Evaluation of Subcutaneous Injection of Erythropoietin on Visual Functions in Patients with Late Onset Optic Neuropathy: A Pilot Clinical Study

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Research Article

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Abstract

Purpose: This pilot study aimed to assess the efficacy of subcutaneous erythropoietin injection on visual functions in patients having late stage optic neuropathy (LSON).

Methods: The study included 20 patients diagnosed with LSON. All patients underwent a detailed history including the onset of the attack, diagnosis of the cause of optic neuropathy, assessment of visual acuity, pupil reaction, and flash visual evoked potential. Systemic erythropoietin injections (Eprex 20000 IU) were administrated subcutaneously once daily for three consecutive days. Cases were followed up for 4 weeks and 12 weeks by recording visual acuity, recording flash visual evoked potential and evaluating the need of second dose of Erythropoietin injection.

Results:

The mean age of the studied patients at presentation was 43.2± 17.3 years. The mean duration of the disease was 5.4± 3 months. There were statistically significant improvements of visual acuity, color vision and VEP parameters after one month ($p<0.001$) with 16 patients showing improvement. The results continued to be statistically significant after three months ($p=0.002$); without having any side effects.

Conclusion:

The subcutaneous erythropoietin may effectively and safely treat the LSON provided that the flash visual evoked potentials recorded at the baseline are within acceptable limits. More well-designed studies are needed to assert upon these results.

Introduction

Optic nerve disorders or optic neuropathies stand among the most common causes for vision loss [1, 2]. Cases with optic neuropathies can get through a disconnection syndrome since once the optic nerve has been damaged, the visual inputs can no longer be tranfered from the eye to the brain to be interpretated [1, 2]. Optic neuropathies can happen suddenly or gradually. Moreover, insult to optic nerve results in progressive retrograde and anterograde degeneration, leading to transsynaptic degeneration in addition to thinning for the visual pathway [1, 3].

The main symptoms are decreased visual acuity and decrease of color vision, with colors appearing washed out in the affected eye. On clinical examination, the optic nerve head may appear edematous in early stages or may have normal appearance. A pale optic disc is a characteristic of long standing optic neuropathy [4]. Full clinical examination is important to rule in optic neuropathy diagnosis. Other tests including visual field testing, electrophysiological testing and neuroimaging are very useful in the overall evaluation [4].

Optic nerve damage can be due to various causes such as inflammation, ischemia, demyelination, infiltration, hereditary, toxic/nutritional causes, compression, glaucoma, neoplasm and other neurological disorders such as stroke and demyelinating disorders [5–7]. Treatment for such issues mainly addresses the underlying etiology but whatever is the cause, as soon as optic nerve atrophy occurs; there is currently no available treatment that is able to reverse this atrophy or the corresponding loss of vision [5, 8].

Most of the ocular approaches for treating optic neuropathies use intravitreal drugs, viral vectors, or cells. This is in near proximity for the retinal ganglion cells not the optic nerve which represents the initial site of injury and is not treating the axons [9]. Updated data showed that myelination and axonal conduction enhancement [10] and oligodendrocyte progenitors transplantation [11] are promising approaches in the treatment of CNS injuries such as optic neuropathies.

Since the discovery of the neurotrophic cytokine erythropoietin (EPO) human gene in 1985 [12], several efforts showed its vital ability in maintaining integrity and functions for various tissues [13, 14]. It is mainly produced from renal cells and to a lesser extent from CNS tissues. It was usually used in hematology to enhance hematopoiesis and used in neurology as neuroprotective cytokine for acute lesions such as traumatic brain injury and stroke to prevent apoptosis [14, 15]. Similarly, it was used in chronic neurodegenerative conditions such as chronic schizophrenia and chronic progressive multiple sclerosis as a neuroregenerative agent to enhance both structural and functional healing [14, 15]. Likewise, EPO have had its access to ophthalmology field after growing evidence for being produced in retinal cells, especially Muller cells [12, 16]. Studies on its safety for the protection of ganglion cell paved the way for trials of using EPO in glaucomas, optic neuritis, diabetic retinopathies, and neuropathies [16–18]. EPO intravenous injection was additionally described for the treatment of methanol induced and traumatic optic neuropathy with relative success [19, 20]. Although intravenous EPO is relatively effective to treat optic neuropathy, severe side effects such as cardiovascular complications, thrombosis, hypertension, and acute pulmonary embolism have been reported [21, 22]. Therefore, this study aimed to assess the safety and efficacy of subcutaneous EPO in the treatment of late stage optic neuropathy (LSON) due to different causes.

