Memantine Treatment in Acute Nonarteritic Anterior Ischemic Optic Neuropathy: A Randomized Clinical Trial

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Abstract

Purpose: To evaluate the effects of memantine on improving visual function in patients with acute nonarteritic anterior ischemic optic neuropathy (NAION)

Methods: This was a prospective, double masked, randomized, clinical trial. The study involved 47 subjects with unilateral NAION of less than 8 weeks duration. Eligible patients were randomly allocated to take either memantine tablets (5 mg daily during the first week and then 10 mg daily for the next two weeks, 25 subjects) or placebo tablets (22 subjects). Baseline visual acuity (VA) tests, pattern visual evoked potential (VEP) and automated perimetry (SITA-standard 24-2) were performed. VA tests were repeated 3 weeks, 3 months and 6 months after initial visit. VEP and automated perimetry were repeated 3 months after initial visit.

Results: At baseline there was no significant difference between the two groups in terms of clinical and laboratory characteristics. After 3 weeks, 3 months and 6 months of treatment, best corrected visual acuity (BCVA) improved by -0.31±0.39, -0.49±0.47 and -0.53±0.48 logMAR in the memantine group respectively and -0.02±0.41, -0.09±0.60 and -0.05±0.67 logMAR in the placebo group respectively (P=0.024, P=0.025 and P=0.017). VEP results demonstrated a reduction of implicit time of -8.32±17.18 ms in the memantine group after 3 months, whereas in the placebo group it increased +5.7±21.60 ms (P=0.043). The change in VEP amplitude was not significantly different between the memantine and placebo groups (P=0.083). The effect of the memantine on mean deviation (MD) and pattern standard deviation (PSD) changes was not significantly different from that of the placebo (P=0.428 and 0.863 respectively).

Conclusion: Treatment of patients who experience acute NAION with memantine may result in significant improvement in BCVA compared with no treatment. The VEP changes seen at 3 months may indicate improved transmission of impulses through the optic nerve.

Keywords: Automated Perimetry, Memantine, Nonarteritic Anterior Ischemic Optic Neuropathy, Visual Evoked Potential


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Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common cause of visual loss from optic nerve diseases among individuals older than 50 years, with an annual incidence rate of 2.3 to 10.2 per 100,000 persons for this population group. Patients with NAION typically present with painless monocular visual loss developing over hours to days. Visual field loss is always present and includes altitudinal defect, central scotoma and generalized depression. A relative afferent pupillary defect (RAPD) is present unless the optic neuropathy is bilateral. The affected optic disk is by definition always swollen. There is no widely accepted treatment for NAION. Although surgical decompression and various medical therapies have been proposed, none has consistently shown to be effective.

NAION is caused by disruption in arterial blood supply to the optic nerve head. This disruption leads to permanent visual loss from ischemic injury to optic nerve axons, ultimately resulting in death of retinal ganglion cells from necrosis and apoptosis. Glutamate is the principal excitatory neurotransmitter in the retina. Retinal ischemia is associated with an increase in the level of extracellular glutamate and excessive activation of N-methyl-d-aspartate (NMDA) type glutamatergic receptors. NMDA-type glutamatergic excitotoxicity has been implicated as a mechanism for ischemic injury to retinal ganglion cells and neurons in many regions of the CNS and drugs that directly antagonize the actions of glutamate have been shown to be neuroprotective.

Memantine is a relatively new drug especially developed for use in moderate to severe dementia and approved by the FDA in 2003 because of its significant efficacy. It is a noncompetitive NMDA receptor antagonist and reduces glutamatergic excitotoxicity. Memantine has also been used for the treatment of Parkinson disease in Europe for the last 2 decades. In fact, the pathogenesis of both dementia and Parkinson disease has been linked to excitotoxic injury induced by excessive glutamate levels in the synaptic cleft and over-stimulation of the NMDA receptor. Memantine has been shown to ameliorate glutamate NMDA-receptor mediated toxicity in both retinal ganglion cells and cortical neurons. There are several studies indicating that memantine is neuroprotective in various in vitro and in vivo animal models of neural cell/brain ischemia as well as glaucoma. Memantine has been shown to reduce the retinal injury in rat ischemia/reperfusion models. In addition, memantine has been shown to be relatively safe and is well tolerated in patients. We have recently shown that memantine significantly improved visual acuity (VA) in a nonrandomized small group of patients with acute NAION.

