ORIGINAL ARTICLE

CITICOLINE IN NON–ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY: PATTERN ELECTRORETINOGRAPHY REVIEW

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ABSTRACT

This study aims to assess 1000 mg citicoline each day given for 60 days on chronic phase NAION (non–arteritic anterior ischemic optic neuropathy) patients. Double masked randomized clinical trial divided the patients into 2 groups: citicoline group (C–NAION) and placebo group (P–NAION). Analysis was done in 17 patients in each group. There were increament of Δ amplitude P50 30 days in C–NAION group (0,775±2,6 μV) and Δ amplitude N95 60 days in C–NAION group (–0,356±2,992 μV) but statistically insignificant compared to P–NAION. Age has a good correlation with Δ amplitude P50 (r = –0.517; p = 0.002). Subjects with 1 risk factor experienced a higher Δ amplitude of P50 than the subjects with more than 1 risk factor (1.856 ± 2.121 μV vs –0.26 ± 2.45; p = 0.025). Citicoline did not show any changes in Retinal Ganglion Cell Thickness. There were improvement of Δ mean deviation 60 days in C–NAION group (3,13±6,467 dB), but statistically insignificant compared to P–NAION. Citicoline tends to increase the Δ amplitude of P50, N95 and mean deviation in chronic phase NAION. Age and the number of risk factors affects the increase of Δ amplitude P50.

Keywords: citicoline, non–arteritic anterior ischemic optic neuropathy, pattern electroretinography, retinal ganglion cell thickness, visual field.

INTRODUCTION

Nonarteritic anterior ischemic optic neuropathy (NAION) is an acute or subacute optic neuropathy due to microcircular ischemia of the retrolaminar anterior optic nerve that is vascularized from the short posterior ciliary artery. This ischemic event will be followed by axon edema which will lead to compartment syndrome and aggravate the incidence of ischemia.[1,2]

In NAION, the main pathology occurs at the level of the optic nerve, concerning the axons of retinal ganglion cells. Initial damage is ischemia in optical disc resulting in hypoxic axon injury as well as manifesting into disc edema. Axon edema causes retrograde axonal transport disturbances particularly the neurotrophic factors of the brain to retinal ganglion cells. This will trigger secondary toxicity and apoptosis. In addition, the presence of oxidative stress, calcium influx and mitochondrial damage also trigger apoptosis.[3] After retinal ganglion cell apoptosis,

retinal nerve fiber layer (RNFL) decline occurs via Wallerian degeneration.[4] This RNFL depletion will manifest as a visual field disturbance and a decrease of visual acuity in chronic phase NAION.[5]

Until now NAION therapy is still empirical. Ischemic Optic Neuropathy Decompression Trial (IONDT), the only level I clinical prospective study for NAION therapy found that there is no benefit from surgical intervention.[6] One large but non–randomized study concluded that oral steroids are indicated for acute phase NAION.[7] Recent neuroprotective therapy received attention because it has the effect of protecting and stimulating the regeneration of neurons, in terms of NAION, retinal ganglion cells. One of the neuroprotective therapies for NAION is citicoline (CDP–choline 5'–diphosphocholine).

Citicolines are intermediates of the phosphatidylcholine synthesis, which is one component of the phospholipid membrane in central nervous system cells. Citicolines play a role in the synthesis of phospholipid membrane cells and help stabilize the intracellular conditions of damaged neurons. Several previous studies have also shown that citicolines have a neuroprotective effect on retinal ganglion cells that are damaged and support regeneration of neuron *in vitro.*[8] Previous study on the administration of citicoline in chronic phase NAION gave satisfactory results but this study has not used a placebo control group.[9]

The development of ophthalmological technology allows us to monitor functional and anatomical response therapy. To evaluate ganglion cell activity, it is necessary to examine pattern electroretinography (pERG). The P50 and N95 waves in pERG reflect the activity of the retinal ganglion cells and the inner layers of the retina.[10] These retinal ganglion cells are affected by the administration of citicoline. In addition, using optical coherence tomography (SD–OCT) spectra–domains we can accurately monitor the retinal ganglion cell thickness. This study aims to determine the effect of citicoline supplementation 1000 mg per day for 60 days on the pattern electroretinography result, ganglion cell thickness and visual field of chronic phase NAION patients.

