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Open Access Journal of Ophthalmology
ISSN: 2578-465X

# Comparison of the Effect of 1000mg and 500mg Oral Citicoline on Visual Field and Ganglion Cell Layer Thickness in Primary Open Angle Glaucoma

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**Research Article**

**Volume 7 Issue 1**

**Received Date:** January 17, 2022

**Published Date:** February 15, 2022

DOI: 10.23880/oajo-16000234

## Abstract

**Purpose:** To compare the effects of 1000 mg and 500 mg oral citicoline on the visual field, retinal nerve fiber layer and ganglion cells layer thickness in well controlled primary open angle glaucoma.

**Methods:** A double blind randomized controlled trial was conducted on 50 subjects (75 eyes). The randomization divided the subjects into two groups, the 1000 mg group and the 500 mg group. The evaluations were performed after 30 days and 60 days intervention by assessing Mean Deviation (MD) and Pattern Standard Deviation (PSD) of Humphrey Visual field as well as retinal nerve fiber layer (RNFL) and Ganglion Cell-Inner Plexiform Layer (GCIPL) on ocular imaging.

**Results:** After 60 days, there was no significant difference between both groups in the MD, PSD, RNFL, and GCIPL values. The median MD increased in the 1000 mg group from -9.96 dB at baseline to -5.0 dB after 60 days and from the intragroup analysis, there was a significant difference (p=0.008). Based on subgroup analysis, there was also significant difference before and after the intervention in the mild glaucoma receiving 500 mg citicoline and in moderate-severe glaucoma receiving 1000 mg citicoline. RNFL and GCIPL thickness in both groups were tended to be stable. A side effect of nausea was found in two subjects who each received a dose of 500 mg and 1000 mg citicoline.

**Conclusion:** There was an improvement in the MD and PSD values in both groups after 60 days of oral citicoline administration, but a significant difference was found in mild glaucoma group receiving 500 mg citicoline and in moderate-severe glaucoma receiving 1000 mg citicoline. The thickness of RNFL and GCIPL in both groups did not decrease after 60 days of citicoline administration.

**Keywords:** Citicoline; Glaucoma; Retinal Ganglion Cell; Visual Field; Pattern Standard Deviation

**Abbreviations:** MD: Mean Deviation; RNFL: Retinal Nerve Fiber Layer; GCIPL: Ganglion Cell-Inner Plexiform Layer; IOP; Increased Intraocular Pressure; POAG: Primary Open Angle Glaucoma; PSD: Pattern Standard Deviation; EMGT: Early Manifest Glaucoma Trial; AGIS: Advanced Glaucoma Intervention Study.

## Introduction

Glaucoma is an eye disorder characterized by glaucomatous optic neuropathy and visual field loss, with increased intraocular pressure (IOP) as the main risk factor. Glaucoma is the second leading cause of blindness in the world after cataract and the first cause of irreversible blindness. In 2013, there were around 64 million glaucoma patients in the world and 3 million of them were blind [1]. At our hospital, 650 cases of primary open angle glaucoma (POAG) were found during 2001-2010 [2].

Various studies have shown that IOP is not the only risk factor involved in the pathogenesis of glaucoma [3]. IOP elevation is not always associated with glaucoma considering that there are a number of patients with high IOP but do not have glaucoma. The management of glaucoma to date is aimed at lowering the IOP consisting of drugs, lasers, and surgery [4,5]. However, those therapies are not always adequate to maintain visual function considering that in some cases progression continues despite controlled IOP so that the target of therapy should not be limited to retinal ganglion cells but also aimed at brain nerves that are prone to degenerate due to glaucoma [6]. Therefore, a complementary therapeutic strategy in the form of neuroprotector agent was considered. One of the neuroprotector agents used in glaucoma therapy is citicoline [7,8].

Previous studies have shown that citicoline has a neuroprotective effect on damaged retinal ganglion cells and supports neuron regeneration in vitro [9]. In addition, various studies both experimental and clinical trials have shown the effectiveness of citicoline in maintaining retinal ganglion cells in the hope of slowing the rate of progression of glaucoma [10-16]. However, those are case-control and retrospective studies; therefore a double-blind randomized trial is needed to confirm the findings. The dose of citicoline used in previous clinical trials ranged from 500-1600 mg per day and until now there is no consensus on the effective dose for glaucoma. Administration via oral route once daily is expected to provide drug adherence (compliance). This study aims to compare the effect of 1000 mg and 500 mg oral citicoline on the visual field and retinal nerve fiber layer (RNFL) and retinal ganglion cells (GCIPL) thickness in POAG [17,18].

