Clinical Trials in Traumatic Optic Neuropathy- An Update

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Introduction

Traumatic optic neuropathy (TON) refers to an acute injury of the optic nerve secondary to trauma. The optic nerve axons may be damaged either directly or indirectly and the visual loss may be partial or complete. TON occurs in 0.5 - 0.6% of patients presenting with closed head trauma.

The pathophysiology of TON is thought to be multifactorial, and some researchers have also postulated a primary and secondary mechanism of injury.TON is categorized as direct or indirect. An indirect injury to the optic nerve typically occurs from the transmission of forces to the optic canal from blunt head trauma. The injury to the axons is thought to be induced by shearing forces that are transmitted to the fibers or to the vascular supply of the nerve. Studies have shown that forces applied to the frontal bone and malar eminences are transferred and concentrated in the area near the optic canal. The tight adherence of the optic nerve's dural sheath to the periosteum within the optic canal is also thought to contribute to this segment of the nerve being extremely susceptible to the deformative stresses of the skull bones. Such injury leads to ischemic injury to the axons of the retinal ganglion cells within the optic canal. This is in contrast to direct TON, which results from an anatomical disruption of the optic nerve fibers from penetrating orbital trauma, bone fragments within the optic canal, or nerve sheath hematomas.

At present, no studies validate a particular approach to the management of TON. There are three management lines for these patients that include 1) observation only; 2) medical treatment with high or mega doses of methylprednisolone; and 3) surgical intervention. The main treatment options for TON include systemic corticosteroids and surgical optic nerve decompression, either alone or in combination. Review and analysis of the literature are complicated by the variety of therapeutic approaches and a lack of randomized, controlled studies on the use of these modalities for TON. Several therapies are used to prevent pathological changes to the optic nerve and preserve retinal ganglion cell (RGC) survival after trauma, however, there is still no standard therapy for TON. This update provides a critical review of current clinical trials in TON, with the aim of clarifying potential treatment strategies for the future.

Clinical Trials

1). National Acute Spinal Cord Injury Study 2 (NASCIS 2):

In 1990, Bracken and colleagues published their findings on the use of mega dose corticosteroid therapy in the NASCIS 2 which was a multicenter clinical trial that evaluated patients with acute spinal cord injury treated with placebo, methylprednisolone, or naloxone. The study showed that methylprednisolone (30 mg/kg loading dose, followed by 5.4 mg/kg/h for 24 hours) started within 8 hours of injury was associated with a significant improvement in both motor and sensory function compared with patients treated with a placebo. The findings of the NASCIS trials significantly influenced clinical practice and led to an increased use of steroids in treating TON. However, the clinical improvement was modest in these studies, and concern existed that the clinical benefit demonstrated for those patients treated in the first eight hours with mega dose steroids was the result of a statistical bias, since the analysis was performed post hoc rather than prospectively.

2). The International Optic Nerve Trauma Study (IONTS):

In 1999, IONTS was published. This is the largest prospective multicentre study of TON published till date. It was a nonrandomized intervention trial that compared visual outcomes for patients with TON treated with observation, systemic steroids, or optic canal decompression. The study included 133 patients who were evaluated and treated within 7 days of the traumatic event, with most of the patients being treated with either corticosteroids (n=85) or surgical decompression of the optic canal (n=33). Follow-up results showed that visual acuity increased by more than 3 lines in 32% of the surgery group, 52% of the corticosteroid group, and 57% of the observation group. However, the study was nonrandomized and uncontrolled, and the small numbers of patients in the observation group (n=9) limited the strength of the study's statistical power. 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.

3). Corticosteroid Randomization After Significant Head Injury (CRASH) Trial:

In 2005, the CRASH trial, which was the largest randomized study, was undertaken to evaluate the effectiveness and safety of mega dose steroids in patients with traumatic brain injury. This study was stopped early due to the significantly increased risk of death in patients that received mega dose steroids at their 6-month follow-up when compared with the placebo group (25.7% vs 22.3%; RR 1.15 CI 1.07 to 1.24; p=0.0001). Although the etiology of the increased risk of death was not determined, the findings of this study should be taken into consideration when managing cases of TON with concurrent traumatic brain injury.

4). 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 Optic nerve injury, and has involved various trophic substances, the use of multiple drugs and gene transfection.

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).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.

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.

References

1. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med. May 17 1990;322(20):1405-11.
2. Edwards P, Arango M, Balica L, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. Lancet. Jun 4-10 2005;365(9475):1957-9.
3. Levin LA, Beck RW, Joseph MP, et al. The treatment of traumatic optic neuropathy: the International Optic Nerve Trauma Study. Ophthalmology. Jul 1999;106(7):1268-77.
4. Steinsapir KD. Treatment of traumatic optic neuropathy with high-dose corticosteroid. J Neuroophthalmol. Mar 2006;26(1):65-7.
5. Steinsapir KD, Goldberg RA, Sinha S, et al. Methylprednisolone exacerbates axonal loss following optic nerve trauma in rats. Restor Neurol Neurosci. 2000;17(4):157-163.
6. Steinsapir KD, Goldberg RA. Traumatic optic neuropathy: an evolving understanding. American Journal of Ophthalmology. 2011;151:928-933.
7. Yu-Wai-Man P, Griffiths PG. Steroids for traumatic optic neuropathy. Cochrane Database Syst Rev. Oct 17 2007;CD006032.
8. Cook MW, Levin LA, Joseph MP, et al. Traumatic optic neuropathy. A meta-analysis. Arch Otolaryngol Head Neck Surg. Apr 1996;122(4):389-92.
9. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. JAMA. May 28 1997;277(20):1597-604.
10. Carta A, Ferrigno L, Salvo M, et al. Visual prognosis after indirect traumatic optic neuropathy. J Neurol Neurosurg Psychiatry. Feb 2003;74(2):246-8.

.11. Levin LA, Beck RW, Joseph MP, et al. The treatment of traumatic optic neuropathy: the International Optic Nerve Trauma Study. Ophthalmology. Jul 1999;106(7):1268-77. .

12. Li KK, Teknos TN, Lauretano A, et al. Traumatic optic neuropathy complicating facial fracture repair. J Craniofac Surg. Sep 1997;8(5):352-5; discussion 356-9.

13. Medeiros FA, Susanna R Jr. Retinal nerve fiber layer loss after traumatic optic neuropathy detected by scanning laser polarimetry. Arch Ophthalmol. Jun 2001;119(6):920-1.

14. Miyahara T, Kurimoto Y, Kurokawa T, et al. Alterations in retinal nerve fiber layer thickness following indirect traumatic optic neuropathy detected by nerve fiber analyzer, GDx-N. Am J Ophthalmol. Aug 2003;136(2):361-4.