Methods

This was a prospective and pilot clinical study (NCT04469777) conducted in the Ophthalmology Department of Alexandria Main University Hospital in Alexandria, Egypt, in the period between June and December 2020. The study included 20 cases presenting with LSON. We followed the tents of the 1964 Helsinki declaration and its later amendments. Institutional review board (the ethical committee of Alexandria University Faculty of Medicine) approval was obtained, and all the patients included in the study signed written informed consent. Patients were enrolled consecutively to the study once the diagnosis of LSON was confirmed. LSON was due to different causes with two cases diagnosed as post optic neuritis, 4 cases as post traumatic optic neuropathy, 3 cases as post papilledemic optic neuropathy, 6 cases as post ischemic optic neuropathy (3 of them had posterior ischemic optic neuropathy and 3

cases had post anterior non arteritic anterior ischemic optic neuropathy), 3 cases as post methanol induced optic neuropathy and 2 cases as glaucomatous.

All patients underwent a detailed history including onset of attack and diagnosis of the cause of optic neuropathy, assessment of visual acuity, pupil reaction, and electrophysiological tests (flash visual evoked potential (VEP) in the affected eye recording P2 implicit time, N2P2 amplitude and SNR ratio) using the Roland Consult electrophysiology and imaging machine (Roland Consult Stasche & Finger GmbH). The test was conducted with the patients sitting and their chin resting on the ganzfield with the untested eye patched. The electrodes were put according to the International Society of Electrophysiology of Vision System (ISCEV) standards (reference electrode (Fz) placed at the forehead, ground electrode (Cz) at the vertex, active electrode (Oz) at approximately 2 cm above the inion (occipital protuberance). All cases were light-adapted (photopic conditions) and the pupils were not dilated. The white flash stimulus (at a rate of 1 – 2 Hz, strength of 3 photopic cd.s.m-2, subtending a visual field of at least 20° and at a distance of 30 cm) was delivered using a Ganzfeld stimulator (with an impedance of \ 10 kX). The VEPs were recorded by an evoked potential inspection device. Peaks were designated as negative and positive in a numerical sequence (N1, P1, N2, P2, N3 and P3).

The patients were scheduled for subcutaneous erythropoietin injection (Eprex 20000 IU) once daily for three consecutive days. Post injection follow-up visit were scheduled after one month. Post injection recording of the visual acuity, color vision and VEP testing that was scheduled as soon as was feasible and was conducted in the same way as the pre injection VEP testing. Then, the patients were evaluated for the need of second course of erythropoietin injections according to the initial improvement on the visual function after the first 3 injections and the patients' desire. The second follow up was after 3 months regardless the need for a second course of erythropoietin injections by recording the visual acuity, color vision and recording VEP in the same way.

Data were analyzed using IBM SPSS software version 20.0. (Armonk, NY: IBM Corp). The normality of distribution of variables was verified using the Kolmogorov- Smirnov. Paired t-test was used for comparison between two periods for normally distributed quantitative variables. Wilcoxon signed ranks test was used for comparison between two periods for abnormally distributed quantitative variables. Significance of the obtained results was judged at the 5% level.

Results

The study included 20 eyes of 20 patients including 12 males and 8 females. The mean & standard deviation (range) of the age of the studied patients at presentation was 43.2± 17.3 (20- 67) years. The mean duration of the disease was 5.4± 3 months. The demographic characteristics of the study participants are presented in Table 1.

