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Review on Diagnosing and Managing Ischemic Optic Neuropathy

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Abstract **Original Research Article**

***Background*:** Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) is the second leading cause of permanent optic nerve-related vision loss in adults. ***Aim*:** This study aimed to evaluate the effectiveness of noninvasive and minimally invasive treatments for AION. ***Methods*:** A systematic literature review was conducted using MEDLINE, EMBASE, and CENTRAL databases from their inception until June 10, 2019, to identify studies reporting the impact of various therapies on visual acuity (VA) and visual field (VF). The weighted mean difference (WMD) with a 95% confidence interval (CI) was calculated for these outcomes. The efficacy of steroids was quantitatively assessed, alongside qualitative evaluations of treatments such as oxygen therapy, steroid plus erythropoietin (EPO), levodopa/carbidopa, memantine, and heparin-induced extracorporeal LDL/fibrinogen precipitation (HELP). ***Results*:** Thirty-two studies were deemed eligible for inclusion. Steroid therapy showed no significant improvement in VA ($p = 0.182$, WMD = 0.14, 95% CI: −0.07, 0.35) or VF ($p = 0.853$, WMD = 0.16, 95% CI: −1.54, 1.86) compared to controls. Qualitative analyses of oxygen therapy, steroid plus EPO, and HELP also showed no significant benefits for VA or VF. However, two studies reported that memantine and levodopa had positive effects on VA. ***Conclusion*:** Our systematic review found no consistently effective treatments for AION, highlighting the need for further research into potential therapies.

Keywords: Nonarteritic Anterior Ischemic Optic Neuropathy (NAION), Visual acuity (VA) and visual field (VF), Steroid therapy, Memantine and levodopa.

INTRODUCTION

Ischemic optic neuropathy (ION) is a significant cause of vision loss, particularly in older adults, and occurs when there is inadequate blood flow to the optic nerve. The optic nerve is essential for transmitting visual information from the eye to the brain, and its damage can lead to permanent visual impairment. ION is classified into two main types: anterior ischemic optic neuropathy (AION) and posterior ischemic optic neuropathy (PION). AION, the more common of the two, affects the anterior part of the optic nerve, while PION involves the posterior segment [1-6].

The pathophysiology of ION primarily revolves around disrupted blood flow in the small arteries supplying the optic nerve. This can result from conditions such as arteriosclerosis, giant cell arteritis (GCA), and systemic hypertension. Non-arteritic AION (NA-AION) is the more prevalent form and is usually associated with conditions like diabetes and high blood pressure. Arteritic AION (A-AION), on the other hand, is most commonly linked to GCA, a potentially life-threatening autoimmune disorder that requires immediate intervention to prevent bilateral blindness and other systemic complications.

Diagnosis of ION involves a comprehensive clinical evaluation. Ophthalmologists rely on patient history, visual acuity tests, and examination of the optic disc for swelling or pallor, a hallmark of AION. Further imaging, including optical coherence tomography (OCT)

and fluorescein angiography, can provide detailed views of the optic nerve structure and blood flow abnormalities. Blood tests, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are crucial in identifying underlying causes like GCA, especially in cases of arteritic ION [7-11].

Management of ischemic optic neuropathy depends on the type and underlying cause. In arteritic AION, prompt treatment with high-dose corticosteroids is vital to reduce inflammation and prevent further vascular damage. Long-term immunosuppressive therapy may be required to manage GCA [12-18]. In non-arteritic cases, treatment options are more limited, as there is no universally effective therapy. Focus is typically placed on managing associated systemic risk factors, such as controlling blood pressure, diabetes, and lipid levels, to reduce the risk of further ischemic events. In some cases, medications like aspirin may be used to reduce the risk of future vascular events [19-27].

While early detection and treatment of arteritic AION can preserve vision in the unaffected eye, the prognosis for visual recovery in either form of ION remains poor. Visual rehabilitation and support, including the use of low-vision aids and counseling, can significantly improve the quality of life for affected individuals. Research into new treatment modalities, including neuroprotective agents and therapies to restore blood flow to the optic nerve, holds promise for improving outcomes in the future [28-38].

In conclusion, ischemic optic neuropathy is a complex and multifactorial condition requiring early diagnosis and targeted management to prevent irreversible vision loss. Understanding the distinct types, their etiologies, and the most effective interventions remains crucial for clinicians in providing optimal care to patients suffering from this debilitating condition.

