Anderson popularized corticosteroids for TON in 1982 based on reports that high doses of intravenous corticosteroids (intravenous methylprednisolone (IVMP) 15-30 mg/kg) improves microcirculation, energy metabolism, post-injury histology and functional outcomes in animal models of spinal cord injury.1-4

Finally there was something in the hands of ophthalmologists who could offer at least something to their patients. However, there are no prospective, randomized trials to attest to its benefit. There were numerous small case series/studies which recommended high dose steroids and their efficacy in better visual outcome. More than 75% of the patients in all these series have been treated with corticosteroids showing a trend towards this modality of treatment.

National Acute Spinal Cord Injury Study (NASCIS II) 1990

The National Acute Spinal Cord Injury Study (NASCIS II) was a step forward in this direction since it was intended to be a controlled study to assess the value of high-dose corticosteroids and optic canal decompression in patients with acute spinal cord injury. This study was a randomized, double-blind, placebo-controlled study where patients were randomly assigned to 1 of 3 treatment arms within 12 hours of injury: high-dose methylprednisolone, naloxone, or placebo. The term high dose corticosteroids referred to the treatment protocol 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. The study propelled widespread use of corticosteroids in TON.

NASCIS II studied intravenous methylprednisolone at 30 mg/kg bolus followed by twenty three hours of infusion at 5.4 mg/kg per hour, compared to naloxone bolus of 5.4 mg/kg with 4.0 mg/kg per hour for 23 hours, and placebo bolus with infusion. After six months, those treated with methylprednisolone within eight hours of spinal cord injury had significant improvement in motor and sensory function compared to placebo. After the eight-hour window, no difference has been demonstrated in neurologic outcome in those given naloxone or methylprednisolone, as compared to placebo. The three groups had similar mortality and major morbidity (delayed healing, gastrointestinal bleed, and wound infection) rates.

In NASCIS III, all patients received intravenous methylprednisolone bolus of 30 mg/kg. The treated patients were subsequently divided into three groups. Group 1 received methylprednisolone infusion at 5.4 mg/kg per hour for twenty four hours, Group 2 the same for forty eight hours, and Group 3 received tirilazad mesylate 2.5 mg/kg bolus infusion every six hours for forty eight hours. The methylprednisolone-treated patients for forty eight hours showed improved motor recovery over those treated with methylprednisolone for twenty four hours. The improvement was significant for those started on methylprednisolone between three and eight hours after spinal cord injury, but they also had more severe infections (sepsis and pneumonia) than the group treated for twenty four hours. Those treated with tirilazad for forty eight hours showed motor recovery equivalent to the patients treated with methylprednisolone for twenty four hours.

International Optic Nerve Trauma Study (IONTS)

The International Optic Nerve Trauma Study (IONTS) is the largest, prospective, multi-centre study of TON published to date (Levin 1999). It was intended to be an RCT but it had to be converted to an observational study after two years due to recruitment failure.

This was a non randomized interventional study which compared the visual outcome of TON treated with...
corticosteroids, treated with optic canal decompression surgery or observed without treatment. A total of 133 patients with initial presentation within 3 days were included in the study and were categorised into three groups: untreated (n = 9), steroids (n = 85), or optic canal decompression surgery (n = 33). The majority of the steroid group had either a megadose (40%) or very high dose regime (18%) and all the participants in the surgical group, except for one, also received steroids.

Follow-up data was available for 104 cases at one month and for 40 cases at six months. After adjustment for the baseline visual acuity, there were no significant differences between the three treatment groups. Visual acuity increased by more than 3 lines in 32% of the surgery group, 57% of the untreated group and 52% of the steroid group. So no clear benefit was found for either corticosteroid therapy or optic canal decompression surgery. There was no indication that either the dose or timing of steroid treatment was associated with an increased probability of visual recovery. The study concluded that neither corticosteroids nor optic canal surgery should be considered the standard of care for the patients with TON.

The point to be noted for 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 TON and the likelihood of spontaneous visual recovery. Also a striking feature is the delay in initiating treatment. Only 62% of the corticosteroid group had their treatment started within 24 hours and only 15% of the surgery group were operated on within 24 hrs.

**Corticosteroid Randomization for Acute Head Trauma (CRASH) trial**

The CRASH study was recently published and its findings are relevant to the present discussion on the role of steroids in TON. This was a multicenter, randomized, placebo controlled study where the effectiveness and safety of steroids was investigated in patients with acute traumatic brain injury who presented within 8 hours of injury. All the patients were randomized to receive either placebo or high dose of intravenous methylprednisolone (2 grams over one hour followed by 0.4 grams per hour for 48 hours). Goal was to recruit 20000 patients from tertiary care eye centers across the globe. The study was stopped at 10008 patients as an increased rate of death among patients with acute head trauma treated with high-dose corticosteroids was reported compared to placebo-treated patients. At six months follow up, the risk of death was higher in the steroid group than in the placebo group (25.7% versus 22.3%; RR 1.15, 95% CI 1.07 to 1.24; P = 0.0001), as was the risk of death or severe disability (38.1% versus 36.3%; RR 1.05, 95% CI 0.99 to 1.10; P = 0.079). There was no evidence that the effect of steroids differed by timing of injury or severity. This landmark trial concluded that steroids should no longer be routinely used in patients with traumatic brain injury.

One thing which has indeed come out of this study is that informed consent for steroids is taken where the patient is informed about the increased mortality issue. The findings of the CRASH study must therefore be seriously considered in the subgroup of TON patients who have co-existing head injuries. The underlying mechanism for the increased mortality in the group treated with steroids remains to be elucidated.

**Toxicity of high dose corticosteroids**

Recent animal studies also suggest that high-dose corticosteroids are toxic to the injured optic nerve. Experimental models of TON have been developed and the most widely used one involves a direct, mechanical crush injury to the rat’s optic nerve (Levkovitch-Verbin). Although one should be cautious when extrapolating evidence from animal studies, these have provided important insights into the pathophysiology of optic nerve injury and effects of steroids.

In two studies, rats treated with various regimes of methylprednisolone were compared with sham controls following an optic nerve crush injury. To mention the most quoted study of those two, Steinsapir et al (Steinsapir 2000), steroids led to more axonal loss than controls, and that there was a significant, dose-dependent decline in axon counts with increasing doses of steroids. However lower doses of steroids were not studied (only 30 to 120 mg/kg).

Some investigators now believe that steroids can exert a negative effect on neuronal survival by suppressing endogenous mechanisms for neuroprotection.

**References**