There were statistically significant improvements of visual acuity (Figure 1), color vision (Figure 2) and VEP parameters (Figure 3, 4) after one month ($p<0.001$) with 16 patients showing improvement. Twelve patients received the second injection of erythropoietin a month later; based on initial improvement and

patients' desire. However, other four patients that did not show significant improvement did not receive the second erythropoietin injection and four patients were satisfied by the encountered improvement and did not wish to take the second dose. The twelve patients that received the second erythropoietin injection continued improvement of visual acuity (Figure 1), color vision (Figure 2) and VEP parameters (Figure 3, 4) that were statistically significant after three months (p=0.002).

The better the initial visual acuity the more significant was the improvement on the visual acuity, those with starting poor visual acuity showed no or little improvement on their visual functions. Moreover VEP parameters at the time of the presentation provide an important prognostic tool for outcome of erythropoietin injection, those with N2P2 amplitude above 3 micrometer and P2 implicit time less than 140 milliseconds and SNR ratio within normal value according to standard stated by international society of electrophysiology of vision (ISCEV) show significant improvement on their visual function after EPO injection but those with marked delay of P2 implicit time, reduced N2P2 below the normal value and reduced SNR showed little or no improvement after erythropoietin injection.

Table (1): Distribution of the studied cases according to different parameters (n=20)

	No. (%)
Sex	
Male	12 (60%)
Female	8 (40%)
Age (years)	
Median (Min. – Max.)	42.5 (20 – 67)
Mean ± SD.	43.2 ± 17.3
Cause	
Post ischemic	6 (30%)
Post traumatic	4 (20%)
Post methanol	3 (15%)
Post papilledemic	3 (15%)
Post papillitic	2 (10%)
Post glaucematous	2 (10%)
Duration of disease (months)	
Median (Min. – Max.)	5 (1 – 12)
Mean ± SD.	5.4 ± 3
SNR ratio of the first recorded VEP	
Normal	14 (70%)
Reduced	6 (30%)

Discussion

This study demonstrated a statistically significant improvement on the visual functions after subcutaneous erythropoietin with no recorded systemic side effects. The three month duration between the baseline and the last follow up was important to confirm the stabilization of the visual function post EPO injection. Scrutiny of the VEP parameters and the initial starting visual acuity in the studied group reveals important prognostic factors for the outcome of erythropoietin injection as shown in our results. The P2 implicit time and the N2–P2 amplitudes improved post erythropoietin injection with successful improvement of the visual acuity and color vision compared to the pre injection findings that was statistically significant over the follow up period.

These promising results of our study are in accordance with previously published studies. For instance, some studies have successfully used EPO in the treatment of indirect traumatic ON at such doses, ranging from 2000 IU (intravitreal) to 10000 IU (intravenous) twice daily for 3 days or even higher doses [23, 24]. In a prospective and noncomparative study, 16 cases with methanol ON were included. All cases received the systemic therapy including metabolic stabilization in addition to detoxification and treatment with intravenous EPO (20000 units/day for 3 days). Similar to our study and counting on the clinical response, some cases received a second course of EPO. IV EPO showed to improve VA in cases with methanol ON and may be a promising treatment according to the results of this study[19]. Another study by Pakravan et al. [20]on 11 cases with ON due to methanol poisoning. The study has a difference in the methods compared to those we used in this study. They used IV EPO 10000 IU twice daily for 5 days. Interestingly, their clinical outcomes were as those shown in our study. Kashkouli et al [25] included 7 cases who received IV EPO (10,000 IU for 3 days) and 8 controls. After 5.8 months, the difference between baseline and final BCVA was significant for those treated with EPO. Moreover, Entezari et al [23] treated 18 cases with IV EPO (20,000 IU for 3 days) and showed that after 3 months, mean BCVA improved significantly.

This study was unique in investigating the therapeutic effect and the safety of subcutaneous EPO injection in the management of LSON due to various causes and setting prognostic factors for the patients that will benefit from erythropoietin injection even after the resolution of the acute attack of optic neuropathy and starting optic atrophy. However, we encountered some limitations. Top of the list is the small sample size and the lack of the control group with different causes of LSON as this was a pilot study. In addition, the follow up period was short but the three months follow up was sufficient to ensure the stabilization of the visual function and that there was no deterioration after the improvement obtained. Moreover, the lack of the structural correlation with OCT and the late onset of starting treatment with erythropoietin injection due to late referral of the cases are also notable limitations that can be avoided in future studies on a larger scales.

