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How Should Patients With Indirect Traumatic Optic Neuropathy Be Treated?

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Although relatively uncommon, indirect traumatic optic neuropathy (TON) often remains visually devastating (1). Numerous treatments have been suggested in the past, particularly surgical optic nerve decompression and high-dose systemic corticosteroids. However, more recent studies have suggested that no treatment might be better than potentially harmful therapeutic interventions, and the management of indirect TON remains highly controversial (1–3).

PRO—Steroids or surgery should be considered in patients with indirect traumatic optic neuropathy: Nicholas J. Volpe, MD

Opening statement

Despite 2 decades of ardent discussion, treatment attempts, clinical trial, and laboratory work, neuro-ophthalmologists have failed to develop a consensus opinion or to design an effective study to answer the question of whether any type of treatment benefits some patients with TON (1–3). This devastating optic neuropathy primarily affects young people in the prime of their life and involves 5 of 100,000 population, a prevalence similar to that of optic neuritis and nonarteritic ischemic optic neuropathy. It is also a common injury encountered in the modern battlefield (4). Unfortunately, there is no class I evidence on the successful treatment of TON to date, and the spontaneous recovery rate from TON makes a comparison with proposed treatments difficult (2,3). There is however a substantial amount of retrospective data and anecdotal experience that favors treatment of these patients, in the absence of severe head trauma, with either steroids and or optic canal decompression. These treatments are relatively safe, have a scientific basis, and ultimately are driven by ‘‘*what would I want if this happened to me*?’’

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Background

TON can result from both direct and indirect trauma. For the purpose of this debate, we define indirect TON as due to trauma to the forehead, brow, or head producing an optic neuropathy as opposed to direct or penetrating ocular or orbital injury to the optic nerve. The latter develops after blows to the face and particularly the forehead and most commonly in the setting of motor vehicles accidents or falls (1). The presumed mechanism of injury involves contusion injury to the optic nerve in the optic canal. Optic canal fractures however are identified in only approximately one third of patients, and therefore identification of a fracture is not necessary for the diagnosis of posterior indirect TON (5). The condition can be associated with any level of visual dysfunction, but generally vision loss is severe. The diagnosis is generally not made when there is injury to the retina, intraocular hemorrhage, or external or initial ophthalmoscopic evidence of injury to the eye or the nerve (1). TON often accompanies severe head injury or multisystem trauma, which at times can make establishing the diagnosis difficult and often precludes gathering meaningful clinical information necessary to study various treatments in a rigorous way.

Pathophysiologic observations that favor treatment

There are a number of reasons to believe that at least mechanistically this should be a treatable condition, recognizing that there is little evidence that any condition associated with any type of acute axonal injury (particularly the optic nerve) can be treated. Posterior indirect TON likely results from 2 factors: 1) the continued forward movement of the eye as the head suddenly decelerates and 2) from transmitted forces from the facial eminencies focally directed to the optic foramen. The combination of these factors leads to compression, stretching, shearing, and contusing of the optic nerve within the confines of the optic canal, where its dura is adherent to the bony walls. The axons may then swell in the tight bony optic canal, where there is no room for expansion (1,5). Therefore, delayed visual loss may result from further compression due to edema within the optic canal or from release of neurotoxic factors at the time of injury. An opportunity for treatment may exist based on a chance to 1) reduce swelling, 2) make more space for the swollen nerve, and 3) use neuroprotective agents of various types, which lessen the damage cascade that is set up at the moment of injury. The use of neuro-protective agents remains the main focus of treatment interventions for other optic neuropathies, including ischemic optic neuropathy and glaucoma.

Historical support for treatment

Several series have reported that between one quarter and one half of patients with untreated TON improve spontaneously (3,6). This high spontaneous recovery rate makes it particularly difficult to detect treatment effect and makes a ‘‘nontreater’’ comfortable and well grounded with his or her recommendation to manage expectantly.

