The Effect of Systemic Erythropoietin and Oral prednisolone on Recent-Onset Non-Arteritic Anterior Ischemic Optic Neuropathy: a Randomized Clinical Trial

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Running title: Effects of systemic erythropoietin and oral prednisolone on acute NAION

Abstract

Background: To evaluate the effect of systemic erythropoietin, as well as oral steroids, in the management of recent onset non-arteritic anterior ischemic optic neuropathy (NAION).

Method: Ninety-nine eyes of 99 patients diagnosed with NAION within 5 days of onset were included in this single masked randomized clinical trial. Thirty-four patients were randomized into group 1 (systemic erythropoietin), group 2 (oral steroids), and group 3 (control). Group A received 10,000 units of erythropoietin twice a day for three days. Group B received oral prednisone 75 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). Functional and structural outcomes were analyzed at 3 and 6 months following treatment. Best corrected visual acuity (BCVA) was the main outcome measure, and mean deviation (MD) of visual field (VF) test and peripapillary retinal nerve fiber layer thickness (PRNFLT) were secondary outcome measures.

Results: The mean BCVA (±SD) at the time of presentation was 1 ± 0.56, 1.01 ± 0.6, and 0.94 ± 0.47 logMAR in groups A, B, and C, respectively (P = 0.140); corresponding values were 0.72 ± 0.45, 0.83 ± 0.46, and 0.78 ± 0.4 logMAR (P = 0.417), and at 6-month follow-up, they were 0.70 ± 0.44, 0.73 ± 0.35, and 0.75 ± 0.39 logMAR, respectively (P = 0.597). Fifty-five percent of patients in group A vesus 34.3% in group B, and 31.2% in group C had an improvement of at least 3 lines in the BCVA values at the 6th-month follow-up visit. (P= 0.04)

The mean deviation (MD) at the time of presentation was 19.67 ± 6.2, 20.83 ± 4.83, and 18.94 ± 6.92 decibels (db), respectively (P= 0.483).The corresponding values at month 3 were 18.22 ± 7.5, 19.82 ± 7.15, and 17.65 ± 7.22 db, (P = 0.848); and at month 6 they were 16.56 ± 7.08, 18.15 ± 6.57, and 15.9 ± 5.97 db, respectively. (P = 0.699) PRNFLT at presentation was 189 ± 58, 193 ± 64, and 199 ± 62 micrometers, respectively (P = 0.779), which decreased to 110 ± 45, 127

± 37, and 119 ± 37 at month 3 (P = 0.423). The corresponding values for month 6 were 88 ± 12, 74 ± 25, and 71 ± 18, respectively. (P = 0.041)

Conclusion: The findings of our study indicate the beneficial effects of systemic erythropoietin in preserving the function and structure of the optic nerve in recent onset NAION.

Keywords: Non-arteritic anterior ischemic optic neuropathy; NAION; Erythropoietin; systemic steroid; Neuroprotection

Introduction

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common cause of acute and sub-acute optic neuropathy in patients over 50 years of age, with an estimated incidence of 2.3 to 10.3 per 100,000 population. [1]

While ischemic pathophysiology is the most cited mechanism for NAION, Parsa and Hoyt have recently proposed a non-ischemic pathophysiology for this condition, attributing NAION to shear force injury following vitreous separation from the optic nerve head.[2] There is no proven effective therapy for NAION. Considering the lack of consensus regarding the exact pathophysiology of NAION, most of the current medical therapeutic approaches are empirical including treatments that address the mechanisms of ischemia, such as thrombosis, insufficient blood supply, and inflammation, or regimens with possible neuroprotective effects. [3–7]

Considering the inflammatory reactions following an ischemic event, [3] investigators have evaluated the role of steroids in NAION, but evidence for their efficacy is lacking. [8]

Erythropoietin (EPO) is a cell-differentiating glycoprotein hormone that has recently attracted much attention as a new therapeutic agent with neuroprotective effects [6-8]. The presence of an EPO receptor in neural tissues that is different from other erythropoiesis receptors is well established. [9] It has been shown that the administration of EPO in patients with diabetic retinopathy can prevent retinal cell death and results in maintenance of blood-retinal barrier function by activating this receptor and extracellular signal-regulated kinase pathway (ERK). [9]

