Efficacy of Memantine in Acute Non-Arteritic Ischemic Optic Neuropathy

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Abstract

Purpose: Evaluation of efficacy of Memantine (N-Methyl-D-Aspartate Receptor Antagonist) on visual function of patients with acute non-arteritic ischemic optic neuropathy (NAION).

Methods: The study was conducted as interventional case series from November 2005 through November 2006 in Farabi Eye Hospital. Twenty-two patients with acute NAION of less than 8 weeks duration entered the study. Memantine was prescribed with a dose of 5 mg per day for the first week and 10 mg per day for the following two weeks. Baseline best corrected visual acuity (BCVA); visual evoked potential (VEP) and visual field was done for all patients. BCVA recording repeated 3 weeks, 3 and 6 months later. VEP and perimetry repeated 3 months after treatment.

Results: After 3 weeks, 3 and 6 months, BCVA improved -0.32±0.40 LogMAR, -0.51±0.49 and -0.51±0.49, respectively (P=0.005, P=0.001 and P=0.001, respectively). VEP recordings after 3 months, demonstrated -8.61±14.51 db mean decrease in implicit time (P=0.019). Amplitude of voltage did not show significant difference with baseline (P=0.10). Perimetry results after 3 months showed that mean deviation (MD) improved 2.77± 3.94 db (P=0.016).

Conclusion: Memantine resulted in significant improvement of BCVA 3 weeks, 3 and 6 months after treatment of acute NAION. Memantine also resulted in significant decrease of implicit time and significant improvement of mean deviation in VEP and perimetry after 3 months.

Keywords: Non-arteritic Ischemic Optic Neuropathy, Memantine, Neuroprotection, Visual Evoked Potential, Perimetry
Introduction
Anterior ischemic optic neuropathy (AION) is the most common optic neuropathy over 50 years of age. The disease reflects ischemic damage of the optic nerve head and presents as sudden unilateral painless loss of vision which occurs during few hours to few days.

Visual field defects are universally present and include the following: altitudinal defects, central scotoma, cecocentral scotoma, and generalized depression.

Relative afferent papillary defect (RAPD) is always present unless the disease is bilateral. Segmental disc edema or disc pallor are both helpful for diagnosis but usually diffuse edema or hyperemic optic nerve head are more common. AION is divided in two groups: arteritic and non-arteritic. Arteritic AION includes those which are related to giant cell arteritis. Non-arteritic form is the most common type (90-95% of cases) and occurs in lower age groups than arteritic form (Mean age of 60).

It is considered that NAION is due to a compromise in the microcirculation of the optic nerve head. Usually optic nerve becomes visibly atrophic within 6-10 weeks.

There are many risk factors predisposing the patient to NAION including: Structural crowding of the optic nerve (disc at risk), systemic hypertension (50%), diabetes mellitus (25%), smoking, vasculitis disorders, hyperlipidemia and migraine.

Untreated NAION generally remains stable but visual improvement of at least 3 lines on Snellen chart has been reported in up to 42% of patients. There is no proven treatment for NAION. Previous treatment modalities such as hyperbaric oxygen, Levodopa and optic nerve sheath decompression surgery (ONSDS) have not been beneficial.

Neuroprotective agents have shown beneficial effects in neurodegenerative processes secondary to ischemia in experimental models. These agents are currently being investigated for treatment of NAION. Memantine (Ebixa, H. Lundbeck A/S, Ottiliavej, DK-2500 Valby, Denmark) is relatively a new drug which is introduced for treatment of moderate to severe dementia. It got FDA approval for moderate to severe dementia in 2003. The drug is a non-competitive antagonist of NMDA receptor and reduces glutamatergic excitotoxicity.

Excitatory neurotransmitter glutamate is the main cause of cell death in acute neurodegenerative disorders of human like stroke or traumatic brain injury. Recent evidence have shown death of retinal ganglion cells are preventable despite damaged cell bodies, also degenerated axons can be regenerated. Preventing death of damaged ganglion cells or neuroprotection is the first step in the management of optic nerve injuries, and this is achieved by inhibiting the process that initiates apoptosis. Injured cells release glutamate; excess of which results in increased level of intracellular calcium and apoptosis. Substances which inhibit release of glutamate from the injured cells or block its absorption or its receptor have probably protective effects.

Indeed, neuroprotective effects of Memantine (an antagonist of NMDA receptor) are proved in animal models. Human studies with Memantine are currently being performed on open angle glaucoma in 10 countries. Memantine is prescribed orally (10 mg coated tablets). The usual dose of the drug is 5 mg per day for the first week; the dose is increased in 5 mg steps each week to reach maximum dose of 20 mg. All previous studies have shown that Memantine is safe and well tolerated.

The rationale for this study was based on the reduction of neuronal damage caused by ischemia with Memantine which is expected to prevent progression of damage. Our purpose was to evaluate neuroprotective effects of the drug in improvement of visual acuity in acute NAION.