There are 2 available options for treatment. One is the use of systemic corticosteroids and the other is the surgical decompression of the optic canal (7). Both target different aspects of the disease process. When used in combination, they may favor a better outcome compared to observation, as demonstrated by a meta-analysis of the available, albeit anecdotal medical literature (8). In injury conditions in which acute swelling and subsequent inflammatory

reaction are undesirable, corticosteroids are well recognized to reduce swelling and inflammation. Indeed, retrospective studies have shown that steroids both in standard doses and in ‘‘megadoses’’ can increase to two thirds the fraction of patients who improve (9,10). Unfortunately, since these reports and the international TON treatment trial, there have been only a few meaningful attempts by neuro-ophthalmologists to report even their anecdotal and retrospective experiences. ‘‘Megadoses’’ steroids gained popularity because of the results extrapolated from traumatic spinal cord injury studies. The National Acute Spinal Cord Injury Trial showed that ‘‘megadoses’’ steroids (30 mg/kg of methylprednisolone load followed by 5.4 mg/kg/hour) reduced permanent deficits in patients with spinal cord injury (11). The mechanism was not believed to be related to glucocorticoid activity but theorized to be the result of reduction in free radical damage and prevention of lipid peroxidation, which is thought to be the final pathway in white matter injury. Steroids in these doses may also enhance blood flow. These studies investigated the treatment of spinal cord injury, not TON, and the most convincing (albeit not statistically significant) benefit was seen when steroids were given within 8 hours of injury (a treatment window that is often difficult to achieve with TON, since its recognition is often delayed outside of the acute injury period). In a post hoc analysis, there was also some evidence that those treated after the 8-hour period fared worse than placebo, but these data and conclusions are of questionable significance (11).

However, these data must be considered in the context of recent evidence that steroids (in ‘‘megadoses’’) may be harmful to the optic nerve in a rat model of crush injury (12) and as well may be contraindicated in patients with severe head trauma because of reduced survival (12,13). The CRASH study (Corticosteroid Randomization After Significant Head Injury) reported that high-dose steroids were associated with reduced survival when given in the context of head injury (14). In this study, 10,008 patients with severe traumatic head injury were randomized, to either ‘‘megadose’’ steroid treatment (2 g of loading dose followed by 0.4 g/hour over 48 hours) or placebo. The mortality rate 2 weeks following the injury was 21.1% in the steroid group and 17.9% in the placebo group ($P = 0.0001$).

Transcranial and extracranial (transethmoidal, transantralethmoidal) surgical decompression of the optic canal have been reported in uncontrolled and retrospective studies to result in up to 70% improvement in patients with TON (6,15). However, there is no class I evidence that demonstrates that this is an unequivocally successful treatment (2). Benefits of optic canal decompression have also been reported in the pediatric population (16). With the increasing availability and training of endoscopic surgeons familiar with the extracranial approach, the complication rate is very low and most centers that use the procedure do so in conjunction with steroid therapy (7,17–19).

Conclusion

Currently, there is no standard of care for the treatment of TON. The International Optic Nerve Trauma Study compared observation to both steroids and canal decompression and found no clear benefit for either modality (6). Vision improved by at least 3 Snellen lines in 57% of the untreated group, 32% of the surgery group, and 52% of the steroid group. However, selection bias and inability to accurately assess patients acutely may have played a

role in the various treatment modalities chosen by the treating physicians. The study confirmed the high rate of significant spontaneous improvement. The following guidelines are offered in the context of nonrigorous evidence supporting the efficacy of steroid treatment, the greater likelihood of benefit from megadose steroids if given within the 8-hour window following injury, and the possible deleterious effect of this treatment. These recommendations are made recognizing the fact that in reality, so little of what we do as neuro-ophthalmologists is based on class I evidence, but how we act is much more often based on the art of medicine and what our individual experiences, the opinions of our specialty's experts, and interpretation of available data would suggest. Admittedly, there is a graveyard of treatments, long abandoned, based on subsequent information that proved these treatments to be useless or even harmful. In TON, observation alone is a reasonable position based on the high spontaneous improvement rate. However, it is also reasonable to offer moderate dose of steroids (250 mg of methylprednisolone QID for 24–48 hours) as an acceptable approach, with the theoretic rationale that improvement may result through reduction of inflammation and edema. ''Megadoses'' steroids (15–30 mg/kg/6 hours) may be cautiously considered in rare cases, but only if initiated within 8 hours of injury and with the understanding that the risk/benefit ratio is unclear. Decisions to use steroids should be made only after discussions with the neurosurgery team concerning their possible adverse effects in patients with severe head injury. In patients who are conscious and can understand the potential risks and possible benefits of this procedure, optic canal decompression should be offered when there is radiologic evidence of a bony fragment or hematoma impinging on the optic nerve. Surgery should be offered in patients with severe vision loss when surgery is being done to repair other facial fractures or in cases of continued visual deterioration with or without steroid treatment. In any patient in whom there is diagnostic un-certainty, such as those with simultaneous globe injury or those with severe head injuries, which make it difficult to assess visual function, we discourage any treatment beyond moderate doses of steroids. In the future, the likely treatment for TON will be a neuroprotective agent. Until then, this will remain an important topic to debate, and more systematic attempts at data collection and treatment studies should again be considered by those experts in this field.

