PERSPECTIVE

Traumatic Optic Neuropathy: An Evolving Understanding

KENNETH D. STEINSAPIR AND ROBERT A. GOLDBERG

• PURPOSE: To critically review the treatment of traumatic optic neuropathy.

• DESIGN: A perspective of clinical and basic science studies related to traumatic optic neuropathy and its treatment.

• METHODS: Published clinical and basic science studies on traumatic optic neuropathy were critically reviewed and interpreted.

• RESULTS: Clinical progress in the treatment of traumatic optic neuropathy is limited by small clinical studies lacking appropriate control groups. The Corticosteroid Randomization for Acute Head Trauma (CRASH) trial found an increased rate of death among patients with acute head trauma treated with high-dose corticosteroids compared to placebo-treated patients (21% vs 18%, $P = .0001$). Recent animal studies also suggest that high-dose corticosteroids are toxic to the injured optic nerve.

• CONCLUSIONS: The Corticosteroid Randomization for Acute Head Trauma study is immediately relevant to the treatment of traumatic optic neuropathy as individuals with traumatic optic neuropathy often have concomitant head trauma. High-dose corticosteroids for traumatic optic neuropathy will result in a measurable loss of life in patients who also have a brain injury. Death has never been an endpoint for traumatic optic neuropathy studies. Given human and animal data suggesting that treatment is harmful and the lack of demonstrated clinical efficacy, corticosteroids should not be used to treat traumatic optic neuropathy. The benefit of optic canal decompression is also unclear. There is a need to identify traumatic optic neuropathy soon after injury to further define the natural history of this injury. This information will provide a basis for assessing potential future treatments for traumatic optic neuropathy. (Am J Ophthalmol 2011;151: 928–933. © 2011 by Elsevier Inc. All rights reserved.)

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IN 1982, ANDERSON AND ASSOCIATES INTRODUCED CORticosteroid treatment of traumatic optic neuropathy to clinical practice.[1] Prior to this, treatment was primarily conservative with anecdotal reports of surgery to decompress the optic nerve. In 1990 high-dose corticosteroids were reported as a successful treatment of acute spinal cord injury. Numerous clinical studies touted the potential value of this treatment, which is also called megadose steroids in the ophthalmic literature, for traumatic optic neuropathy. On this basis, ophthalmologists widely embraced high-dose corticosteroids as therapy for traumatic optic neuropathy.[2] Unfortunately, these clinical studies were small case series lacking appropriate controls.

The International Optic Nerve Trauma Study was intended to be a controlled study to assess the value of high-dose corticosteroids and optic canal decompression.[3] Enrollment was limited, however, and the study was converted to an interventional case series. The authors of this study, drawing on their data and a review of the literature, concluded that there was no clear evidence that corticosteroids or optic canal decompression produced better outcomes than no treatment. In the absence of clear evidence, clinicians were encouraged to make individualized choices among these treatment options. Since the publication of the International Optic Nerve Trauma Study in 1999, several lines of evidence now suggest that treatment of traumatic optic neuropathy with high-dose corticosteroids may be harmful rather than helpful. Corticosteroids and optic nerve decompression for treatment of traumatic optic neuropathy are the focus of this perspective.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

TRAUMATIC OPTIC NEUROPATHY IS AN ACUTE INJURY OF the optic nerve with disruption of visual function. Specific causes include motor vehicle and bicycle accidents, head trauma from falls and falling debris, assault, stab and gunshot wounds, endoscopic sinus surgery mishap, recreation-associated trauma, and seemingly trivial injuries.[2] Traumatic optic neuropathy is part of the spectrum of head trauma. Historic series suggest that traumatic optic neu-

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ropathy is seen in 0.5% to 2% of head injuries[4]; however, traumatic optic neuropathy is more common in the setting of craniofacial fractures.[5] In the first 6 years of operations Iraqi and Enduring Freedom, 30 484 troops were wounded in action.[6] Of these, 523 had globe or orbital adnexal combat injuries that required tertiary care. This included 103 cases of traumatic optic neuropathy, accounting for nearly 20% of the ocular combat injuries.[6] Almost half of these cases (48%) were indirect optic nerve trauma. The incidence of loss of consciousness at the time of traumatic optic neuropathy is reported as 20% to 75% depending on the series.[7,8] Prognosis for visual recovery is poor for patients presenting with no light perception vision and orbital fractures,[9] afferent pupillary deficits that exceed 2.1 log units,[10] and flash visual evoked potentials that are less than 50% of the unaffected optic nerve.[11]

Traumatic optic neuropathy is classified as direct when the nerve is injured directly by a projectile, knife, or other object that penetrates the orbit to damage the optic nerve. Indirect optic neuropathy is diagnosed when the injury to the nerve results from the nonpenetrating effects of trauma, including hemorrhage, edema, and concussion. Indirect traumatic optic neuropathy has been the subject of more clinical research than direct injury. This may reflect the increased opportunity for visual recovery associated with indirect traumatic optic neuropathy.

