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Should steroids be offered to patients with nonarteritic anterior ischemic optic neuropathy (NAION)?

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Abstract

The treatment of nonarteritic anterior optic neuropathy remains very limited and disappointing. Recent publications have suggested that oral steroids as well as intravitreal injections of steroids might be helpful to accelerate resolution of disc edema and improve visual outcome. However, the use of steroids to treat acute NAION remains largely debated.

Keywords

Nonarteritic anterior optic neuropathy; steroids; intravitreal injections; treatment

Steroids should be offered to patients with nonarteritic anterior ischemic optic neuropathy (NAION). Andrew G. Lee, MD

Opening statement

It remains an inconvenient truth that to date there is no proven effective therapy for nonarteritic anterior ischemic optic neuropathy (NAION). This situation is frustrating to both the patient and the clinician. Although we can make recommendations to these patients for improving general health and for treating their vasculopathic risk factors (e.g., blood sugar, cholesterol, blood pressure, diet, exercise, tobacco cessation, sleep apnea treatment) the lack of an effective therapy for NAION remains a major issue for neuro-ophthalmologists. A number of older and more recent reports have suggested that steroids might be useful in NAION (1-3). Indeed, many physicians are currently offering steroids to patients as a treatment option for NAION.

To begin, although there have been a number of scattered case reports on the use of intravitreal steroids in NAION (4-6) the data for intravitreal steroids is even weaker than for systemic steroids and I currently do not offer this option to patients. The data on intravitreal

^{*}Both authors have contributed equally to this manuscript.

steroids are at best anecdotal and at worst potentially dangerous or misleading. I therefore shall confine the remainder of my discussion to my current practice and the issue of systemic corticosteroids and NAION.

Sohan S. Hayreh MD, an acknowledged expert in the field, has devoted a great deal of time and effort in his career to the study of NAION. In a recent publication (3) Hayreh and Zimmerman investigated systematically the possible therapeutic role of systemic corticosteroid therapy in NAION. Although it is obvious that a randomized controlled clinical trial is the best means to answer the question of efficacy for systemic or intravitreal steroids in NAION, prior attempts by Dr. Hayreh and others have not been successful in obtaining funding or performing a Grade 1 prospective study. The Hayreh and Zimmerman study was a patient choice study that included 613 consecutive patients (n = 696 eyes) seen at the University of Iowa Hospitals and Clinics from 1973 to 2000. Of the study cohort, 312 patients (n = 364 eyes) voluntarily opted for systemic corticosteroid therapy and 301 patients (n = 332 eyes) chose no treatment for NAION. At the initial visit all study patients underwent detailed ophthalmic and medical histories and a comprehensive ophthalmic evaluation by Dr. Hayreh. Snellen visual acuity, and Goldmann perimetry were performed on all patients and improvement in visual function was the primary outcome measure. The treatment group received oral prednisone 80 mg daily for two weeks followed by a tapering dose (70 mg for 5 days, 60 mg for 5 days, and 5 mg reductions thereafter every 5 days). The median follow-up was 3.8 years. 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%) visual improvement. The odds ratio of improvement 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 was 2.06 (95% CI: 1.24, 3.40; p = 0.005). Drs. Hayreh and Zimmerman concluded that NAION “treated during the acute phase with systemic corticosteroids resulted in a significantly higher probability of improvement in visual acuity (p = 0.001) and visual field (p = 0.005) than in the untreated group.”

I believe that this is evidence that cannot be completely ignored and that patients deserve the opportunity to hear about the results of this study in an objective manner from a trusted source. In my own practice I explain to patients the results of the Hayreh and Zimmerman study and the controversial components. We review the difference between a patient choice methodology (such as Dr. Hayreh's work) and a randomized, prospective, placebo controlled clinical trial. I believe that the Hayreh and Zimmerman study is useful for hypothesis generating but I acknowledge that for “hypothesis testing” a randomized clinical trial is necessary. One of the worst things that can happen to a patient with an untreatable disease like NAION is for the physician to say “Nothing can be done”. Admittedly, I am in a “data free zone” for some of my current practices, but much of medicine remains outside the realm of Grade 1 evidence. In addition, I acknowledge that corticosteroids have significant systemic side effects and they are most certainly not benign, especially in elderly or vasculopathic patients for whom steroids might worsen hypertension or diabetes, the suspected risk factors for NAION.

