

Mean Deviation (MD)

The visual field parameter consistent throughout all six studies was the change in MD. Participants who were subjected to Citicoline, whether administered

intramuscularly, topically or orally, were noted to either have a trend of improvement or minimal change in the MD. According to Lanza, et al (2019), the treatment group showed significantly higher values of MD than did those recorded in the control group (at 18 months and 24 months). In a similar study by Arrico, et al (2020), the mean MD of the treatment group improved from a baseline value of -14 dB to -11 dB at 12 months. The mean MD improved further to -9 dB at 24 months and this change was statistically significant, but there were no additional statistically-significant improvements after 24 months. In the control group, mean MD continued to deteriorate from a baseline value of -14 dB to -15 dB after 36 months. Conversely, in the 24-month study by Ottobelli, et al (2013), fluctuations in the MD were observed at 4 month (after the treatment period) and at 6 month (after the washout period) intervals. However, these changes were consistently less than 1.0 dB and were not statistically significant. Similarly, in a 6- month study by Parisi, et al (2015) that measured MD values at months 4 and 6, the results indicated a change from baseline of less than 1.0 dB, reflecting minimal visual field loss. Another study by Parisi (2005) noted improvement from baseline at 96 months. The authors of Parisi (2005) and Parisi, et al (2015) did not conduct statistical evaluation of the changes in MD because the power of their studies were primarily based on the main electrophysiological parameters and because of the presence of inter-individual variability at baseline. They suggested that to detect significant differences in visual field measures, a larger cohort of OAG patients would be necessary. In Parisi, et al's (2019) study, although there was slight improvement at 4 months, it lacked statistical significance.

MD is the preferred parameter for assessing visual field progression in glaucoma because it relies on raw data, providing a direct and objective measure. Since MD is calculated using age-matched cohorts, it offers a clearer comparison of an individual's visual field against normative values. In contrast, PSD depends on patterns derived from available points, which can be influenced by confounding factors that might not be associated with glaucoma. This makes MD a more reliable indicator for tracking disease progression, as it reflects overall changes in visual function more accurately than PSD.

Pattern Standard Deviation (PSD)

PSD was another visual field parameter analyzed in three studies (Parisi, et al, 2015; Parisi, et al, 2019; Arrico, et al, 2020). There was a trend toward improvement in PSD values observed across two studies. According to Arrico, et al (2020), subjects in the treatment group showed a significant decrease of mean PSD values over the entire follow-up period (13 dB to 11 dB after 36 months). In the control group, mean PSD values continued to deteriorate. Parisi, et al (2015) observed an improvement in PSD at the end of the treatment period compared to the control group, but after the 2-month washout period the MD value changed by less than 1.0 dB compared to baseline, suggesting regression after discontinuation of Citicoline. However, the authors did not perform statistical analysis due to the previously mentioned reasons. Parisi, et al's (2019) findings showed that the PSD value improved from baseline, however it failed to achieve statistical significance.

PSD is global metric that assesses local changes, but it is not the ideal visual field index for monitoring glaucoma progression. Although PSD can provide information about local damage, it peaks around -12 dB, suggesting significant impairment. As glaucoma advances and affects both hemifields, the PSD value may actually decrease due to a floor effect. This occurs because the focal defect becomes less pronounced relative to other areas of damage, leading to similar PSD values in individuals with mild and advanced glaucoma. Thus, PSD is not a reliable indicator of disease progression.

Mean Sensitivity (MS)

MS was another parameter explored by Parisi, et al's (2019). Their findings showed that the MS value improved from baseline, but like the MD and PSD values, it did not reach statical significance.

Mean Progressive Rate (MPR)

MPR was the main visual field parameter in the study by Parisi, et al (2015). The MPR of the treatment group improved by 0.38 dB as compared to the control group which worsened by 0.10 dB. However, statistical analysis was not performed on these results.

Rate of Progression (RoP)

The primary visual field parameter in the research conducted by Ottobelli, et al (2013) was the RoP. The mean RoP significantly changed from -1.1 dB/year in

the 2 years before study inclusion to -0.15 dB/year at the end of the study.

Benefit of Extended Treatment Durations

The study on intramuscular Citicoline (Parisi, 2005) provided insufficient data to draw definitive conclusions. Similarly, studies on topical Citicoline with short treatment durations of 4 months did not yield significant results (Parisi, et al, 2015; Parisi, et al, 2019). However, studies on oral Citicoline showed more promising outcomes, with significant improvements in the RoP becoming evident at 24 months. This was demonstrated by Ottobelli, et al (2013) and further supported by our meta-analysis of Lanza, et al (2019) and Arrico, et al (2020), where 24-month follow-up results were statistically significant. This suggests that longer treatment durations may be necessary to observe the potential therapeutic effects.

The need for prolonged treatment durations to observe therapeutic effects is well-supported in the literature, particularly for chronic conditions like glaucoma. For example, Weinreb, et al (2004) noted that significant effects of glaucoma treatments often emerge only after extended periods due to the slow progression of the disease. Similarly, Heijl, et al (2002) emphasized the necessity of long follow-up periods to accurately assess the efficacy of glaucoma therapies. The findings from Ottobelli, et al (2013), along with the meta-analyses by Lanza, et al (2019) and Arrico, et al (2020), align with this perspective, underscoring the importance of 24-month follow-ups in evaluating the sustained therapeutic effects of interventions like Citicoline.

