

Do you give neuroprotective/alternative drugs to manage normal tension glaucoma?

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Neuroprotective Drugs for NTG: **A Yes Perspective**

Nilo Vincent FlorCruz, MD

Several landmark trials such as the Early Manifest Glaucoma Trial (EMGT) and the Advanced Glaucoma Intervention Study (AGIS) showed that intraocular pressure (IOP) is a major risk factor in glaucoma progression. Lowering IOP slows down glaucoma progression and this applies to normal tension glaucoma (NTG) as well. We can say that lowering IOP offers some form of neuroprotection.

Then again, there are pressure-dependent and pressure-independent risk factors in the development of glaucoma. Several clinical trials have shown glaucoma progression occurs despite significant decreases in IOP either by the use of anti-glaucoma drops, laser, or surgery. Addressing these pressure-independent factors would also help in treating glaucoma and is another form of neuroprotection. The use of neuroprotective drugs may offer some added benefits not only in patients with NTG but also in other glaucoma patients who are progressing despite good IOP control.

Ginkgo biloba is the most commonly studied agent for neuroprotection in glaucoma. Two randomized controlled clinical trials compared the effect of *Ginkgo* versus placebo on visual field progression in patients with NTG.^{1,2} Findings from

both studies show that intake of *G. biloba* for 4 weeks resulted to a much slower visual field progression.

A retrospective study from Korea looked into the effect of *G. biloba* extracts given along with anti-glaucoma eye drops on visual field progression in NTG patients.³ Although retrospective in nature with a sample size of 42 patients, study follow-up duration of 12 years is noteworthy since visual field changes in glaucoma occur in the long term. Study findings showed a slower rate of visual field progression based on the mean deviation, pattern standard deviation, and the visual field index after treatment with *G. biloba* extracts. No ocular or systemic side effects were reported.

Brimonidine is another possible neuroprotective agent. Results of the Low-Pressure Glaucoma Treatment Study (LoGTS) showed that there was less visual field progression in NTG eyes treated with brimonidine compared to timolol even when the IOPs at baseline and at the end of the two-year follow were almost the same in both groups.⁴

Based on these studies, IOP is not the only risk factor that causes glaucoma progression. Lowering IOP is still the tried and tested treatment for glaucoma. But for NTG patients who have worsening visual fields, brimonidine and *Ginkgo biloba* may help. Our search continues for medications that can not only prevent glaucoma progression but could also reverse the disease.

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Neuroprotective Drugs for NTG:**A No Perspective****Maria Zita Meriales, MD**

Neuroprotection is a treatment strategy to keep retinal ganglion cells alive and functional. It is an intervention independent of intraocular pressure (IOP) reduction directed at maintaining neuronal survival. In glaucoma, retinal ganglion cell death is irreversible. Retinal ganglion cell death is a complex process and is triggered by different mechanisms. Mechanisms implicated are genetic mutations or polymorphisms, activation of the excitotoxic glutamate cascade, alteration of the mitochondrial function, excess free radical production, and reduction of energy production. Neuroprotection strategies have evolved based on these potential root causes. These strategies include genetic therapy, neurotrophic support, stem cell therapy, and bioenergetic support.

In glaucoma, IOP lowering is the only clinically proven strategy to prevent progression. Treatment modalities to lower IOP can be considered as a means to eliminate the stressor which is elevated pressure. Several randomized clinical trials (Ocular Hypertension Treatment Study, Collaborative Normal Tension Glaucoma Study, Early Manifest Glaucoma Trial, Advanced Glaucoma Intervention Study, and the Collaborative Initial Glaucoma Treatment Study) have shown that lowering IOP offers protection against visual field loss.

Neuroprotection, by definition, is strictly a non-IOP-reduction-related treatment. Current evidence has not shown any topical or oral neuroprotective agents to be effective in preventing retinal ganglion cell death or preserving visual field in open angle glaucoma.

