Ophthalmol Ina 2024;Vol. 50(1):71-80

LITERATURE REVIEW

ANATOMICAL AND FUNCTIONAL OUTCOME IN THE MANAGEMENT OF NON-ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY

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ABSTRACT

Introduction: *Non-arteritic anterior Ischemic optic neuropathy refers to condition in which damage to the anterior optic nerve is presumed to be secondary to ischemia of the anterior part of the optic nerve. This condition is irreversible, and the visual prognosis is generally guarded. To date, there is no definitive high-grade evidence for an effective treatment of NAION. The purpose of this literature review is to assess the results of currently published literatures regarding the management of non-arteritic anterior ischemic optic neuropathy, taking anatomical and functional outcomes into consideration.*

Methods: *A comprehensive literature search was conducted using online databases (PubMed, EBSCO, Clinical Key, and Google Scholar) using relevant search terms. Included studies were selected based on predefined inclusion criteria.*

Results: *Systemic and locally-administered corticosteroid indicated various responses, as well as anti-VEGF, however suggesting no positive effects. Rho-kinase as a vasodilator improved visual acuity in a small study. Erythropoietin and cytidine diphosphocoline (citicoline) suggested visual acuity improvement, while only citicoline improved visual field improvement and prevent further RNFL thinning, in non-randomized controlled studies.*

Conclusion: *No high-quality evidence of intervention has been shown to enhance both anatomical and functional outcome. Many studies were also insufficient to conclude. Further studies are needed, including neuroprotective and novel vasodilator agents.*

Keywords*: non-arteritic anterior ischemic optic neuropathy, visual acuity, visual field, retinal nerve fiber layer thickness, electrophysiology*

INTRODUCTION

Ischemic optic neuropathy refers to a group of condition in which damage to the optic nerve is presumed to be secondary to ischemia of the anterior part of the optic nerve. Anterior ischemic optic neuropathy will further be classified into non-arteritic (NAION), or arteritic (AAION). NAION is the second most common optic neuropathy after glaucoma, caused by short posterior ciliary arteries impairment that supply the anterior portion of the optic nerve head. It is most commonly occurred in older age, more than 50 years old. Annual incidence of NAION varied from 2,3 to 10,2 cases per 100.000.[1–3] NAION is an irreversible, painless, and acute vascular failure of the optic nerve. It is characterized by sudden loss of visual acuity and visual

field. The visual prognosis is generally guarded. Prevention of compartment syndrome to reduce secondary damage to axons, protection of retinal ganglion cells from death (anti-apoptosis), and even the use of regenerative medicine, such as stem cell therapy, are all potential strategies for the future treatment of NAION. No conclusive results have been obtained despite the availability of literature on NAION as well as numerous therapies that have been proposed and tested for non-arteritic anterior ischemic optic neuropathy over the years. Despite the widespread belief that damage to the optic nerve is irreversible, we would like to investigate current management strategies as well as relevant literature published in recent years to elucidate the most plausible management strategies for this condition.

METHODS

Literature search was conducted from online databases, including PubMed, EBSCO, Clinical Key, and Google Scholar. We utilized various combinations and search strategies that are related to our clinical question, that is "non-arteritic anterior ischemic optic neuropathy". We expanded the searching strategies using [Mesh] terms. The searching strategy was limited to articles written in English or Indonesian; and also involving only human subject. The inclusion criteria were studies that reported at least one of this outcome: visual acuity, parameters obtained with optical coherence tomography (OCT), visual field-related parameter, or electrophysiology parameter. Information extracted from every study including author(s), study year, number of subjects, intervention, duration of the follow-up, and outcome(s) of the study.

Treatments are classified into three groups: group A - treatment that is intended to alleviate the optic nerve edema; group B - treatment that is intended to act upon blood vessel, that is anti-thrombotic or vasodilator; and group C - treatment that is intended to limit neuronal or axonal injury, or to offer neuroprotective effects.

Initially, 41 studies were found using the search strategy. Twenty two studies met our inclusion criteria, which then further included in this study. Study characteristics and results were summarized in the following tables, classified by their respective outcomes (visual acuity, visual field, retinal nerve fiber layer thickness, and electrophysiology).