Regression During Washout Periods

In the study by Parisi, et al (2015), the MD value initially improved after the first 4 months of treatment. However, following a 2-month washout period, the MD change was less than 1.0 dB compared to baseline, indicating minimal overall visual field loss. For PSD, a reduction of more than 1.0 dB with respect to baseline was observed. After the 2-month washout, the PSD value changed by less than 1.0 dB from baseline, indicating minimal change. Notably, these findings were not statistically analyzed, as this study primarily focused on the MPR as the outcome.

The study by Ottobelli, et al (2013) showed that the MD value either decreased or remained stable (-0.9 to 0.3) compared to baseline following each 4-month treatment period. After each 2-month washout period, the MD value generally regressed towards baseline levels. Despite these observations, none of the MD changes at any follow-up points throughout the 24-month study were statistically significant. These fluctuations in the MD value show how the MPR is a more appropriate measure of visual field progression changes long-term.

It is important to note that the 24-month study by Lanza, et al (2019) and the 36- month study by Arrico, et al (2020), both of which included 2-month washout periods, did not report data immediately following the 4-month treatment periods. Lanza, et al collected data every 6 months, while Arrico, et al collected data every 12 months. Incorporating data immediately after the 4-month treatment periods could have helped validate the initial treatment-phase outcomes observed by Ottobelli, et al (2013) and Parisi, et al (2015).

Secondary Outcomes

Intraocular Pressure

All six studies also looked at the effect of Citioline on IOP. In the studies evaluating the effect of intramuscular Citicoline (Parisi, 2005) and topical Citicoline (Parisi, et al, 2015; Parisi, et al, 2019), no significant changes in IOP were detected. However, among the three studies assessing oral Citicoline, only Ottobelli, et al (2013) reported a significant reduction, noting a mean IOP approximately 1 mmHg lower during follow-up compared to a baseline measurement of 15.5 mmHg. Notably, patients with baseline IOP >15 mmHg experienced significantly faster progression rates (-0.25 dB/year) than those with IOP <15 mmHg (-0.05 dB/year).

Despite the observed reduction in IOP, there is currently insufficient evidence to conclude that a 1 mmHg decrease can effectively slow progression rates. The treatment guidelines established by the Early Manifest Glaucoma Trial indicate that a 25% reduction in IOP is necessary to lower the relative risk of progression by 50%, emphasizing that the degree of IOP reduction is strongly dependent on baseline IOP levels (Heijl, et al, 2002).

Side Effects of Citicoline

All studies monitored potential adverse events related to Citicoline, including conjunctival

hyperemia, corneal microabrasions, lesions of the conjunctiva and cornea, dry eye, and variations in tear quality or quantity, as specified by Parisi, et al (2019).

None of the studies reported any side effects linked to its administration, whether intramuscular, topical, or oral. Additionally, Parisi and colleagues (2019) evaluated whether topical Citicoline would have any systemic side effects, particularly on blood systolic pressure, but found no significant changes. This demonstrates that Citicoline has a favorable safety profile even with long-term use of up to 36 months.

RNFL Thickness and GCC Thickness

In addition to assessing functional parameters through SAP, the study by Lanza, et al (2019) also examined morphological parameters using OCT in glaucomatous patients treated with oral Citicoline. After 12 months of therapy, the mean RNFL thickness and the mean GCC thickness in the treatment group were significantly greater than in the control group. These measurements remained stable in follow-up visits, while the RNFL and GCC thickness in the control group significantly declined over time. The authors provided evidence supporting the idea that OCT can be particularly valuable in the early detection of glaucoma, as outlined in the glaucoma continuum model by Weinreb, et al (2004). This model emphasizes that glaucoma progression begins with structural changes that are often detectable before significant functional loss occurs.

Furthermore, Lanza, et al (2019) observed that OCT demonstrated greater sensitivity in detecting the neuroprotective effects of oral Citicoline, identifying these effects six months earlier than SAP. The authors propose that if future studies can confirm these findings, it would imply that Citicoline therapy could be beneficial for patients at all stages of glaucoma, not just in advanced cases. One possible explanation for this is that SAP may not reveal the initial structural changes that precede detectable functional impairment, making it more effective in later stages of the disease when visual field loss is more pronounced. Therefore, integrating OCT into clinical practice allows for a more comprehensive understanding of glaucoma's progression, facilitating earlier diagnosis and treatment based on morphological evidence, while reserving SAP for monitoring progression in later stages.

Additionally, the study of Lanza, et al (2019) found no significant correlation between the baseline SAP and OCT parameters and their changes during the follow-up period, suggesting that the benefits seen with OCT were not reflected in the SAP results. The lack of correlation between changes observed in OCT and SAP measurements points to a potential gap in how functional and structural assessments reflect the disease's progression. This finding underscores the importance of using multiple assessment tools within the glaucoma continuum model to capture the full spectrum of glaucoma progression and the effects of treatment, reinforcing the need for tailored approaches to patient management.