The aim of the current randomized clinical trial was to compare the effects of memantine on VA, visual field and visual evoked potential (VEP) findings with placebo in patients with acute NAION.

Methods

This prospective randomized double-masked clinical trial was registered at http://www.anzctr.org.au as ACTRN12607000181404. Subjects with acute visual loss from unilateral NAION of less than 8 weeks duration were enrolled. Inclusion criteria were as follows: acute onset of painless loss of vision, localized or generalized swelling with or without pallor of the optic nerve head, flame-shaped hemorrhages, arterial narrowing without venous congestion, a RAPD, and a visual field defect.

This study was performed with informed consent and following all the guidelines for experimental investigations required by the investigational review board and ethics committee of Tehran University of Medical Sciences.

The main exclusion criteria were: age<40 years, elevated sedimentation rate as well as presence of systemic signs and symptoms consistent with arteritic AION, diabetic retinopathy, uncontrolled glaucoma, or conditions other than NAION that could contribute to the visual loss, drug history such as anti-convulsants, barbiturates, neuroleptics, amantadine, hydrochlorothiazide and history of renal insufficiency.

At baseline, eligible subjects were randomly assigned to receive either memantine or placebo, in a masked fashion. All patients underwent a complete ophthalmic...
examination including manifest refraction to determine best corrected visual acuity (BCVA) by ETDRS chart and expressing acuity in logMAR scale, visual field testing using a Humphrey automated perimeter (24-2 SITA-standard program), slit-lamp examination, tonometry, evaluation of pupillary responses to light stimulation, and funduscopic examination with a fully dilated pupil using an indirect ophthalmoscope and/or a 78-diopter biconvex indirect lens with the slit-lamp biomicroscope. All patients were referred to a cardiologist for assessment of cardiovascular status, including measurement of blood pressure. Laboratory evaluation including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), fasting blood sugar (FBS), cholesterol, triglyceride, blood urea nitrogen (BUN) and creatinine measurements were done for all subjects at baseline. VEP (pattern VEP if possible), and color fundus photography were performed at baseline. Fluorescein angiography was done if necessary.

For suspicion of an intracranial mass lesion, demyelinating disease, or other neurologic conditions, a neurologic consult was obtained and neuroimaging performed. Each subject received either memantine (Ebixa®) tablets (5 mg daily for first week and 10 mg daily for the next 2 weeks) or placebo taken in the same manner. Both placebo and memantine tablets were made similar in appearance by putting memantine tablets into a capsular shell containing lactose monohydrate/microcrystal cellulose. Placebo capsules contained only lactose monohydrate/microcrystal cellulose. Both the patient and the treating physician were masked to the drug being dispensed. Medical and ophthalmologic data, including BCVA and funduscopic examination with a fully dilated pupil using an indirect ophthalmoscope and/or a 78-diopter biconvex indirect lens with the slit-lamp biomicroscope. All patients were referred to a cardiologist for assessment of cardiovascular status, including measurement of blood pressure. Laboratory evaluation including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), fasting blood sugar (FBS), cholesterol, triglyceride, blood urea nitrogen (BUN) and creatinine measurements were done for all subjects at baseline. VEP (pattern VEP if possible), and color fundus photography were performed at baseline. Fluorescein angiography was done if necessary.

Thus, the minimum number of subjects necessary to detect a clinically meaningful difference to a power of 80% and a risk of 5% and a loss to follow up of 20% was 44.

Statistical analysis was performed by the T-test and the $\chi^2$ test with SPSS software version 11.5. The level of significant for all analyses was set at $P<0.05$.