MATERIAL AND METHODS

This study is a double masked randomized clinical trial. This research was conducted in Neuro–ophthalmology (NO) Division FKUI–RSCM Kirana. The study was done in November 2016–April 2017 after obtaining approval of FKUI–RSCM ethics committee Numbered 1066/UN2.F1/ETIK/2016 and LB.02.01/X.2/0005/2017. This research was followed the tenets of the Declaration of Helsinki.

The inclusion criteria for this study were patients aged 20–70 years, clinically diagnosed NAION by at least 1 NO division consultant with an onset of ≥6 weeks, best corrected visual acuity with snellen ≥ 1/60 and willing to participate in this study by signing informed consent. In bilateral NAION, examination of the study was performed on one eye with the closest onset of 6 weeks.

The exclusion criteria of this study were media refraction opacities such as LOCS III> 3, macular and other papillary disorders, glaucoma history and intraocular inflammation, taking other supplements in the last 2 weeks, clinically and or with OCT papillary detected optic disc edema.

The sample size was calculated based on previous studies measuring the amplitude of N95 PERG wave in NAION patients. From the previous research, the standard deviation was 55%.[9] The researcher determined the minimum clinical difference value that was considered as significant as 0,55. Using the sample formula for unpaired numerical analytic test, we got 16 samples for each group. Consecutive sampling was performed.

We performed baseline data collection and laboratory outcomes related to risk factors, standard ophthalmological examination and pERG examination following the International Society for Clinical Electrophysiology of Vision (ISCEV) standard[11], visual field examination with Humphrey HFA II–i 750, 24–2 threshold and examination of ganglion retinal cell thickness with OCT Cirrus™ panomap mode. This examination was performed pre–intervention, 30 days and 60 days after intervention. The subjects will be randomized to group A (received citicoline 1000 mg) or group B (received placebo). During the study, subjects continued to take systemic drugs and did not take other multivitamins. Patients who experienced side effect were requested to stop the supplementation and came to control the day after.

RESULTS

The subjects included at the beginning of the study were 38 subjects. Figure 1 shows the plot of the research subject. The analysis was performed on 34 subjects. Table 1 shows the basic characteristics of the two groups. Table 2 shows the results of pERG examination, retinal ganglion cell thickness and visual field prior to intervention in both groups. There were no significant differences between the two groups

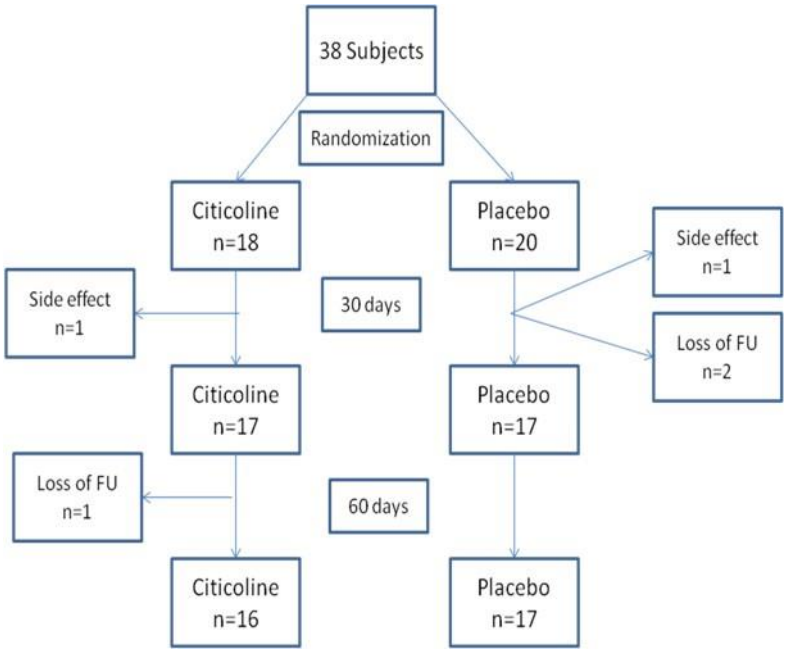

Figure 1. Plots of research subject

Table 1. Baseline characteristic (n=34 subjects)