CON—No treatment should be offered to patients with indirect traumatic optic neuropathy: Leonard A. Levin, MD, PhD

Opening statement

Neuro-ophthalmologists are uncomfortably familiar with the use of therapies that subsequently turn out to be ineffective (or worse, harmful) when tested in randomized clinical trials. The poster trial for this effect is the Ischemic Optic Nerve Decompression Trial, which showed that fenestration of the optic nerve sheath did not help nonprogressive nonarteritic anterior ischemic optic neuropathy (NAION) (20). The results from this study stopped the use of optic nerve sheath fenestration in NAION. Similarly, the frequent use of standard-dose oral corticosteroids for optic neuritis was virtually halted after the Optic Neuritis Treatment Trial suggested a higher recurrence rate in patients treated in that way when compared to high-dose intravenous corticosteroids or placebo (21). Similar trials have demonstrated ineffective treatment results using brimonidine for NAION (22) and Leber hereditary optic neuropathy (23).

Given this experience, on what basis could an experienced and ethical physician advocate treating patients with indirect TON, a disease for which not only is there minimal data for efficacy from nonrandomized trials (24) but also the most commonly used treatment (corticosteroids) is actually harmful (12,14,24,25)? Treatment of this disorder is complicated by several factors: its natural history includes both dramatic improvement and worsening, its incidence is relatively low, and it is difficult to obtain accurate baseline data regarding vision of 10 patients with recent head trauma. Clearly, only a randomized clinical trial would inform us of how to treat TON, but such a trial would likely be difficult to carry out if change in visual function was the primary end point. Some disease-therapy combinations are simply resistant to study (26).

A solution to this conundrum may come as our ability to correlate structural and functional measures of optic neuropathy improves. At present, visual function is the end point that all major stakeholders (patients, their physicians, and regulatory agencies) consider primary. However, structural end points do not require as much patient attentiveness, have high intra- and intersession reliability, and correlate quite well with functional end points or prognosis (27). These attractive features have led to the use of retinal nerve fiber layer thickness as a surrogate measure for pilot clinical trials of neuroprotective agents (e.g., : a randomized, double-blind, placebo-controlled, multicenter study of the effects of glatiramer acetate). Studies testing various therapies for indirect TON could take advantage of advances in imaging structural end points and might even include imaging of individual retinal ganglion cells (28,29). Success in such a pilot study could lead to enthusiasm for a proper clinical trial for TON. Until then, we have little to offer our patients besides encouragement and hope.

Rebuttal: Nicholas J. Volpe, MD

Dr. Levin is one of the world’s experts in the field of neuroprotection and has spent more time than most of us studying TON, both from the standpoint of the best approach to designing experiments and compounds for neuroprotection and the best approach to treatment. Once again I would highlight that we are in agreement that there is simply no class I evidence to support the treatment of TON patients with corticosteroids. I also agree and strongly endorse his conclusions that ultimately we will have a much better understanding on how to treat all types of optic nerve disorders when we can perfect our structural measurements of the optic nerve and tie them tightly to visual function. This will eliminate the inaccuracies associated with subjective vision testing and all the limitations that have been discussed regarding the difficulty in examining and qualifying visual deficits in patients with TON. Ultimately, the answer to how to best treat this condition will come from studies in which testing modalities are able to assess the viability and function of optic nerve axons at presentation and during follow-up with different treatments.

Dr. Levin accurately points out, as did I, that a number of treatments have been abandoned in neuro-ophthalmic practice as a result of prospective randomized clinical trials. His implication is that only with laboratory or clinical evidence should any therapy be used. This argument would fall short in other clinical situations in neuro-ophthalmology in which our individual and collective experiences, based on the clinical management of patients, dominate our decision making. One such example is in the management of idiopathic

intracranial hypertension. Most experts would consider acetazolamide as the treatment of choice in patients with early and moderate vision loss. The use of this treatment, based on a sound physiologic principle, has never been rigorously tested but is now the subject of a recently initiated prospective randomized treatment trial. While I acknowledge that the argument for neuroprotection from ‘‘megadoses’’ of steroids is not substantiated by any laboratory or clinical trial evidence, I would offer that in this situation, conventional doses of steroids may well be helping reduce tissue edema in the tight confines of the optic canal regardless of whether they have any neuroprotective effect. Similarly, this may be the mechanism by which optic canal decompression may also be helpful.