Depending on the nature of the event, impact forces are loaded into the optic nerve within milliseconds (range, 1.5 to 19 ms).[12] The shock wave can fracture the optic canal. Static loading studies suggest that compression of the superior orbital rim is transferred and concentrated in the orbital roof and optic canal.[1] The optic nerve is fixed within the optic canal, which contributes to the vulnerability of the nerve in this location.[13] Coup-contrecoup forces whip mobile portions of the optic nerve against fixed structures, causing injury. Violent rotation of the globe can result in partial or complete optic nerve avulsion. Finite analysis modeling suggests that rapid globe rotation is associated with an abrupt rise in intraocular pressure, a factor in globe rupture at the optic nerve head.[14]

Traumatic optic neuropathy is also classified anatomically based on distinct clinical presentations associated with injury location. Partial or complete optic nerve head avulsion presents with intraocular hemorrhage at the optic nerve head and disruption of optic nerve head anatomy. Anterior optic nerve trauma is presumed when there is loss of vision with disruption of circulation at the optic nerve head. The trauma affects the nerve at a site anterior to where the ophthalmic artery enters the optic nerve. Unilateral or asymmetric bilateral posterior traumatic optic neuropathy is a clinical diagnosis that should be considered when visual loss following trauma cannot be explained by other ocular injuries and there is a relative afferent pupillary defect even though the fundus appears normal. In bilateral injury, absence of a relative afferent pupillary defect suggests that the nerves are comparably damaged. Posterior injuries involve the optic nerve proximal to where the ophthalmic artery enters the optic nerve in the orbit to the optic chiasm. The most common sites of injury are the foramina of the optic canal, the optic canal, and under the falciform dural fold that drapes the edge of the anterior clinoid process.[13]

Walsh[13] described the process of contusion necrosis that results from shearing injury to the axons and microvasculature, and this process is thought to be the basis for injury in these cases. What follows are postinjury biochemical cascades that exacerbate the initial damage.[4] Most cases of visual loss are immediate; however, delayed visual loss is documented in 10% of cases.[3] Treatment with surgery and corticosteroids is intended to limit secondary injury.

HIGH-DOSE CORTICOSTEROIDS

IN THE NEUROSURGICAL LITERATURE, THE TERM *high-dose corticosteroids* refers to the treatment protocol of intravenous methylprednisolone used to treat acute spinal cord injury in the Second and Third National Acute Spinal Cord Injury Studies (NASCIS II and NASCIS III).[15,16] The protocol consisted of a loading dose of 30 mg/kg followed by a continuous intravenous infusion of 5.4 mg/kg per hour for 24 or 48 hours.[15,16] The ophthalmic literature refers to this protocol as megadose corticosteroids. Investigators have used a range of methylprednisolone regimens to treat traumatic optic neuropathy. As classified by Levin and associates,[3] methylprednisolone regimens include megadose (greater than 5400 mg/d), very-high-dose (2000 to 5400 mg/d), high-dose (500 to 1999 mg/d), moderate-dose (100 to 499 mg/d), and low-dose treatment (below 100 mg/d). For purposes of clarity and consistency with the neurosurgical literature, in the discussion to follow, intravenous methylprednisolone of 30 mg/kg loading followed by a continuous intravenous infusion of 5.4 mg/kg per hour for 24 or 48 hours will be referred to as high-dose rather than megadose treatment. In the discussion of other protocols, the actual dose will be cited (eg, 250 mg/d of methylprednisolone rather than moderate dose).