Results

A total of 47 patients with NAION were enrolled. 25 subjects were in the memantine group and 22 subjects were in the placebo group. Tables 1 and 2 summarize the demographic data and results of the study. The mean±one standard deviation is provided. The demographic and ocular characteristics of the subjects at baseline were similar between the two groups.

The mean duration of symptoms from the onset of NAION to the initiation of treatment was 19.8±11.6 days (ranging from 4 to 42 days) in the memantine group and 17.8±11.6 days (ranging from 5 to 50 days) in the placebo group ($P=0.548$). Distribution of risk factors between the two groups was similar (Table 1). Over all, systemic hypertension was found in 25 subjects (53.2%), diabetes in the 18 subjects (38.3%) and hyperlipidemia in 11 subjects (23.4%).
**Table 1.** Comparison of baseline characteristics in memantine group with control group

<table>
<thead>
<tr>
<th></th>
<th>Memantine group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>57.2±8.4 yrs</td>
<td>59.8±8.2 yrs</td>
<td>0.298</td>
</tr>
<tr>
<td>Number (gender)</td>
<td>25 (17 M : 8 F)</td>
<td>22 (14 M : 8 F)</td>
<td>0.753</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (36.0%)</td>
<td>9 (40.9%)</td>
<td>0.730</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (52.0%)</td>
<td>12 (54.5%)</td>
<td>0.861</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>5 (20%)</td>
<td>6 (27.3%)</td>
<td>0.557</td>
</tr>
<tr>
<td>Visual loss duration</td>
<td>19.8±11.6 days</td>
<td>17.8±11.6 days</td>
<td>0.548</td>
</tr>
<tr>
<td>Initial logMAR acuity</td>
<td>1.27±0.80</td>
<td>1.28±0.75</td>
<td>0.966</td>
</tr>
<tr>
<td>Initial VEP implicit time</td>
<td>129.43±14.80 ms</td>
<td>129.29±19.66 ms</td>
<td>0.979</td>
</tr>
<tr>
<td>Initial VEP amplitude</td>
<td>6.55±4.58 µv</td>
<td>8.82±7.44 µv</td>
<td>0.236</td>
</tr>
<tr>
<td>Initial mean deviation</td>
<td>-18.10±7.07 db</td>
<td>-21.49±6.90 db</td>
<td>0.140</td>
</tr>
<tr>
<td>Initial pattern standard deviation</td>
<td>9.39±5.22 db</td>
<td>9.65±3.39 db</td>
<td>0.856</td>
</tr>
</tbody>
</table>

SD: Standard deviation

**Table 2.** Comparison of endpoint values in different timepoints in memantine group with control group

<table>
<thead>
<tr>
<th></th>
<th>Memantine group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Week logMAR acuity</td>
<td>0.94±0.64</td>
<td>1.25±0.74</td>
<td>0.150</td>
</tr>
<tr>
<td>3-Month logMAR acuity</td>
<td>0.78±0.54</td>
<td>1.16±0.76</td>
<td>0.071</td>
</tr>
<tr>
<td>6-Month logMAR acuity</td>
<td>0.73±0.53</td>
<td>1.11±0.75</td>
<td>0.090</td>
</tr>
<tr>
<td>3-Month VEP implicit time</td>
<td>118.96±20.35 s</td>
<td>135.83±11.83 s</td>
<td>0.008</td>
</tr>
<tr>
<td>3-Month VEP amplitude</td>
<td>5.72±4.39 µv</td>
<td>7.11±5.99 µv</td>
<td>0.441</td>
</tr>
<tr>
<td>3-Month mean deviation</td>
<td>-15.17±7.64 db</td>
<td>-21.53±6.68 db</td>
<td>0.019</td>
</tr>
<tr>
<td>3-Month pattern standard deviation</td>
<td>10.44±4.31 db</td>
<td>9.99±3.51 db</td>
<td>0.752</td>
</tr>
<tr>
<td>Change in logMAR acuity at 3-weeks</td>
<td>-0.31±0.39</td>
<td>-0.02±0.41</td>
<td>0.024</td>
</tr>
<tr>
<td>Change in logMAR acuity at 3-months</td>
<td>-0.49±0.47</td>
<td>-0.09±0.60</td>
<td>0.025</td>
</tr>
<tr>
<td>Change in logMAR acuity at 6-months</td>
<td>-0.53±0.48</td>
<td>-0.05±0.67</td>
<td>0.017</td>
</tr>
<tr>
<td>Change in VEP implicit time at 3-months</td>
<td>-9.29±17.30 ms</td>
<td>5.70±21.60 ms</td>
<td>0.031</td>
</tr>
<tr>
<td>Change in VEP amplitude at 3-months</td>
<td>-0.40±2.95 µv</td>
<td>-2.67±4.04 µv</td>
<td>0.067</td>
</tr>
<tr>
<td>Change in mean deviation at 3-months</td>
<td>2.37±5.27 db</td>
<td>0.85±5.42 db</td>
<td>0.428</td>
</tr>
<tr>
<td>Change in pattern standard deviation at 3-months</td>
<td>0.96±5.60 db</td>
<td>0.67±3.17 db</td>
<td>0.863</td>
</tr>
</tbody>
</table>

