Title: Should Patients with Optic Neuritis Be Treated with Steroids?

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Abstract

Purpose of review: Optic neuritis is the most common cause of optic neuropathy in young adults. High-dose intravenous corticosteroids (IVCS) were established as the standard of treatment for acute optic neuritis via the Optic Neuritis Treatment Trial (ONTT), with its first findings published more than 20 years ago. Subsequent studies have further clarified the role of corticosteroids in the treatment of acute optic neuritis.

Recent findings: Recent clinical research has confirmed existing knowledge of the efficacy and limitations of corticosteroids in the treatment of optic neuritis. Recent studies have examined the role of race, route of administration, and combination of IVCS with other therapies. Current evidence continues to support high-dose IVCS as the cornerstone of treatment of acute optic neuritis.

Summary: High-dose IVCS are effective in hastening visual recovery in acute typical optic neuritis, but do not affect the final visual outcome. In optic neuritis patients, IVCS may delay progression to clinically definite multiple sclerosis (CDMS) at 2 years, but not at 5 or 10 years. It is reasonable to recommend high-dose IVCS for acute optic neuritis patients with significant vision loss, severe pain, and/or white matter lesions on brain MRI in whom the potential for benefit outweighs the risks.

Keywords: Optic neuritis, steroids, corticosteroids, multiple sclerosis
Abbreviations

CDMS: clinically-definite multiple sclerosis; CRION: chronic relapsing inflammatory optic neuropathy; IV: intravenous; IVCS: intravenous corticosteroids; MR: magnetic resonance; MRI: magnetic resonance imaging, NMO: neuromyelitis optica; ONTT: optic neuritis treatment trial; PLEX: plasma exchange

Introduction

Optic neuritis is defined as dysfunction of the optic nerve related to inflammation. It is the most common cause of optic neuropathy among young adults and is the presenting sign of multiple sclerosis in approximately 20-25% of cases (1). The clinical hallmarks of typical optic neuritis include subacute, central vision loss in one eye that may progress over 1-2 weeks, accompanied by pain with eye movements in > 90% of cases, a relative afferent pupillary defect in unilateral cases, and impairment of color vision out of proportion to visual acuity. Optic neuritis is a clinical diagnosis, but magnetic resonance imaging (MRI) of the brain and orbits is useful, both in confirming the presence of optic nerve inflammation and in screening for radiographic evidence of multiple sclerosis (Figure 1). MRI has also proven to be the single best predictor of the future risk of multiple sclerosis in patients with optic neuritis (2).

Since the publication of the Optic Neuritis Treatment Trial (ONTT), a multicenter, prospective, randomized, placebo-controlled clinical trial in which intravenous corticosteroids (IVCS) and oral steroids were evaluated in patients with acute optic neuritis (3), IVCS have been routinely used in the treatment of acute optic neuritis. The
necessity of treatment of idiopathic demyelinating optic neuritis is debatable, as IVCS have been demonstrated to hasten visual recovery and potentially temporarily delay the onset of multiple sclerosis, but have failed to show an effect on long-term visual outcomes. The aim of this article is to review recent evidence and offer reasonable criteria to guide the use of IVCS in the treatment of acute optic neuritis.

Corticosteroids for Optic Neuritis

Glucocorticosteroids exert their immunosuppressant effects via a variety of cellular mechanisms relevant to optic neuritis, at both genomic and nongenomic levels, with effects on blood-brain barrier integrity, leukocyte chemotaxis, immunoglobulin production, macrophage activation, and cytokine production, among others (4,5). Corticotrophin and cortisone were used with some benefit in a variety of neurologic disorders, including optic neuritis, in an uncontrolled study published in 1952, without any definite conclusions regarding efficacy (6). Over the next several decades, others also evaluated steroids in the treatment of optic neuritis and suggested a possible benefit (7,8). In 1988, the results of a small trial of 12 patients with optic neuritis treated with high doses of intravenous methylprednisolone was published, all of whom showed improvement (9). These studies paved the way for the ONTT, which has arguably influenced the treatment of acute optic neuritis more than any other published clinical trial (3).