Methods
The study design was interventional case series. Patients with acute NAION of less than 8 weeks duration were enrolled from November 2005 through November 2006. All patients with sudden unilateral loss of vision, segmental or diffuse disc edema, pallor of the edematous disc, flame shaped hemorrhages around the disc, arterial narrowing without engorgement of veins, RAPD in acute phase of the disease (<8 weeks) and visual field defects compatible with NAION were included. We excluded those with age less than 40 years, pregnancy, lactation, complete optic atrophy, systemic
signs and symptoms like headache, fever which are in the favor of arteritic AION, history of using anti epileptics, barbiturates, neuroleptic agents, amantadine, hydrochlorothiazide and history of renal failure. Eligible patients signed an informed consent. The study protocol was approved by Institutional Review of Board and ethics committee of Tehran University of Medical Sciences.

All patients underwent complete ophthalmic examination including: manifest refraction, BCVA recording (ETDRS chart), slit lamp examination, tonometry, RAPD checking, funduscopy with full dilated pupils (indirect ophthalmoscopy or biomicroscopy with 90 or 78 biconvex lenses). All the patients referred to a cardiologist for evaluation of cardiovascular system and blood pressure monitoring.

The following laboratory tests were checked for all patients: Complete Blood Count (CBC); Erythrocyte sedimentation Rate (ESR); C-reactive Protein (CRP); Fasting Blood Sugar (FBS); Cholestrol / Triglyceride; Blood Urea Nitrogen (BUN) and Creatinine. Visual evoked potential (VEP) (pattern VEP if possible), perimetry (SITA standard c-24) and fundus photography was done for all patients. Fluorescein angiography was done if necessary or other possible diagnoses were to be ruled out.

In bilateral cases, suspicious space occupying lesions of the brain or suspicious demyelinating disease and other neurologic conditions, neuroimaging and neurologic consult was done for the patients. Memantine was prescribed 5 mg per day for the first week and 10 mg per day for the following two weeks. All the patients completed the 3 week-course of treatment. Those who did not complete the time, were excluded from the study. BCVA measurement repeated 3 weeks, 3 months and 6 months after treatment. VEP and perimetry repeated 3 months after treatment.

Two main parameters of VEP were evaluated: implicit time and amplitude of P100 or P2 waves. Two parameters were also evaluated in perimetry: mean deviation (MD) and pattern standard deviation (PSD).

**Statistical analysis**

Response to treatment was defined as any degree of improvement from the baseline. Statistical level of significance was preset at 0.05. Data were analyzed using SPSS software version 14.0. Paired T-test was used for comparison of the quantitative variables before and after treatment.

**Results**

Twenty two eyes of 22 patients with acute NAION enrolled the study. The demographic and ocular characteristics of the patients at baseline are shown in table 1. Hypertension was seen in 12 (54.5%), diabetes mellitus in 8 (36.4%), hyperlipidemia in 5 (22.7%) and disc at risk in one patient (4.5%).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>56.70±8.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
</tr>
<tr>
<td>Involved eye</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>9</td>
</tr>
<tr>
<td>Left</td>
<td>13</td>
</tr>
<tr>
<td>Manifest refraction</td>
<td>+0.29±0.68</td>
</tr>
</tbody>
</table>

One of the patients did not complete the course of treatment and excluded the last analysis.

Four patients demonstrated mild adverse effects: dizziness in 2, hypertension crisis which controlled with medication in 2 others. No serious adverse effect was seen at all.

**Visual acuity**

Mean baseline BCVA was 1.25±0.86 LogMAR. After 3 weeks mean BCVA improved -0.32±0.40 LogMAR (P=0.005). After 3 and 6 months, mean BCVA improved -0.51±0.40 LogMAR (P=0.001) (Figure 1 and Table 2).
Figure 1. Efficacy of Memantine on BCVA in acute NAION

Table 2. Baseline BCVA and its changes 3 weeks, 3 and 6 months after treatment

<table>
<thead>
<tr>
<th>BCVA (LogMAR)</th>
<th>Number</th>
<th>Mean±SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22</td>
<td>1.25±0.86</td>
<td>-</td>
</tr>
<tr>
<td>Change after 3 weeks</td>
<td>21</td>
<td>-0.32±0.40</td>
<td>0.005</td>
</tr>
<tr>
<td>Change after 3 months</td>
<td>19</td>
<td>-0.51±0.49</td>
<td>0.001</td>
</tr>
<tr>
<td>Change after 6 months</td>
<td>19</td>
<td>-0.51±0.49</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Pattern VEP

VEP was done for all patients at baseline. In six patients, flash VEP was done instead of pattern type because of low vision (Finger Count<1 meter). Implicit time and amplitude of P100 wave or p2 wave (in conditions of flash VEP) were measured.

Mean baseline implicit time was 128.59±13.4 ms. Mean baseline amplitude was 6.12±3.5 uv.