Variable	Citicoline	Placebo	p
Number of patients	17	17	
Age (year)	57,59±8,846	53,88±5,499	0,154*
Gender			0,303#
• Female	7 (41,2%)	10 (58,8%)	
• Male			
Onset (weeks)	10 (58,8%)	7 (41,2%)	0,522**
BCVA (logMar)	32(16–108)	24(12–104)	0,862**
DM (Y/N)	0,4(0–1,7)	0,4(0–1,7)	0,486#
Hypertension (Y/N)	9/8	11/6	1#
Dyslipidemia (Y/N)	10/7	10/7	1##
Hypercoagulation (Y/N)	13/4	13/4	0,132#
	7/10	3/14	

* unpaired–T test ** Mann–Whitney test # Chi–Square test #Fisher test

Table 2. Pre–intervention data

	Citicoline	Placebo	p
Amplitude P50 (µV)	4,824±3,26	5,641±3,082	0,458*
Amplitude N95 (µV)	–5,235±3,667	–5,853±3,05	0,597*
Retinal ganglion cell thickness (µm)	58,65±9,546	58,82±15,977	0,969*
Mean deviation (dB)	–18,193±8,883	–19,515±9,924	0,739*
Pattern standard deviation (dB)	10,093±3,21	10±4,071	0,952*

* unpaired–T test

Table 3. Comparison of Δ amplitude P50 and N95 ; Δ retinal ganglion cell thickness 30 days and 60 days post–intervention in both groups

	Citicoline	Placebo	p
Δ amplitude P50 30 days (µV)	0,775±2,6	–0,282±2,42	0,182*
Δ amplitude N95 30 days (µV)	–0,1(–7–12)	0,9(–4,9–5,3)	0,459**
Δ amplitude P50 60 days (µV)	0,1(–3–10,9)	0(–2,3–4,1)	1**
Δ amplitude N95 60 days (µV)	–0,356±2,992	–0,671±3,37	0,779*

Δ retinal ganglion cell thickness 30 days (μm)	0(–3–4)	–1(–8–12)	0,384*
Δ retinal ganglion cell thickness 60 days (μm)	0(–7–9)	–1(–7–44)	0,571*

* unpaired–T test ** Mann–Whitney test

Table 3 shows the comparison of Δ examination results after 30 days and 60 days of intervention. Delta examination results obtained from the difference of measurement results after the intervention (30 days and 60 days) and pre–intervention data. Clinically, Δ amplitude of P50 was increasing 0.775 μV at 30 days of citicoline and 0.1 μV on 60 days of citicoline administration. This was not experienced by the placebo group. Clinically the N95 amplitude in the citicoline group also improved (more minus) by –0.356 μV after 60 days of administration. This becomes statistically insignificant due to the width of the standard deviation.

We tried to find correlation between age and amount of risk factor of research subject to Δ amplitude. Researchers found moderate to strong correlation between age and Δ amplitude P50 ($r = –0.517$; $p = 0.002$). The correlation is negative meaning that the older subject, has a smaller Δ amplitude P50. The researchers also tried to find the basic characteristics of patients who experienced an increase of P50 amplitude at 60 days by ≥ 0.55 μV and found that the age of the study subjects who improved were younger (50.25 ± 5.578 years) than those who were not improving (58.67 ± 6,894 years), ($p = 0.001$).

Similarly, the number of risk factors determines the Δ amplitude of P50 in 30 days where in the study, subjects with the number of risk factors only one, had a greater increase of P50 amplitude compared to subjects with more than one risk factor. The result of Δ amplitude P50 30 days in the group with 1 risk factor was 0.669 ± 2.57 μV while group with more than 1 risk factor was –0.182 ± 2,492 μV. Likewise Δ amplitude of P50 60 days in the group with 1 risk factor was 1.188 ± 3.22 μV while group with more than 1 risk factor was 0.2 ± 2.067 μV. Furthermore, as many as 12 subjects (70.6%) in the citicoline group had more than one risk factor while in the placebo group there were only 6 subjects (35.3%) who had more than one risk factor.