Treatment of traumatic optic neuropathy with high-dose methylprednisolone was widely embraced by the ophthalmic community with the publication in 1990 of the results of the Second National Acute Spinal Cord Injury Study. This study was a randomized, double-blind, placebo-controlled study of patients with acute spinal cord injury, which was published in the *New England Journal of Medicine*.[15] Patients were randomly assigned to 1 of 3 treatment arms within 12 hours of injury: high-dose methylprednisolone, naloxone, or placebo. The study concluded that patients with acute spinal cord injury treated with high-dose methylprednisolone within 8 hours of injury have a statistically significant improvement in motor and sensory function compared with placebo, nal-

oxone, or high-dose methylprednisolone treatment started more than 8 hours after trauma. Critics of the Second National Acute Spinal Cord Injury Study argue that stratifying the corticosteroid-treated patients based on the 8-hour time frame was chosen as a result of post hoc data analysis. When the 8-hour stratification is removed, corticosteroid-treated patients have worse outcomes overall compared with those receiving placebo.[17]

Since 1990, there have been 43 studies of traumatic optic neuropathy that have enrolled at least 10 patients, for a total of 1906 patients. Of these, 1442 were treated with corticosteroids alone or corticosteroids plus optic canal surgery. Unfortunately, each of these studies is relatively small. In some cases, conclusions are limited by the changing approach to patient recruitment evident in the literature. Compared with older studies, these reports have larger numbers of patients identified and treated more quickly after trauma.

Two studies from the Massachusetts Eye and Ear Infirmary highlight the effect of early diagnosis. The first is by Lessell,[18] who reported 33 cases of traumatic optic neuropathy seen from 1976 to 1987. In this series, 6 (18%) of the patients initially had no light perception vision and 9 (27%) had visual improvement. Contrast this with a study from the same institution published just 1 year later by Joseph and associates.[19] They reported 14 unilateral cases of traumatic optic neuropathy seen in a 16-month period between April 1987 and October 1989. Of these, 5 patients (36%) presented with no light perception vision. All patients were seen within 1 week, and 5 (36%) underwent optic canal surgery within 24 hours of their trauma. Overall, 11 patients (79%) had visual improvement. These studies, from a single institution, demonstrate the complexity of interpreting the traumatic optic neuropathy literature. It took 11 years to accumulate 33 cases of traumatic optic neuropathy in Lessell's series, but just 16 months to accumulate another 14 cases in the series by Joseph and associates.

This disparity raises several questions. Did the community incidence or referral patterns of traumatic optic neuropathy change? It is more likely that study investigators made a greater effort to identify patients with acute traumatic optic neuropathy presenting to their institution. Did the treatment in the second series account for the improvement in outcome, or was it simply the result of identifying a cohort with traumatic optic neuropathy closer in time to the initial injury, thereby increasing the opportunity for spontaneous visual improvement? It is likely that early diagnosis biased the second study toward a more favorable outcome irrespective of treatment. Conversely, as time from injury increases, the probability of visual recovery decreases.

This set of articles is not unique in presenting conflicting information that creates confusion in the literature. In the study by Chou and associates,[20] the authors described 58 patients with traumatic optic neuropathy. They concluded that patients treated with high-dose corticosteroids had better outcomes than untreated patients. Untreated patients, however, did not present to the authors until 3 weeks after injury on average. In contrast, patients treated with corticosteroids alone presented, on average, within 2 weeks of trauma; and those who had surgery plus corticosteroids presented, on average, within 3 days of trauma. Time to study recruitment rather than treatment protocols may account for the difference in outcomes in this particular study.[2]

The International Optic Nerve Trauma Study analyzed 133 patients with traumatic optic neuropathy who had vision assessed within 3 days of their trauma.[3] The striking feature of this study is the bias toward treatment. Of 133 patients, 125 received corticosteroids in varying doses, and 33 of those also had optic canal surgery. This bias for treatment means that we do not know the natural history of traumatic optic neuropathy and the likelihood of spontaneous visual recovery. Without a control group of untreated patients with traumatic optic neuropathy identified at a time frame comparable to that of treated patients, it is impossible to conclude that medical or surgical intervention makes a difference. The authors of the International Optic Nerve Trauma Study stated there was "sufficient evidence to conclude that neither corticosteroids nor optic canal surgery should be considered the standard of care for patients with traumatic optic neuropathy."[3] They suggested it was reasonable for clinicians to make empirical treatment decisions with their patients. Since the findings of the International Optic Nerve Trauma Study were released in 1999, several new lines of evidence now suggest that treating traumatic optic neuropathy with high-dose corticosteroids is harmful rather than helpful.[21]

The Corticosteroid Randomization After Significant Head Injury (CRASH) trial was a multicenter, randomized, placebo-controlled study of high-dose methylprednisolone therapy for acute head trauma, published in the journal *Lancet* in 2004.[22] Patients were randomly assigned within 8 hours of trauma to treatment with either placebo or high-dose methylprednisolone (30 mg/kg loading followed by an infusion of 5.4 mg/kg per hour) for 48 hours. The goal was to enroll 20 000 patients, but the study was halted at 10 008 patients. Safety monitoring data revealed a higher risk of death from all causes 2 weeks after trauma in the corticosteroid-treated patients (21% vs 18% mortality, $P = .0001$). This is 1 excess death for every 31 patients with head trauma treated.[23] This finding has prompted neurosurgeons to abandon the use of high-dose corticosteroids after head trauma. The CRASH trial has immediate implications for treating traumatic optic neuropathy given the high incidence of concomitant head trauma.