VEP: Visual evoked potential
Visual acuity

Mean baseline BCVA was 1.27±0.80 logMAR (ranging from 0.24 to 2.60 logMAR) in the memantine group and 1.28±0.75 logMAR (ranging from 0.04 to 0.60 logMAR) in the placebo group (P=0.966).

Three subjects (1 subject in the memantine group and 2 subjects in the placebo group) discontinued drug before completion of treatment and were excluded from further analysis. Side effects were seen in 4 subjects in the memantine group. Dizziness appeared in 2 subjects and there was a crisis of systemic hypertension in 2 subjects which was controlled with medication. No other serious side effect was seen.

Forty-four subjects completed 3 weeks of follow-up. After 3 weeks, mean BCVA improved -0.31±0.39 logMAR in the memantine group (24 subjects) and -0.02±0.41 logMAR in the placebo group (20 subjects). The difference of VA between the two groups was statistically significant (P=0.024, Figure 1). At 3 weeks of follow-up 10 subjects (41.7%) had a VA improvement of ≥0.3 logMAR in the memantine group compared to 3 (15%) subjects in the control group (P=0.054).

At 3 months of follow-up, the difference of mean BCVA from baseline was -0.49±0.47 logMAR in the memantine group (22 subjects) and -0.09±0.60 logMAR in the placebo group (18 subjects). The difference of VA between the two groups was statistically significant (P=0.025). At 3 months of follow-up 13 subjects (51.9%) had a VA improvement in the memantine group compared to 7 (38.9%) subjects in the control group (P=0.204).

Thirty-six subjects completed 6 months of follow-up. In memantine group (21 subjects), mean difference of BCVA from baseline was -0.53±0.48 logMAR and in the placebo group (15 subjects) was -0.05±0.67 logMAR. The difference of VA between the two groups was statistically significant (P=0.017). At 6 months of follow up 13 subjects (61.9%) had a VA improvement in the memantine group compared to 5 (33.3%) subjects in the control group (P=0.091).

Figure 1. Comparison of best corrected visual acuity between the memantine and control groups at baseline, 3 weeks, 3 months, and 6 months of follow-up.
**Pattern visual evoked potential**

VEP was performed for 42 subjects (5 subjects were not cooperative) at baseline and implicit time \([P100 \text{ millisecond or } P2 \text{ (flash VEP)}]\) and amplitude (\(\mu v\)) were evaluated.

It was not possible to perform pattern VEP in 15 subjects (6 in the memantine group and 9 in the placebo group) because of low vision, therefore flash VEP was done in this group and implicit time (P2) and amplitude were evaluated.