Neither citicoline nor placebo did show changes in ganglion cell thickness after 30 and 60 days of intervention. This means that in patients with atrophy NAION phase, the thickness of ganglion cells is already depleted and static. This can be seen in table 3.

Table 4. Comparison of visual field 30 days and 60 days post–intervention in both groups

	Citicoline	Placebo	p
Δ *Mean deviation* 30 days (dB)	0(–7,26–8,66)	0(–18,08–5,62)	0,689**
Δ *Pattern standard deviation* 30 days (dB)	0(–0,17–3,59)	0(–0,98–2,61)	0,382**
Δ *Mean deviation* 60 days (dB)	0,068±2,178	0,384±3,202	0,741*
Δ *Pattern standard deviation* 60 days (dB)	0,068±2,178	0,384±3,202	0,741*

* unpaired–T test **Mann–Whitney test

Table 4 showed that after 60 days of citicoline administration, there was improvement of mean deviation compared to the placebo group. This becomes statistically insignificant due to the width of the standard deviation.

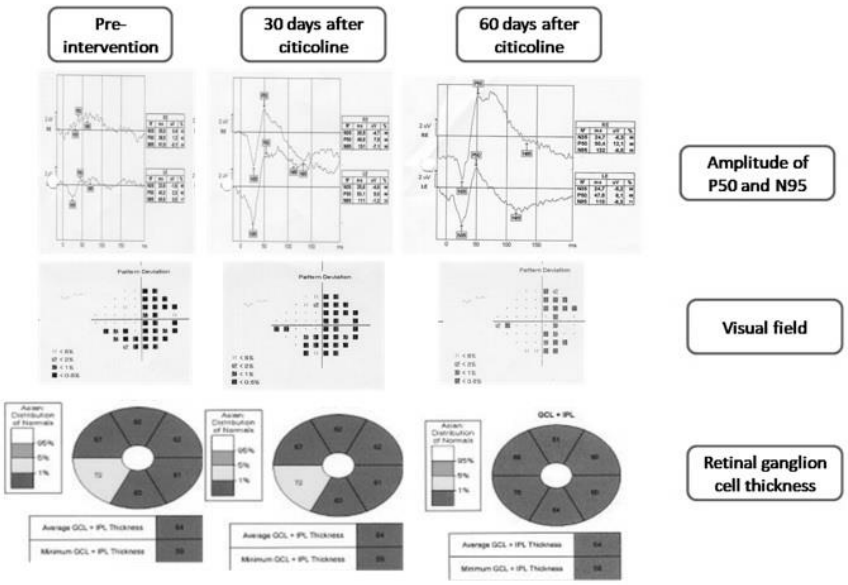

Figure 2. Example of P50–N95 amplitude and visual field improvement in one of subject, Patient A, male, 41 years old, in citicoline group.

Total subjects in the study amounted to 38 subjects. After the randomization table was opened, there were headache and nausea side effects in 2 subjects (1 subject in the citicoline group and 1 subject in the placebo group). Both of these subjects did not continue the study.

DISCUSSION

There was a paradigm shift in which the ganglion cell damage was known used to be irreversible, it is now believed to be repairable. It takes years for retinal ganglion cell to degenerate, so pharmacological intervention can be applied at this time to prevent total retinal ganglion cell death. One of the most common pharmacological interventions used in NAION patients in our practice is citicoline.

In the beginning of this study, the two groups were in the same condition. A good masking

method in patients, examiners and researchers ensures that both treatment and measurements are similar. This was proved by the non–significant differences in the basic characteristics and amplitude of P50 and N95 on pERG examination, retinal ganglion cell thickness in OCT panomap and mean deviation and pattern specific deviation at Humphrey at the beginning of the study.