An increasing body of evidence suggests the beneficial effects of EPO on vision problems, such as traumatic optic neuropathy, methanol poisoning optic neuropathy, optic neuritis, and NAION. [10–13] Our previous prospective study failed to demonstrate any beneficial effect of systemic steroid or combined steroid and EPO in the visual outcome of NAION patients. [14] However, the inclusion window for our study was 14 days, which could adversely affect the outcome of neuroprotection. In this prospective randomized clinical trial, we aimed to examine the therapeutic effects of systemic corticosteroids and EPO therapy alone on visual outcome of recent-onset (within 5 days) NAION.

Materials and Methods

This randomized clinical trial was performed at the neuro-ophthalmology units of Labbafinejad Medical Center and Torfe Eye Center from September 2015 to March 2017. The study was approved by the ethics committee of the Ophthalmic Research Center (reference number: IR.SBMU.ORC.REC.1397.18) and followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from each participant after explaining the research objectives, possible side effects, and benefits.

NAION was diagnosed based on the following criteria: (1) sudden and painless visual loss associated with relative afferent pupillary defect, which was not related to any other neurological or systemic diseases; (2) optic disc edema in clinical examination which was confirmed by measuring the retinal nerve fiber layer thickness (RNFLT) using optical coherence tomography; (3) visual field defect related to optic neuropathy.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured for all patients to exclude arteritic AION. Brain and orbital MRI was performed in case of other suspected conditions.

BCVA measurement, slit lamp biomicroscopy, tonometry, fundoscopy, visual field testing, and OCT were performed at the initial presentation and then were repeated 1,3, and 6 months after the intervention. BCVA was measured by a certified blind examiner using a Snellen chart and was converted to logMAR for statistical analysis. Peripapillary OCT (Cirrus Zeiss Cirrus HD-OCT, Carl

Zeiss Meditec Inc.) was done to measure the peripapillary retinal nerve fiber layer thickness. The standard SITA 24-2 field test was performed using Humphrey visual field analyzer (HFA; Model 750; Carl Zeiss Meditec, Inc., Dublin, CA, USA).

Exclusion criteria were as follows: (1) glaucoma or any ocular, neurological or systemic disease that can affect vision and visual fields; (2) abnormal laboratory findings, including abnormal ESR and serum CRP; (3) history of eye surgery; (4) history of receiving any treatment for NAION; (5) systemic conditions such as diabetes or uncontrolled high blood pressure; (6) contraindications to systemic steroids such as active infection, acute gastric ulcer, and immune deficiency; (7) contraindications for the administration of systemic EPO, such as polycythemia; (8) unwillingness to participate in the study. Prior to intervention, counseling was provided for all patients by an internist. Furthermore, all patients were examined for possible side effects and complications of systemic EPO and prednisolone administration.

The sample size calculation was performed based on the difference in BCVA between groups. The study was designed with a sample size of 32 patients in each group to detect a difference of 0.3 logMAR with a significance level of 0.05 and a power of 80%.

Randomisation was performed on the day of first presentation. Assignments were generated by a computer programme employing a random permuted block algorithm. Randomisation was performed by a biostatistician and the sequence was concealed from the investigators. The patients were randomized into three groups: Group A received 10,000 units of erythropoietin twice a day for three days. Group B received oral prednisone 75 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). In addition, all subjects in the second group received 300 mg of ranitidine daily. Group C was control and did not receive any intervention.

Blood pressure was monitored before, during and after the EPO injection, and the injection was stopped if blood pressure was increased during the injection. Routine tests including blood pressure measurement and laboratory parameters including complete blood count (CBC), blood glucose, blood urea nitrogen (BUN), creatinine and serum electrolytes were evaluated daily for three days, and then twice a month. All patients in group B were routinely monitored for side effects of systemic steroids including bi weekly blood glucose and blood pressure.

