

Systemic corticosteroids in nonarteritic ischemic optic neuropathy

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Nonarteritic ischemic optic neuropathy (NAION) is one of the most prevalent optic nerve disorders seen in ophthalmic practice. The role of corticosteroid therapy in NAION remains a highly controversial area of debate in ophthalmology. This brief review will provide an overview of the current clinical evidence on this topic as well as some comment on the medical debate.

Key words: Controversies, steroid in nonarteritic ischemic optic neuropathy, systemic corticosteroid in nonarteritic ischemic optic neuropathy

Access this article online

Website:

www.ijo.in

DOI:

10.4103/0301-4738.146015

Quick Response Code:



Nonarteritic ischemic optic neuropathy (NAION) is the most common nonglaucomatous optic nerve disorder in patients above the age of 50.^[1,2] NAION presents most commonly with acute, painless, and unilateral variable visual acuity loss, a visual field defect (often inferior nasal or altitudinal scotomas), a relative afferent pupillary defect, and segmental or diffuse hyperemic disc edema on fundoscopic examination.^[2,3] The pathogenesis of NAION is thought by many authors to be multifactorial, occurring in the setting of transient hypoperfusion of the optic nerve head secondary to systemic disturbances (i.e., nocturnal hypotension, diabetes, hypertension, arteriosclerosis, vasospasm, or vasoactive medications) that reduce the autoregulatory capacity of the optic disc.^[3-5] A small cup to disc ratio seen in a majority of patients with NAION is thought to render the optic disc further susceptible to fluctuations in local perfusion pressure and “disc crowding,” in which ischemic swelling of axons leads to compression of capillaries in a restricted optic disc space.^[5,6] With crowding of the optic disk, a “vicious cycle” may occur in which compression of the surrounding capillaries induce further ischemia that ultimately results in ischemia of the optic nerve head.

The concept of systemic corticosteroids as a viable treatment option for NAION began in the 1960s and 1970s when several anecdotal case series demonstrated improved visual outcomes in patients with NAION on steroid therapy.^[7,8] The efficacy of

steroid therapy has been attributed to decreased compression of capillaries in the optic nerve head by decreasing edema and increasing blood flow to the optic nerve head, thereby improving the function of the surviving but nonfunctioning optic nerve axons.^[3] Several recent anecdotal case reports have suggested therapeutic benefits with intravitreal steroid injections in NAION, but the data are so sparse that a conclusion cannot be made on this route of steroid administration, which may in fact be harmful.^[9-11] In addition, to date, there exist no studies on the applicability of intravenous and peribulbar steroid administration in NAION. Thus, we have purposefully chosen to focus on the use of oral corticosteroids in NAION in this manuscript.

The Evidence

Some of the earliest evidence of improved visual outcomes in patients with NAION on oral systemic steroids comes from case series published in the 1960s and 1970s. Foulds showed improvement in visual acuity in 11 of 13 (85%) patients treated with high dose corticosteroid therapy (60 mg prednisone) compared to 5 of 13 (45%) patients who remained untreated.^[7] Hayreh further reported improvement in visual acuity in 6 of 8 (75%) patients treated with 40–80 mg of oral prednisone therapy when compared to 1 of 6 (17%) untreated patients.^[8] These initial studies, however, were criticized for a lack of randomization, inadequate controls, and small sample sizes, rendering it difficult to draw substantive conclusions. In addition, similar studies had shown no benefit with corticosteroid therapy in patients with NAION.^[12]

In 2008, Hayreh and Zimmerman published a large “prospective patient choice” study that included 613 consecutive patients ($n = 696$ eyes) seen at the University of Iowa Hospitals and Clinics from 1973 to 2000.^[13] Of the study cohort, 312 patients ($n = 364$ eyes) opted for systemic corticosteroid therapy and 301 patients ($n = 332$ eyes) chose no treatment for NAION. Patients who opted for treatment were initially given 80 mg of prednisone daily for 2 weeks, followed by a taper every 5 days to 70 mg, 60 mg, and then

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Manuscript received: 28.06.14; **Revision accepted:** 27.08.14

decreasing the dose by 5 mg every 5 days to 40 mg until the optic disk edema was no longer present. Prednisone was rapidly tapered off completely following resolution of disk edema. At 6 months from the onset of the NAION, 69.8% of eyes with an initial visual acuity of 20/70 or worse and seen within 2 weeks of onset in the treated group had visual acuity improvement (95% confidence interval (CI): 57.3%, 79.9%). This was in contrast to the control group of untreated patients who had a 40.5% (95% CI: 29.2%, 52.9%) incidence of visual improvement. The odds ratio of improvement with treatment was 3.39 (95% CI: 1.62, 7.11; $P=0.001$). Likewise, for visual field improvement at 6 months from onset of NAION, in the treated group for those seen within 2 weeks of onset with moderate to severe initial visual field defect, there was improvement in 40.1% (95% CI: 33.1%, 47.5%) compared with 24.5% (95% CI: 17.7%, 32.9%) in the untreated group. The odds ratio for visual field improvement with treatment was 2.06 (95% CI: 1.24, 3.40; $P=0.005$). Hayreh and Zimmerman concluded that NAION treatment during the acute phase with systemic corticosteroids resulted in a significant improvement in visual acuity ($P=0.001$) and visual fields ($P=0.005$).^[13]