Mean baseline implicit time was 129.43±14.80 ms in the memantine group (22 subjects) and 129.29±19.66 ms in the placebo group (20 subjects). Mean baseline amplitude was 6.55±4.58 \(\mu v\) in the memantine group (22 subjects) and 8.82±7.44 \(\mu v\) in the placebo group (20 subjects). The difference of implicit time and amplitude between the two groups was not statistically significant (Table 1).

At 3 months of follow-up VEP was done in 34 subjects. Difference of mean baseline implicit time from follow up was -9.29±17.30 ms in the memantine group (19 subjects) and 5.70±21.60 ms in the placebo group (15 subjects). At 3 months of follow-up, the implicit time decreased in the memantine group, however, it increased in the control group (Table 2). The change in VEP implicit time at 3 months of follow-up was statistically significant between the two groups (P=0.031).

There was a decrease of VEP amplitude in both groups. However, the reduction of amplitude in the memantine group was less than that of placebo group (P=0.067).

**Automated perimetry**

Perimetry program of SITA-standard C2-24 for all subjects (47 subjects) at base line were done, however, only in 39 subjects perimetry were reliable. In this study reliability indices were defined as follows: False negative <12%, False positive <4% and Fixation loss <20%. Common visual filed defect patterns were inferior altitudinal pattern in 12 subjects (27.3%), general depression in 8 subjects (18.2%), double arcuate pattern in 6 subjects (13.6%), superior altitudinal pattern in 3 subjects (6.8%), and nasal altitudinal pattern in 3 subjects (6.8%).

In the memantine group (21 subjects) the mean of the initial MD and mean of the initial PSD were -18.10±7.07 db and 9.39±5.22 db respectively. In the control group (18 subjects), the mean of initial MD and mean of initial PSD were -21.49±6.90 db and 9.65±3.39 db respectively. There was no significant difference in the magnitude of the initial MD PSD between the two groups (Table 1).

At 3 months of follow-up perimetry results were not reliable in 7 subjects; thus only in 32 subjects perimetry was evaluated. In memantine group (17 subjects) the mean of the 3 months MD and mean of the 3 months PSD were -15.17±7.64 db and 10.44±4.31 db respectively. In control group (15 subjects), the mean of 3 months MD and mean of PSD were -21.53±6.68 db and 9.99±3.51 db respectively.

The difference between baseline and 3-months follow-up MD was 2.37±5.27 db in the memantine group and 0.85±5.42 db in the control group which was not significant between the two groups (P=0.428)(Table 2).

The difference between baseline and 3-months follow-up PSD was 0.96±5.60 db in the memantine group and 0.67±3.17 db in the control group which was not significant between the two groups (P=0.863).

**Discussion**

We performed this randomized clinical trial because of the lack of widely accepted treatment for NAION and the strong clinical and histological evidence of the neuroprotective effects of memantine in animal models of neuronal and retinal ischemia.\(^{13-27}\) Neuroprotection is an important issue in the field of ischemic/hypoxic damage and several clinical trials are currently underway, investigating neurological as well as ophthalmologic disorders.\(^{30,31}\) Therefore, memantine seemed an appropriate treatment in patients with NAION. One of the main challenges with neuroprotective agents is the time of administration. Experimental studies suggest that they are most effective when given shortly after ischemic onset, or even in advanced cases.\(^{31,32}\) Therefore, the clinical reality of delayed presentation and diagnosis of patients with AION represents a major problem to the application of neuroprotective
agents. The initial ischemic injury in the NAION, however, is often followed by further progression of damage due to cascade of apoptotic processes. In addition, some 25% of affected eyes show stepwise progression of optic nerve ischemia and visual deterioration in the coming next 6 months. This provides the unique opportunity to administer a therapeutic agent before additional ischemic events occur. Interestingly, it has been speculated that the neuroprotective effects of memantine are more likely to be related to the modulation of slow apoptotic cell death processes rather than to the limitation of acute necrosis.