Normality of data was assessed by the Kolmogorov-Smirnov test and Q-Q diagrams. Data were described using descriptive statistics including mean, standard deviation (SD), median, and range. Data were analyzed using ANOVA, Kruskall-Wallis and chi-square tests. Multi-variable comparison was performed using the general linear method. A change of 0.3 logMAR (equivalent to three lines in the Snellen visual acuity chart) was considered to be clinically significant.

All statistical analyses were carried out using the IBM SPSS Statistics (version 25) at the significance of 0.05.

Results:

Initially, a total of 129 patients with recent-onset NAION were considered for enrolment in our study. The main reasons for exclusion were declining to participate (10 patients), ocular comorbidities (2 patients), previous intraocular surgery (2 patients) and systemic conditions precluding systemic EPO or steroid therapy (16 patients). A total of 99 patients were finally randomized into the study arms. While 34 patients were enrolled in group A, thirty-three and 32 patients were included in groups B and C, respectively. One patient in group A was excluded from final analysis following globe rupture 3 weeks after NAION. One patient was excluded from final analysis in group B as he moved to another city. Mean ages (±SD) of participants were 63.2 (±6.1), 62.1 (±3.2), and 62.5 (±5.1) years respectively. (P=0.679) Baseline values of BCVA, MD and RNFL did not differ significantly between the three groups (P>0.05) (Table 1).The mean BCVA (±SD) at the time of presentation was 1 ± 0.56, 1.01 ± 0.6, and 0.94 ± 0.47 logMAR in groups A, B, and C, respectively (P = 0.140)

At month 3, the corresponding values were 0.72 ± 0.45, 0.83 ± 0.46, and 0.78 ± 0.4 logMAR (P = 0.417), and at 6-month follow-up, they were 0.70 ± 0.44, 0.73 ± 0.35, and 0.75 ± 0.39 logMAR, respectively (P = 0.597) (Table 2) There was no statistically significant difference between months 3 and 6, which implies stabilization of the visual acuity by month 3. Considering the cutoff point of three lines from Snellen chart or 0.3 logMAR change in visual acuity, 54.5% of patients in group A, 34.3% in group B, and 31.2% in group C had an improvement in the BCVA values at the 6th-month follow-up visit. (P= 0.04)

The mean deviation (MD) at the time of presentation was 19.67 ± 6.2, 20.83 ± 4.83, and 18.94 ± 6.92 decibels (db), respectively (P= 0.483). The corresponding values at month 3 were 18.22 ± 7.5, 19.82 ± 7.15, and 17.65 ± 7.22 db, (P = 0.848); and at month 6 they were 16.56 ± 7.08, 18.15 ± 6.57, and 15.9 ± 5.97 db, respectively. (P = 0.699) (Table 3) Although visual acuity tended to stabilize at month 3, the improvement of visual field MD index continued up to at least 6 months after disease onset.

PRNFLT at presentation was 189 ± 58, 193 ± 64, and 199 ± 62 micrometers, respectively (P = 0.779), which decreased to 110 ± 45, 127 ± 37, and 119 ± 37 at month 3 (P = 0.423). The corresponding values for month 6 were 88 ± 12, 74 ± 25, and 71 ± 18, respectively. (P = 0.041) PRNFLT decreased significantly in each group (P < 0.0001 in the three groups, Table 4).

Results of ANCOVA showed a statistically significant difference in PRNFLT between the study groups after three months (P=0.041). Post-hoc evaluation showed that PRNFLT was significantly thicker in group A compared to other groups. (P=0.044).

None of our patients showed polycythemia or high blood pressure during the injection period and during the 6 months of follow-up. Three patients in group B developed transient hyperglycemia, which was managed with lifestyle modification and normalized after steroid was tapered off. Recurrence of NAION or occurrence of disease in the fellow eye did not happen in our study participants during the course of study.

Discussion:

This randomized clinical trial demonstrated the functional and structural benefits of systemic erythropoietin in the management of recent-onset NAION. Almost half of the patients group A had a significant improvement in their visual acuity at 6-month follow-up, which was higher than the steroid group and reported natural course of NAION. [15,16]

To date, no definitive high-grade evidence for effective treatment of NAION exists. There are few randomized clinical trials regarding the management of NAION. [17,18] These studies have provided the highest level of evidence so far but failed to demonstrate any benefit from optic nerve fenestration, intravenous steroids, and normobaric oxygen in the management of NAION.

