Neuroprotection in the Treatment of Glaucoma

Astrianda Nadya Suryono
Department of Ophthalmology, Faculty of Medicine, Universitas Indonesia

Abstract
Glaucoma is a neurodegenerative disease with certain characteristics of progressive damage of the optic nerve, loss of retinal ganglion cells (RGC) and their axons, accompanied by typical visual defect. Increased intraocular pressure (IOP) is the main risk factor for glaucoma. Some study stated that RGC death is still progressing despite the use of IOP-lowering medications. The main aim of glaucoma treatment remains to lower IOP, however neuroprotective agents have gained increased interests due to its effects to prevent or slow down the rate of RGC death other than IOP-dependent mechanisms. Production of glutamate and nitric oxide is known as one of the contributing factors of RGC death, and neuroprotective agents that work by targeting the production of glutamate and nitric oxide can be a valuable option to prevent further RGC death.

Keywords: neuroprotective agents, glaucoma treatment, retinal ganglion cells death, glutamate, nitric oxide

INTRODUCTION
Glaucoma is a neurodegenerative disease characterized by progressive damage of the optic nerve, as well as loss of retinal ganglion cells and their axons.1,2 Retinal ganglion cells (RGC) which forms the optic nerve carries visual impulse from the eye to the brain. When glaucoma occurs, there will be loss of retinal ganglion cells, therefore the transfer of information from eye to the brain will be disrupted and visual field defect will occur.3 There are two main classifications of glaucoma, open-angle glaucoma (OAG) and angle-closure glaucoma (ACG). OAG is a chronic, progressive optic nerve disease and the most common form of glaucoma which usually asymptomatic. OAG could be accompanied with increased IOP, which occurs in primary open-angle glaucoma (POAG), or in normal IOP, which is normotension gluacoma. The other main glaucoma type, ACG, usually has abrupt onset and specific signs and symptoms, such as increased IOP, pain in the orbital region, scleral injection, blurred vision, headache, halo sign, nausea, and vomiting.3

Glaucoma is one of the leading causes of irreversible blindness in the world. With more than 60 million people affected and its prevalence is projected to increase to reach 111.8 million in 2040, glaucoma is one of the important public health concerns in the world.7,8

The optic nerve damage in glaucoma is irreversible because of the inability of RGC to divide and regenerate.9,10 The increased IOP in glaucoma patients will cause distortion in lamina cribrosa which preventing neurotropic factors from the brain to reach RGCs which eventually will cause apoptosis of RGCs. Some study stated that optical nerve damage in glaucoma still progressing even though the patients already undergo IOP-lowering therapy.11-13 For example in patients with normo-tension glaucoma, the eyes are postulated to...
undergo ischemia which induces excitotoxic substance increase, such as glutamate in the vitreous, which will activate the NMDA receptor and signal the apoptosis cascade of the cells. Therefore, neuroprotective agent is important in preserving RGC as well as optic nerve neuronal structure and function. Some of the cellular mechanism that results in RGC death could be a target for neuroprotective agents, such as production of glutamate and nitric oxide, which caused by production of external nerve-derived risk factors, low nutritional factors in nerve cells, loss of intracellular self-repair process, and generation of intracellular destructive process. Though the reduction of IOP is still considered to be the most promising mechanism to prevent further glaucomatous damage to the nerve, neuroprotective agents such as N-methyl D-aspartate (NMDA) receptor antagonists, antioxidants, *Ginkgo biloba* extract, etc. has been investigated in several studies to prove their potential effects to prevent further nerve damage in the glaucomatous eyes.

**Neuroprotection in the treatment of glaucoma**

Any interventions aimed to prevent the death of RGCs and protect the optic nerve is considered as neuroprotection for glaucoma. There are more than 100 candidates of neuroprotective agents which have been tested and had very low success rate, the drugs failed to demonstrate efficacy, acceptable safety, or patients benefit.

The pharmacological agents used for neuroprotection in treatment of glaucoma are:

1. Antiglaucoma Medication
   a. Alpha-2 adrenergic agonists
b. Prostaglandin analogues
c. Beta-blockers
d. Carbonic anhydrase inhibitors
e. Rho-kinase (ROCK) inhibitors

2. Antioxidants
   a. Ginkgo biloba extracts
   b. NMDA-receptor antagonists
c. Citicoline
d. Melatonin
e. Coenzyme Q10 (CoQ10)

3. Vasodilators
   a. Calcium channel blockers (CCBs)

Antiglaucoma medication

Lowering the IOP is still the treatment of choice to prevent further damage of optic nerve and RGCs, which makes the antiglaucoma medication one of the neuroprotective agents in managing glaucoma.

• **Alpha-2 adrenergic agonists**

There are some hypotheses that a third generation of alpha-2 adrenergic agonist, brimonidine tartrate has neuroprotective effects through its antiapoptotic properties. It causes vasodilatation in retinal arterioles and increases ocular blood flow. Study by Evans, *et al.* (2003) showed that patients in brimonidine group had 50% better RGCs survival than patients in timolol group, however, patients in brimonidine group were less likely to have improvement in visual field compared to timolol group. In study by Krupin *et al.* (2011), patients in brimonidine group showed improvement in contrast sensitivity compared to the other therapeutic group. Sena and Lindsley (2017) reviewed a randomized control trial in two treatment group, brimonidine 0.2% and timolol 0.5%, both groups were followed up until 4 years after the start of the treatment and it suggested that brimonidine treatment may slow and prevent progression of visual field loss compared with timolol, even though there are a lot of missing data in brimonidine group. This missing data in brimonidine group could be caused by ocular allergy as an adverse effect in brimonidine use.

