Traumatic Optic Neuropathy Therapy: an Update of Clinical and Experimental Studies

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Introduction

Traumatic optic neuropathy (TON) occurs in 0.5 – 5% of patients in the USA presenting with closed head trauma.1 Damage to the optic nerve (ON) causes immediate shearing of and induces secondary swelling in a proportion of retinal ganglion cell (RGC) axons, accompanied by subsequent RGC degeneration.2 Multiple therapies are used to prevent pathological changes to the ON and preserve RGC survival after trauma, however, there is still no standard therapy for TON. This update provides a critical review of current clinical trials and experimental progress in TON, with the aim of clarifying potential treatment strategies for the future.

Clinical treatment

At present, there are four main treatment options for TON: conservative management; administration of steroids; surgical decompression; and a combination of surgery and steroid treatment. Since 1980, there have been at least 18 studies of TON in a total of 841 patients. Among these patients, 353 were treated with corticosteroid therapy, 114 with conservative management and 354 with surgery (Table 1).3 – 20

CONSERVATIVE MANAGEMENT

In conservative management, patients are monitored and no treatment is administered after ON injury. The natural history of TON has not been studied prospectively, but it has been reported that spontaneous recovery may occur in at least 30% of patients.21 One prospective study showed 40% spontaneous visual
<table>
<thead>
<tr>
<th>Reference and year</th>
<th>No. patients in case study</th>
<th>Corticosteroids</th>
<th>Conservative therapy</th>
<th>Surgery</th>
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<td>Matsuzaki et al.(^3) 1982</td>
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<td>Seiff 1990</td>
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<td>Joseph et al.(^6) 1990</td>
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<td>Entezari et al.(^20) 2007</td>
<td>31</td>
<td>16</td>
<td>68.8%</td>
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</table>

*Combination of surgery and steroid treatment.
improvement in children with TON following ON injury.\(^7\)

**SYSTEMIC ADMINISTRATION OF STEROIDS**

Steroids have antioxidant capabilities and can inhibit free radical-induced lipid peroxidation during nerve trauma. Since the early 1980s, steroids have been used to reduce abnormal swelling after ON injury and improve visual recovery. The Second and Third National Acute Spinal Cord Injury Studies compared the effects of placebo, steroids or methylprednisolone (MP) administered within 12 h of injury and indicated that treatment with MP results in a significant improvement in motor function.\(^22,23\) Sheng et al.\(^24\) found that high-dose MP could inhibit apoptosis of RGCs in ON injured rats through the up-regulation of Bcl-2 and down-regulation of Bax.

The observed benefits of MP in the treatment of spinal cord trauma and in experimental rat models do not, however, seem to extend to the treatment of TON. A randomized, double-blind, placebo-controlled clinical trial compared the effect of intravenous high-dose corticosteroid therapy with placebo in the treatment of recent TON. This study confirmed earlier findings that there is no difference in improvement in visual acuity between intravenous high-dose corticosteroids and placebo.\(^20\) Ohlsson et al.\(^25\) observed the effects of MP treatment in experimental crush-injured rats and did not detect any effect of MP on RGC survival, axonal regeneration or visual function. Current evidence, therefore, indicates that steroids do not provide any obvious benefit over conservative management.\(^26\)

The adverse effects of steroids should also be considered. The Corticosteroid Randomisation After Significant Head Injury (CRASH) study evaluated the effectiveness and safety of steroids in patients with acute traumatic brain injury. At 6 months of follow-up, the risk of death was higher in the steroid group than in the placebo group.\(^27\)

**SURGICAL DECOMPRESSION**

Optic canal decompression plays a role in the management of compressive optic neuropathies, complicating mass lesions arising from the intracalvarium, and has been advocated in many retrospective reports. Recently, Ohlsson and Svensson\(^28\) reported that early decompression of the injured ON reduces axonal degeneration and improves functional outcome in adult rats. There is little evidence, however, to support the assertion that these cases actually benefit more from surgery.\(^29\) The International ON Trauma Study is the largest prospective multicentre study of TON published to date.\(^13\) It analysed 133 people with indirect TON who were treated within 7 days of injury. After adjustment for baseline visual acuity, no clear benefit was found in favour of either corticosteroid therapy or optic canal decompression surgery. These results and the existing literature provide sufficient evidence to conclude that neither corticosteroids nor optic canal surgery should be considered as standard care for patients with TON. It is, therefore, clinically reasonable to decide whether to treat, or not treat, on an individual patient basis.

Recently, a cadaveric study showed that transphenoidal medial wall decompression of the ON canal with dural sheath opening may induce physical damage to the nerve.\(^30\) The authors suggested that any hypothetical value in dural–arachnoid sheath opening must be weighed against the potential for damage to the ON caused by the surgical intervention.
Experimental studies
Injury to RGCs in adult mammals results in primary damage that causes changes in the release of neurotransmitters, depletion of growth factors and local inflammation. Thus, the primary lesion is often compounded by a gradual secondary loss of undamaged neurons due to apoptosis in its vicinity. The prevention of human RGC apoptosis has been a crucial strategy for the experimental treatment of ON injury, and has involved various trophic substances, the use of multiple drugs and gene transfection.