I tend to steer patients away from steroids if they have minimal or mild visual loss from their NAION, severe or brittle diabetes or hypertension, active infections, or significant ulcer disease history. On the other hand, for patients with 20/70 or worse visual acuity whom I see within 2 weeks of onset of NAION and who do not have significant risks for steroid related

side effects, I do offer them the opportunity to choose or decline steroid treatment. Inevitably patients who are told that “nothing can be done” will find the long list of purported therapies for NAION including the steroid literature. I would much prefer them to ask me questions and receive an informed opinion rather than getting all of their information from the Web. I do not tend to offer steroids to patients with 20/70 or better vision, who have risks for steroid use, or who are greater than 2 weeks since onset. Ironically, however, in the past I have also offered steroids to patients with optic disc edema from NAION in whom no visual loss has occurred (i.e., “incipient NAION”) as I believe the rationale for steroid-induced reduction of disc edema and any potential “compartment syndrome” mechanism, steroid neuroprotective effects, and membrane stabilization effects might have greater validity prior to visual loss. I also give stronger consideration to steroids for monocular patients or the uncommon patient with bilateral simultaneous or sequential, but proven, NAION.

Additionally, the steroid controversy is interesting to me because although we call it ischemic optic neuropathy, unlike giant cell arteritis related arteritic ischemic optic neuropathy, the entity of NAION may not be solely ischemic in mechanism (7-11). Inflammatory, mechanical, and venous etiologies have all been postulated and the potentially beneficial effects of corticosteroids cannot be dismissed on the grounds of lack of efficacy in other ischemic disorders like cerebrovascular stroke. In summary, I believe that until a randomized clinical trial is performed, the decision for steroids in NAION should be an individual one that is made by the patient and not the doctor. In my opinion, the role of the physician in this setting is to reduce risk factors for future events, to give hope for the future, to provide information for an informed decision, and to act as a trusted source for risk-benefit decision making in a controversial area.

Steroids should not be used to treat nonarteritic anterior ischemic optic neuropathy. Valérie Biousse, MD

Opening statement

Although numerous practitioners recommend steroids to treat acute nonarteritic anterior ischemic optic neuropathy (NAION) [1], this practice is not based on any level I evidence and is potentially dangerous [2]. Not being able to offer a treatment to patients with potentially blinding disorders is very difficult and frustrating, and it takes much longer to make a NAION patient understand why “no treatment” is a reasonable option than to write a prescription for steroids. This might explain why approximately 10% of physicians reported treating NAION with oral steroids and 19% of neurologists chose high-dose intravenous steroids in a recent survey [2]. Since this survey was conducted, a large case-series proposing oral steroids for acute NAION was published [3], followed by a few case reports suggesting that intravitreal injections of steroids might also be used to treat acute NAION [4-6]. These reports leave room for debate as to whether patients with acute NAION should receive steroids or not.

Because the pathophysiology of NAION remains elusive, it is difficult to propose informed hypotheses regarding acute treatment of NAION [1,7]. Small vessel circulatory insufficiency of the optic nerve head is the most widely accepted pathophysiology of NAION, but the mechanism of ischemia remains uncertain [7-11]. The optic nerve head is supplied by an anastomotic arterial circle (derived from the short posterior ciliary arteries) with distinct upper and lower halves, consistent with the altitudinal defects often seen in NAION [12]. Fluorescein angiography studies provide the most compelling indirect evidence that circulatory insufficiency in the paraoptic branches of the short posterior ciliary arteries is the primary cause of NAION; however, no adequate systematic histopathologic

studies of these vessels have been performed, and it is not known whether there is associated atherosclerotic change or thrombosis [8]. Levin and Danesh-Meyer [11] even recently proposed that NAION may primarily be a venous disease; however, this theory remains speculative.

A number of good studies in the neurologic literature have shown that steroids do not improve the outcome of patients with acute arterial or venous cerebral ischemia [13,14]. Indeed, it has even been suggested that steroids can be detrimental to patients with acute cerebral ischemia and should not be prescribed [13,14]. The same concerns may apply to NAION, which is a presumed vascular disorder, most often occurring in older patients who have vascular risk factors [15-17].

