Controversial Issues in The Treatment of Traumatic Optic Neuropathy: A Journey Through Historical Course

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ABSTRACT

Traumatic optic neuropathy (TON) can occur by either direct injury or an indirect way which can develop secondary to transfer forces occurring due to trauma in frontal and maxillary bones to optic canal. The involvement of productive individuals at younger age groups makes it more important. Since TON is accompanied by multiple traumas, the diagnosis of TON is generally challenging and delayed in these patients usually requiring ICU follow-up. The treatment in patients diagnosed as TON is one of the most controversial issues in neuro-ophthalmology. The clinical experiences on treatment of TON have been built on 'National Spinal Cord Injury Study II and III2 trials rather than small cases series and the results had been found satisfactory. On the other hand, the concerns about translation of results from studies on spinal cord injury treatment to optic nerve injuries have been increased with the results of 'International Optic Nerve Trauma Study' showing no difference between groups underwent observation, steroid treatment or optic canal decompression. Additionally, the results from 'Medical Research Council-Corticosteroid Randomisation After Significant Head Injury' study, which showed statistically significantly higher mortality rates within first two weeks of mega-dose steroid treatments compared to placebo groups, have promoted us to review our treatment protocols.

As similar to stroke and degenerative neurological disorders, the efficiency of neuroprotective agents have been investigated and molecules like erythropoietin are promising.

The major challenges in the treatment of TON are high spontaneous recovery rates due to the nature of the disorder and lacking of class I evidence from multi-center, randomized, prospective, double-blind studies comparing different treatment modalities.

This review aimed to summarize different studies which form our preferences in treatment of TON.

Key Words: Traumatic optic neuropathy, Treatment, Neuroprotection**.**

The Ocular Trauma Classification group has attempted to classify both anterior and posterior segment traumas and to establish treatment algorithms.[1] Although therapeutic approaches are less controversial in anterior segment traumas, there is no widely accepted consensus on the treatment of posterior segment traumas such as traumatic optic neuropathy (TON).[2] The TON can be defined as impairment in optic nerve functions such as loss of vision and visual field or color vision disorders as result of blunt or penetrating injuries of optic nerve.[3] Optic nerve injury can occur in 0.5-7% of closed head injuries and it has been reported that it may reach up to 2.5% in cases with mid-facial trauma.[4, 5] The TON, where men aged 20-40 years comprise majority of cases, often results from motor vehicle accidents, cycling injuries and falls.

The major difference affecting prognosis results from mechanism of injury in pathogenesis traumatic optic neuropathy. In cases with direct traumatic optic neuropathy, avulsion and compression occur in optic nerve through penetrating trauma of optic nerve while compartment syndrome occurs by transfer of forces following closed head injury at frontal and maxillary bone region to optic canal localized at ala minor of sphenoid bone and compression of optic nerve in the canal in cases with indirect traumatic optic neuropathy. In general, stretch and impaired circulation of optic nerve axons, altered cerebrospinal fluid circulation and reduction or interruption of retroaxonal conduction can be implied in the development of TON. The difference in the pathogenesis can influence on both prognosis and treatment. Spontaneous recovery is common in cases

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with indirect traumatic optic neuropathy while it is less common in those with direct traumatic optic neuropathy. The difference in the pathogenesis brings therapeutic alternatives and debates on these alternatives, making the issue one of the most controversial fields in neuro-ophthalmology.[6-7] Given its pathophysiology, the goal of treatment should be to relieve edema at axonal structures that form optic nerve; improve circulation; create space for optic nerve compressed within optic canal; and protect structures which did not become fully dysfunctional against cytotoxic substances. In the literature, follow-up, steroid therapy, optic canal decompression, optic nerves sheath fenestration, neuroprotective therapies and their combinations are defined in the treatment of TON.[8] Although there are controversies on different treatment modalities, there is no consensus on timing, dose, effectiveness and adverse events of steroid treatment which has been proven to be effective in different types of optic neuropathies. In this review, therapeutic modalities used in the treatment will be discussed based on current literature together with historical process.

Steroids in the treatment of TON

Steroids have been used in the treatment of TON as they reduce inflammation and edema and neuronal/axonal loss resulting from locally elevated hydrostatic pressure within optic canal; enhance blood supply, particularly in high doses; prevent free radical formation and lipid peroxidation induced by free radicals; and decrease intracellular Ca^{+2} levels. The role of steroids in the treatment of TON was addressed in details in Cochrane reviews.[9] Although many studies about steroid therapy in TON, there is only a single double-blinded, placebo-controlled, randomized study.[10] The major causes of controversies about steroid therapy include insufficient number of cases, lack of a certain protocol based on experience of clinician, various doses and types of steroids used in the treatment and differences in time from trauma to treatment among others.