• **Prostaglandin analogue**

Prostaglandin analogues (PGA) have substantial IOP reduction with relatively few side effects and are usually the recommended first-line treatment for glaucoma. PGA offers better control of IOP fluctuation over 24 hours rather than beta-blockers. Latanoprost use in animal model has shown neuroprotective effect on glutamate-induced RGC death *in vitro* and axotomy-induced optic neuropathy mimicking glaucoma. Studies by Sit, *et al.* (2006) and Quaranta, *et al.* (2008) shown that latanoprost has better IOP reduction and ocular perfusion pressure improvement effects than bimatoprost, which is an important feature in the treatment of normotension glaucoma.

• **Beta-blockers**

The neuroprotective effects of beta-blocker such as betaxolol and nonselective beta-blockers such as metipranolol and timolol are produced by reduction in sodium and calcium influx through voltage-sensitive channels, which responsible for ischemia/reperfusion injury and related to the release of glutamate and subsequent activation of NMDA receptors. Levobetaxolol has greater capacity to block sodium and calcium influx, therefore it is suggested to have better neuroprotective effect than timolol. Betaxolol neuroprotection effect is mediated by blockade of voltage-gated calcium channels and it also has demonstrated effect of increasing blood velocity in human optic nerve head.

• **Carbonic anhydrase inhibitors**

Carbonic anhydrase inhibitor such as dorzolamide and brinzolamide could lower the IOP by blocking carbonic anhydrase enzymes which is essential in producing aqueous humor. It also has neuroprotective effect which is not correlated to the IOP by inducing vasodilatation of the blood vessels, therefore increasing the retinal perfusion.

• **ROCK inhibitors**

Elevated levels of rho enzymes have been observed in glaucomatous eyes. ROCK is serine/threonine kinase which plays role in cells...
migration, proliferation, and survival. Blockage of ROCK will increase the ocular blood flow and promote axonal degeneration. Some examples of the ROCK inhibitors are fasudil and netarsudil.26-28

Antioxidants

• **Ginkgo biloba extracts**
  Ginkgo biloba extract which mainly consists of flavonoids and terpenoids has antioxidant effects that is thought to play role in combating oxidative damage and apoptosis-mediated damage in RGCs. *Ginkgo biloba* also has stabilizing effects on microcirculation and mitochondrial membrane, it also has vasodilatation effect on the blood vessels.1-2

• **NMDA receptor antagonists**
  In patients with glaucoma, there is a significant amount of glutamate release in the vitreous which will trigger the NMDA receptor to facilitate calcium influx and stimulate the proapoptotic factors. This suggests that there is association between excessive release of glutamate with neuronal cell death in the retina in patient with glaucoma. However, NMDA receptor activity is essential for normal neuronal function. One of NMDA noncompetitive open channel blocker, memantine, has neuroprotection effect which will works by only blocking excess NMDA receptors that activated by glutamate, without affecting the normal activity of other NMDA receptor.29-32

• **Citicoline**
  Citicoline is composed by ribose, cytosine, pyrophosphate, and choline, which act as intermediate endogenous compound in the synthesis of membrane phospholipids. Citicoline increases neurotransmitter such as noradrenaline, serotonin, and acetylcholine, that provides protective effect on RGC. Citicoline could be administered through parenteral and oral route, which has similar effects. A multicenter study stated that there was reduction of rate of visual field loss progression in patient with progressive glaucoma after administration of citicoline oral solution, therefore we can suggest the bioavailability of citicoline oral solution is similar as parenteral administration.2-2 Parisi, et al. (2015), confirmed that citicoline eye drops three times daily significantly improved electroretinogram pattern and visual-evoked potential compared to baseline.33

• **Melatonin**
  Melatonin is reported to have antioxidant and antiscavenging properties, it is also suggested to have ocular hypotensive properties. Agomelatine, one of melatonin analogues, is currently under investigation to prove the IOP-lowering and neuroprotective effects in both human and animal trials.34-37

• **CoQ10**
  Coenzyme Q10 is an important component of mitochondrial respiratory chains which also act as lipid-soluble antioxidant. Using an animal model, it was shown that intraocular COQ10 administration reduces glutamate increase and promotes neuroprotection in patients with glaucoma. Topical treatment solution of CoQ10 and vitamin E has effects on minimizing retinal damage and RGC loss, it also shown to inhibit the PTP formation and cytochrome c which could help preventing the RGC death.5

Vasodilators

CCBs
  Lomerizine and nilvadipine have shown promising neuroprotective effects. CCB alters calcium influx across membrane and regulate the calcium intracellular. It generally dilutes the isolated ocular vessels and increases ocular blood flow, however, there are concern about CCB-related systemic hypotension which can worsen the retinal ischemia due to reduction of OPP.38

Conclusion

There is a raising interest for research regarding the use of neuroprotective agents in the treatment of glaucoma, however there are some challenges in proving whether the neuroprotective agent could be used in human. Most of the neuroprotective agents are still in preclinical stage of research, such as NMDA-receptor blockers, alpha-2 adrenergic agonist, CCBs, *Ginkgo biloba* extract, and others. Studies to evaluate the combination of neuroprotective agents and conventional therapy in glaucoma is needed to prove the benefit of neuroprotective agents to prevent RGCs death, therefore improving patients’ outcome.
DAFTAR PUSTAKA

DAFTAR PUSTAKA