To recapitulate, this study puts the recommended regimen for subcutaneous erythropoietin injection to obtain maximal effect with no systemic side effects. Further studies are recommended to prove the outcome obtained in our study.

Declarations

Availability of data and material:

The data used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest

The authors declare no competing financial issues.

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Nothing to be acknowledged

Consent for publication

There is no identifying information about participants available in the article**,** so this issue is not applicable.

Ethical approval

All procedures performed in this study which involve human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Clinical Trials Registration

NCT04469777 (July 2020)

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Figures

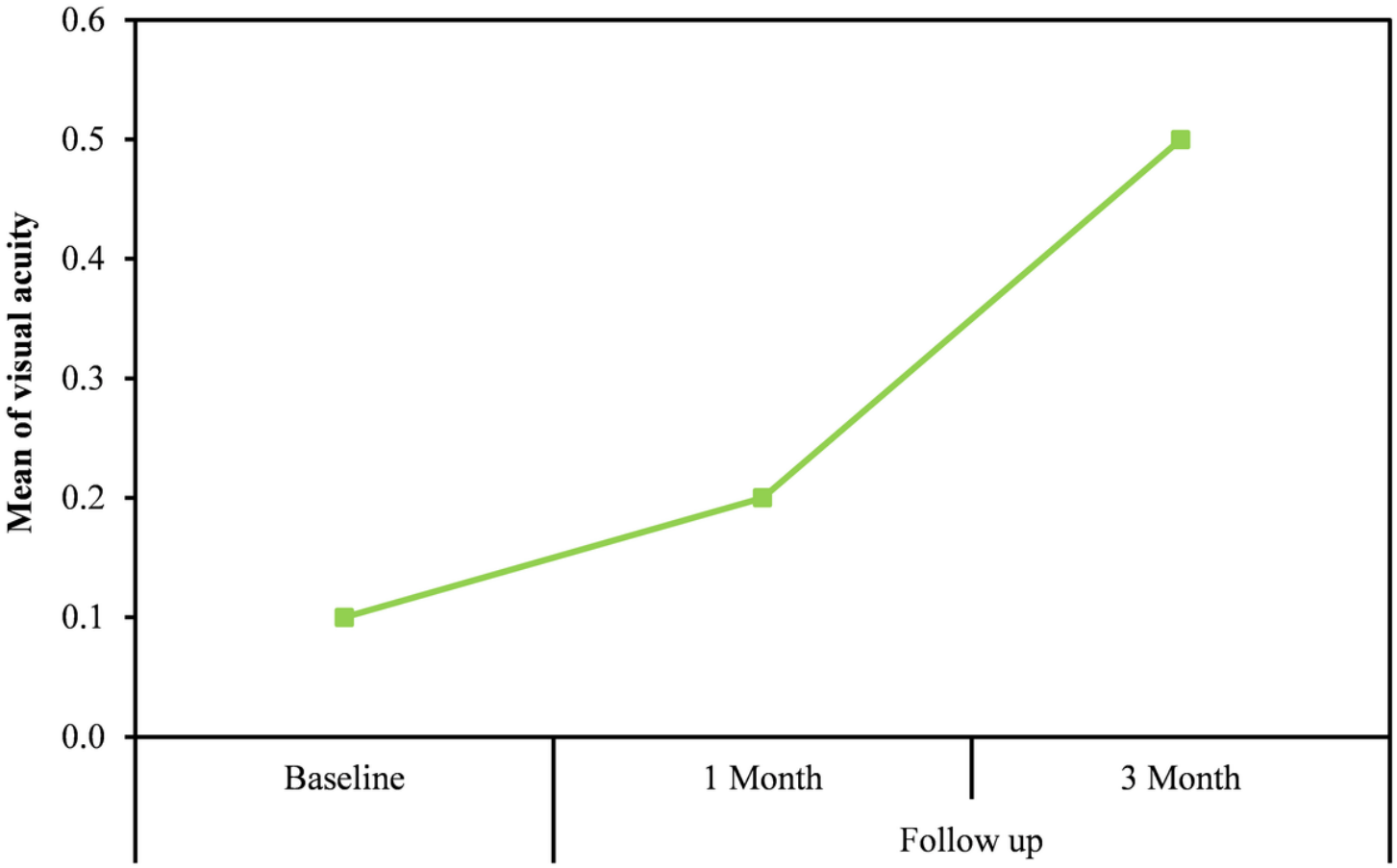

Figure 1

Comparion between the three studied periods according to visual acuity

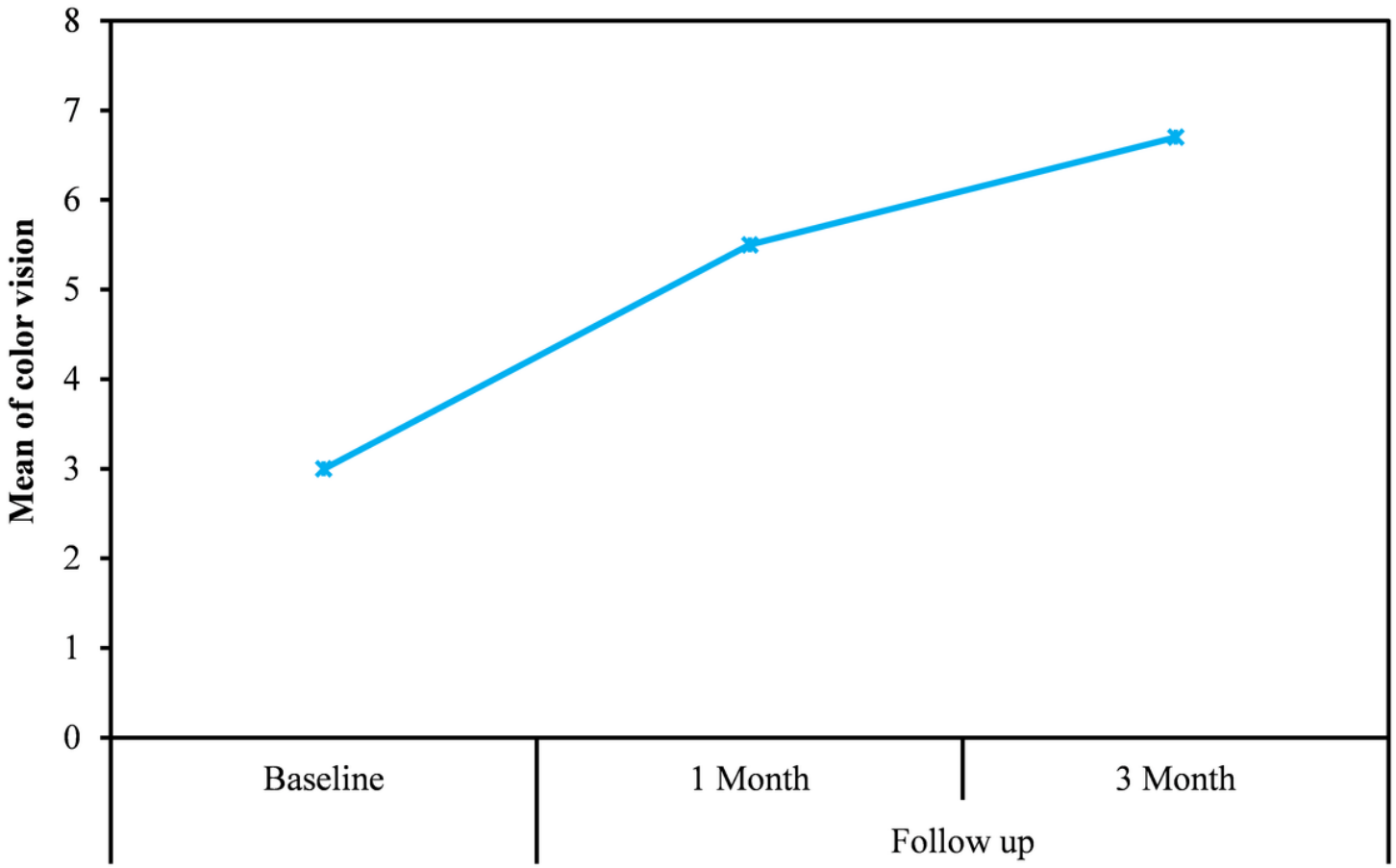