## Methods

This research is a double blind randomized clinical trial allocating the subjects into two groups, each receiving either 1000 mg or 500 mg oral citicoline. The population for this study were patients with POAG with controlled IOP who visited the Glaucoma Outpatient Service in Cipto Mangunkusumo hospital.

Inclusion criteria included 18-65 years of age, diagnosed with POAG, best corrected visual acuity at least 0.02, the IOP was controlled based on target pressure, and subjects were cooperative to undergo examination procedures, by signing an informed consent. Subjects would be excluded if subject had normal tension glaucoma; there was a significant opacity of the refractive media; abnormalities of the retina, macula or optic nerve head from causes other than glaucoma; disorders or diseases that affect visual pathway; intraocular inflammation; and taking other neuroprotective agents in the past two weeks. The drop-out criteria consisted of the patient's IOP >21 mmHg, intolerable side effects of the drug, absence at the scheduled follow-up time, withdrawal during the study, and not taking the drug for three consecutive days.

All subjects consumed one dose of oral citicoline per day for 60 days and were evaluated after 30 days and 60 days of drug administration. Subjects were asked about complaints related to side effects and underwent visual acuity examinations, complete ocular examination including IOP, visual field examination with Humphrey Visual Field Analyzer, and examination of the thickness of retinal ganglion cells and retinal nerve fiber layers by SD-OCT. Both eyes would be analyzed if met the inclusion criteria [19].

The statistical analysis was carried out by SPSS 20.0 (IBM corp). Comparison of data value before and after the intervention was using repeated ANOVA test (normal distribution) or Wilcoxon test (abnormal distribution). To compare the mean significance we used unpaired T test in normal data or Mann-Whitney test (abnormal distribution). Test to evaluate the correlation was Pearson test (normal distribution) or Spearman test (abnormal distribution). The significance of p value was <0, 05.

## Results

A total of 50 subjects met the inclusion and exclusion criteria at the beginning of the study. The randomization process divided patients into two groups, 1000 mg dose group and the 500 mg dose group with each group consisted of 25 subjects. After 30 days, there were two dropouts due to side effects and after 60 days, two subjects were lost to follow up. If both eyes of the subject meet the criteria, then



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the data is taken from the two eyes of the subject so that the total number of eyes is 75 eyes, consist of 36 eyes in the 1000 mg dose group and 39 eyes in the 500 mg dose group [20].

The baseline characteristics of the subjects of this study can be seen in (Table 1). The mean age of subjects in the 1000 mg dose group was 58.0 years; while in the 500 mg dose group was 57.1 years. A total of 20 subjects had systemic disease with hypertension and/or diabetes mellitus.

| Variable | 1000 mg n=25 | 500 mg n=25 | p |
|---|---|---|---|
| Gender | | | 0.765 |
| Male | 17 | 16 | |
| Female | 8 | 9 | |
| Laterality | | | 0.281 |
| Bilateral | 11 | 14 | |
| Unilateral Systemic disease | 14 | 11 | 0.853 |
| Yes | 12 | 8 | |
| None | 13 | 17 | |
| Age (year)* | 58.0±9.0 | 57.1±10.3 | 0.738 |

*mean±SD

**Table 1:** Baseline characteristics of the subjects (n=50).

The cup-disc ratio of the study participants varied from CDR 0.4-0.5 to 0.9-1.0 with a mean vertical CDR of 0.8 in both groups. BCVA in both groups was considered good with a median of 0.0 (LogMAR) in the 1000 mg dose group and a median of 0.1 (LogMAR) in the 500 mg dose group. During the study there was no deterioration in visual acuity in any subjects. Based on clinical characteristics, there was no significant difference between the two treatment groups both in terms of disease severity, CDR, initial IOP, and BCVA as shown in Table 2.