Objective

We aimed to analyze the efficacy of the noninvasive and minimally invasive therapeutic options of AION.

METHODOLOGY

Our meta-analysis was conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and was registered in PROSPERO Inter- national Prospective Register of Systematic Reviews (registration number CRD42018102521). Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were applied to report our results [30]. We deviated from the protocol in that we also nar- ratively analyzed non-comparative studies, because we wanted to show a more complex view about therapeutic difficulties.

Eligibility Criteria

We created our scientific question following the population-intervention-control- outcomes (PICO) framework: (P) our population consisted of patients with nonarteritic anterior ischemic optic neuropathy, (I) who received a therapeutic intervention (corti- costeroids or levodopa with carbidopa or erythropoietin, pentoxifylline, brimonidine, memantine, prostaglandin E1, ranibizumab, bevacizumab, oxygen, heparin-induced extra- corporeal LDL/fibrinogen precipitation (HELP), Fasudil), (C) compared with no treatment or placebo, and our (O) outcomes were improvement of visual acuity (VA), change in visual field (VF), and retinal nerve fiber layer (RNFL) thickness. Studies were included in our qualitative synthesis if they reported the mentioned therapeutic interventions even if they were not comparative studies. Studies that used the Humphrey visual field analyzer were included in our quantitative analysis of VF. We compared the mean deviation (MD) values of these studies. Studies in which the treatment was not initiated within 1 month after the onset of NAION or that applied surgical interventions were excluded.

Search and Selection Strategy

Our systematic search was performed in MEDLINE (via PubMed), EMBASE and CENTRAL (Cochrane Central Register of Controlled Trials) from inception to 10 June 2019. Our search query was '((non-arteritic OR nonarteritic) AND anterior AND ischemic AND optic AND neuropathy) OR NA-AION OR N-AION OR NAION'. No search filters were applied.

The results of our search were imported to and processed with the EndNote X7.4 soft- ware (Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates automatically and manually, the studies were screened by title, then by abstract, and finally by full text by two independent investigators (K.L., V.G.). Disagreements were resolved by consensus.

Data Extraction

Numeric data were extracted independently by two reviewers (K.L. and V.G.) and entered into a purpose-designed Excel datasheet (Office 365, Microsoft, Redmond, WA, USA). We extracted data of the author of the study, year of publication, study design, details of the intervention, length of follow-up, number of patients, and the outcomes: VA, VF, and RNFL thickness, before the treatment and after at specified times. Any discrepancies were resolved by consensus.

Statistical Analysis

For data synthesis, we used the methods recommended by the working group of the Cochrane Collaboration [31]. Random effects-models by DerSimonian and Laird [32] were used to conduct a meta-analysis to assess the effect of different therapies on VA and VF. In the case of VA as a continuous