Initially widely used in acute cerebral injuries to reduce cerebral edema, steroids are currently limited to treating cerebral edema associated with brain tumors and bacterial meningitis. Over the past decade, studies have shown that the efficacy of steroids in acute spinal cord injury is limited and that steroids should not be prescribed to patients with acute traumatic brain injury or traumatic optic neuropathies [18]. Although steroids are commonly used in numerous ocular disorders, including selected ocular vascular disorders, it is important to emphasize that the main purpose of the steroids in various ocular vascular disorders is to reduce retinal edema, a major cause of visual loss in diabetic retinopathy and retinal vein occlusion [19]. Although a recent study utilizing optical coherence tomography (OCT) demonstrated that 8 of 76 patients with NAION examined within 4 weeks of visual loss had subfoveal fluid, likely responsible for some of the reversible visual loss [20], the primary cause of irreversible visual loss in NAION is direct damage to the optic nerve [7]. Administration of steroids to reduce macular edema does not seem necessary in most cases of NAION.

Patients with a small cup to disc ratio are predisposed to NAION and are said to have a “disc at risk” [21-23]. It has been suggested that swelling within the confines of a tight disc may produce a “compartment syndrome” [23]. The crowded axons swell in the restricted space, and capillaries and other small vessels among the nerve fibers are compressed, resulting in cytotoxic and vasogenic edema that worsens infarction and tissue loss. A number of medical and surgical interventions have been proposed to shorten the duration of disc edema, presumably to stop this vicious circle and treat the compartment syndrome [1,7]. Optic disc edema is by definition present in NAION and characteristically persists a few weeks [7,23]. A recent study showed that the median time (25–75th percentile) to spontaneous resolution of optic disc edema from onset of visual loss was 7.9 (5.8–11.4) weeks [23]. Resolution time was longer in diabetics than in non-diabetics ($p=0.003$), and multi-factor analysis showed that worse initial visual field defects ($p<0.0001$) and acuity ($p=0.04$) were associated with faster resolution [23]. There is, however, no evidence that decreasing the duration of disc edema improves visual outcome.

Interestingly, the rationale for the use of steroids in NAION comes from a study from the late 1960's that postulated that steroids would decrease capillary permeability, thereby inducing faster resolution of disc edema [24]. This, in turn, would reduce compression of capillaries in the optic nerve head and improve blood flow, restoring the function of surviving, but non-functioning, ischemic axons. In that study [24], improvement in visual acuity occurred in 11 of 13 (85%) patients treated with systemic steroids (60 mg prednisone daily), compared to 5 of 11 patients (45%) not treated. In 1974, Hayreh [25] reported improvement in visual acuity in 75% of 8 treated NAION eyes, compared to 17% of 6 untreated eyes. Neither study was randomized, and it is difficult to draw conclusions from so few subjects. There have been no studies using high dose intravenous steroids in NAION and no randomized, controlled studies investigating the role of oral or intravitreal

corticosteroid therapy [1]. The current controversy was triggered by a recent report by Hayreh and Zimmerman [3] supporting the use of oral steroids to treat acute NAION and a few anecdotal reports of NAION patients treated with intravitreal injections of triamcinolone [4-6,26,28].

The recent large Hayreh and Zimmerman study [3] suggested that oral prednisone might improve the visual acuity and visual acuity of patients with NAION. In this nonrandomized study, patients self-selected their treatment and the examiner was not blinded to treatment. Despite the large number of patients, these two major causes of bias severely limit the validity of the study. In those patients treated with steroid therapy within 2 weeks, the median time to optic disc edema resolution was 6.8 weeks, compared to 8.2 weeks in untreated cases ($p<0.0001$). However, the untreated group had more vascular risk factors (especially diabetes), making it impossible to objectively interpret the results. Indeed, the earlier resolution of disc edema seen in the treated group is particularly subject to selection bias, since diabetics were much less likely to be treated, and the authors' own data have previously demonstrated that disc edema persists longer in diabetics [23].