The amplitude of the P50 and N95 waves is a component which is more sensitive to retinal changes than the implicit time, so we only analyze the amplitude Δ P50 and N95.[12] There is a 10–80% decrease in pERG amplitude in patients with optic neuropathy, where in the normal population the amplitude P50 and N95 ranges from 2–4μV.[11]

In this study, we found an amplitude improvement trend of P50 (0.775 ± 2.6 μV) and N95 (–0.1 (–7–12) μV) as well as improved visual field in terms of mean deviation (3.13 ± 6.467 dB) at citicoline groups. Citicoline has been shown to increase the synthesis of phosphatidylcholine and other cell membrane phospholipids such as phosphatidyethanolamine and phosphatidylserine. This counteracts the mechanism of neural apoptosis of ganglion cells that occurs in NAION patients. Another mechanism of action is to stabilize the intracellular state of the retinal ganglion and decrease the activity of the enzyme phospholipase A2 (PLA2) and clusterin expression and also increase Bcl–2 expression aimed at preventing retinal ganglion cell apoptosis. Furthermore, citicoline also stimulates the dopaminergic system known as neurotransmitters in the retina.[13]

In this study, there was still a measurable physiological fluctuation in the examination of pERG and visual field in the placebo group. This is in contrast to a study by Levin et al who found no morphological and physiological changes after 6 weeks of NAION (atrophy phase).[4] This indicates that although the number of ganglion cells tends to be stable, its function can still fluctuate and autorepair itself.

In this study, there was no statistically significant difference due to the wide standard deviation of subjects. The standard deviation included in the sample calculations at the beginning of the study was 0.55 μV according to the study by Parisi et al[9], whereas the standard deviation of our study results was 3.05–3.667 μV.

Overall, there was a significant correlation between the age and Δ amplitude of P50 at 30 and 60 days. In addition, it was found that subjects with clinical improvement Δ amplitude P50 ≥ 0.55 μV were younger than those without improvement. It is interesting that citicoline has different effects of phosphatidylcholine formation between young and old patients. As is known, phosphatidylcholine is an important component that maintains the integrity of cell membranes and their repair. In old age there is a decrease of phosphatidylcholine in brain

membrane cells due to aging process. A study using magnetic resonance spectroscopy protein to measure the concentration of choline in the cytosol before and after the administration of oral citicoline found that choline resonance in patients with younger age increased, whereas in old age, decreased. This may be the result of the cytidin component of citicoline increasing the incorporation of brain choline in the phosphatidylcholine of the cell membrane so that its resonance decreases in old age.[14]

We found that the subjects with more than 1 risk factor had a smaller amplitude compared to those with only one risk factor. This applies to both the citicoline and placebo groups. The number of risk factors in NAION patients have more role to determine the patient's prognosis (improvement of amplitude P50) than whether the risk factor is controlled. Rusenberg et al in his findings reported that diabetes and hypertension led to dendritic axon edema and reduced retinal ganglion cell count.[15] Similarly, Idiculla et al found that dyslipidemia was associated with reduced number and function of retinal ganglion cells.[16] Percentages of subjects with more than one risk factor were found higher in citicoline group. This may explain why the increase of Δ amplitude of P50 in the citicoline group did not differ significantly with the placebo group.

This study is the first study to evaluate the effect of oral citicoline versus placebo with a double–masked randomized method in NAION patients. The method of this research is double–masked randomization, so the researcher expects the basic characteristic variable which can become confounding factor evenly divided between the two study groups. The difficulty is to monitor the daily food intake of patients such as subjects consuming food sources containing choline, such as eggs, red meat and nuts but until now there has been no further research on the amount of these foods and its choline levels in blood.[17]

Another weakness of this study is the width of the standard deviation in the study subjects. This happens because the number of samples is inadequate and the sampling is consecutive, thus less reflecting the population. Ideal side is difficult because of limited research time and few cases. Selection of research subjects in terms of age and number of risk factors also need to be considered. Another obstacle is the diverse level of education of subjects requiring different learning curve in following the direction when the examination, especially the subjective one such as Humphrey.

CONCLUSION

Citicoline supplementation tends to improve the Δ amplitude of P50 and N95 and Δ mean deviation in chronic phase NAION. The age and the number of risk factors are those that affect the increase of Δ amplitude P50. Citicoline supplementation did not show changes

in retinal ganglion cell thickness. Citicoline supplementation can be used safely in chronic phase NAION.

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Authors have no interest to declare

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Figure legend

Figure 1 Plots of research subject

Figure 2 Example of P50–N95 amplitude and visual field improvement in one of subject, Patient A, male, 41 years old, in citicoline group.

Table legend

Table 1 Baseline characteristic (n=34 subjects).