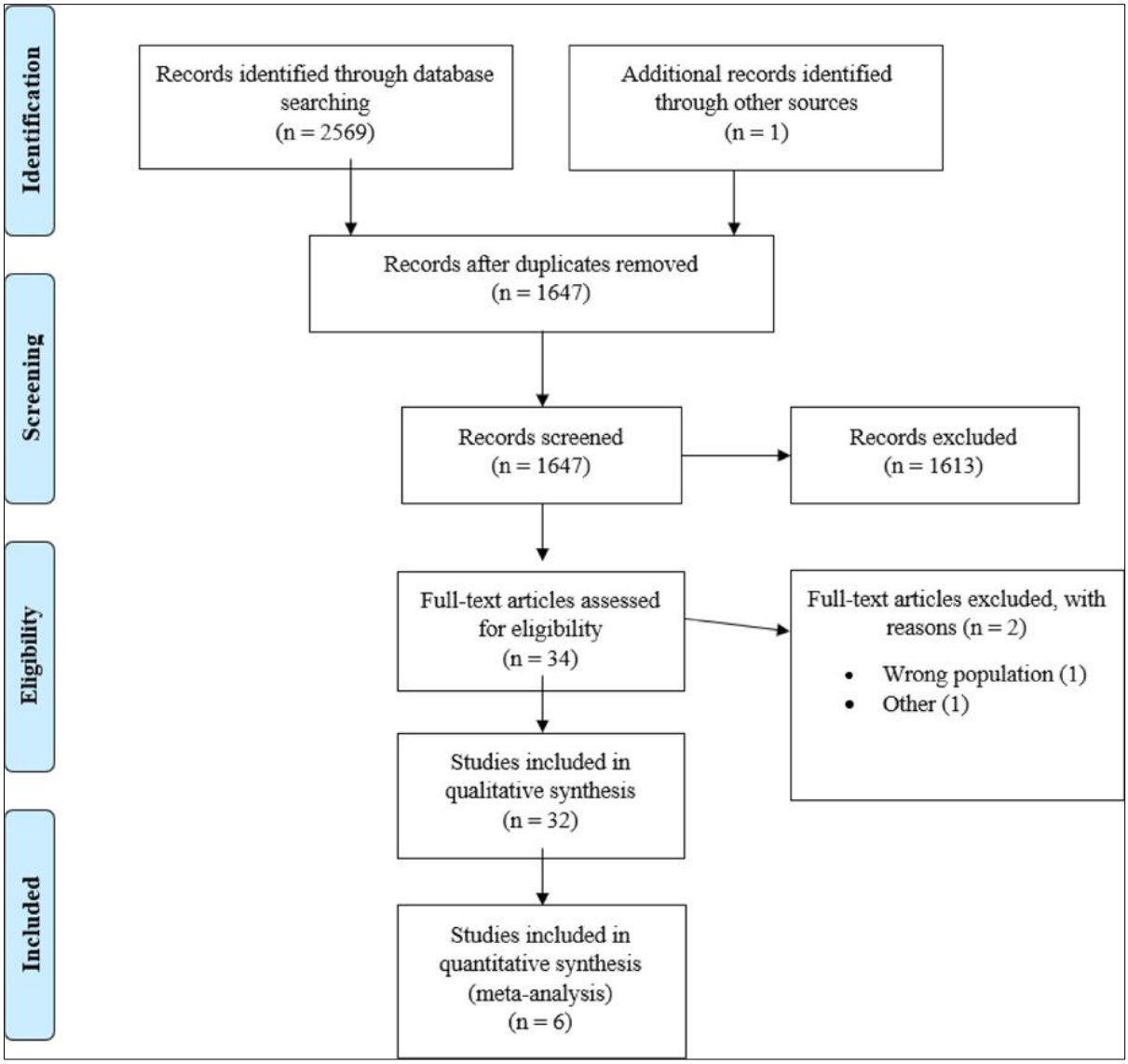
variable, weighted mean difference (WMD) and 95% confidence interval (CI) of logMAR values were estimated. The VA was reported in LogMAR values in all but one study, in which data had to be converted to LogMAR values [33].

For VA as a categorical variable, 'improved' and 'not improved' categories were used to calculate pooled odds ratios with 95% CI. In case of VF as a continuous variable WMD and 95% CI of mean deviation values were estimated. Because in some studies there were no events observed, we performed a continuity correction recommended in the Cochrane Handbook and proposed by Sweetin *et al*., [34] to overcome the difficulty of dividing by 0. We calculated WMD for the therapies and outcomes with sufficient data for the analysis. The other studies were summarized narratively.

When the number of studies was sufficient for statistical analysis, publication bias was evaluated by visual inspection of funnel plots and test f H0. Heterogeneity was tested using Cochrane's Q and I2 statistics.

We performed all meta-analytic calculations with STATA 16 statistical software (STATA Corp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC.).

The results of the literature search are illustrated by the flowchart in Figure 1. A total of 2570 articles were identified and 32 of these were included in qualitative synthesis and 6 of these with 524 patients in quantitative analysis.



A total of 2570 articles were identified and 32 of these were included in qualitative synthesis and 6 of these with 524 patients in quantitative analysis.