Our study was a double blind randomized clinical trial and there was no significant difference in the clinical characteristics of subjects between the two groups. Also, there was no significant difference between the initial VA and visual field indices. Our data indicate that memantine tablets with the dose of 5 mg daily for the first week and 10 mg daily for the next 2 weeks in the subjects with NAION causes significant improvement of VA and visual field indices. Our data suggest that daily oral administration of memantine may promote visual recovery by enhancing neuronal function in retina, lateral geniculate nucleus, or visual cortex. Dopamine also

The VEP is a particularly useful tool which reflects the bioelectrical activity of the visual pathways in response to visual stimuli. Consistent with the course of NAION, we found an increase in the implicit time of placebo subjects. Interestingly, there was a significant reduction of implicit time in the memantine group. Although memantine did not improve the amplitude and both groups had reduction of amplitude, the degree of amplitude reduction in the memantine group was less than placebo group. Our findings are consistent with those of Hare et al who have shown that daily oral administration of memantine in the monkey model of experimental glaucoma results in less VEP amplitude reduction and treatment with memantine is without significant effect on the normal function of the retina and central visual pathways.

Memantine did not show a significant improvement in the automated perimetry parameters such as MD or PSD compared with placebo. One of the shortcomings of our study was its low sample size. It is possible that a significant difference could have existed in the proportion of improved visual fields between treated and control subjects but this fact was not identified because our sample size was small. The other limitation was that memantine was prescribed for only 3 weeks with maximum dosage of 10 mg. It is possible that more promising results could be obtained with longer durations of treatment as it has been elicited in studies in patients with dementia.

Loss of retinal ganglion cells is a hallmark of many ophthalmic diseases including anterior ischemic optic neuropathy. Neurotoxicity is caused by excessive stimulation of receptors for excitatory amino acids. In particular, the amino acid glutamate has been shown to act as a neurotoxin which exerts its toxic effect on retinal ganglion cells predominantly through the NMDA subtype of glutamate receptor. Over-activation of NMDA receptors causes excessive Ca influx into the cell, mitochondrial dysfunction and production of free radicals leading to necrotic and apoptotic cell death. In addition increased NMDA receptor mediated Ca influx can elevate energy demand further, enhance depolarization, trigger further Ca increase and favor release of endogenous glutamate. The systemic administration of memantine may act on NMDA receptors located in the retina. Memantine produces reversible open-channel block of NMDA receptor associated channels. The kinetics of memantine action in the channel results in block of excessive NMDA receptor activity but sparing of physiological receptor activity. Moreover, it has been reported that memantine inhibits ATP-dependent K+ conductances in dopamine neurons of the substantia nigra pars compacta. This latter effect ultimately results in an increase of dopamine release in the striatum. Dopamine may promote visual recovery by enhancing neuronal function in retina, lateral geniculate nucleus, or visual cortex. Dopamine also
may alter the metabolic milieu of the retina and vitreous, thereby preventing ischemic neuronal injury mediated by excessive levels of the excitatory amino acid glutamate.\textsuperscript{10,38-40} It has been reported that administration of levodopa may improve vision loss in recent-onset of NAION.\textsuperscript{38}

Recently Hayreh and Zimmerman have reported that treatment of NAION patients with systemic corticosteroids during the acute phase, results in a significantly higher probability of improvement in VA and visual field compared with untreated patients.\textsuperscript{41} It has been postulated that the faster resolution of optic disk edema with corticosteroid results in progressive decrease of compression of the capillaries in the optic nerve head, better blood flow in the capillaries, improved circulation in the optic nerve head and finally improved function of the surviving but not functioning hypoxic axons.\textsuperscript{41}

The neuroprotective effects of memantine suggested by our study and other experimental studies, implies memantine as a promising adjunctive treatment to corticosteroids in patients with NAION. However further larger clinical trials with prolonged and maximum tolerable dosages of memantine are needed to confirm the efficacy of memantine on NAION.

Conclusion

Three weeks course of treatment with memantine in patients with NAION causes significant improvement of VA and implicit time of VEP when administered within 8 weeks of onset of NAION. Further investigations are needed to prove the efficacy of memantine in NAION patients.

References