Ophthalmol Ina 2024;Vol. 50(1):71-80

Table 1. Visual acuity outcome

Study	Treatment modalities	Maximum follow-up duration	BCVA difference and its clinical significance
Treatment Modality A			
Chen et al[6] (2019)	Steroid vs control (Triamcinolone, prednisolone, methylprednisolone), either intravitreally, intravenously, or orally administered	Range: 6 months - >9 months	Mean difference BCVA: -0.02 [-0.10 - 0.06] – not statistically significant I^2 = 0% Z = 0.40
Rebolleda et al[7] (2013)	80 mg prednisolone PO vs control	6 months	Not significant (p = 0,28)
Yaman et al[8] (2008)	4 mg triamcinolone acetonide intravitreal	3 months	No statistical test possible
Kinori et al[9] (2014)	1 g methylprednisolone intravenous vs control	Treatment: 22.7±23.4 months Control: 36.2±24.2 months	Treatment p = 0.80 Control p = 0.10 Treatment vs Control: 0.30
Hayreh et al[10] (2008)	80 mg prednisone PO initially vs control	3.8 years	At 6 mo: Treatment: improved in 69.8% (57.3-79.9) Control: improved in 40.5% (29.2-52.9) OR = 3.39 (1.62 - 7.11), p=0.001
Saxena et al[3] (2018)	80 mg prednisolone PO vs placebo	6 months	Treatment: p = 0.003 Control: p = 0.01 Treatment vs Control: 0.78
Radoi et al[4] (2013)	4 mg triamcinolone actenoide intravitreal vs control	6 months	%improvement of VA >1 line Treatment: 71%; Control: 13% p = <0,005 %improvement of VA >3 lines Treatment: 29%; Control: 7% p = 0.08
Alten et al[11] (2014)	Intravitreal dexamethasone implant (Ozurdex®)	3 months	Snellen VA Chart 3 eyes: Baseline: 20/100; 20/100; and 20/50 – at 3 months: 20/80; 20/400; 20/60 ,respectively
Rootman et al[5] (2013)	1,25 mg bevacizumab intravitreal vs control	6 months	Not significant (p = 0.33)
Bennett et al[12] (2007)	1.25 mg bevacizumab intravitreal	10 days	Improved, but no statistical test possible
Treatment Modality B			
Sanjari et al[13] (2016)	0.025 mg rho-kinase (Fasudil) intravitreal	3 months	Significant (p = 0.004)
Prokosch et al[14] (2014)	1 mg/kg BW fluocortolone PO + 300 mg pentoxyphillin intravenous vs pentoxyphillin intravenous	6 months	After 3 days: p<0,002 After 6 months: p<0,001)
Steigerwalt et al[15] (2008)	40 mg 6-methylprednisolone +80 μg PGE_1 **vs** 100 mg aspirin PO + 25 mg prednisone PO	2 months	Significant (p = 0.001)
Treatment Modality C			

Nikkhah et al[16] (2020)	(A) 2 x 10.000 IU erythropoietin intravenous, (B) 75 mg prednisolone PO, or (C) placebo	6 months	p (A vs B vs C) = 0.597
Pakravan et al[17] (2017)	(A) 1 g methylprednisolone intravenous + 10.000 IU rhEPO intravenous; (B)) 1 g methylprednisolone intravenous; (C) control	6 months	p = 0.802
Modarres et al[18] (2010)	2000 IU erythropoietin (Eprex®) intravitreal	6 months	p < 0.001
Parisi et al[19] (2019)	500 mg citicoline PO (NAION)^{NC} vs control (NAION)^{NN} vs control (healthy)^{C}	9 months	p = 0.0031
Lyttle et al[20] (2016)	3x (25 mg carbidopa + 100 mg levodopa) PO vs control	6 months	p < 0.005
Johnson et al[21] (2000)	3x (25 mg carbidopa + 100 mg levodopa) PO vs control	6 months	p = 0.012
Wilhelm et al[22] (2006)	Topical 0,2% brimonidine tartrate (Alphagan®) vs control	3 months	p = 0.54
Fazzone et al[23] (2003)	Topical 0,2% brimonidine	3 months	p = 0.49
Aghdam et al[24] (2021)	300 µg granulocyte-colony stimulating factor (G-CSF) intravitreal	12 months	p = 0.278