Although steroid therapy in treatment of TON dates back to 1980s,[11] detailed data has come from 'National Spinal Cord Injury Study (NASCIS-II)'.[12] This was the first study with multicenter, randomized, double-blinded design. In the study, intravenous bolus of 30 mg/kg methyl prednisolone was given to eligible patients recruited to the study within first 8 hours after trauma; followed by 5.4 mg/kg/hour methyl prednisolone over 23 hours and significant differences were reported in motor functions in patients treated using steroid therapy within 8 hours when compared to controls received placebo and those treated beyond 8 hours.[12] In extension study NASCIS-III, early treatment and treatment extended up to 48 hours were evaluated. It was reported that extending treatment up to 48 hours had no superiority to 24-hours treatment in patients treated within first 3 hours but extended treatment was more effective regarding motor and functional recovery in the group treated between hours 3 and 8 and outcomes were poorer in treatment beyond 8 hours when compared to placebo group.[13] The promising results in these studies were translated to patients with TON, forming clinical treatment practices. The main criticism to promising NASCIS studies are that the patients in NASCIS studies had spinal cord injury not optic nerve injury and that patients with TON could not be treated within first 8 hours in general, emphasizing need for randomized, double-blinded, placebo-controlled studies including patients with optic nerve injury. There are ongoing concerns about treatments beyond 8 hours in particular, given that steroids do not reduce effects of macrophages and prevent lipid peroxidation; and, more importantly, they impair normal regenerative process of tissue. The 'International Optic Nerve Trauma Study (IONTS)' by Levin et al. is the most reliable prospective, multicenter study in this context.[14] In the study, it was shown that there was no significant difference in final visual acuity and visual acuity gain between untreated patients, those received steroid therapy and those underwent optic canal decompression. The most important criticism to the study is that the study was started as a randomized clinical trial but it was turned into observational study due to challenges in recruitment of patients. In addition, the study has some limitations including treatment of patients in different time points within first 7 days, variations in steroid regimens and additional steroid treatment given to all but one patients in the surgery group. Although there are many studies supportive the outcomes in the literature, the most important data came from only randomized, double-blinded, placebo-controlled study on role of steroid therapy in TON by Entezari M et al.[10] The study was supportive for IONTS study, reporting no significant difference in final visual acuity and visual acuity gain between steroid group (16 patients) and placebo group (15 patients). In a case report by Mermut et al., high-dose (1000 mg/day) intravenous methyl prednisolone over 3 days was given to 2 patients with TON (aged 14 years and 15 years); followed by 1 mg/day oral prednisolone over 11 days; however, no improvement was detected in visual acuity after steroid therapy.[15]

The attitude towards steroid therapy in which efficacy could not be demonstrated clearly has changed by Medical Research Council-Corticosteroid Randomisation After Significant Head Injury (MRC-CRASH) study. In the study on10,008 patients with head injury recruited within first 8 hours, it was shown that all-cause mortality rate during

first two weeks was significantly higher in the patients who received methyl prednisolone for 48 hours when compared to placebo group16 In addition to increased mortality, severe morbidities such as acute pancreatitis, gastrointestinal bleeding, acute psychotic episode, hypertensive crisis, diabetic ketoacidosis, pneumonia, sepsis and wound site problems can be seen with high-dose (500-1999 mg/day) and mega-dose (5400 mg/day) steroid therapies.

Yazici et al. assessed efficacy of steroid therapy by giving mega-dose (2000-5000 mg/day) and high-dose (1000 mg/day) intravenous methyl prednisolone to 5 patients and 4 with TON, respectively. No steroid-related complication was developed in patients given steroid and authors reported successful outcome with high-dose steroid in TON; however, it was suggested that corticosteroid therapy could be ineffective in patients without light perception at time diagnosis or those with delayed diagnosis.[17] In a case report demonstrating efficacy of corticosteroid therapy in the treatment of TON, Soylev et al. reported an improvement in visual acuity in 5 of 11 cases after high-dose (1000 mg/day) intravenous methyl prednisolone for 3 days. Authors found favorable outcomes in cases given mega-dose (2000-5000 mg/day) intravenous methyl prednisolone, emphasizing the importance of early diagnosis and timely treatment for success of corticosteroid treatment.[18]

Role of surgical interventions in treatment of TON

In optic canal decompression (OCD) surgery, it is aimed to decompress optic nerve compressed within optic nerve and relieve optic nerve damage caused by bone fragments in optic canal fracture and prevent ischemia by restoring optic nerve circulation. Optic nerve sheath incision and Zinn annulus dissection performed as adjunct to optic canal decompression were reported in case of edema and hematoma.[19] Although OCD has long been used, there is no randomized, clinical trial emphasizing benefits of OCD. As similar to difference in the practices for steroid therapy, OCD is also performed by different approaches such as transcranial, transethmoidal, endonasal and sublabial based on surgeon's experience and timing for surgical intervention also show variation; in addition, steroid therapy given can mask efficacy of surgical treatment and spontaneous recovery rate of 40-60% in cases with indirect TON raises questions whether spontaneous recovery contributes to efficacy of surgical treatment.

