Steroids in the treatment of nonarteritic anterior ischemic optic neuropathy
A PRISMA-compliant meta-analysis

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Abstract
Background: Non-arteritic anterior ischemic optic neuropathy (NAION) is the common cause of acute and subacute optic neuropathy in adults over the age of 50. Steroid administration in NAION seems to be in practice and is advised frequently by neurologists. The controversy regarding steroid usage in NAION is far from settled, with strong opinions on both sides. Despite a large amount of articles on this topic, but the results have not always been consistent. To address this gap, we decided to conduct a meta-analysis of all available published studies in order to better understand the effectiveness of steroids in treating NAION.

Objectives: To identify the effectiveness of steroids in treating NAION.

Methods: We performed a meta-analysis using databases, including PUBMED EMBASE, and the Cochrane library, to find relevant studies. The weighted mean difference (WMD) was determined for BCVA in steroid and nonsteroid groups.

Results: Eight studies were included and summarized in this analysis. The studies included 720 eyes (392 NAION eyes and 328 eyes of normal controls). Heterogeneity among these studies was low ($I^2$=0%). Because of the presence of heterogeneity, we conducted a fixed effects model to assess the effect of steroids on visual acuity in patients with NAION. The meta-analysis clearly demonstrated that in NAION, steroids did not significantly improve visual acuity (WMD = 0.02 [95% CI: −0.10 to 0.06], $Z=0.40$, $P=0.69$). After sensitivity analysis via the leave-one-out method, WMD was not significantly changed.

Conclusions: Our meta-analysis found that steroids do not significantly improve visual acuity in NAION. In view of their long list of side effects, attempts at reversing ischemia should not involve the use of steroids.

Abbreviations: BCVA = best-corrected visual acuity, CI = confidence interval, IONDTR = Ischemic Optic Neuropathy Decompression Trial, NAION = non-arteritic anterior ischemic optic neuropathy, NOS = Newcastle-Ottawa Scale, RCTs = randomized clinical trials, SD = standard deviations, WMD = weighted mean difference.

Keywords: meta-analysis, nonarteritic anterior ischemic optic neuropathy, steroids

1. Introduction
Nonarteritic anterior ischemic optic neuropathy (NAION) is a common cause of acute and subacute optic neuropathy in adults over the age of 50 years old, and often results in severe visual loss.[1] It is thought to result from ischemic damage to the anterior optic nerve, which is predominantly supplied by the posterior ciliary arteries.[2] It is estimated that 2 to 10 persons per 100,000 people have NAION (~1500–6000 new cases per year in the United States).[3,4] The mechanisms involved in the development of optic disc ischemia in NAION are uncertain. Pathogenetically, the development of NAION is caused by hypoperfusion of the optic nerve head circulation, as well as transient occlusion of the capillaries of the posterior ciliary arteries, leading to ischemia of the optic nerve head.[5] There is no established treatment for NAION.[4] Numerous agents and procedures have been suggested for the treatment of NAION treatment, but most have not produced encouraging results.[4]

The earliest evidence of the beneficial effects of steroid treatment for NAION came from case series published in the late 1960s.[6] Experimental evidence obtained in a rodent model also showed that steroids exert neuroprotective effects on retinal ganglion cell survival in NAION.[5,7] A study published in 2007 provided strong support for the beneficial effects of steroids in NAION. A large, noncontrolled, retrospective study by Hayreh included 613 patients (696 eyes) treated with oral steroids over a period of 27 years.[8] Despite the heavy weighting and influence of the early Hayreh study, little other evidence, outside anecdotal evidence, has demonstrated that steroids provide any benefit in NAION. Outcomes of smaller trials have suggested that subtle benefits, at most, are achieved, but they also often demonstrate severe side effects. Indeed, steroids are selected by many
physicians as a treatment option for NAION. A survey by Atkins et al showed that steroid administration is often applied in NAION and even frequently advised by neurologists.\textsuperscript{[5]} Recently, two randomized clinical trials (RCTs) were performed to investigate the effect of steroids on the course of NAION. Interestingly, the results showed that steroid use did not result in better final visual outcomes and potentially had harmful effects.\textsuperscript{[3,9]} The controversy regarding steroid usage in NAION is far from settled, and there are strong opinions on both sides. Despite a large number of articles on this topic, to the best of our current knowledge, no published meta-analysis has focused on the effects of steroids in the treatment of NAION. To address this gap, we conducted a meta-analysis of all available published studies to improve understanding of the effectiveness of steroids in treating NAION.

2. Methods

2.1. Search strategy

We conducted a literature search using three databases (PUBMED, EMBASE, and Cochrane library) to identify records potentially relevant for this analysis, using the following search terms: (steroid OR corticosteroid) AND (ischemic optic neuropathy). A manual search was performed by checking the reference lists of the identified original reports and reviewing the relevant articles to identify studies not initially included in the computerized databases. The final search was carried out on April 4, 2019. The language was limited to English. Since all the data of this meta-analysis were collected from published literature and no patient consent were need, the ethical approval and written consent were not necessary in this study.