| Variable | 1000 mg n=36 eyes | 500 mg n=39 eyes | p |
|---|---|---|---|
| Glaucoma severity | | | 0.442 |
| Mild | 14 | 20 | |
| Moderate | 8 | 5 | |
| Severe | 14 | 14 | |
| BCVA (LogMAR)* | 0.0(0.0-0.5) | 0.1(0.0-1.0) | 0.921 |
| Baseline IOP (mmHg)** | 14.2±3.0 | 13.55±3.0 | 0.349 |
| Vertical CDR** | 0.81±0.16 | 0.80±0.16 | 0.871 |

* median (minimum-maximum), ** mean±SD

**Table 2:** Clinical characteristics of the eyes (n=75).

During the study period the IOP of all subjects were controlled, with the mean IOP in the 1000 mg dose group was 14.2 mmHg (beginning of study) and 12.6 mmHg (after 60 days) and IOP in the 500 mg dose group was 13.5 mmHg (beginning of study) and 13.8 mmHg (after 60 days).

To find out whether the initial conditions of the two groups were equivalent, comparison of the baseline data for Mean Deviation (MD) and Pattern Standard Deviation (PSD) as well as the thickness of the RNFL and GCIPL of the two groups was performed. In addition to the average RNFL thickness, measurements were also performed on the four quadrants (inferior, superior, nasal, and temporal). Table 3 shows that the two groups have the same baseline.



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| Variable | 1000 mg (n=27 eyes) | | 500 mg (n=33 eyes) | | p |
|---|---|---|---|---|---|
| | Mean/Med | SD/Range | Mean/Med | SD/Range | |
| MD (dB)* | -9.96 | -31.9 | -5.67 | -34.1 | 0.746 |
| PSD (dB)* | 6.8 | 1.1-14.8 | 3 | 0.8-13.7 | 0.296 |
| RNFL average (mm) | 76.3 | ±16.5 | 76.5 | ±19.2 | 0.961 |
| RNFL inferior (mm)* | 79.5 | 47.0-145.0 | 83 | 12.0-145.0 | 0.746 |
| RNFL superior (mm)* | 97.5 | 44.0-140.0 | 88 | 15.0-145.0 | 0.436 |
| RNFL nasal (mm) | 66.8 | ±12.4 | 65.5 | ±12.8 | 0.652 |
| RNFL temporal (mm) | 61.6 | ±16.5 | 65.1 | ±14.3 | 0.336 |
| GCIPL average (mm) | 67.3 | ±14.6 | 71 | ±11.3 | 0.219 |
| GCIPL minimum (mm) | 57.6 | ±17.7 | 60.9 | ±14.8 | 0.385 |

*Mann Whitney test, MD= Mean Deviation, PSD= Pattern Standard Deviation, RNFL= retinal nerve fiber layer; GCIPL= ganglion cell-inner plexiform layer

**Table 3**: Group parameters at baseline.

After 30 days and 60 days, there was no significant difference in MD and PSD values between both groups. However, there was a change in median MD in the 1000 mg dose group from -9.96 dB at the start of the intervention to -5.0 dB after 60 days (p = 0.008). After the intragroup analysis was carried out in the 1000 mg dose group using the Wilcoxon test, there were significant differences at the time of the initial examination and 30 days (p = 0.004) and the initial examination and 60 days (p=0.002). While in the 500 mg group, despite the improvement of the MD values based on intragroup analysis, the significant difference was only seen between MD in the initial examination and after 60 days of intervention. The median visual field defects of the two groups before and after the intervention can be seen in Table 4.

| Variable | 1000 mg | 500 mg | p* |
|---|---|---|---|
| MD (dB) | | | |
| Baseline | -9.96 (-31.6-0.3) | -5.67 (-34.5-(-0.4)) | 0.746 |
| 30 days | -6.2 (-31.5-0.85) | -6,9 (-31.4-0.93) | 0.631 |
| 60 days | -5.0 (-30.6-0.73) | -4.7 (-34.5-0.68) | 0.954 |
| PSD (dB) | | | |
| Baseline | 6.8 (1.1-14.8) | 3.0 (0.8-13.7) | 0.296 |
| 30 days | 4.8 (1.3-15.4) | 5.7 (1.1-13.5) | 0.881 |
| 60 days | 4=.2 (1,0-14,4) | 2.9 (1,0-12,3) | 0.538 |