After 3 months VEP repeated in 19 patients. The difference of implicit time from that of the baseline was -8.61±14.1 ms (P=0.019) (Figure 2). Mean change of amplitude was -0.98±0.42 uv (P=0.10).

Nearly all patients showed a mild increase of implicit time in the sound eye (the healthy eye with normal BCVA and visual field).

Figure 2. Efficacy of Memantine on implicit time of VEP in acute NAION

Perimetry

Humphrey automated perimetry (SITA standard C2-24) was done for all patients at baseline. Reliability criteria were as follows: false negative less than 12%, false positive less than 4% and fixation loss less than 20%. The results were reliable in 19 cases. The most common visual field defects in order of frequency were: inferior altitudinal in 5 (26.35), generalized depression in 5 (26.3%), double arcuate in 3 (15.8%), superior altitudinal in 2 (10.5%), central scotoma, central island of vision, superior scotoma, superior altitudinal concurrent with inferior arcuate each in one patient.

After 3 months, four of the perimetry tests were not reliable, so only results of 15 patients were analyzed. Mean change of MD was -2.77±3.94 db (It means 2.77 db of improvement) (P=0.016) (Table 3 and Figure 3).

Mean change of PSD was -0.01±1.96 db (P=0.985) (Table 3).

Table 3. Baseline and 3 months after treatment perimetry parameters

<table>
<thead>
<tr>
<th>Perimetry</th>
<th>N</th>
<th>Mean±SD</th>
<th>Significance (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base line mean deviation (db)</td>
<td>19</td>
<td>-18.95±6.62</td>
<td></td>
</tr>
<tr>
<td>Base line pattern standard deviation (db)</td>
<td>19</td>
<td>10.22±3.37</td>
<td></td>
</tr>
<tr>
<td>DIF MD</td>
<td>15</td>
<td>-2.77±3.94</td>
<td>0.016</td>
</tr>
<tr>
<td>DIF PSD</td>
<td>15</td>
<td>-0.01±1.96</td>
<td>0.985</td>
</tr>
</tbody>
</table>
Discussion

As mentioned previously, there is no proven treatment for NAION and previous treatment modalities like hyperbaric oxygen, Levodopa and optic nerve sheath decompression surgery (ONSDS) have not been beneficial even in the last one deterioration of visual acuity after treatment has been reported.\(^1\) Neuroprotective agents have shown beneficial effects in neurodegenerative processes secondary to ischemia or optic nerve crush in experimental models.\(^1,8\) Prevention of death in damaged ganglion cells or neuroprotection is the first step in treatment of optic nerve injuries.\(^3\) Neuroprotective effect of the drug Memantine (NMDA receptor antagonist) has been proved in animal models.\(^3,9-12\) In the current study efficacy of Memantine in acute phase of NAION was evaluated.

Our results showed that Memantine with a dose of 5 mg per day for the first week and 10 mg per day for the following two weeks, results in significant improvement of visual acuity 3 weeks (-0.32±0.40 LogMAR), 3 months and 6 months (-0.51±0.49 LogMAR) after treatment (P=0.005, P=0.001 and P=0.001); although not all of this is related to the drug. As we know, untreated NAION generally remains stable after reaching to the minimum level of vision but visual improvement of at least 3 lines on Snellen chart (equal to -0.3 LogMAR) has been reported in up to 42% of patients.\(^1\) In the current study BCVA improvement equal to -0.51 LogMAR was seen after 6 months; it seems much better than the natural course of the disease and probably is related to drug effects. We can not conclude definitely that the drug has caused this much improvement however and for definite conclusion a clinical trial should be done.

We also found that implicit time decreased significantly 3 months after treatment. In a study by Torman et al on nine patients with AION, they found only decrease of amplitude and no change of implicit time was reported.\(^13\) This is in contrary to our study which in all patients we found both decrease of amplitude and increase of implicit time.

The above study also showed significant improvement of mean deviation (2.77 db) in perimetry 3 months after treatment (P=0.016). Although there are no prospective studies regarding visual field changes in the natural course of AION, it has been mentioned that spontaneous improvement is less likely.\(^1\) Again we can say that probably Memantine has caused this degree of improvement although a clinical trial is needed to confirm the data. Memantine did not result in improvement of amplitude neither the PSD.

To our knowledge there is no similar study in human evaluating efficacy of Memantine in acute NAION and the current study is the first one. Power of our study was doing it for the first time and limitation of our study was its design as case series with no control group. Another limitation of our study was duration and dosage of Memantine use which was prescribed only for 3 weeks and with the maximum dose of 10 mg; maybe in larger doses and with longer duration treatment we could get much better results. It is recommended to do clinical trials with larger sample size and also longer duration and larger doses of treatment.

Indeed, our study was the first pilot study in human that showed possible positive effects of Memantine in acute NAION which needs more studies to be proved.

Conclusion

It seems that Memantine as a neuroprotective drug is effective in acute phase of NAION but more clinical trial studies should be done for definite results..
References