The Optic Neuritis Treatment Trial
The ONTT included 457 patients between the ages of 18 and 46 with visual symptoms lasting 8 days or less and history and examination findings consistent with optic neuritis. Each patient was randomized to one of three study arms: placebo, 250 mg of intravenous methylprednisolone every 6 hours for 3 days followed by oral prednisone at 1mg/kg for 11 days, or oral prednisone at 1mg/kg for 14 days. The treatment regimen in both the intravenous and oral corticosteroid groups included a four-day oral taper. Treatment with intravenous methylprednisolone was associated with a more rapid recovery of visual function. Methylprednisolone showed the most benefit within the first 15 days of followup, but by 6 months, the visual outcome of the intravenous methylprednisolone group was only slightly better than placebo (3). By one year, there was no difference in visual outcome in any of the groups (10). Unexpectedly, oral prednisone treatment was associated with an approximately two-fold higher rate of recurrent optic neuritis during 6 to 24 months of followup (27%) than either the intravenous methylprednisolone group (13%) or the placebo group (15%). At ten years, the rate of recurrence of optic neuritis was still higher in the oral prednisone group than in the IV methylprednisolone group, but was no longer significantly different from placebo (11). At two years, the rate of progression to clinically-definite multiple sclerosis (CDMS) was lower in the intravenous methylprednisolone group than either the placebo or oral steroid groups, although there was no difference in the rates of multiple sclerosis between groups at 5 years (12). During the trial, only two out of 151 patients in the IV methylprednisolone group experienced serious, but transient, side effects: one with acute pancreatitis, and the other with acute transient depression.
The results of the ONTT have been interpreted as showing that IVCS are well-tolerated and hasten visual recovery following acute optic neuritis, intermediate doses (1 mg/kg/day) of oral prednisone alone increase the risk of recurrence of optic neuritis, and intravenous steroids may delay the onset of CDMS within the first two years after optic neuritis.

A recent meta-analysis of high-dose IVCS in the treatment of optic neuritis reiterated the findings of the ONTT in that it found no effect of IVCS on visual outcomes at 6 months or one year (13).

Factors in the Response to Corticosteroid Treatment for Optic Neuritis

No studies have suggested that any specific subgroup of patients with typical acute optic neuritis is more likely to benefit from treatment with corticosteroids than another. A recent reanalysis of data from the ONTT with regard to self-reported black race/ethnicity showed black patients had worse vision at the onset of optic neuritis and recovered at a faster rate than white patients, but the final vision was still worse in black patients. No interaction between race/ethnicity and treatment modality was found for either intravenous or oral steroids. Therefore, it is very unlikely that black race/ethnicity plays any significant role in the efficacy of steroid treatment for acute optic neuritis (14).

Effect of Corticosteroids on the Risk of Optic Neuritis Recurrence
The finding of an increased risk of optic neuritis recurrence following treatment with intermediate doses of oral prednisone in the ONTT has been the subject of criticism due to the purported lack of a plausible biological explanation, a marginal p value for the finding, disagreement with the results of an earlier published study, and alteration of the a priori assumptions of the trial to reach this conclusion (15). Subsequent publications have addressed some of these criticisms. A retrospective, single-center study of risk factors for idiopathic optic neuritis recurrence in Chinese patients found a higher rate of recurrence in patients with unilateral optic neuritis (40%, vs 12% for bilateral optic neuritis) and those treated with intermediate-dose (equivalent of ≤ 100 mg oral prednisone/day) corticosteroids (42%, vs 25% for > 100 mg/day; p = 0.045) (16). The authors postulated that genomic effects of corticosteroids, mediated by alterations in gene transcription, are most prominent at doses ≤ 100 mg daily, while non-genomic effects predominate at doses > 100 mg daily, accounting for the difference in efficacy and optic neuritis recurrence risk between high-dose and intermediate-dose corticosteroids. It is a now commonly accepted standard of practice that intermediate-dose oral corticosteroids alone are not used in the treatment of typical acute optic neuritis.

High-dose Oral Corticosteroids

Although the ONTT showed no role for intermediate-dose (1 mg/kg daily) oral prednisone, there is limited data to support the use of high doses of oral prednisone in the treatment of optic neuritis (17). Sixty patients were included in a single-center,
randomized, placebo-controlled trial that evaluated oral methyprednisolone at a dose of 500 mg daily for three days, followed by a 10 day oral taper. There was a beneficial effect on vision at one and three weeks following the initiation of treatment, but not at 8 weeks, and there was no increased risk of demyelinating events in the treated group at one year (17). The potential for decreased costs and ease of administration associated with high-dose oral instead of intravenous corticosteroids has prompted interest in further research regarding the efficacy of high-dose oral corticosteroids for the treatment of optic neuritis. A clinical trial has been completed evaluating optic neuritis recovery following randomized treatment with equivalent doses of intravenous or oral corticosteroids, although the results have not yet been published (NCT01524250, clinicaltrials.gov). Based on currently available data, high-dose oral corticosteroids appear to be a reasonable consideration in the treatment of acute optic neuritis when IVCS are contraindicated or not available.