Table 2. Visual field outcome

Study	Treatment modalities	Maximum follow-up duration	Visual field difference and its statistical significance
Treatment Modality A			
Rebolleda et al[7] (2013)	80 mg prednisolone PO vs control	6 months	ΔMD: p = 0.213 ΔPSD: p = 0.07
Yaman et al[8] (2008)	4 mg triamcinolone acetonide intravitreal	3 months	No difference, but no statistical test possible
Kinori et al[9] (2014)	1 g methylprednisolone intravenous vs control	Treatment: 22.7±23.4 months Control: 36.2±24.2 months	Quadrant analysis Treatment: p = 0.10 Control: p = 0.50 MD analysis Treatment: p = 0.20 Control: p = 0.90
Hayreh et al[10] (2008)	80 mg prednisone PO initially vs control	3.8 years	Treatment: improved in 40.1% (33.1-47.5) Control: improved in 24.5% (17.7-32.9) OR = 2.06 (1.24 - 3.40), p=0.005
Radoi et al[4] (2013)	4 mg triamcinolone actenoide intravitreal vs control	6 months	MD, p<0.003
Alten et al[11] (2014)	Intravitreal dexamethasone implant (Ozurdex®)	3 months	MD, p = 0.40
Rootman et al[5] (2013)	1,25 mg bevacizumab intravitreal vs control	6 months	No statistical test possible

Bennett et al[12] (2007)	1.25 mg bevacizumab intravitreal	10 days	No statistical test possible
Treatment Modality B			
Sanjari et al[13] (2016)	0.025 mg rho-kinase (Fasudil) intravitreal	3 months	MD, p = 0.005
Prokosch et al[14] (2014)	1 mg/kg BW fluocortolone PO + 300 mg pentoxyphillin intravenous vs pentoxyphillin intravenous	6 months	MD, p=0.297
Treatment Modality C			
Nikkhah et al[16] (2020)	(A) 2 x 10.000 IU erythropoietin intravenous, (B) 75 mg prednisolone PO, or (C) placebo	6 months	(A) p = 0.001 (B) p = 0.01 (C) p = 0.04 p (A vs B vs C) = 0.699
Pakravan et al[17] (2017)	(A) 1 g methylprednisolone intravenous + 10.000 IU rhEPO intravenous; (B)) 1 g methylprednisolone intravenous; (C) control	6 months	(A) p = 0.033 (B) p = 0.037 (C) p = 0.207 p (A vs B vs C) = 0.825
Modarres et al[18] (2010)	2000 IU erythropoietin (Eprex®) intravitreal	6 months	MD, p = 0.60
Parisi et al[19] (2019)	500 mg citicoline PO $(NAION)^{NC}$ vs control $(NAION)^{NN}$ vs control $(healthy)^{C}$	9 months	NC vs NN p < 0.005
Lyttle et al[20] (2016)	3x (25 mg carbidopa + 100 mg levodopa) PO vs control	6 months	MD, p = 0.23
Johnson et al[21] (2000)	3x (25 mg carbidopa + 100 mg levodopa) PO vs control	6 months	MD, p = 0.83
Wilhelm et al[22] (2006)	Topical 0,2% brimonidine tartrate (Alphagan®) vs control	3 months	MD, p = 0.23
Aghdam et al[24] (2021)	300 µg granulocyte-colony stimulating factor (G-CSF) intravitreal	12 months	MD p > 0.05 PSD p > 0.05