The rationale for intravitreal steroids is presumably the same as for systemic steroids. The advantages of local over systemic administration of steroids are obvious and include a potential greater effect on the retina (and optic nerve head) and reduced systemic complications. To date, 3 reports [4-6] have included 9 eyes with NAION treated with 4 mg of intravitreal triamcinolone acetonide (similar to what is routinely used in macular edema [19]) within 4 to 22 days of onset. The first report included 4 NAION patients with severe visual loss (20/200 or worse) within 22 days of onset [4]. The visual outcome was compared to 6 consecutive patients with NAION who received no treatment. All patients completed at least 9 months of follow-up. In the treated group, the mean improvement in visual acuity was 6.2 Snellen lines at the final visit. Optic disc swelling markedly decreased by the first post injection week and had disappeared by 3 weeks in all eyes. In the non-treated group, the mean improvement in visual acuity was 1.3 lines at the final visit, and optic disc swelling resolved between 4 to 12 weeks. The authors concluded that intravitreal triamcinolone acetonide 4 mg provided better recovery of visual acuity and more rapid resolution of optic disc swelling, but no visual field improvement was seen in this small sample. This report was criticized by Hayreh [26] who emphasized that changes in fixation strategy may explain why the visual acuity improved, while the visual fields did not. He also emphasized that although intravitreal triamcinolone has the advantage of fewer systemic side effects, it may result in persistent increased intraocular pressure that may worsen optic nerve damage. Since this first report, 5 other reported NAION patients (4 from Turkey [5] and 1 from Korea [6]) have received intravitreal triamcinolone acetonide 4 mg, 4 to 10 days after visual loss. All patients experienced some visual improvement and the authors suggested that triamcinolone improved disc edema [5,6]. However, a previous report from Germany [27] described 3 patients treated with a much higher dose (20 mg) of intravitreal triamcinolone within 1 week of visual loss. One eye developed triamcinolone-induced ocular hypertension and visual acuity did not improve in these patients.

NAION remains frustrating for clinicians and often devastating for patients. The pathophysiology remains unclear, and it is uncertain whether any treatment will be effective for NAION [1]. The role of steroids remains controversial, and although steroids (particularly intravitreal steroids) might accelerate resolution of disc edema, there is currently no evidence that a shorter duration of disc edema is associated with improved visual outcome [28]; additionally, the benefits of steroids on possible associated macular edema are probably very limited clinically. Results of recent studies need to be interpreted carefully and controversy should be seen as stimulus to expand our research on the

pathophysiology and treatment of NAION rather than proof that steroids are an effective treatment for acute NAION [28].

I do not currently recommend the use of steroids (intravenous, oral, or intravitreal) to treat acute NAION, and I limit their use to those rare cases with presumed arteritic AION. I also believe that even oral steroids are potentially dangerous in this population with vascular risk factors. Should steroids be shown to be an effective and safe treatment for acute NAION, then intravitreal administration might be the route of choice, as in numerous other ocular diseases. I would prefer to see improvement in NAION animal models, allowing for better evaluation of potential effects of steroids and other future therapies, before even considering a multicenter clinical trial.

Rebuttal: Andrew Lee, MD

Dr. Biousse nicely outlines the con side of the controversy. I have no problem with the facts that she elucidated, namely that there is no grade 1 evidence (i.e., randomized controlled clinical trial) for the use of steroids in NAION. The “absence of proof of efficacy” however is not the same as “proof of the absence of efficacy”. I readily acknowledge that there is a “junk yard” in medicine littered with treatments touted as effective anecdotally for multiple conditions which are only later found to be ineffective or even harmful. Nevertheless many treatments which have been proven to be effective in a large randomized clinical trial had their humble start in anecdotal case reports, case series, or observational cohorts.

The idea that reduction of macular edema might be one mechanism for the improvement in NAION after steroids is intriguing and macular high resolution OCT might show that subretinal fluid is a more common cause of visual loss in NAION than we think. After all to paraphrase Goethe, “we only look for what we know and we only find that which we look for.” Finally, and perhaps most compelling I do not believe that it is the role of the physician to decide what treatments should or should not be offered to or withheld from the patient. Today's patients are more informed, are more technology savvy, and are more engaged in their care than in generations past. My patients in Houston want to know about all the available treatments including the proven, the unproven, and yes, the controversial. I believe that it is my role to inform, to advise, and in some cases to recommend one or more options but I don't think it is my role to decide what they should do. The litmus test in my opinion is “What would you do if it was your eye?”

Rebuttal: Valérie Biousse, MD

Dr Lee acknowledges being in a “data free zone” when treating patients with NAION. The history of medicine is filled with examples of treatments administered to thousands of patients without strong evidence, that later turned out not only to be ineffective, but also harmful. Optic nerve sheath decompression for NAION [29], corticosteroids for traumatic optic neuropathy and traumatic brain injury [18], oral steroids for acute optic neuritis [30], systematic anticoagulation for cerebral ischemia [13], and indiscriminatory carotid endarterectomy [13] are only a handful of these examples. I never tell a patient that there is nothing to do and I carefully weigh treatment options; however I do not prescribe a treatment based on a patient's request. Indeed, one of the roles of physicians is to decide what treatments should or should not be offered to patients, most of whom do not have the experience or training to make such decisions. It is because we as physicians have such an enormous responsibility, that we need to be as rigorous as possible in our recommendations. Modern medicine is about evidence, which remains weak in NAION.

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