2.2. Inclusion criteria

The following inclusion criteria were applied in this meta-analysis: independent retrospective or prospective study that assessed the use of a corticosteroid to treat NAION that (1) assessed best-corrected visual acuity (BCVA) in patients with NAION, and (2) had sufficient data available to estimate WMD with 95% CI.

2.3. Exclusion criteria

If the study met the following selection criteria, it was excluded: abstracts from conferences, full text without raw data available for retrieval, duplicate publications, letters, and review articles. Studies published in a language different from English were excluded.

2.4. Data extraction

Two investigators independently extracted the data. Disagreement was resolved by discussion. For each study, we extracted information on the authors of each study, the year of report, the study design, the patient population, the number of eyes, the medication(s) given, their dosage and treatment duration, and BCVA. When studies reported data for several time intervals, we selected the one with the longest follow-up period for analysis. BCVA was measured in logMAR units. ETDRS letter scores were converted to logMAR units according to the formula logMAR = 1.7–0.02 × letter score.\textsuperscript{[10]} Snellen visual acuities were converted to logMAR units according to the methods described by Holladay et al.\textsuperscript{[11]} If ranges were provided instead of standard deviations (SD), the corresponding SD was calculated according to the method described by Hozo et al.\textsuperscript{[12]}

2.5. Qualitative assessment

The quality of nonrandomized studies was evaluated using the Newcastle–Ottawa Scale (NOS) in this meta-analysis.\textsuperscript{[13]} In this method, a study is judged on three categories: selection (four items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each). A nine-point scale of the NOS (range, 0–9 points) has been developed for the evaluation of results.\textsuperscript{[14]} In the NOS, poor, medium, and good quality are scored as 0–3, 4–6, and 7–9, respectively. Studies with NOS scores above 4 points were included in the final analysis. To analyze the quality of the RCTs, the Jadad scale was applied.\textsuperscript{[15]}

2.6. Statistical analysis

All statistical analyses were performed in Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark) using extracted values for the mean, SD, and sample size. The weighted mean difference (WMD) was determined for BCVA in the steroid group and nonsteroid group, and the outcome was reported with a 95% CI. \( P < .05 \) was considered statistically significant in the test for an overall effect. Heterogeneity was explored using the \( Q \)-test to calculate the \( I^2 \) statistic. In cases of low statistical heterogeneity (\( I^2 < 30\% \)), the fixed effects model was applied to the data. Given the low number (<10) of studies included in our meta-analysis, we chose not to test for publication bias to avoid the possibility of drawing a misleading conclusion.\textsuperscript{[16]} Sensitivity analysis was performed via the leave-one-out method.\textsuperscript{[17]}

3. Results

The study selection protocol used in this meta-analysis is shown in Figure 1. A total of 1444 articles were initially identified, and eight of these studies were included in this analysis; the studies are summarized in Tables 1 and 2.\textsuperscript{[3,5,8,9,18–21]} All patients received treatment within 14 days (or median <14 d) of onset. In the Hayreh published study, we extracted only the data on patients treated within 14 days for whom visual acuity was available at 6 months from the initial visit.\textsuperscript{[8,22]} Two of the studies tested triamcinolone, two tested prednisolone, one tested prednisone, one tested methylprednisolone combined with prednisone, and two tested methylprednisolone combined with prednisolone.

According to the NOS used for quality assessment, three nonrandomized studies had moderate quality scores of 5 or 6, while three nonrandomized studies had high quality scores of 7. When the quality of the RCTs was assessed according to the Jadad scale, the scores were 5 and 7, respectively. Overall, the risk of bias in the included studies was low, and all eight studies were deemed acceptable in the analysis (Table 1).

The trials in this meta-analysis examined 720 patient eyes with NAION (Figure 2). Heterogeneity among these studies was low (\( I^2 = 0\% \)). Because of the presence of heterogeneity, we conducted a fixed effects model to assess the effect of steroids on visual acuity in patients with NAION. This comparison clearly demonstrated that steroids in NAION did not significantly improve visual acuity (WMD = -0.02 [95% CI: -0.10 to 0.06], \( Z = 0.40, P = .69 \)). After a sensitivity analysis performed via the
Records identified through database searching (n=1444)
Pubmed:362
Embase:1057
Cochrane library:25

Additional records identified through other sources (n=0)

Records after duplicates removed (n=1209)

Records screened (n=1209)

Records excluded (n=1180)

Full-text articles assessed for eligibility (n=29)

Full-text articles excluded, with reasons (n=21)
- not RCT or CCT (n=14)
- not English (n=6)
- Date inefficiency (n=1)

Studies included in qualitative synthesis (n=8)

Studies included in quantitative synthesis (meta-analysis) (n=8)

Figure 1. Flow diagram describing the identification and selection of relevant studies for the present meta-analysis.