Not every traumatic optic neuropathy patient will have a brain injury, so the mortality rate associated with corticosteroid treatment will be lower than that seen in patients with primary head trauma. No study of high-dose methylprednisolone therapy for traumatic optic neuropa-

thy has used death as a study endpoint because death in this setting has always been attributed to the underlying head trauma. Traumatic optic neuropathy studies exclude these patients. Since the CRASH trial, informed consent for high-dose corticosteroid therapy for traumatic optic neuropathy must include information on the increased mortality to be expected from this treatment. Recognizing the existence of a higher mortality rate associated with treating traumatic optic neuropathy with high-dose corticosteroids, ophthalmologists should look to affirmative evidence balancing the potential risks of treatment.

Not only do we lack evidence for the efficacy of high-dose corticosteroids, there are now several animal studies that show high-dose corticosteroids to be directly toxic to injured optic nerve. Steinsapir and associates[24] studied the treatment of experimental optic nerve injury with methylprednisolone in doses ranging from 30 to 120 mg/kg, compared with a saline-treated group. The saline-treated animals retained statistically significantly greater numbers of axons than the corticosteroid-treated animals. The second research study was a double-insult study by Ben Simon and associates.[25] They found that head trauma preceding optic nerve injury was neuroprotective. Furthermore, treatment of the animals with high-dose methylprednisolone (30 mg/kg) after the optic nerve injury resulted in a loss of the protective effect associated with the head trauma. This neuroprotective effect was preserved when the animals were treated with low-dose methylprednisolone (1 mg/kg). Finally, Diem and associates[26] demonstrated that methylprednisolone (20 mg/kg) was detrimental in an animal model of inflammatory optic neuropathy. Optic nerve inflammation is a different entity than traumatic optic neuropathy but may share common postinjury biochemical cascades.[4] Corticosteroids may paradoxically interfere with adaptive mechanisms that limit the spread of secondary injury.[4] No animal models of indirect traumatic optic neuropathy demonstrate a benefit for corticosteroids at any dose.[21]

Clinical evidence does not support the use of high-dose corticosteroids for traumatic optic neuropathy. This treatment increases mortality in patients with head trauma. Animal studies show the treatment to be toxic to injured optic nerve. There is no reason to subject our patients to this treatment. The potential loss of life associated with high-dose corticosteroids in the setting of head trauma is not counterbalanced by clinically meaningful benefits. Without new and compelling research data, high-dose corticosteroids for traumatic optic neuropathy should be abandoned.

This naturally raises the question about whether lower dosages of methylprednisolone could be safe and effective. The answer is that no clinical or animal studies have shown any convincing evidence that methylprednisolone is effective for treating traumatic optic neuropathy at any dose. Clinical enthusiasm to use corticosteroids for treatment of traumatic optic neuropathy without any evidence that it may be helpful must be weighed against our new understanding that the treatment can actually be harmful. Whether methylprednisolone is safe when administered in a dosage below 20 mg/kg every 6 hours cannot be answered. The absence of data needed to answer this question does not provide a rationale for conducting human experimentation, given the risk of potential harm. Further clinical experimentation with alternate corticosteroid protocols would be difficult to support ethically without compelling, new animal data justifying such a treatment approach or, at the minimum, establishing that such treatments do not cause harm. Ben Simon and associates[25] found that high-dose methylprednisolone (30 mg/kg) interfered with an optic nerve neuroprotective effect seen following head trauma. Methylprednisolone given at 1 mg/kg did not block the neuroprotective effect. This does not imply that methylprednisolone even at this lower dose is safe or effective for treating traumatic optic neuropathy.

Following trauma, clinicians may have reasons other than the treatment of traumatic optic neuropathy for considering corticosteroid therapy. To cite just one hypothetical example, we lack evidence to conclude that a kidney transplant recipient with a diagnosis of traumatic optic neuropathy who requires long-term prednisone therapy to control graft rejection should have the prednisone regimen discontinued. In the absence of better information, it seems prudent to limit such treatments to the equivalent of 1 mg/kg every 6 hours of methylprednisolone in the presence of concomitant acute traumatic optic neuropathy.