Figure 2

Comparion between the three studied periods according to color vision

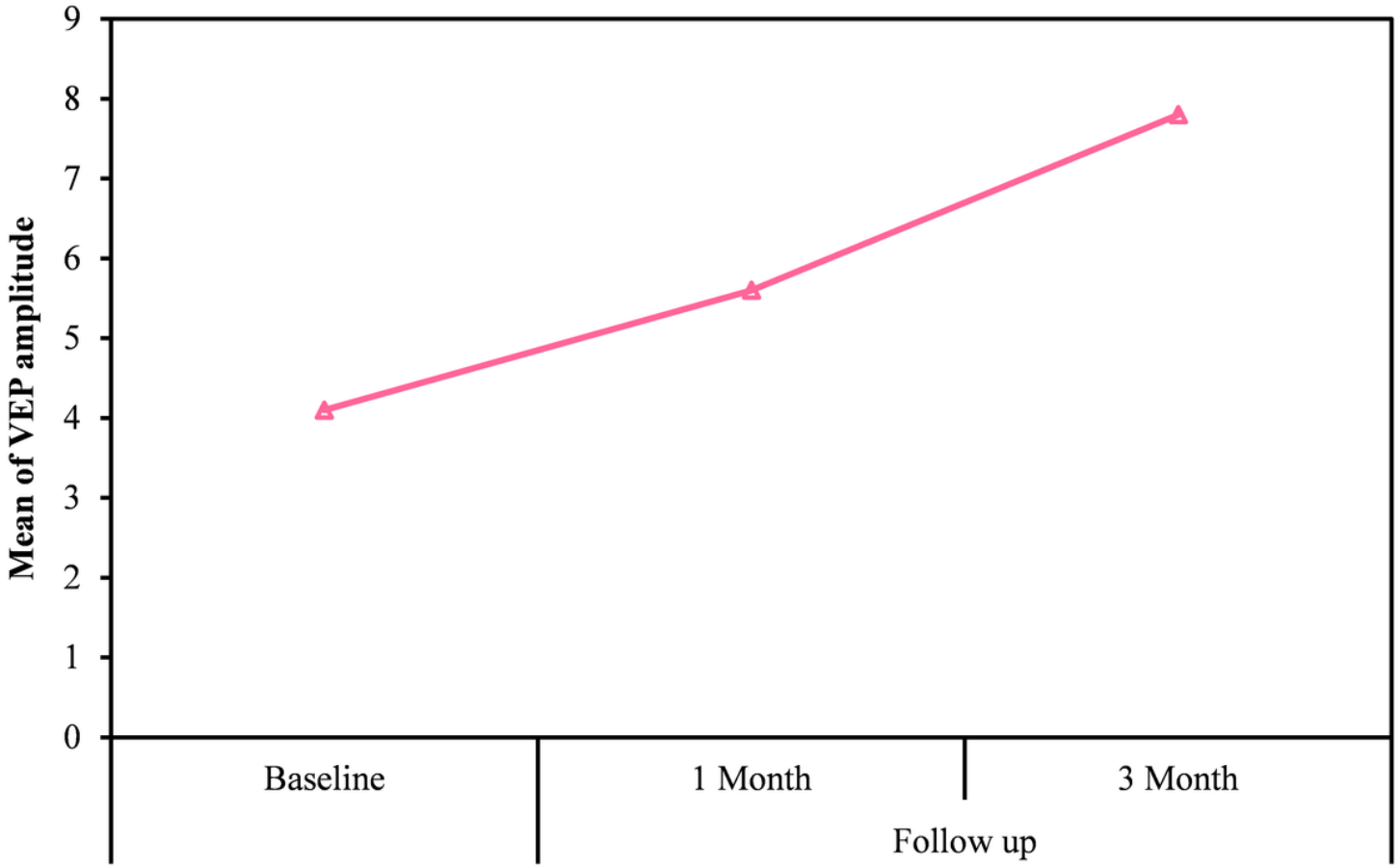

Figure 3

Comparion between the three studied periods according to VEP amplitude

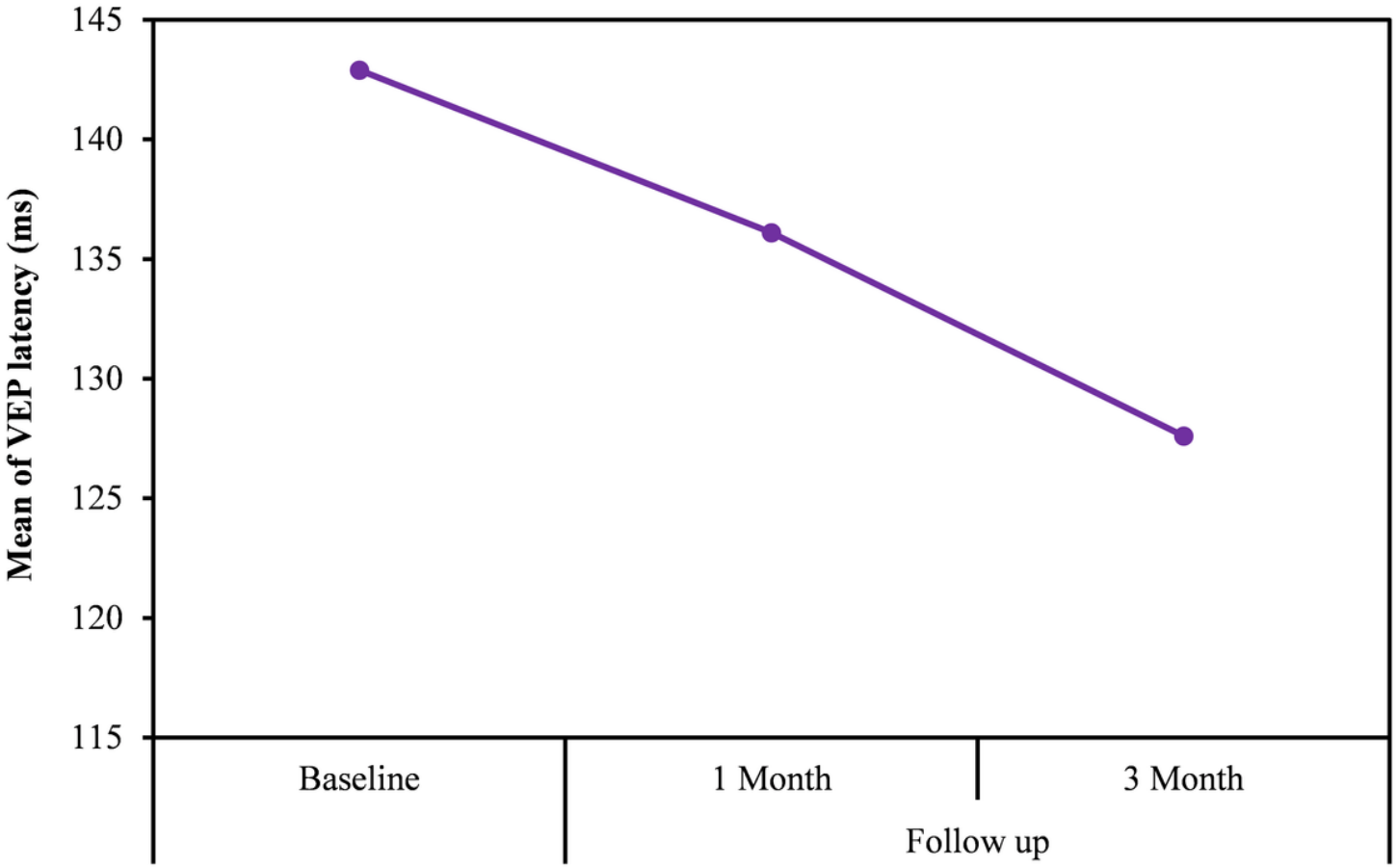

Figure 4

Comparion between the three studied periods according to VEP latency (ms)