Frankly, I feel that the argument that steroids are harmful falls short in some ways. In each of the examples cited, it was their effect on laboratory rats, their use in other diseases, or their use in a group of patients with severe head trauma that found steroids to be harmful. As clinicians dealing with isolated TON, we are certainly not dealing with laboratory animals and in many situations not dealing with patients who also have severe head injuries. However, I do agree that based on the CRASH data, steroids should be contraindicated in the setting of severe head injury.

I believe Dr. Levin and I agree that we are a long way from having an ideal and clearly effective treatment. There is no sound clinical trial evidence to support the treatment of TON, and the clinical course is highly variable making it difficult to test such a treatment. We both agree that structural measurements of optic nerve function will aid us in the future design of clinical trials to test possible treatments. Where our opinions differ is largely based on whether in patients with isolated TON and the absence of severe head injury, we can safely use moderate doses of steroids and optic canal decompression in an effort to lessen the damage to the optic nerve. Lacking class 1 evidence, I believe this decision on personal experience and non-rigorous retrospective data is reasonable at this time.

Rebuttal: Leonard A. Levin, MD, PhD

Dr. Volpe cogently and accurately summarizes the critical literature describing the presentation, pathophysiology, and treatment of indirect TON. I have no disagreement with what he writes, and more specifically, I agree with him that there is no evidence based on prospective randomized studies to support a choice of any specific therapy vs observation. He is correct that in a meta-analysis that my colleagues and I performed 15 years ago (8), we concluded that surgery or corticosteroids were superior to observation. However, the results of the International Optic Nerve Trauma Study (6) published 3 years later reached the opposite conclusion in a concurrent (albeit nonrandomized) observational study.

I contend that his recommendation for treatment with corticosteroids and/or surgery is based less on scientific evidence than the fact that he is an ethical and caring physician who desires the best for his patients, and as he writes, ‘‘*what would I want if this happened to me?*’’ But the critical question is not what would the physician want if the situation were reversed, but what would the patient want. An equally ethical and caring position is that without laboratory or clinical evidence of efficacy with a therapy, withholding these therapies (observation alone) is indicated. Given that laboratory evidence and the CRASH study

demonstrate significant potential risks of high-dose corticosteroids, one can strongly justify recommending no therapy.

Dr. Volpe correctly states that ‘‘there is little evidence that any condition associated with any type of acute axonal injury (particularly the optic nerve) can be treated.’’ This statement is supported by level 1 clinical evidence for memantine in Alzheimer disease (3), riluzole in amyotrophic lateral sclerosis (4), and most recently, brimonidine in normal-tension glaucoma (5). On the other hand, there are dozens of animal studies demonstrating neuroprotective effects of drugs and other therapies on optic nerve crush and transection, which are preclinical models of TON.

This discrepancy between results in the clinic and the laboratory has 2 sources. First, most animal studies examine the effects of the treatment on survival of the cell soma (the retinal ganglion cell), but the survival of the axon is equally important (6). The development of axoprotective drugs is a lacune in our therapeutic armamentarium, and without attending to the axon, there is unlikely to be visual improvement in most optic neuropathies. Second, therapies that work in cell culture or animal models frequently fail in human trials. This disconnect arises from a variety of reasons inherent to translational research that we have called the ‘‘Lost in Translation’’ problem (6). In other words, there may be a good reason why it has been difficult to find effective therapies for indirect TON and provides further justification for pilot studies using a structural end point, such as retinal nerve fiber layer thickness.

In summary, there is inadequate evidence from clinical trials to support any specific treatment for indirect TON, and animal and clinical studies suggest that one such treatment, high-dose corticosteroids, may even be harmful. On the other hand, laboratory research continues to entice us with the possibility of using neuroprotective and axoprotective therapies. The best approach is to focus our efforts on finding more efficient ways of testing treatments in clinical trials using novel end points and trial designs, and thereby increase our chances of having an effective therapy to offer our patients.

Conclusion: Andrew G. Lee, MD, and Valérie Biousse, MD

Once again, the lack of class I evidence makes it difficult for expert neuro-ophthalmologists to agree on the treatment of a well-recognized entity, such as indirect TON. This controversy emphasizes the importance of randomized clinical trials, without which the debate will continue.

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Dr Levin has served as a paid consultant and received honoraria for lectures relating to neuroprotection with respect to several pharmaceutical companies. He also has patents issued or pending on neuroprotective therapies, which are assigned to the Wisconsin Alumni Research Foundation.

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