Table 1: Characteristics of the studies

Study, Year	Study Design	Interventions	No.of Participants	VA Follow-Up (Months)
Rebodella *et al.*, 2013 [4]	retrospective cohort study	prednisolone PO	10	6
		untreated	27	
Pakravan *et al*., 2016 [1]	randomized clinical trial	iv. methylprednisolone, prednisolone PO	30	6
		100% normobaric oxygen	30	
		untreated	30	
Kinori *et al*., 2014 [6]	retrospective cohort study	iv. methylprednisolone, prednisolone PO	24	22
		untreated	24	36
Steigerwalt *et al.*, 2008 [7]	prospective cohort study	i.v methylprednisolone+ PGE1	8	6
		prednisolone PO	7	
Pakravan *et al*., 2017 [5]	prospective cohort study	iv. methylprednisolone + EPO, prednisolone PO	40	6
		iv. methylprednisolone, prednisolone PO	43	
		untreated	30	
Radio *et al*., 2014 [8]	retrospective cohort study	intravitreal triamcinolone	21	6
		untreated	15	
Kaderli *et al*., 2007 [9]	retrospective cohort study	intravitreal triamcinolone	4	12–15
		untreated	6	9–12
Hayreh *et al*., 2008/1 [10]	retrospective cohort study	prednisolone PO	312	6
Hayreh *et al*., 2008/2 [38]		untreated	301	
Saxena *et al*., 2018 [11]	randomized, double-blind placebo-controlled trial	prednisolone PO	19	6
Prokosch *et al*., 2014 [14]	randomized controlled trial	iv+per os pentoxifylline	30	6
		iv+per os pentoxifylline + fluocortolone	30	
Vidovic *et al*., 2015 [12]	prospective case series	methylprednisolone PO	38	6
Yaman *et al*., 2008 [13]	case series	intravitreal triamcinolone	4	3
Modarres *et al.*, 2011 [19]	prospective case series	intravitreal EPO	31	6
Johnson *et al*., 1996 [15]	randomized, double-masked placebo-controlled trial	levodopa/carbidopa	10	6
		untreated	10	
Lyttle *et al*., 2015 [18]	retrospective cohort study	levodopa/carbidopa	33	8
		untreated	26	
Simsek *et al*., 2005 [16]	randomized, placebo-controlled trial	levodopa/carbidopa	12	11
		untreated	12	10
Johnson *et al*., 2000 [17]	retrospective cohort study	levodopa/carbidopa	18	6
		untreated	19	
Bajin *et al*., 2011 [27]	retrospective case series	intravitreal ranibizumab	4	3
Saatsi *et al*., 2013 [28]	retrospective case series	intravitreal ranibizumab	17	12
Prescott *et al*., 2012 [39]	retrospective case series	intravitreal bevacizumab	5	inconsistent
Rootman *et al.*, 2013 [29]	non-randomized controlled trial	intravitreal bevacizumab	17	6
		untreated	8	
Fazzone *et al*., 2003 [20]	retrospective cohort study	topical brimonidine	14	2–3
		untreated	17	

Study, Year	Study Design	Interventions	No.of Participants	VA Follow-Up (Months)
Wilhelm *et al.*, 2006 [21]	randomized, double masked, placebo-controlled trial	topical brimonidine	11	3–3,5
		untreated	18	
Haas *et al*., 1997 [24]	randomized, controlled trial	HELP	19	3
		hemodilution	21	
Ramunni *et al.*, 2005 [25]	case series	HELP	11	3
Haas *et al*., 1994 [40]	retrospective case series	hemodilution	24	24
Guerriero *et al.*, 2009 [26]	prospective case series	LDL apheresis	10	6
		conventional therapy	10	
Bojic *et al*., 1994 [41]	case series	hyperbaric oxygen	9	6
Aftab *et al*., 2006 [23]	prospective interventional pilot study	iv Heparin, Warfarin PO	24	6
Sanjari *et al*., 2016 [42]	case series	intravitreal Fasudil	13	3
Esfahani *et al*., 2011 [22]	randomized, double-masked controlled trial	memantine PO	25	6
		untreated	22	

First, A study analyzed VA as a continuous variable. They imported or converted every VA value in LogMAR and in all the studies included, the follow-up period lasted for at least 6 months.