The Cochrane systematic review included studies for neuroprotection which involved the excitotoxic pathway (N-methyl-D-aspartate antagonist), α -2 adrenergic agonists (brimonidine), calcium channel blockers, brain-derived neurotrophic factor (BDNF) to brain, anti-oxidants and free radical scavengers, *Ginkgo biloba* and other natural antioxidants, and nitric oxide synthase inhibitors.¹

The European Glaucoma Society likewise supports that the only approach effective in preserving visual function is lowering IOP. Improvement in ocular blood flow and the use of neuroprotective agents have no conclusive evidence.² However, the search for other potential neuroprotective agents continues because of the observation that field loss can still occur even though IOP has been lowered. Most of these treatment modalities are still experimental such as gene therapy which aims to correct a fundamental molecular basis of the disease or prevent the transmission of the pathogenic mutation.³ Neurotrophic factors have also been demonstrated to be neuroprotective by promoting axon regeneration and enhancing neuronal cell function while stem cell therapy aims to regenerate endogenous cells in vivo.⁴

Therapies that target excitotoxicity, i.e. memantine and brimonidine, have also been studied for glaucoma. Excitotoxicity refers to cell death resulting from toxic excitatory amino acids.⁵ Glutamate is the major excitatory neurotransmitter in the central nervous system and prolonged exposure to it contributes to the injury and death of neurons because of the excessive influx of ions into the cell (glutamate cascade). Memantine, is a noncompetitive N-methyl-D-aspartate receptor antagonist which blocks glutamate toxicity.⁶ However, in a randomized placebo controlled clinical trial, oral memantine failed to show any benefit compared to placebo in reducing visual field loss.⁷ Brimonidine, an α -2 adrenergic receptor agonist can also modulate glutamate toxicity. The Low-Pressure Glaucoma Study reported lowered incidence of visual field progression with the brimonidine group vs timolol group. However, significant dropout was noted in the brimonidine group which could have masked a subgroup of progressing patients. The study was reviewed to have a high attrition bias, and the certainty of evidence for the outcomes is very low.⁸

Natural antioxidants and vitamin supplement, which includes *Ginkgo biloba*, are possibly the most

cost-effective. However, the effects are not easily measured, and their use need further studies.⁹

For an agent to be considered as neuroprotective, the following has been the proposed criteria: (1) it has to have a receptor target in the retina or optic nerve; (2) it triggers a pathway that enhances resistance to stress/injury; (3) it reaches the site at pharmacologic doses; and (4) its neuroprotective activity is demonstrated in clinical trials.¹⁰

Most of the proposed neuroprotective agents have demonstrated retinal ganglion cell protection in animals models. However, these hypotheses should be tested with large-scale randomized clinical trials. Neuroprotective agents have been successful in the laboratory but have yet to have definite clinical translation and no compound has reached a sufficient level of evidence to be considered as a neuroprotectant in glaucoma.^{2,11}

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Consolidating the Evidence

Alexander Reyes, MD

What evidence would you require to prescribe calcium channel blockers (CCB) for glaucoma neuroprotection? A study suggests that CCBs may increase ocular blood flow in patients with open angle glaucoma.¹ Additionally, CCBs improve visual function, offer *in vitro* protection of neurons undergoing apoptosis and necrosis, provide neuroprotection in experimental cerebral ischemia models, and neuroprotection of retinal ganglion cells and photoreceptors in experimental animals.

In a hypertensive patient on a β -blocker for hypertension, I would occasionally contact the internist to ask if the patient could be shifted to a CCB for possible neuroprotective effect. However, a study done to look for systemic medications associated with glaucoma found that CCBs were most strongly associated with glaucoma while β -blockers seemed protective.² So there are risks to prescribing strong measures without solid evidence from randomized controlled studies to back it up.

On the other hand, the Low-Pressure Glaucoma Study showed a 9% progression rate for brimonidine versus a 30% progression rate for timolol.³ In my opinion, the high dropout rate in the brimonidine group does not weaken this impressive finding. Brimonidine has a high allergy rate. A higher dropout rate was anticipated at the study onset which is why the brimonidine group was larger at the beginning. In my practice, I tend to favor brimonidine in normal pressure glaucoma patients for possible neuroprotective effect.

Still that study is 7 years old and there has been nothing concrete since then. It may be interesting to look at what neurologists are trying to do to help their patients with Alzheimer's disease and senile dementia. Interestingly, exercise seems to be getting a lot of attention here but the mechanisms are complex involving cardiorespiratory health, improved microcirculation, mitochondrial quality, telomere length, and neurotrophic factors such as brain-derived neurotrophic factor. These involve multiple molecular mechanisms and pathways.⁴ Perhaps this is why the search for a single molecule has been unsuccessful. It may not be possible to duplicate these mechanisms with a single drug or molecule.

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