OPTIC NERVE DECOMPRESSION

IT HAS BEEN HYPOTHESIZED THAT SWELLING OF THE OPTIC nerve within the fixed and limited confines of the optic canal could compromise blood supply to the nerve within the canal. This could exacerbate tissue ischemia and cause further damage to the injured optic nerve. The optic nerve can swell following trauma. As Walsh[13] pointed out, it is unknown how much swelling is needed to compromise the nerve. Despite this uncertainty, swelling is commonly cited as a rationale for performing optic canal decompressive surgery. Early reports of optic canal decompression were not promising.[27,28] Studies in the 1970s from Japan suggested that traumatic optic neuropathy was relatively common and responsive to optic canal decompressive surgery.[29] In retrospect, the numbers of cases in these studies and their reported rates of success were anomalously high, and the basis for diagnosing traumatic optic neuropathy is questionable.[3,4,9]

Since the early 1980s, the rate of reported spontaneous visual improvement for untreated cases of traumatic optic neuropathy has ranged from 0% to 67%.[20,30] Treatment studies during this same period commonly combine both corticosteroids and optic canal decompression. Rates of postoperative visual improvement range from 0% to

76%.[31,32] Cook and associates[33] analyzed 46 of these studies, including 244 cases. They concluded that treatment with corticosteroids, optic canal decompression, or combined treatment results in a higher rate of visual recovery than no treatment. This study, however, failed to consider the changing nature of how patients are identified for inclusion into these studies.[2] Instead of examining patients who present for assessment days, weeks, or even months after visual loss attributable to traumatic optic neuropathy, contemporary investigators have the opportunity to assess and treat patients within hours of their trauma. As just noted, there is a high rate of spontaneous visual recovery following traumatic optic neuropathy. This biases relatively recent studies that emphasize treatment toward a more favorable outcome when compared with older studies.[21]

Presently, we do not know the natural history of untreated traumatic optic neuropathy and the rate of spontaneous visual recovery when traumatic optic neuropathy is identified within hours of injury. Without this information, it is impossible to determine the benefit of subjecting patients to optic nerve surgery or, for that matter, any treatment. It is important to understand that a subset of patients may exist who will benefit from surgery, but we do not yet know which patients are likely to benefit. Research is needed to identify predictive biological markers that decrease unnecessary optic canal surgery and increase the likelihood that surgery is beneficial. It is also possible that optic canal decompression provides no measurable benefit over spontaneous visual recovery.

Patients with visual compromise from optic nerve sheath hematoma may be one example of a subset more likely to benefit from surgery. Anecdotal reports suggest that patients with progressive visual loss associated with the finding of an enlarged optic nerve sheath attributable to intra-sheath hemorrhage respond favorably to optic nerve sheath decompression.[4] Although this is a rare clinical circumstance, the value of intervention appears to be less controversial than that of optic canal decompression.[4,34]

CONCLUSIONS

FINALLY, WHAT SHOULD BE DONE FOR YOUR TRAUMATIC optic neuropathy patients? Patients and their families deserve a thorough and frank discussion of the basis for visual loss and our current understanding of the condition. In the absence of new information, corticosteroids should not be used to treat traumatic optic neuropathy. Individual circumstances may require the use of corticosteroids for other clinical reasons in the setting of traumatic optic neuropathy. Based on admittedly limited data, anti-inflammatory doses of corticosteroids (eg, oral prednisone, 60 to 100 mg/d) are likely safe in this setting. Again, this is cited as a guideline when other concomitant clinical issues warrant the use of corticosteroids. This should not be misinterpreted as an endorsement for low-dose corticosteroids as a treatment of traumatic optic neuropathy.

In the absence of imaging studies suggesting an optic nerve sheath hemorrhage, an uncommon clinical circumstance, surgery should be reserved for conscious patients with delayed visual loss, or whose vision does not improve in the first 4 days, provided there is a flash visual evoked potential that is at least 50% of the normal eye, or there is an afferent pupillary deficit less than 2.1 log units. It is worth noting that optic canal fractures may be a marker for how much force had an impact on the nerve rather than an indication for surgery.

The message that high-dose corticosteroids may be harmful appears to be taking hold. Lee and associates[35] published a prospective study of 121 patients with traumatic optic neuropathy seen in the United Kingdom between November 2004 and November 2006. Of these patients, 75 (65%) received no initial treatment, which suggests a trend toward conservative management. Going forward, we need a natural history study of this condition in which patients are recruited into the study within hours of their injury, to learn all we can about the rates of spontaneous visual recovery. These data are essential to judge the effects of any proposed treatment of traumatic optic neuropathy that may emerge in the future.

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