Timing of Corticosteroid Administration in Optic Neuritis

Determination of the optimal timing of corticosteroid treatment in optic neuritis has been elusive. The ONTT addressed the effect of intravenous and oral steroids within 8 days of symptom onset, and the effects of more acute or delayed treatment of optic neuritis with corticosteroids are not fully known. Treatment of optic neuritis with corticosteroids during the presumed hyperacute phase was evaluated in a prospective case series of patients with a history of optic neuritis and recurrence of pain in either eye (18). Eight patients were evaluated in the presumed hyperacute stage of optic neuritis, prior to the
onset of vision loss. Five of the eight patients underwent MR imaging, and all five demonstrated optic nerve enhancement. Treatment with high-dose intravenous steroids was given immediately, and no vision loss occurred in any of the patients, suggesting that corticosteroid treatment during the painful phase of presumed optic neuritis, before the onset of vision loss, may prevent vision loss.

Corticosteroids in the Treatment of Atypical Optic Neuritis

Atypical optic neuritis may be differentiated from typical optic neuritis by progressive unilateral or bilateral visual loss, poor visual recovery, lack of eye pain, hemorrhages or exudates on funduscopic examination, and relapse after steroid withdrawal (19). Atypical optic neuritis may be a manifestation of neuromyelitis optica (NMO), autoimmune optic neuropathy, chronic relapsing inflammatory optic neuropathy (CRION), neuroretinitis, or optic neuropathy associated with systemic diseases such as connective tissue diseases, vasculitides, or sarcoidosis. Although data from prospective randomized clinical treatment trials do not exist for corticosteroids for atypical optic neuritis, retrospective case series and expert opinion suggest that visual outcomes may be poor if left untreated (1), and high-dose IVCS are often the preferred treatment.

Optic neuritis associated with NMO is typically treated with high-dose IVCS, a practice adopted from the treatment of idiopathic optic neuritis, despite the lack of a clinical trial evaluating its efficacy specifically in NMO (20). The efficacy of high-dose IVCS (IVCS) was recently evaluated in comparison with plasma exchange (PLEX) plus IVCS in acute
NMO relapses (21). This nonrandomized retrospective study found disability scale scores were more likely to be at or below their baseline in the PLEX plus IVCS group than in the IVCS alone group at 6-18 months followup. Despite relapses of NMO being less responsive to high-dose corticosteroids than relapses of multiple sclerosis (21), high-dose IVCS are considered standard therapy in the treatment of NMO relapses.

Patients with autoimmune optic neuritis, which has included patients with laboratory evidence of a systemic collagen vascular disease, in one series responded very favorably and often dramatically to high-dose corticosteroids (22). In a retrospective case series of 15 patients considered to have CRION, which is considered to differ from typical optic neuritis by its steroid-dependent and relapsing course, all were described as having a “clear and prompt response to treatment with systemic corticosteroids” (23). High-dose intravenous or oral corticosteroids are considered as part of the treatment guidelines for recurrent neuroretinitis, which typically presents with optic disc edema followed by an exudative maculopathy (“macular star”) (24). Infectious causes of optic neuritis are rare, but may include syphilis, Lyme disease, tuberculosis, West Nile virus, and others (25). There are no clinical trial data on the effect of corticosteroids in infectious optic neuritis. High-dose corticosteroids are considered a first-line treatment for most forms of atypical optic neuritis.

Corticosteroids in Pediatric Optic Neuritis

Unlike in adult optic neuritis, pediatric optic neuritis most often presents with funduscopic abnormalities, including optic disc edema and retinal exudates. A greater
proportion of patients with severe and/or bilateral vision loss is also characteristic of pediatric optic neuritis (26,27). Children with optic neuritis tend to recover faster than adults and a higher percentage involve secondary causes than in adults (28). Despite the lack of prospective clinical data in children to support its use, high-dose intravenous methylprednisolone is considered first-line treatment for pediatric optic neuritis by extension from the ONTT, as affected children often present with impairment of visual acuity severe enough to justify its use. Following IVCS, a prolonged oral corticosteroid taper over 2-6 weeks is common, as some experts believe there is an increased rate of relapse with early cessation of corticosteroids (27,29,30). One recent small retrospective study of 26 consecutive pediatric patients with optic neuritis treated for 3 days with intravenous methylprednisolone compared those treated with an additional two weeks of oral corticosteroids to those treated for more than two additional weeks. Final visual acuity, side effects, and relapse rates did not differ between the two groups with a mean follow-up of 70 weeks. This study included potential for selection bias with longer courses of corticosteroids given to patients exhibiting poor recovery.

Future Research

Despite an abundance of useful data gathered from the ONTT and other clinical trials and case series, important questions remain regarding the use of corticosteroids in the treatment of optic neuritis, such as the optimal dose, timing, specific formulation, and route of administration (31,32) and whether there may be a subgroup of patients with
optic neuritis in whom high-dose corticosteroid treatment results in persistent, long-term clinical improvement.