Steroid therapy is by far the most studied treatment for NAION. The rationale for its potential therapeutic effect is presumed faster resolution of the optic nerve edema and reestablishment of optic nerve head blood supply. [19,20]The largest study on the role of steroid therapy on the course of NAION was a patient choice study by Hayerh and Zimmerman on 696 consecutive patients seen at the University of Iowa Hospitals and Clinics from 1973 to 2000. [19] In their cohort, 312 patients (n = 364 eyes) chose to receive oral prednisone 80 mg tapering off within 30 days.

The odds ratio of improvement in BCVA and MD was 3.39 and 2.06, respectively. While they concluded that the treatment 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), the study was limited by its lack of randomization. The steroid therapy was offered to our patients considering its role in reducing post-ischemic edema and damage caused by secondary compartment syndrome. However, we did not observe any benefit from oral steroids regarding the improvement of the final visual outcomes of patients with recent onset NAION within the 6-month follow-up period. Furthermore, our study showed that oral steroids did not hasten the resolution of the optic disc edema when compared with the control group. These findings are in line with the results of previous studies that demonstrated IV steroids was not superior to observation alone in the management of recent onset NAION. .[14,21]

The lack effective therapies targeted at reversing ischemia in our randomized clinical trial as well as previous studies may call into question the proposed role of ischemia and resulting inflammation in this neuropathy. In fact, Parsa and Hoyt recently pointed out that no evidence has ever been put forth to implicate ischemia in so-called “NAION” and that this designation represents a misnomer. [2] Static vitreopapillary traction having already been well known to be able to produce optic disc elevation as well as surface vessel telangiectasia with potential hemorrhages, [22] these investigators also proposed a dynamic pathophysiologic mechanism whereby shear forces generated during brisk vitreous separation of the epipapillary membrane could cause axonal damage in the peripapillary and papillary areas.

It is now well established that EPO has neuroprotective effects through direct neuroprotection, anti-apoptotic, anti-inflammatory, and antioxidant effects, glia cell protection and improvement

of blood flow to the damaged tissue. [23–26] Intravitreal injection of EPO resulted in significant improvement of visual acuity in 55% of NAION patients, [12] however, this study was limited by lack of control group.

Peripherally administered EPO can readily cross the blood-brain barrier and potentially target various aspects of NAION pathogenesis such as the promotion of angiogenesis, apoptosis of RGC, secondary damage mechanism such as antioxidants, and promoting axonal regeneration. In our previous study, we failed to demonstrate any benefit from combined systemic EPO and corticosteroid in acute NAION. [14]

We argued that high-dose steroid in that study inhibited not only proinflammatory cytokines but also neuroprotective growth factors such as glial-derived neurotrophic factor, brain-derived neurotrophic factor, and NT-3. [27] Moreover, steroid is shown to blunt EPO receptors' up-regulation. [28] The inclusion window for our prior study was 14 days, while any neuroprotective effect has greater validity prior to visual loss. In the current study, NAION with less than 5 days of onset was included as some experimental studies have indicated that RGC apoptosis starts within 5 days of ischemia and advocated the earlier administration of neuroprotective agents. [28]

The present randomized clinical trial prospectively evaluated the outcome of intravenous EPO, and of oral steroid, in the management of recent onset NAION. One limitation of this study is the exclusion of diabetic patients. Since we wished to have actual randomization, and yet could not ignore the high risks associated with systemic steroids in diabetic patients, we decided to exclude diabetic patients from our study. We believe, however, that the results of this study could be generalized to diabetic patients.

In summary, our findings revealed the beneficial effects of systemic EPO in recent onset NAION. This study showed that if systemic EPO is started within 5 days of onset of NAION, it results in better visual outcome and protects against loss of retinal nerve fiber layers. The absence of any demonstrated benefits in this randomized controlled trial, as well as in previous studies, leads us to conclude that in view of their long list of side effects, attempts targeted at reversing ischemia by systemic steroid could well be unwarranted.

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Table 1. Baseline characteristics of three study groups.