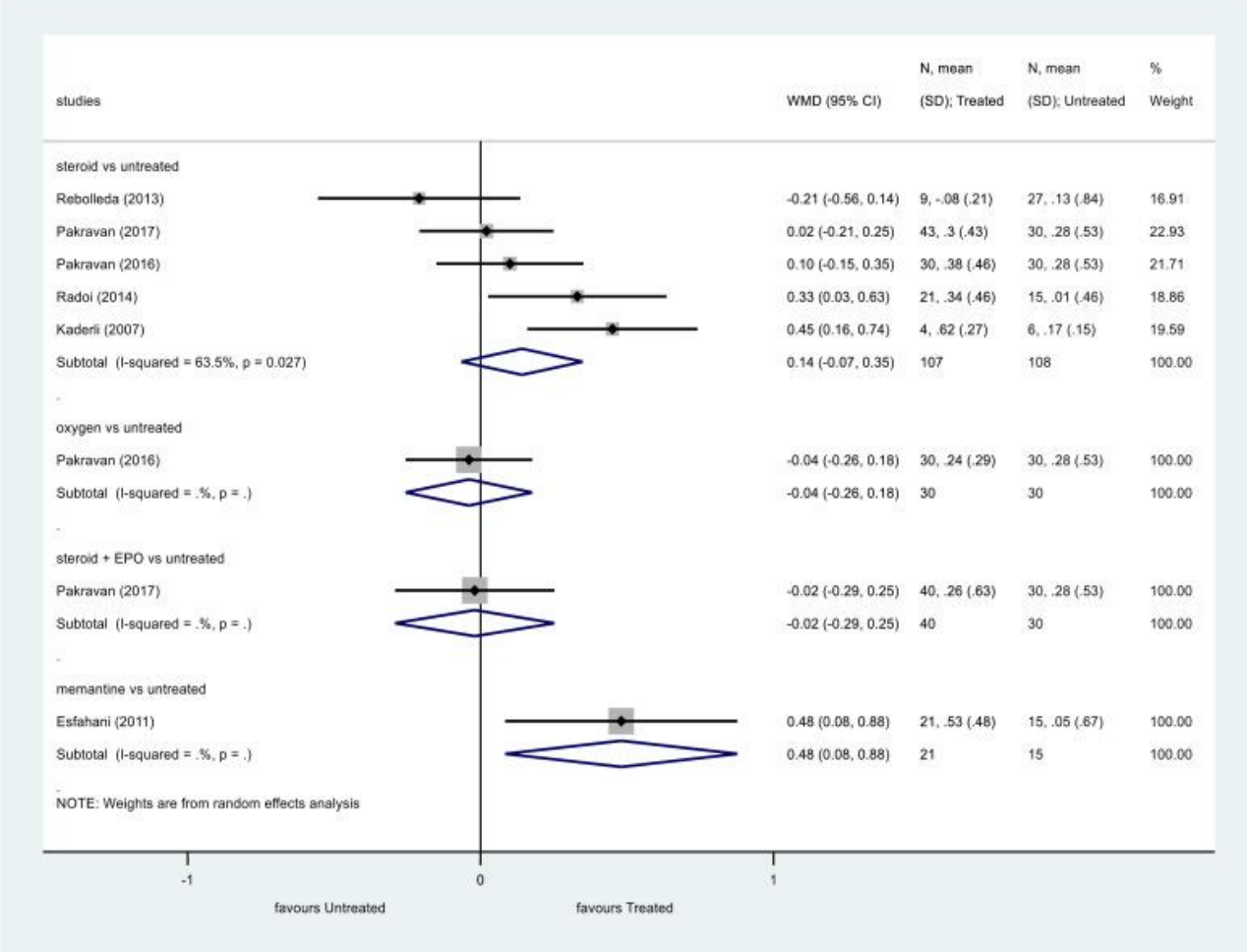


Figure-1: Comparison of interventions to no treatment regarding visual acuity

The VA of patients treated with steroids did not show significant improvement at the end of the follow-up compared to the control group (p = 0.149, OR = 1.77, 95% CI: 0.81, 3.84). Heterogeneity was moderate among these studies, too (I2 = 58.3%, p = 0.035).