In some case series, it was reported that steroid therapy has no benefit in cases with progressive loss of vision and that transcranial OCD should be performed, particularly in cases with prolonged latency and low amplitude on visual evoked potential tests, even in the absence of optic canal fracture on CT scan and time to surgery has no effect on treatment response.[20-21]

Leaving aside the case series including 400 patients by Fukado, which reported surgical decompression is highly beneficial,[22] the most important source is IONTS study in TON as similar to steroid therapy and showed that, at a follow-up of one month, visual acuity was poorer in surgery group when compared to untreated group or steroid group but the difference did not reach statistical significance.[14] Again, on month 1, there was no significant among 3 groups regarding visual acuity gain of ≥3 lines. The results were also valid for 3-months follow-up. Again, it was also reported that steroid therapy in addition to OCD has no advantageous compared to OCD alone.[23]

The OCD can be performed by neurosurgeons or ETN specialists but it is not fully harmless. In the IONTS study, cerebrospinal fluid leakage was developed in 10% of cases while meningitis in one case.[14] Given vulnerability of optic nerve and presence of internal carotid artery and ophthalmic artery traces within surgical field in cases undergoing sheath incision, the surgical procedure should have to be performed by experienced surgeons.

Role of neuroprotection and novel potential therapies in the treatment of TON

Neuroprotection, known as protection of neural tissue against oxidative stress products resulting from trauma and ischemia, is promising in the treatment of acute diseases such as stroke, head injury or spinal cord trauma and chronic disorders such as Alzheimer's disease and Parkinson disease. Although numerous molecules have been tested in laboratory and clinical trials, only riluzole and memantine were approved for amyotrophic lateral sclerosis and moderate-to-severe Alzheimer's disease by US Food and Drug Administration, respectively.[24] As a reflection of these trials, efficacy of neuroprotective agents have been investigated in neuro-ophthalmology, ,it was shown that alpha-2 receptor agonist brimonidine tartrate did not decrease risk for involvement of contralateral eye in Leber hereditary optic neuropathy and that there was no significant difference although visual acuity gain was greater than placebo in cases with non-arteritic anterior ischemic optic neuropathy (NAAION).[25-26] In TON, it was shown that target damage is ganglion cell complex (GCC) composed of ganglion cell layer and inner plexiform layer and that there is a thinning in outer nasal and inferior quadrants of GCC within 3 weeks before onset of changes in retinal nerve fiber layer on optical coherence tomography studies.[27] In TON, many molecules, mainly

steroids, have been investigated to protect GCC against ischemia, oxidative stress and cytokines. Erythropoietin (EPO), shown o be effective in the treatment of NAAION, is one of the molecules investigated in the treatment of TON.[29, 30] In animal models, EPO is being evaluated as a neuroprotective agent in stroke, mechanical trauma, exotoxic damage and neuro-inflammation. In a study by Entezari et al., 20,000 units of EPO was given to TON patients within first 2 weeks and a significant improvement was shown in visual acuity on months 1 and 3 when compared to baseline in 18 patients.[30] As similar to efficacy reported in the treatment of NAAION, the optimum dose, mode of administration, duration and drug concentration at optic nerve are unclear. It will be appropriate to wait results of ongoing multi-center, randomized clinical trial which compares EPO, steroid therapy and placebo.

CONCLUSION

Although pathogenesis of traumatic optic neuropathy is well-known and reproduced in animal models, its treatment remains to be one of the most controversial issues in the neuro-ophthalmological disorders. There is no class I evidence from multi-center, randomized, prospective, study showing effectiveness of steroids in which mechanism of action is best-known and OCD which is thought to be effective on pathogenesis. Given the higher rate of spontaneous recovery during natural course of disease, high mortality rates in patients with head injury who received mega-dose steroid therapy and complications of OCD which hasn't been proven to be effective, it is apparent that there is a need for randomize, prospective, double-blinded, placebo-controlled studies to establish definitive treatment. It will be most appropriate approach to avoid mega-dose steroid therapy in TON patients with severe head injury and to prefer high-dose regimens (50-1999 mg/day) with known anti-edematous, anti-inflammatory and anti-oxidant effects if needed given better understanding of adverse effects of high-dose regimen and to prefer surgical treatment together with referral to experienced centers in patients with progressive loss of vision and unresponsiveness to steroid therapy and to encourage use of safety belt and helmet based on principle of preventing disease with unknown treatment.

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