Variable		Total	Group A	Group B	Group C	P-value
Age	Mean ± SD	62.6 ± 5.2	63.2 (±6.1)	62.1 (±3.2)	62.5 (±5.1)	0.679†
Gender	Female	30 (30.9%)	6 (18.2%)	14 (42.4%)	10 (32.3%)	0.105*
	Male	67 (69.1%)	27 (81.8%)	19 (57.6%)	21 (67.7%)	
BCVA (Log MAR)	Mean ± SD	0.92 ± 0.56	1 ± 0.56	1.01 ± 0.6	0.74 ± 0.47	0.140‡
MD	Mean ± SD	19.82 ± 6.02	19.67 ± 6.2	20.83 ± 4.83	18.94 ± 6.92	0.483†
RNFL	Mean ± SD	186.96 ± 62.1	169.02 ± 58.29	192.61 ± 63.55	199.48 ± 62.05	0.122†

BCVA: best corrected visual acuity. MD: mean deviation. NFLT: nerve fiber layer thickness. † Based on ANOVA ‡ Based on Kruskal-Wallis test. * Based on Chi-Square test

Table 1. BCVA variation in the study groups through time

Time	Variable	Total	Group A	Group B	Group C	P-value
Baseline	Value	0.92 ± 0.56	1 ± 0.56	1.01 ± 0.6	0.94 ± 0.47	0.140‡
Month 3	Value	0.74 ± 0.44	0.72 ± 0.45	0.83 ± 0.46	0.78 ± 0.4	0.417¥
	Change from Base	-0.18 ± 0.4	-0.19 ± 0.45	-0.18 ± 0.48	-0.16 ± 0.24	
	P change from base§		0.029	0.027	<0.001	
Month 6	Value	0.69 ± 0.4	0.70 ± 0.44	0.73 ± 0.35	0.75 ± 0.39	0.597¥

	Change from Base	-0.25 ± 0.4	-0.22 ± 0.51	-0.31 ± 0.37	-0.22 ± 0.28	
	P change from base§		0.029	0.005	0.002	
	P change from month3§		0.781	0.269	0.792	

Data are expressed as mean ± SD.
‡ Based on Kruskall-Wallis test.
¥ Adjusted for the baseline, based on ANCOVA
§ Based on Linear mixed model, adjusted for the multiple comparison based on the Sidak method.

Table 2. MD values and variation in the study groups through time

Time		Total	Group A	Group B	Group C	P-value
Baseline	Value	19.82 ± 6.02	19.67 ± 6.2	20.83 ± 4.83	18.94 ± 6.92	0.483†
Month 3	Value	18.59 ± 7.27	18.22 ± 7.5	19.82 ± 7.15	17.65 ± 7.22	0.848¥
	Change from Base	-1.92 ± 5.6	-1.99 ± 4.27	-1.72 ± 7.98	-2.05 ± 3.71	
	P change from base§		0.017	0.491	0.012	
Month 6	Value	16.87 ± 6.54	16.56 ± 7.08	18.15 ± 6.57	15.9 ± 5.97	0.699¥
	Change from Base	-3.61 ± 4.82	-4.08 ± 4.54	-3.03 ± 6.08	-3.68 ± 3.78	
	P change from base§		0.001	0.019	<0.001	
	P change from month3§		0.066	0.084	0.040	

Data are expressed as mean ± SD.
† Based on ANOVA.
¥ Adjusted for the baseline, based on ANCOVA
§ Based on Linear mixed model, adjusted for the multiple comparisons based on the Sidak method.

Table 4. NFLT values and variations in the study groups through time

Time		Total	Groups A	B	C	P-value
Baseline	Value	191 ± 62	189 ± 58	193 ± 64	199 ± 62	0.779†
Month 3	Value	119 ± 40	110 ± 45	127 ± 37	119 ± 37	0.423¥
	P change from base§		<0.001	<0.001	<0.001	
Month 6	Value	81 ± 20	88 ± 12	74 ± 25	71 ± 18	0.041¥
	P change from base§		<0.001	<0.001	<0.001	
	P change from month3§		<0.001	<0.001	<0.001	