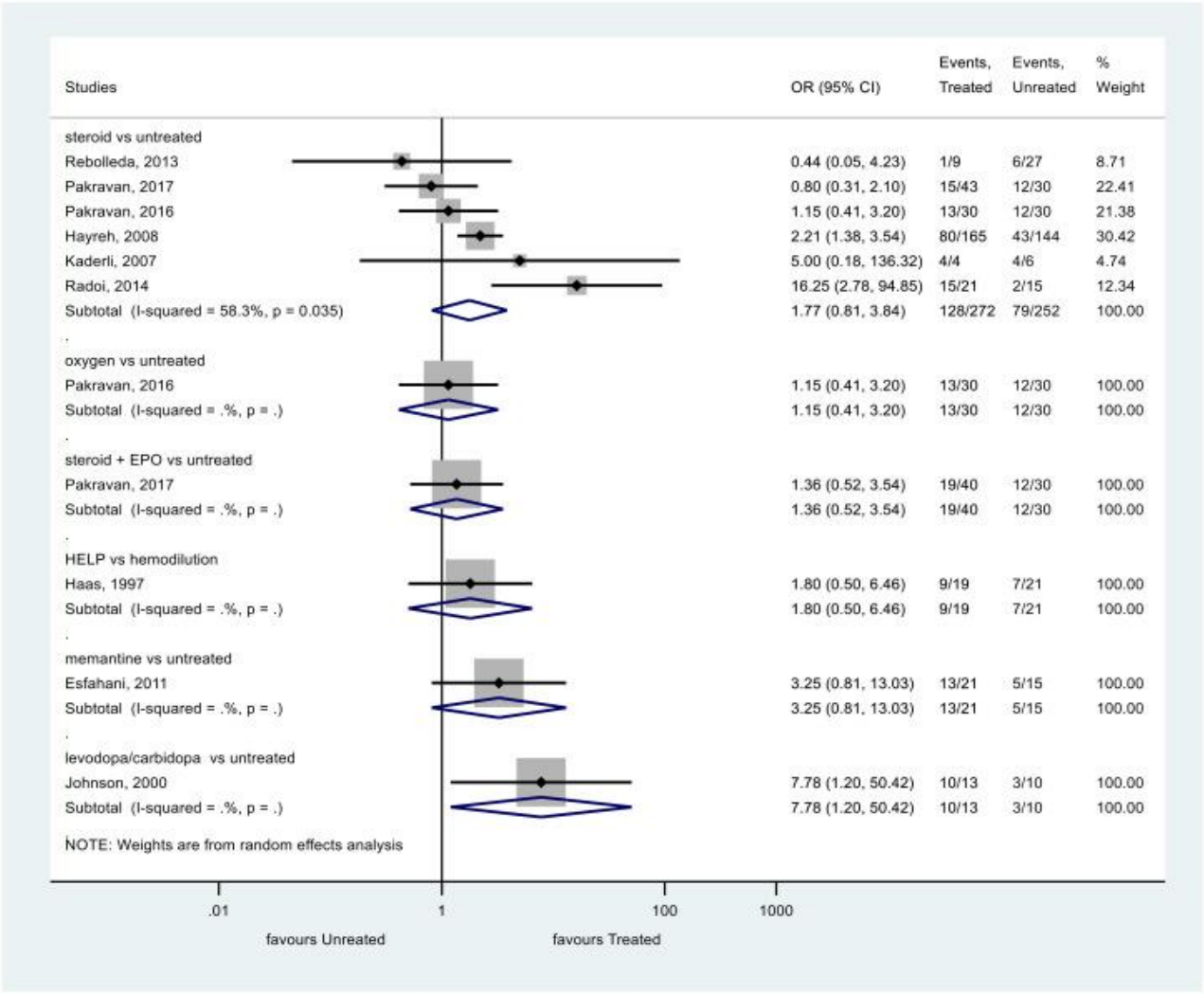


Figure-2: Comparison of interventions to no treatment regarding visual acuity

Table-2: GRADE of evidence of our results for visual acuity as a continuous variable

Outcomes	Anticipated Absolute Effects * (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Certainty of the Evidence (GRADE)	Comments
	Risk with Untreated	Risk with Treated				
Steroid vs. untreated follow up: range 6 months to 15 months	The mean steroid vs. untreated was 0 logMAR	WMD 0.14 logMAR higher (0.07 lower to 0.35 higher)	-	215 (5 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	
Oxygen vs. untreated	The mean oxygen vs. untreated was 0	WMD 0.04 lower (0.26 lower to 0.18 higher)	-	60 (1 RCT)	⊕◯◯◯ VERY LOW [d,e]	
Steroid+EPO vs. untreated	The mean steroid+EPO vs. untreated was 0	WMD 0.02 lower (0.29 lower to 0.25 higher)	-	70 (1 observational study)	⊕◯◯◯ VERY LOW [d,e]	

Memantine vs. untreated	The mean memantine vs. untreated was 0	WMD 0.48 higher (0.08 higher to 0.88 higher)	-	36 (1 RCT)	⊕◯◯◯ VERY LOW [d,e]	