*Mann-Whitney test

**Table 4:** Comparison of the median values of visual field parameters before and after intervention.

To see further whether there is a difference in the value of the MD and PSD between both groups, a subgroup analysis was performed based on the severity of glaucoma using the Mann Whitney Test. For the category of moderate glaucoma because there were only a few eyes in each group, it was combined with eyes with severe glaucoma. Table 5 shows the comparison of the median MD and PSD values in each group with mild glaucoma and moderate-severe glaucoma. The results of the subgroup analysis based on the severity and time of examination showed a significant difference in the MD value in the mild glaucoma receiving 500 mg citicoline after 30 and 60 days of administration. In moderate-severe glaucoma, a significant difference in MD values on subjects receiving 1000 mg citicoline.



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| Severity | Dose 1000 mg | | Dose 500 mg | | p* |
|---|---|---|---|---|---|
| | Median | Range | Median | Range | |
| Mild glaucoma | | | | | |
| MD baseline | -1.98 | -5.75 | -3.15 | -5.27 | 0,061 |
| MD 30 days | -1.5 | -5.9 | -1.94 | -6.32 | 0,316 |
| MD 60 days | -1.81 | -5.13 | -1.81 | -5.84 | 0,423 |
| p** | 0.168 | | 0.012 | | |
| PSD baseline | 2.14 | 1.09-9.10 | 2.08 | 1.32-3.59 | 0,930 |
| PSD 30 days | 1.95 | 1.26-5.33 | 1.7 | 1.07-7.45 | 0,841 |
| PSD 60 days | 1.86 | 0.99-7.08 | 1.65 | 1.16-4.94 | 0,679 |
| p** | 0.133 | | 0,070 | | |
| Moderate-severe glaucoma | | | | | |
| MD baseline | -18,44 | -31.58-(-6,10) | -22.9 | -34,54-(-7,84) | 0,094 |
| MD 30 days | -13,39 | -25,15-(-4,88) | -21.72 | -31,39-(-8,39) | 0,027 |
| MD 60 days | -13,47 | -27,67-(-2,23) | -19.55 | -34,50-(-8,38) | 0,172 |
| p** | 0.023 | | 0.113 | | |
| PSD baseline | 10.26 | 2.19-14.79 | 10.61 | 0.76-13.71 | 0,937 |
| PSD 30 days | 8.68 | 2.28-15,42 | 10.1 | 5,63-13,31 | 0,297 |
| PSD 60 days | 9.3 | 1,32-14,43 | 10.33 | 0,95-12,34 | 0,509 |
| p** | 0.368 | | 0.731 | | |

*Mann Whitney test, **Friedman test

**Table 5:** Comparison of the median values of visual field parameters based on disease severity.

Table 6 shows the mean or median thickness of the RNFL and GCIPL for each group during the study. There was no significant difference in the mean RNFL thickness (average) and RNFL quadrant between the 1000 mg group and the 500 mg group both at the initial examination, at 30 days, and at 60 days after intervention. After conducting intragroup analysis in each group using the Wilcoxon test, there was no significant difference between times of examination. It was seen that in both groups the RNFL thickness at baseline, after 30 days, and after 60 days tended to be stable, except in the 1000 mg dose group the median thickness of the superior RNFL decreased.

| Variable | 1000 mg | D500 mg | p |
|---|---|---|---|
| RNFL average (mm) | | | |
| Baseline | 76.3±16.5 | 76.5±19.2 | 0.761* |
| 30 days | 76.6±16.1 | 77.4±18.4 | 0.856* |
| 60 days | 78.4±16.3 | 77.6±19.2 | 0.863* |
| $p^{(ANV)}$ | 0.852 | 0.966 | |
| RNFL inferior (mm) | | | |
| Baseline | 79.5 (47.0-145.0) | 83.0 (12.0-145.0) | 0.746^ |
| 30 days | 80.0 (46.0-140.0) | 79.0 (49.0-139,0) | 0.699^ |
| 60 days | 81.0 (50.0-149.0) | 83.5 (46.0-145.0) | 0.845^ |
| $p^{(FR)}$ | 0.078 | 0.244 | |
| RNFL superior (mm) | | | |
| Baseline | 97.5 (44.0-140.0) | 88.0 (15.0-145.0) | 0.436^ |