Table 1
 Characteristics of the studies included in this meta-analysis.

| Study          | Study design                  | NAION duration | Medication   | Treatment pattern                                      | Follow-up (months) | Score |
|----------------|-------------------------------|----------------|--------------|---------------------------------------------------------|--------------------|-------|
| Kaderli 2007   | Retrospective comparative study | <14 d          | Triamcinolone| Intravitreal injection of 4 mg/0.1 mL                    | >8                 | 6*    |
| Hayreh 2008    | Retrospective comparative study | <14 d          | Prednisone   | 80 mg daily for 2 weeks, then tapered to 70 mg for 5 days, decreased by 5 mg every 5 days until stopping | 6                  | 6*    |
| Rebolloeda 2013| Retrospective comparative study | <14 d          | Prednisolone | 80 mg daily for 2 weeks, then tapered to 70 mg for 5 days, decreased by 5 mg every 5 days until stopping | 6                  | 7*    |
| Kinori 2014    | Retrospective comparative study | <14 d          | Methylprednisolone | 1 g/day for 3 days, followed by oral prednisone (1 mg/kg) for 11 days | 6          | 7*    |
| Radoi 2014     | Retrospective comparative study | Median (<14 d) | Prednisolone | Intravitreal injection of 4 mg/0.1 mL                   | 6                  | 6*    |
| Pakravan 2016  | Prospective, randomized clinical trial | <14 d          | Methylprednisolone | 1 g/day for 3 days, followed by oral prednisone (1 mg/kg) for 10 days | 6                  | 5†    |
| Pakravan 2017  | Prospective, non-randomized comparative study | <14 d          | Methylprednisolone | 1 g/day for 3 days, followed by oral prednisone (1 mg/kg) for 10 days | 6                  | 7*    |
| Saxena 2018    | Prospective, randomized, double-blind placebo clinical trial | Median (<14 d) | Prednisolone | 80 mg daily for 2 weeks, then tapered to 70 mg for 5 days, decreased by 5 mg every 5 days until stopping | 6                  | 7†    |

* Quality of studies assessed by Newcastle-Ottawa Scale (NOS).
† Quality of studies assessed by Jadad.
leave-one-out method, we found that the WMD was not significantly changed.

4. Discussion

In this meta-analysis, we summarized findings presented in the clinical literature on the effects of steroid administration on NAION patients. The results revealed that there was no significant change in BCVA after steroid administration. The rationale for the use of steroids in NAION is based on a study published in the late 1960s in which several anecdotal case series demonstrated improved visual outcomes in patients with NAION treated with steroid therapy.[6] Theoretically, the effect of steroid therapy could be attributed to decreased compression of capillaries in the optic nerve head as a result of decreased edema and increased blood flow to the optic nerve head.[23] Based on these results, steroids are selected as a treatment option for NAION by many physicians, although conflicting results regarding its benefit have been reported over the past 2 to 3 decades.[8,24]

However, this meta-analysis demonstrates that steroids do not significantly improve visual acuity in NAION. If they act on optic disc edema, steroids should decrease the compression of capillaries in the optic nerve head.[23] Hence, the administration of steroids should result in effects similar to those achieved by optic nerve decompression surgery, which may be beneficial for optic disc edema. Regrettably, the Ischemic Optic Neuropathy Decompression Trial (IONDT), which was a randomized, single-blind, multicenter trial for NAION sponsored by the National Eye Institute, showed that surgical intervention provided no benefit.[25]

A number of questions have arisen regarding the pathogenesis of NAION with regards for whether it is solely ischemic in etiology, in which case, NAION should be steroid-responsive.[26] Furthermore, a study showed that the median time (25–75th percentile) to spontaneous resolution of optic disc edema from the onset of visual loss was 7.9 (5.8–11.4) weeks.[27] Although steroids might accelerate the resolution of optic disc edema, there is no evidence of a link between a shorter duration of optic disc edema and visual outcomes.[26,28] Moreover, a randomized double-blind clinical trial also showed that the use of steroids in acute NAION did not significantly improve visual acuity, although it did significantly improve the resolution of optic disc edema.[9]

Nonetheless, several limitations of this meta-analysis should be acknowledged. In the past, a large number of scattered case reports have been published on the use of steroids in NAION. This practice is not founded on any level I evidence and is

![Figure 2. Forest plot demonstrating comparison of steroids versus nonsteroid in NAION on visual acuity. CI = confidence interval, IV = inverse variance, SD = standard deviation.](image-url)
The meta-analysis showed that steroids did not significantly improve visual acuity in NAION. In view of the long list of steroid side effects, steroids should not be used to reverse ischemia.

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