DISCUSSION

Corticosteroids have antiedematous, antiphlogistic effects, can decrease capillary permeability, and decrease compression of capillaries in the optic nerve head, improving blood flow and restore the function of surviving ischemic axons in NAION [43]. Our meta-analysis of 6 studies for VA and 3 for VF demonstrated that steroids did not improve VA and VF significantly. However, the results of a study by Hayreh *et al*., [10] provided support for the beneficial effect of steroids. They found that oral corticosteroid therapy resulted in a significantly higher probability of improvement in VA. Two studies with intravitreal steroid therapy (triamcinolone injection) [8, 9] showed significant improvement of VA and VF, although one of them had a small number of cases [9]. The effect of steroid and pentoxifylline was also described in a study showing that fluocortolone in combination with pentoxifylline has a beneficial effect on VA, but there was no significant difference in the VF [14]. In contrast to the aforementioned studies, Rebolleda et al. and Kinori et al. reported no functional difference between the steroid and the untreated groups [4, 6]. Moreover, a randomized, double-blind clinical trial supports our findings, as it concluded that steroids did not improve the VA significantly at 6 months. Unfortunately, we could not include this study in our meta-analysis due to missing data about the initial and final VA and VF values of the patient groups [11]. Pakravan *et al*., evaluated the efficacy of normobaric oxygen therapy in addition to steroids [1]. Their findings did not reveal beneficial effects of either steroids or oxygen for the management of NAION compared to placebo. Steigerwalt et al. used PGE1 with steroids [7], but we did not include it in our analysis because the control group also received steroids. They found that VA improved in the cases treated with PGE1 compared to the control group. We found a meta-analysis published by Chen et al. which investigated only steroid therapy in NAION. Their article also supports the results of our meta-analysis, that steroids do not significantly improve VA [43]. Our meta-analysis investigated not only steroid therapy but we also examined the VF in addition to VA. Our results suggest that steroids did not significantly improve VA or VF in NAION.

Levodopa crosses the blood–retinal barrier to increase retinal dopamine level. Dopamine is a neurotransmitter, neuromodulator, and neuroprotective agent. There are some studies about the effects of levodopa on visual function in patients with NAION. Lyttle *et al*., found that levodopa improved central VA [18]. Johnson *et al*., [17] published VA improvement results in patients with 20/40 VA or worse, 76.9% in the levodopa group and 30% of the control group had improved VA. Johnson *et al*., [15] found improvement of VA among patients receiving levodopa and carbidopa despite a long-standing visual loss; however, this study refers to earlier publications, which stated that visual improvement might have been occurred because of the spontaneous resolution of NAION. In contrast with what Johnson found, in the study by Simsek et al., there was no improvement in VA either in the study or the placebo group, suggesting that levodopa and carbidopa therapy cannot restore a long-standing visual loss [16]. Unfortunately, these studies could not meet our eligibility criteria for the quantitative synthesis, therefore we could not perform the meta-analysis of their results.

Moderres *et al*., published a study where 31 patients received intravitreal injection of erythropoietin solution and it showed improvement in VA. Neuroprotection is a therapeutic strategy in the treatment of NAION. EPO reduces apoptosis in retinal ganglion cells [19]. Pakravan *et al*., [5] compared the effect of steroid therapy alone or in combination with systemic EPO for the treatment of NAION. They found no beneficial effect in either group, similar to our results.

Topical brimonidine tartrate is an alpha-adrenergic agonist agent, which has a neuroprotective effect for retinal ganglion cells. We found two studies [20, 21] that examined the effects of brimonidine tartrate as a treatment of NAION, but they did not find an improvement of visual function. Wilhelm's double-masked, randomized, placebo-controlled trial was not included in our analysis due to the ambiguity in the patient number in the treatment groups.

Memantine is a noncompetitive NMDA receptor antagonist and it relieves glutamate NMDA-receptor mediated toxicity in retinal ganglion cells. Analyzing the results of Esfahani *et al*., [22] as a continuous variable we found that memantine improves VA compared to the control group.

HELP improves rheologic status of tissues. We found four publications about HELP and hemodilution [24, 25, 26, 40]; one of these was analyzed statistically, a prospective, randomized, controlled study by Haas *et al*., which suggested the HELP system is more effective than hemodilution in the treatment of NAION.

Multiple embolization may play a role in the development of NAION. We found publications investigating the efficacy of anticoagulants and thrombolytics. The recanalization rate in response to thrombolytic therapy improves as a vessel narrows [44].

Aftab *et al*., found that patients with NAION did benefit from anticoagulation with heparin and warfarin [23].

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