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| | | | |
|---|---|---|---|
| 30 days | 90.0 (48.0-146.0) | 93.0 (5.0-150.0) | 0.864^ |
| 60 days | 91.0 (42.0-144.0) | 91.0 (17.0-155.0) | 0.561^ |
| $p^{(FR)}$ | 0.83 | 0.132 | |
| RNFL nasal (mm) | | | |
| Baseline | 66.8±12.4 | 65.5,±12.8 | 0.652* |
| 30 days | 67.7±13.8 | 67.7±14.0 | 0.994* |
| 60 days | 69.9±10.2 | 66.9±13.6 | 0.299* |
| $p^{(ANV)}$ | 0.56 | 0.766 | |
| RNFL temporal (mm) | | | |
| Baseline | 61.6±16.5 | 65.1±14.3 | 0.336* |
| 30 days | 63.4±15.5 | 63.6±14.6 | 0.953* |
| 60 days | 61.5±14.7 | 65.5±16.0 | 0.262* |
| $p^{(ANV)}$ | 0.856 | 0.828 | |
| GCIPL average (mm) | | | |
| Baseline | 67.3±14.7 | 71.0±11.3 | 0.219* |
| 30 days | 67.9±15.0 | 70.9±12.0 | 0.341* |
| 60 days | 68.5±14.7 | 71.4±10.9 | 0.343* |
| $p^{(ANV)}$ | 0.947 | 0.984 | |
| GCIPL minimum (mm) | | | |
| Baseline | 57.6±17.7 | 60.9±14.8 | 0.385* |
| 30 days | 57.0±19.2 | 60.6±16.3 | 0.388* |
| 60 days | 58.2±18.4 | 61.2±16.5 | 0.480* |
| $p^{(ANV)}$ | 0.96 | 0.987 | |

*Unpaired t-test, p(ANV) = ANOVA, ^Mann Whitney, p(FR) = Friedman

**Table 6:** Comparison of mean/median of OCT parameters.

In the mean GCIPL thickness and minimum GCIPL after drug administration for 30 days and 60 days, there was no significant difference between the two groups. Based on intragroup analysis, there was also no significant difference in the results of the examination before and after in each group. Table 6 shows that in both groups the average GCIPL thickness and the minimum GCIPL tend to be stable.

In this study, the changes in MD and PSD values after 30 and 60 days of intervention were calculated in the 1000 mg and 500 mg dose groups. The delta of each parameter was obtained from the difference between the results after intervention and the initial data. there was no difference in each parameter before and after the intervention between both groups. There was almost no change in RNFL and GCIPL showing that the thickness tended to be stable. The comparison of the change in each parameter after 30 days and 60 days between the two groups can be seen in (Table 7).



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| Changes | Dose 1000 mg | Dose 500 mg | p |
|---|---|---|---|
| ΔMD 30 days (dB) | 0.38 (-3.0-5.8) | 0.69 (-3.6-5.3) | 0.577 |
| ΔMD 60 days (dB) | 0.51 (-3.3-3.7) | 0.82 (-2.6-4.0) | 0.632 |
| ΔPSD 30 days (dB) | -0.15 (-7.3-2.7) | -0.20 (-3.2-11,.2) | 0.787 |
| ΔPSD 60 days (dB) | -0.41 (-10.4-1.7) | -0.12 (-3.0-7.1) | 0.376 |
| ΔRNFL average 30 days (mm) | -1 (-28-29) | 1 (-10-21) | 0.134 |
| ΔRNFL average 60 days (mm) | 0 (-13-29) | 0 (-6-27) | 0.568 |
| ΔGCIPL average 30 days (mm) | 0 (-8-20) | 0 (-13-14) | 0.791 |
| ΔGCIPL average 60 days (mm) | 0 (-12-12) | 0 (-10-8) | 0.402 |
| ΔGCIPL minimum 30 days (mm) | 0 (-29-23) | 0 (-16-34) | 0.762 |
| ΔGCIPL minimum 60 days (mm) | 0 (-11-10) | 0 (-25-23) | 0.435 |

Mann-Whitney test

**Table 7:** Comparison of changes in parameters after intervention.

The only side effect of the drug was nausea in two subjects, one receiving 1000 mg dose and the other receiving 500 mg. After the consumption of the drug discontinued, the side effect subsided.

