

SYMPOSIUM ON THE TREATMENT OF TRAUMATIC OPTIC NEUROPATHY RESOLVED: CORTICOSTEROIDS SHOULD NOT BE USED

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The treatment of indirect traumatic optic neuropathy (TON) has been controversial, especially since the natural history of the condition has been difficult to elucidate. Early series were biased toward more severe cases with poor prognosis for spontaneous recovery, while more recent literature includes a higher percentage with milder injury and better prognosis. In recent years, Lessell¹ reported 5 of 25 untreated cases with substantial visual improvement, Seiff² 5 of 15, Cook et al³ 11 of 49, and the International Optic Nerve Trauma Study (IONTS)⁴ 57%; these data make attribution of visual improvement to a treatment modality more difficult. Moreover, the relative rarity of TON has relegated therapeutic reports to small case series, and the single major attempt at a randomized clinical trial of therapy (IONTS) was unsuccessful due to recruitment issues.

The mechanisms of injury in central nervous system (CNS), and by extension, optic nerve trauma include primary (1. mechanical disruption of tissue by shear or other force and 2. interruption of vascular supply), in which damage is immediate and probably irreversible; and secondary (1. vasospasm, 2. tissue swelling with compression within the optic canal, with axonal injury and further ischemia, and 3. subsequent cell death mechanisms, including free radical production and excitotoxicity), in which damage develops later and theoretically may be prevented or mitigated. Such secondary injury is the focus of this review.

The mechanisms of action for corticosteroids in traumatic CNS injury include 1. membrane stabilization (reduction of extracellular edema), 2. anti-inflammatory, and 3. antioxidant and other proposed neuroprotective mechanisms. At lower and at so-called "high-dose" levels (eg 500-2000 mg/day methylprednisolone), membrane stabilization and anti-inflammatory effects probably predominate, while at "mega-dose" levels (eg > 4200 mg/day methylprednisolone), neuroprotective effects may come into play.

The use of corticosteroids in TON has been based on reports of benefit in CNS trauma. However, the well-documented beneficial effect of corticosteroids in reduction of edema in CNS neoplasms has been less rigorously documented in CNS injury. The North American Spinal Cord Injury Study (NASCIS I) showed no substantial benefit from standard dose corticosteroids after spinal cord injury. However, the NASCIS II⁵ did demonstrate that megadoses (4200mg/day), if administered during the 1st 8 hours after injury, resulted in improved long term function when compared to controls. Based in large part on these data, several studies were undertaken to assess a possible benefit of high or megadoses for TON. Anderson et al⁶ reported 3 of 6 cases improved after dexamethasone doses up to 200 mg/day. Seiff² reported visual improvement in 13 of 21 patients treated with 80 mg dexamethasone/day. Mauriello et al⁷ reported 9 of 16 patients improved after 2000 mg methylprednisolone/day. Spoor et al⁸ reported improvement in 7 of 9 treated with 80 mg dexamethasone/day and in 12 of 13 patients after doses of up to 7200 mg/day methylprednisolone (megadoses). These reports were all small, nonrandomized studies with varying criteria for entry, time to treatment, dosage, and measurement of effect. While promising, the limitations in methodology excluded definitive conclusions regarding treatment effect.

The IONTS was developed to assess the benefit for visual outcome of corticosteroid treatment or optic canal decompression surgery versus observation. Although obstacles to recruitment precluded its completion as a randomized clinical trial as originally planned, the data obtained illuminated the lack of evidence for treatment effect of corticosteroids. In the 133 enrolled subjects, no significant differences were detected between the groups, with 57% of the untreated group showing increase in visual acuity by at least 3 Snellen lines versus 52% of those treated with corticosteroids. Treatment groups included 5 levels of therapy, ranging from "low dose" (<100mg methylprednisolone/day, 6% of patients), "moderate dose" (100-499 mg/day, 9% of patients), "high dose" (500-1999 mg/day, 19% of patients), "very high dose" (2000-5399 mg/day, 18% of patients), and "megadose" (\geq 5400 mg/day, 40% of patients); dosage was not a significant differentiating feature in visual recovery. The study concluded that although power was insufficient to allow comparisons between levels of treatment, that there was sufficient power for the overall treatment group (58% of which received > 2000 mg/day) to show that a beneficial effect was not demonstrated with corticosteroid therapy.

Moreover, the systemic risks of megadose corticosteroid therapy are well known, and include immunosuppression, psychosis, impaired glucose metabolism, and poor blood pressure control. Further, several reports of possible corticosteroid-induced CNS injury have surfaced. Steinsapir et al⁹ reported exacerbation of rat optic nerve axonal loss after crush injury with administration of high dose methylprednisolone vs control (saline).

Re-evaluation of the NASCIS II data suggested that administration after the 8 hour window could result in a worse prognosis. The CRASH (Corticosteroid Randomisation After Significant Head injury) study compared rate of death after head injury in >10,000 patients treated with megadose (11.6 gram/day) methylprednisolone vs controls¹⁰. Results indicated a significant increase in death risk at 2 weeks and in both death and disability risk at 6 months following injury. While the cause of the increased death rate was unproven, the lack of benefit in reducing mortality and morbidity was clear. These conclusions were supported by other studies in the Cochrane Review¹¹ of 2009.

In summary, recent studies have shown:

- a. That TON has a significant spontaneous improvement rate;
- b. That evidence for improvement following corticosteroid use is based on small series with nonstandardized methodology;
- c. That the largest and least methodologically limited study showed no benefit for the use of corticosteroids over observation; and
- d. High dose and megadose corticosteroids may be harmful in CNS injury, including TON.

We therefore cannot support the use of this treatment modality in TON.

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