Although this study represents the most comprehensive study to date on the role of systemic corticosteroids in NAION, several criticisms have been directed at the lack of true randomization and masking in the study design.^[14-18] Although there was no statistically significant difference in patient characteristics, some critics of this study have emphasized the potential for problems in the allocation to the untreated and treated groups due to the lack of true randomization in this patient choice study and that these differences could produce potentially unrecognized selection bias.^[16-18] In response to these criticisms, Hayreh stated that his study met all crucial criteria for “conventional” randomization, including similar sample sizes between treatment and control groups (51% voluntarily opted for systemic steroid therapy and 49% opted for no treatment) and there was no statistically significant initial differences between the two groups in terms of visual acuity, visual fields, and systemic diseases apart from hypertension.^[3,19-21] Furthermore, significant differences between the two groups (age and hypertension) were believed to be accounted for in the statistical analysis by including them as covariates in the logistic regression model, with no apparent statistical impact on visual outcome (age, $P=0.8$; hypertension, $P=0.6$).

In contrast, Rebolleda *et al.* reported a different nonrandomized case series of 10 patients with NAION treated with 80 mg of prednisone and 27 untreated patients with NAION that demonstrated no statistical differences between the two groups in terms of visual outcome.^[16] While the authors acknowledge statistical limitations in their study (including much smaller samples sizes than those used in Hayreh and Zimmerman’s study), Rebolleda *et al.* reported steroid-related complications in 3 of 10 (30%) patients treated with corticosteroids, namely steroid-induced depression, hyperglycemia, ocular hypertension, and pulmonary embolism. The authors emphasized that corticosteroids are not benign pharmacological agents and that steroid therapy must be administered in consideration of the risk-benefit ratio and side-effect profile in any patient.^[16,17] In a subsequent correspondence, Hayreh criticized this study for being too small to yield a meaningful conclusion and suggested that the results were misleading with regards to the actual

prevalence of systemic steroid-related complications seen in general ophthalmic practice.^[21]

The Debate

A recent survey by Atkins *et al.* that included 350 neuro-ophthalmologists, 340 general ophthalmologists, 322 neurologists, and 583 optometrists showed that approximately 10% of those surveyed offered steroid therapy to patients with NAION and interestingly that approximately 19% of neurologists surveyed administered high-dose intravenous steroids in patients with NAION.^[22] A discussion by Lee and Biousse highlights several key points on both sides of the corticosteroid debate.^[15] Lee argued that patients should learn about Hayreh and Zimmerman’s 2008 findings, the differences between a patient choice study and a prospective randomized clinical trial, and be aware of the controversy surrounding the study’s conclusions. In the age of the internet, Lee argued that it was better that patients receive an informed opinion from their physician on the “pros and cons” of corticosteroid therapy in NAION rather than learn about potential therapies on their own accord. At the same time, however, he recommended steering patients away from corticosteroid therapy if they did not meet the original Hayreh and Zimmerman study criteria of visual acuity <20/70, presented >2 weeks after onset, or had significant contraindications to corticosteroid use (i.e., brittle diabetes, hypertension, peptic ulcer disease). Despite the risks of treatment some diabetic and hypertensive patients with NAION may still be amenable to steroid therapy if managed in coordination with a primary care physician.^[21] Given the controversy surrounding the role of corticosteroid therapy in NAION, many clinicians believe that any final decision should be made by the patient and that the role of the physician is to provide the patient with the knowledge necessary to make an informed risk-benefit decision.

In the same article, Biousse offered a counter argument that there is no level 1 evidence (i.e., prospective, randomized, double-masked, controlled clinical trial with high statistical power, and sufficient sample size) for the use of corticosteroids in NAION.^[15] Biousse also pointed out that a number of questions have arisen regarding the pathogenesis of NAION as solely ischemic in etiology and thus, whether or not NAION is steroid-responsive. In this context, she argued that without a clear biologic rationale for treatment, the risks of corticosteroid therapy outweigh any potential benefit. In contrast to the arguments of Lee, Biousse believed that it is the role of the physician to decide what treatments should or should not be offered to patients, especially given the fact that most patients lack any medical education or training.

Concluding Remarks

The controversy regarding steroid usage in NAION is far from settled, with strong opinions on both sides. Until there is a large prospective randomized controlled study on this subject, the debate on corticosteroid therapy remains, at least in part, a philosophical one, with ethical, fiduciary, legal, and social considerations in addition to scientific, statistical, and medical ones. Indeed, it is most apparent in controversies such as this one the competing roles of shared decision-making and professional paternalism in a healthcare environment with the continual evolution of the physician-patient relationship. Although there remains no clear answer in this controversy, we believe that the work of Hayreh and others supporting

steroids in NAION should be considered in consultation with the patient and their providers. In the absence of definitive prospective randomized, double-masked, controlled clinical trial we believe that it remains the duty of the physician to act as both caretaker and educator to fulfill his/her professional duties in a conscionable and ethical manner for patients with NAION.

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Cite this article as: Al-Zubidi N, Zhang J, Spitze A, Lee AG. Systemic corticosteroids in nonarteritic ischemic optic neuropathy. *Indian J Ophthalmol* 2014;62:1022-4.

Source of Support: This work was supported in part by an unrestricted grant from Research to Prevent Blindness (RPB) to the University of Texas Medical Branch, Galveston, Texas, USA, **Conflict of Interest:** None declared.