## Discussion

At the beginning of the study, there was no significant difference in the baseline characteristics of the subjects between the 1000 mg group and the 500 mg group. Risk factors that can affect the progression of glaucoma include IOP, older age, and a worse initial Mean Deviation. The mean age of subjects in the 1000 mg group was 56.1 years, while the mean age of subjects in the 500 mg group was 57.7 years. This is similar to the results of previous studies which show that POAG is more prevalent at over 40 years of age [3,21]. In addition, various studies have shown that old age is a risk factor for the progression of glaucoma [22].

One of the inclusion criteria in this study was controlled IOP considering that IOP is a major risk factor for the progression of glaucoma. In addition to performing IOP examination at each visit, subjects were always asked about adherence to antiglaucoma therapy. If at each visit, the result of the examination showed an increase in IOP or the subject needed additional antiglaucoma therapy and even surgery, then the patient was excluded from the study so that it could be minimized that IOP fluctuations were not a confounder in this study [23]. The mean IOP at the beginning of the study was 14.2 mmHg in the 1000 mg cytolin group and 13.4 mmHg in the 500 mg group and was stable until the end of the study. During the study, none of the patients had IOP above 21 mmHg. Based on the Early Manifest Glaucoma Trial (EMGT), patients with IOP above 21 mmHg have a 1.77 higher risk of developing visual field progression [5]. This is also shown by the Advanced Glaucoma Intervention Study (AGIS) which recommends that IOP be controlled below 18 mmHg in advanced POAG patients who have undergone surgical intervention to prevent visual field deterioration [24].

One of the output parameters in this study is Mean Deviation (MD). When the MD values were compared between both groups, there was no significant difference after 30 days and 60 days of drug administration. However, after 30 days and 60 days of drug administration, based on intragroup analysis, there was a significant improvement in the MD value in the group receiving 1000 mg citicoline.

In this study, MD and PSD data varied between both groups because subjects with various degrees of severity were included. The wide range of values indicates heterogeneous data. One interesting thing seen after conducting subgroup analysis based on the degree of glaucoma severity, there was a significant difference in the MD values of the 500 mg group with mild glaucoma after intervention. It was also found that in moderate-severe glaucoma group receiving 1000 mg dose. This could lead to a possibility that a larger dose might be beneficial to patients with a more severe glaucoma and this findings need to confirmed on a larger sample with a longer follow-up.

Previous studies that also used visual field parameters and assessed the effectiveness of 500 mg of oral cytolin, included studies conducted by Ottobelli L, et al. [12]. This study evaluated the effect of citicoline on the rate of progression of visual field loss. Patients w receiving 500 mg oral citicoline daily for two years showed a reduction in the rate of progression of glaucoma. Lanza M, et al. [16] also showed that the administration of 500 mg oral citiocoline can slow the rate of progression of glaucoma. After 18 months of citicoline administration, there was a significant difference



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in MD of patients who received citicoline compared to the control group who received placebo. The MD values appeared stable at the next follow-up examination up to 24 months compared to the control group who tended to experience worsening MD.

Other outcome parameters in this study were the thickness of the RNFL and GCIPL. Damage in glaucoma primarily affects retinal ganglion cells and their axons and causes progressive thinning of the RNFL with changes in the structure of the optic nerve head. In the majority of cases, the loss of ganglion cells results in a reduction in the thickness of the RNFL which ultimately results in visual field defects [25].

In this study, the mean RNFL thickness and quadrant RNFL thickness (inferior, superior, and nasal, temporal) were measured. The RNFL for each quadrant was measured because in glaucoma RNFL thinning occurs generally starting from the inferior quadrant, followed by the superior, nasal, and temporal quadrants (if following the ISNT rule based on the neuroretinal rim), although the ISNT rule cannot always be applied to the thickness of the RNFL [26,27]. Both groups showed a value that tended to be stable except for the superior RNFL in the 1000 mg group which showed a decrease in the thickness of the RNFL, although statistically the decrease was not significant. SD-OCT is a tool that has good reproducibility between visits. In Cirrus SD-OCT, differences of 7μm or more in the superior and inferior quadrants (or> 4μm in the mean RNFL) between scans exceed the tolerance for variability and suggest a change [28]. Another study by Leung CK, et al. [29] Inter-visit reproducibility on the SD-OCT device was 4.86 m at the mean RNFL and ranged between 4.31 m (temporal) and 22.01 mm (6 o'clock direction).