A recently published review on the investigation of acute optic neuritis called for consensus in the investigation of patients with acute optic neuritis in the context of new imaging, laboratory and electrophysiological techniques (33). Organized implementation of new techniques in the evaluation of optic neuritis is likely to lead to meaningful new data, which could help answer lingering questions regarding the role of corticosteroids in the treatment of optic neuritis.

**Conclusion**

Two main benefits are often cited as rationale for treatment of acute typical optic neuritis with IVCS: hastening of visual recovery and a lower rate of progression to clinically-definite multiple sclerosis (CDMS) at 2 years, but not at 5 years (3,34). The potential for bias confounding interpretation of the data suggesting a lower rate of progression to CDMS in the short-term has been raised (15).

As with any treatment, the approach to whether or not to implement a specific therapy relies on an accurate understanding of the potential risks and benefits. The ONTT demonstrated relatively good tolerability of high-dose intravenous methylprednisolone, although patients should be informed of potential adverse effects, including sleep disturbances, mood changes, gastrointestinal upset, facial flushing, psychosis, and hyperglycemia (35).
After a discussion with the patient regarding potential risks and benefits, it is reasonable to recommend high-dose IVCS to patients with acute optic neuritis with bilateral or significant unilateral vision loss, severe pain, T2 hyperintensities on MRI that predict a higher short-term risk of development of CDMS, or features of atypical optic neuritis (Figure 2). High-dose corticosteroids may help prevent poor visual outcomes in atypical optic neuritis, but the excellent visual prognosis in typical optic neuritis coupled with the lack of definitive permanent benefits of high-dose IVCS make the treatment of typical optic neuritis optional, but helpful in selected cases characterized by significant vision loss, severe pain, and/or T2 white matter hyperintensities on brain MRI.

**Key Points**

- IVCS hasten the recovery of visual function in typical acute optic neuritis and may decrease the risk of development of CDMS at 2 years, but not at 5 or 10 years
- It is reasonable to offer high-dose IVCS in patients with typical acute optic neuritis with significant vision loss, severe pain, and/or T2 white matter hyperintensities on brain MRI
- No permanent beneficial effects of high-dose IVCS have been demonstrated in typical acute optic neuritis trials, emphasizing the role of IVCS as an optional, but potentially very helpful, treatment for typical acute optic neuritis
- Untreated atypical optic neuritis may lead to irreversible vision loss and urgent treatment with corticosteroids may help prevent poor visual outcomes
Intermediate-dose oral corticosteroids (1mg/kg/day prednisone equivalent) have no role in the treatment of typical acute optic neuritis

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Conflicts of interest

None
References and Recommended Reading

● of special interest

●● of outstanding interest

   ● A thorough review of typical and atypical optic neuritis.


   This study reanalyzed original data from the ONTT with regard to race/ethnicity and found that although black patients with optic neuritis present with worse vision, recover more quickly, and have a worse final visual outcome, black race/ethnicity does not appear to play a role in the response of optic neuritis to corticosteroids.


   Retrospective study suggesting an elevated risk of optic neuritis recurrence in Chinese patients treated with intermediate-dose oral corticosteroids, which are believed to act via genomic effects, as opposed to high-dose corticosteroids which act principally via nongenomic effects.


   Intravenous corticosteroids plus plasma exchange appear to outperform corticosteroids alone in the treatment of acute relapses of neuromyelitis optica.


● This small study suggests no difference in pediatric optic neuritis outcomes between patients treated with a two week oral steroid taper vs. a greater-than-two-week oral steroid taper after treatment with 3 days of high-dose intravenous corticosteroids.


●● This article highlights recent advancements in the evaluation of the structure and function of the visual pathways in optic neuritis patients and proposes
standard care and research protocols likely to help further standardize the future evaluation of optic neuritis.


Figure Legends

Figure 1. MRI findings associated with optic neuritis. A) T1 post-contrast fat suppressed axial images showing enhancement of the proximal intraorbital portion of the right optic nerve (arrows). B) T1 post-contrast fat suppressed coronal images showing enhancement of the intraorbital right optic nerve. C) T2 FLAIR axial brain sequence in the same patient showing areas of T2 hyperintensity in the periventricular cerebral white matter in a pattern consistent with the patient’s known multiple sclerosis. None of the lesions were enhancing on post-contrast images.

Figure 2. Weighing the potential risks and benefits of high-dose IV corticosteroid treatment of acute optic neuritis. High-dose corticosteroids are most likely to be helpful in patients with optic neuritis with significant vision loss, significant pain, acute symptom onset (< 8 days), T2 hyperintense white matter lesions on brain MRI, or features of atypical optic neuritis. The clinician must weigh the potential for benefit against possible adverse effects before making a treatment recommendation. Cost and availability of treatment may not directly impact the risk:benefit ratio, but may influence the advisability of treatment.