GLUTAMATE INHIBITORS
Glutamate is the major excitatory transmitter in the eye and induces RGC apoptosis via binding to N-methyl-D-aspartate, α-amino-3-hydroxy-5-methylisoxazolepropionate (NMDA) and kainate receptors in the ON. It has been reported that many substances that block NMDA receptors, including memantine, phenytoin and dizocilpine (MK801), provide significant protection of RGCs after experimental ON injury in adult rats and mice.

NERVE GROWTH FACTORS
The rationale for supplying neurotrophins to axotomized RGCs is that their death might be related to the loss of retrogradely supplied trophic factors. Many reports have shown that axotomized RGCs can be rescued by the experimental addition of several neurotrophic factors, including fibroblast growth factor-2 (FGF-2), brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF). For example, BDNF helps to support the survival of existing neurons and encourages the growth and differentiation of new ones. Chen and Weber reported that BDNF could increase the density, cell size and mean percentage of surviving ganglion cells in ON-injured cats. CNTF, a cytokine expressed by glial cells that acts as a survival factor for motor and sensory neurons, has been used in patients with neurodegenerative diseases.

CRYSTALLIN
Crystallin is a member of the small heat-shock protein family and has the potential to act as an anti-inflammatory agent in the neuroprotective process. We have previously shown that α-crystallin reduces RGC death in vitro and after ON injury in vivo. Recently, Fischer et al. found that crystallins of the β/γ-superfamily mimic the effects of lens injury and promote axon regeneration. Being able to increase naturally occurring crystallins may, therefore, provide significant protection for RGCs after experimental ON injury.

NITRIC OXIDE AND TNF-α INHIBITORS
Nitric oxide is a small, diffusible, highly-reactive molecule that acts as a pro-apoptotic modulator and alters the expression of apoptosis-associated proteins. Previous studies showed that administration of nitric oxide synthase (NOS) inhibitors enhanced RGC survival and delayed retrograde degeneration of RGC axons after axotomy. Tumour necrosis factor-α (TNF-α) is one of the primary cytokines that induces apoptosis in a host of cell types. Tezel et al. found that TNF death receptor signalling is involved in the secondary degeneration of RGCs following ON injury. The inhibition of TNF death receptor signalling may, therefore, be an effective strategy to protect RGCs in neurodegenerative injuries.

IMMUNE SYSTEM AND NEUROPROTECTION
The integrity of the peripheral immune
system is a key factor in the ability to prevent neurodegenerative conditions. There are two forms of immune response that can be activated under certain circumstances: (i) adaptive immunity, normally induced by T cells; and (ii) innate immunity, which involves the action of blood or resident macrophages.

Fisher et al. found that immunization with non-encephalitogenic myelin peptides triggered an immune response that slowed down the degeneration of RGCs. Cop-1 is a synthetic polymer that partially cross-reacts with myelin-related self-proteins and has been approved by the US Food and Drug Administration for the treatment of multiple sclerosis. Vaccination with Cop-1 has been found to result in significant neuroprotection in rat models of ON crush and chronic glaucoma. It seems, therefore, that T cell-based protective autoimmunity may promote recovery of the damaged ON and translating this potential treatment into clinical trials is a desired next step.

Macrophages, the major immune effector and phagocytic cells in the central nervous system (CNS), seem to play a decisive role in helping axonal re-growth after injury. Intravitreal injection of two macrophage activators, oxidized galectin-1 and zymosan, strongly enhanced the regeneration of transected RGC axons beyond the ON crush site in adult cats.

OTHER POTENTIAL TREATMENTS
The increase in intracellular calcium, via the activation of caspases and other substances and pathways within the neuron, plays an important role in apoptosis in the ON. It has also been reported that administration of lomerizine, a new calcium channel blocker, alleviates secondary degeneration of RGCs induced by ON crush in rats, presumably by improving the impaired axoplasmic flow. Erythropoietin (EPO) is responsible for the regulation of red blood cell production and has proved neuroprotective in CNS injury. Intravitreal EPO significantly increased RGC somata and axon survival between the eye and transection site, through Jak2/Stat3 and PI3K/AKT pathway activation, indicating its potential as a therapeutic agent for neuroprotection and regeneration.

Minocycline, which is mainly used to treat bacterial infections including pneumonia, has also been reported to enhance significantly the survival of RGCs after TON and in experimental glaucoma by delaying the apoptosis pathway.

Conclusion
With regard to current clinical trials, neither the systemic administration of steroids nor surgical decompression has proved particularly beneficial in the treatment of TON. Clinicians must make individual decisions regarding how best to restore their patients’ visual function. On the other hand, it seems that regeneration of the ON has been successfully promoted in laboratory settings with substances that slow down RGC apoptosis and promote axon re-growth. Much work still needs to be done, however, to translate these multiple and novel strategies into treatments that can be used in the clinical setting.

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Conflicts of interest
The authors had no conflicts of interest to declare in relation to this article.
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References
28 Ohlsson M, Svensson M: Early decompression

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