The mean RNFL thickness in the 1000 mg and 500 mg dose groups before intervention were 76.3μm and 76.5 μm. These figures were not much different when compared to the results of the study by Hammel N, et al. [30] which showed the RNFL thickness of 73.9μm. When compared between both groups, there was no significant difference in the thickness of the RNFL at the start of the study and after 60 days of citicoline administration. The thickness of the RNFL in both groups appeared relatively stable from the start to the end of the study.

In this study, the average thickness of GCIPL and minimum GCIPL in 1000 mg the group was not significantly different from the 500 mg group. This thickness value is similar to that of a study conducted by Hammel N, et al. [30] with an average GCIPL thickness of 69.4μm and a minimum GCIPL of 62.5μm. From the initial examination to the examination after 60 days, it was found that the GCIPL thickness values were stable in both groups. Delta GCIPL, both mean and minimum, also did not show any significant differences between both groups.

Based on the results of OCT in a study conducted by Lanza M, et al. [16], it was found that the thickness of the nerve fiber layer (RNFL) and retinal ganglion cells (GCIPL) was higher in patients receiving citicoline compared to the placebo group. Changes in the thickness of the RNFL were only seen after 6 months of 500 mg citicoline administration. The thickness of the RNFL and GCIPL in patients who received citicoline was more stable over time at the next examination, while in the placebo group RNFL and GCIPL decreased. A recent study by Rossetti L, et al. [31] showed that adding citicoline drops to POAG patients slows progression in mild-moderate glaucoma patients, characterized by a lower rate of visual field progression (change in mean deviation) in patients given citicoline drops than in patients in the group placebo. In patients who received citicoline drops, changes in the thickness of the RNFL were also less than in the placebo group.

During the study, the side effects of citicoline were also monitored. In this study, there were two patients who experienced the side effects of nausea after each taking 500 mg and 1000 mg of citicoline for 3 days. In terms of its safety profile, choline is a substance with very low toxicity. Concomitant administration of cytidine (in the form of cytidine) further reduces the toxicity index by up to 20 times. A study assessing the effectiveness and safety of oral citicoline at a dose of 500-4000 mg per day in 4,191 acute ischemic stroke patients showed that side effects occurred in 0.73% of patients with symptoms related to the nervous system and gastrointestinal symptoms [32]. Oral citicoline generally is well tolerated [33].

This study was the first double-blind randomized clinical trial to compare oral citicoline between doses of 1000 mg and 500 mg in POAG. This study also used output parameters with the Humphrey Visual Field and OCT examination, modalities which are standard examinations for glaucoma patients who are routinely performed in daily practice. It is hoped that the results of this study can be used as a basis for further research which results can be applied in clinical practice. In this study, structural examinations were not limited to the thickness of the RNFL, but also the thickness of GCIPL using SD-OCT which has good reproducibility and produces images with better resolution and fewer artifacts [34].

The drawbacks of this study were the small number of samples and the short duration of follow-up. The sampling process encountered obstacles due to limited research time and the decreasing number of patient visits in the era of the COVID-19 pandemic. In addition, there was also subject heterogeneity in terms of the severity of glaucoma and visual field defects so that there was variability in the MD and PSD values. However, this picture is actually a more realistic



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picture and can represent the patient population seeking treatment at Glaucoma Clinic in the tertiary hospital. In order to increase the reliability of the perimetric examination results, it is recommended that the initial data be checked twice at different times.

## Conclusion

There was an improvement in the MD and PSD values in both groups after 60 days of oral citicoline administration, but a significant difference was found in mild glaucoma group receiving 500 mg citicoline and in moderate-severe glaucoma receiving 1000 mg citicoline. The thickness of RNFL and GCIPL in both groups did not decrease after 60 days of citicoline administration.

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