Table 3. Retinal nerve fiber layer thickness outcome

Study	**Treatment modalities**	**Maximum follow- up duration**	**ΔRNFLt and its statistical significance**
Treatment Modality A			
Rebolleda et al[7] (2013)	80 mg prednisolone PO vs control	6 mo	Δp (overall) = 0.394
Saxena et al[3] (2018)	80 mg prednisolon PO vs control	6 mo	p(S) = 0.63, p(N)= 0.53, p(I)= 0.77. p(T) = 0.71
Radoi et al[4] (2013)	4 mg triamcinolone actenoide intravitreal vs control	6 mo	p(S) = 0.0017, p(N)=0.1, p(I)=0.067 p(T)=-0.36
Rootman et al[5] (2013)	1,25 mg bevacizumab intravitreal vs control	6 mo	p = 0.33
Treatment Modality B			
Sanjari et al[13] (2016)	0.025 mg rho-kinase (Fasudil) intravitreal	3 months	p = 0.003

Treatment Modality C			
Nikkhah et al[16] (2020)	(A) 2 x 10.000 IU erythropoietin intravenous, (B) 75 mg prednisolone PO, or (C) placebo	6 months	p(A,B,C) = 0.041
Pakravan et al[17] (2017)	(A) 1 g methylprednisolone intravenous + 10.000 IU rhEPO intravenous; (B)) 1 g methylprednisolone intravenous; (C) control	6 months	p(A,B,C) = 0.147
Parisi et al[19] (2019)	500 mg citicoline PO (NAION)^{NC} vs control (NAION)^{NN} vs control (healthy)^{C}	9 months	NC vs NN p=0.164 p=0.044 p=0.054 p=0.040 p=0.864
Lyttle et al[20] (2016)	3x (25 mg carbidopa + 100 mg levodopa) PO vs control	6 months	p = 0.75
Aghdam et al[24] (2021)	300 µg granulocyte-colony stimulating factor (G-CSF) intravitreal	12 months	Pre-Post p<0.001

Table 4. Electrophysiology outcome

There were three studies, i.e Saxena et al[3], Alten et al[25], and Parisi et al[1924] reporting electrophysiology study results in their respective original articles.

Study	Treatment modalities	Electrophysiology parameter	Electrophysiology outcome and its statistical significance
Saxena et al[3] (2018)	80 mg prednisolone PO vs placebo (Treatment Modality A)	VEP amplitude (µV)	p = 0.02
		VEP latency (msec)	p = 0.04
Alten et al[11] (2014)	Intravitreal dexamethasone implant (Ozurdex®) (Treatment Modality A)	VEP amplitude (1°) at 3 mo	Reduction during entire observation up to 6 months of three patients included
		VEP amplitude (15') at 3 mo	Reduction during entire observation up to 6 months of three patients included
Parisi et al[19] (2013)	500 mg citicoline PO (NAION)^{NC} vs control (NAION)^{NN} vs control (healthy)^{C} (Treatment Modality C)	60' pERG P50-N95 amplitude (□V) 60' VEP P100 implicit time (msec) 60' VEP N75-P100 amplitude (□V) 15' pERG P50-N9 amplitude (□V) 15' VEP P100 implicit time (msec) 15' VEP N75-P100 amplitude (□V)	NC vs NN p < 0.005

DISCUSSION

There has been no evidence-based study on medical or surgical procedures that is effective enough to overcome NAION. The main prevention is to manage the risk factor such as hypertension, dyslipidaemia, diabetes mellitus, or hypercoagulable state. Sleep apnea has

also been identified as a potential risk factor for NAION. The underlying mechanism is believed to involve intermittent hypoxia and subsequent reoxygenation, which can lead to vascular endothelial dysfunction and increased susceptibility to ischemic events, including NAION. In general, if the patient is in the acute phase (edema of optic nerve head), methylprednisolone administration may be considered, but if the patient is already on chronic phase (atrophy disc) which generally occurs 6-11 weeks after the onset, then steroids are no longer indicated.[26] Kernstock27 et al explained that in patient with NAION, functional deficits were present directly after onset, and mainly did not change relevantly further on.