Electrophysiological Parameters

In the studies examining electrophysiological parameters following Citicoline treatment, significant improvements were reported by Parisi (2005) in both VEP and PERG parameters after the initial treatment periods, with sustained enhancements noted even after a washout. Extended treatment periods further improved these parameters compared to pre-treatment and control conditions. Similarly, Parisi, et al (2015) found significant increases in PERG P50-N95 and VEP N75-P100 amplitudes, along with a significant reduction in VEP P100 implicit times. However, after a washout period, both PERG and VEP values returned to baseline levels, and the control group exhibited no significant changes throughout the study. In Parisi, et al (2019), Citicoline treatment resulted in significant increases in PERG P50-N95 amplitude and reductions in VEP P100 implicit time, although this study did not include a washout period. The authors suggested that glaucomatous visual field defects may arise from two functional impairment sources: 1) at the retinal level, indicated by abnormal PERG responses reflecting the bioelectrical activity of ganglion cells and their fibers, and 2) at the post- retinal level, evidenced by irregular VEP responses and delays in retino-cortical time.

It is expected that glaucoma patients will exhibit abnormal electrophysiologic parameters, which aligns with the findings from the studies by Parisi, et al (2005, 2015, 2019). Research has consistently shown that glaucoma can lead to changes in VEPs and ERGs, indicating compromised retinal function and neural conduction along the visual pathway (Redjak, et al, 2003, Parisi, et al, 2008, Rossi, et al, 2022). These abnormalities in electrophysiologic measures often

correlate with disease severity and can provide insights into underlying neural damage (Senger, et al, 2019). Moreover, alterations in parameters such as PERGs have been associated with structural changes in the retina, such as thinning of the RNFL and degeneration of ganglion cells (Bowd, et al, 2010). These structural changes provide indirect evidence of retinal damage that can lead to functional impairments, reinforcing the expectation of electrophysiologic abnormalities in glaucoma patients. Thus, the observed findings from Parisi, et al (2005, 2015, 2019) are consistent with the broader literature on the electrophysiologic impact of glaucoma.

Best Corrected Visual Acuity

There were three studies that examined the BCVA of the subjects. Parisi, et al (2015) and Parisi, et al (2019), both of which evaluated Citicoline eye drops, did not detect any significant changes in BCVA. The study by Arrico, et al (2020) found that the mean BCVA increased in the therapy group receiving oral Citicoline improved from a mean baseline value of 0.9 up to a value exceeding 1, whereas the mean BCVA in the control group receiving oral placebo continued to decline at each visit. However, it was not specified whether this difference was statistically significant.

While Arrico, et al (2020) reported improvements in BCVA in the therapy group receiving oral Citicoline, these findings should be interpreted with caution. This may not reflect a true clinical benefit, especially considering that the study did not specify whether the difference was statistically significant. Furthermore, the glaucoma continuum model suggests that early changes in the disease may primarily involve structural alterations rather than functional ones (Weinreb, et al, 2004). In glaucoma, visual acuity may not be significantly impacted until central vision is affected, indicating that BCVA alone is not an ideal measure for assessing disease progression or treatment efficacy.

Limitations

Several limitations should be acknowledged when interpreting the results of this study. First, only two out of the six studies were eligible for inclusion in the meta- analysis, limiting its statistical power. The primary limitation of this systematic review, however, was the heterogeneity in study designs and methodologies among the included studies. This review comprised a mix of randomized controlled trials and non- randomized studies, introducing variability in overall study quality. Furthermore, different visual field testing devices were employed across studies, namely the HFA 24-2 and 30-2. Although the difference in the areas tested by these devices is minor, and the results are generally comparable for most clinical purposes, it is important to consider the specific device used when interpreting and comparing study outcomes.

Lastly, secondary outcomes varied across studies, leading to inconsistencies due to differences in the parameters assessed. Significant findings were noted in some studies for electrophysiological parameters, RNFL, and GCC, with only one study reporting a significant outcome for IOP. In contrast, others, such as BCVA and CCT, did not demonstrate significant changes. While this review emphasizes the positive influence of Citicoline on the functional aspects of glaucoma progression, these inconsistencies suggest that further investigations are warranted to elucidate its impact on other glaucoma-related metrics, the interplay between functional and structural changes in glaucoma, and overall disease management.

CONCLUSION

This study contributes to emerging evidence that Citicoline is a promising adjunctive therapy for POAG, demonstrating a favorable trend in stabilizing or slightly improving visual field parameters, particularly with longer treatment durations of oral Citicoline up to 24 months. The absence of adverse effects further supports its consideration as a safe and viable dietary supplement for managing this disease. From a broader health perspective, oral Citicoline may be an affordable and valuable addition to conventional glaucoma treatment. However, the variability in methodologies and outcomes underscores the need for further research, focusing on standardized treatment protocols, including visual field testing methods, dose, duration, and administration routes. It is hoped that the results of this study will lay the groundwork for longer-term studies to assess the sustainability of Citicoline's effects and, eventually, serve as a basis for its application in clinical practice.

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