The highest quality evidence included in this study is a meta-analysis by Chen et al6 using steroid with various route of administration, which reported visual acuity as their only outcome. However, it turns out to be not statistically significant, with range of follow up between 6 to 9 months in the individual studies included in that meta-analysis. There were two other studies evaluating systemic corticosteroid, but administered per orally. A large retrospective study by Hayreh et al[10] offered 613 consecutive patients the option of treatment with 80 mg of oral prednisone for 2 weeks followed by a tapering dose until resolution of the optic disc edema. They concluded that in long term follow-up, visual acuity is markedly improved pcompared with control group, with the odds of visual acuity improvement is nearly twice as much as in control group. However, this study should be interpreted with caution since it was non-randomized and also the untreated group had more vascular risk factors, including diabetes, indicating a possible bias from unmeasured health factors related to self-selection for treatment. Steroids are thought to exert anti-inflammatory effects, which may theoretically alleviate optic nerve swelling and inflammation associated with NAION. However, the use of steroids in NAION is controversial due to concerns about potential adverse effects such as exacerbation of systemic conditions like diabetes and hypertension, as well as the lack of robust clinical trials demonstrating significant long-term benefits. The study conducted by Rebolleda et al[7] did not find improvements in visual acuity or mean deviation of visual field, despite noting a significant improvement in pattern standard deviation, in the group that received orally administered steroids. Additionally, there was no observed change in retinal nerve fiber layer (RNFL) thickness. Prospective controlled trials assessing intravitreal bevacizumab, intravitreal bevacizumab combined with triamcinolone, and sub-tenon methylprednisolone also failed to demonstrate any statistical differences between the treatment and control groups at final follow-up. Rootman et al[5] failed to demonstrate improvement in functional outcome as well as anatomical outcome using intravitreal bevacizuamb.

Several therapies have been evaluated to address the presumed vasodynamic factors that contribute to the development of NAION. These include administration of Prostaglandin E2[15], pentoxifylline[14] and intravitreal injection of a rho-kinase inhibitor[13] Sanjari et al[13] published a study involving 13 eyes, that were intravitreally injected, concluding that Rho-kinase significantly improved visual acuity and visual field pre and post- treatment. Sugiyama[28] reported that intravenous Fasudil improved the impairment of a rabbit optic nerve head blood flow, through a nitric oxide synthase inhibitor, while having no effect on normal rabbit ONH blood flow.[28] Prokosch et al[14] study included pentoxiphylline, a non-selective phospodiesterase inhibitor which hypothetically not only a vasodilator, but also improving red blood cell deformability[29]. However, the study did not compare pentoxiphylline to non- pentoxiphylline arm, instead adding fluocortolone (corticosteroid) compared to only pentoxiphylline group.

Neuroprotection is a fast-expanding field, with various clinical trials for neurological and ophthalmological diseases currently underway. Modarres et al[18], 31 patients with NAION received unilateral intravitreal erythropoietin injection (2000 units) within one month of onset of NAION. Visual acuity improvement occurred in 61 percent of patients within the first month. Vision continued to improve up to three months and then deteriorated. Citidine diphosphocoline (CDP-choline 5'-diphosphocholine or Citicoline) is being considered as a promising therapeutic option for NAION. A pilot study published by Parisi et al[30] suggested both neuroenhancer effect and neural conduction improvement, with statistically significant alleviation in visual acuity and visual field, with various effects on retinal nerve fibre layer thickness. G-CSF is a new neuroprotective agent evaluated in a prospective interventional case series by Aghdam et al[24]. In this study, 14 eyes of 14 patients with NAION received intravitreal injection of G-CSF within two weeks of the onset. While the drug was found to be safe, the beneficial effect only lasted a month.

Exploration of innovative treatment modalities, such as QPI-1007 (a modified small interfering RNA) and oral endothelin-1 receptor antagonists, which are registered for ongoing clinical treatment, has been undertaken. However, as of now, no results from these investigations have been published.

CONCLUSION

Most previously published reports on treatment for NAION are limited by retrospective designs, non-standardized methods of data collection or measurement, relatively small sample sizes, and variable (usually relatively short) lengths of follow-up. no intervention has been shown to enhance visual results in a randomized, controlled trial. Many studies were also

insufficient to conclude. While neuroprotection is a fast-expanding field, with various clinical trials for neurological and ophthalmological diseases currently underway, there are various agents that are promising, but currently not backed up with reasonably high-quality evidence. Novel vasodilating agents should also be considered in the future research.

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