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Adding erythropoietin to intravenous methylprednisolone in acute treatment of attacks of neuromyelitis optica spectrum disorders: A randomized controlled trial

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system (CNS) that prompts immediate potent treatment. Delaying treatment could leave debilitating sequelae. As erythropoietin (EPO) has shown neuroprotective effects, we studied the effects of adding EPO to intravenous methylprednisolone (IVMP) in patients with acute attacks of NMOSD.

Methods: NMOSD cases with acute attacks were included. Cases of optic neuritis (ON) and those with myelitis were separated. After randomization [with block sizes of 2 (1:1 ratio)], the patients in the intervention group received IVMP 1000 mg/day and intravenous (IV) EPO 20000 U/day for five days. IVMP 1000 mg/day and normal saline (NS) were administered in the control group. Staged eye score and motor forces were evaluated in the patients with ON and myelitis, respectively, at the time of the attack and three months later. Primary patient allocation and clinical assessments were blinded to the physicians.

Results: Mean age of participants was 53.87 ± 11.53 years. At follow-up, in the ON arm, the median improvement in staged eye score was 2 in the control and 5 in the intervention group.

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The difference was significant (P < 0.001). In the myelitis group, none of the patients in the control group had improvement in motor forces. All the patients in the intervention group showed substantial improvement with minimal or no remaining weakness. The difference was statistically significant (P = 0.029).
Conclusion: The results show the possible benefit of adding EPO to the classic IVMP in attacks of NMOSD in both visual and motor aspects.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system (CNS) that prompts immediate treatment. Most of the patients are women, between 30 to 50 years old.[1] The majority (around 90%) have the antibody against aquaporin 4, a channel for water transportation in specific sites of the CNS.[2] It mostly involves the spinal cord and optic nerves, both of which could have devastating impacts on the patients' lives. Optic neuritis (ON) in NMOSD is more severe than multiple sclerosis (MS) and could cause permanent vision loss. Myelitis attacks could cause necrotizing, longitudinally extensive lesions with poor recovery, leaving the patient paretic or incontinent. The classic "Lazarus effect" highlights the importance of early potent intervention to minimize the long-term sequelae of the disease.[3] To date, steroids and plasma exchange (PLEX) are the mainstays of NMOSD treatment in acute attacks.[4] Considering their efficacy,[5] the need for more efficient treatments is felt.

Erythropoietin (EPO) is a hormone mainly secreted from peritubular cells in the kidneys. Its primary role is to prevent apoptosis of the erythroid cells. It also enhances the maturation and proliferation of erythroid progenitor cells.[6] Its safety is well-approved as a treatment for anemia. In addition, studies have shown its role in neurogenesis and neuroprotection against oxidative stress.[7] Its potential anti-apoptotic, antioxidant, and anti-inflammatory effects on neurons have made it a candidate for treating neurologic conditions such as Parkinson's disease,[8] Alzheimer's disease,[9] epilepsy,[10] cerebral ischemia,[11] traumatic brain injury,[12] and diabetic neuropathy.[13]

Regarding demyelinating diseases, there is growing preclinical and clinical evidence that it may be a promising treatment alternative.[14-19] But to our knowledge, no study has been conducted in patients with NMOSD. We studied the effects of adding EPO to intravenous methylprednisolone (IVMP) in patients with acute attacks of NMOSD.

Materials and Methods

Patients: Overall, 20 NMOSD cases with acute attacks, admitted in Sina Hospital (a tertiary center in Tehran, Iran), between 2018 and 2020, were included. Diagnosis of NMOSD was made by a specialist in CNS demyelinating diseases, based on NMOSD diagnostic criteria 2015.[20] Patients with a history of anemia, malignancy, uncontrolled hypertension, stroke, myocardial infarction, renal failure, and those with hemoglobin levels upper than 17 were excluded. Attack was defined as a new focal neurologic deficit in a patient with NMOSD, lasting for more than 24 hours, not explained by infection.

Randomization: Thirteen cases of ON and seven patients with myelitis were separated. Then in each group, cases were allocated randomly into intervention or control arms, by a general practitioner. Block randomization with block sizes of 2 (1:1 ratio) was used.

Intervention: The patients in the intervention group received IVMP 1000 mg/day and intravenous (IV) EPO 20000 U/day for five days. IVMP 1000 mg/day and normal saline (NS) (as sham therapy) were administered in the control group for five days as well. All the patients were admitted to the neurology ward throughout the treatment period.

Clinical assessment: Symptoms and signs such as staged eye score (Table 1) and motor forces were evaluated by a neurology resident in the patients with ON and myelitis, respectively, at the time of the attack and three months later. The data were recorded in the patients' files. Follow-up was performed by the same neurology resident in the NMOSD clinic of Sina Hospital, three months after admission. Any new complaint after drug administration was recorded, looking for any known or unknown side effects.

Table 1. Definition of staged eye scores

Visual acuity	Staged eye score
1/2	1
1/2.5	2
1/3	3
1/4	4
1/5	5
1/6	6
1/8	7
Finger count	8
Hand motion	9
Light perception	10
No light perception	11

Blinding: Primary patient allocation and clinical assessment were blinded to the physicians. Only the responsible nurses were aware of the treatment groups.

SPSS software (version 26, IBM Corporation, Armonk, NY, USA) was used. Data from ON and myelitis groups were evaluated separately. Basic differences between the intervention and control groups were checked. Changes in staged eye score and motor forces after treatment were compared. Fisher's exact test (for parametric data), Mann-Whitney U test, and Moses test of extreme reactions (for nonparametric factors) were applied as needed.

Ethical issues: Informed consent was gained from all the patients before enrollment. The possible benefits and harms were explained. The proposal was approved by the Ethical Committee of Tehran University of Medical Sciences (ethical code: IR.TUMS.MEDICINE.REC.1398.360).

Results

Twenty patients with acute NMOSD attacks were admitted to our center during the study period. All of them agreed to take part in the study. All participants tested positive for anti-aquaporin-4 antibody [enzyme-linked immunosorbent assay (ELISA) technique was applied]. For nine patients, it was the first presentation of the disease. For those with prior history of the disease, the median disease duration was 3 years [interquartile range (IQR): 2-10] and median Expanded Disability Status Scale (EDSS) was 1 (1-3.25). Of all participants, seven presented with acute myelitis, and 13 presented with ON (Table 2).

In the ON group, four (30.8%) were men and nine (69.2%) were women. According to randomization, five patients received IVMP and NS, while the other eight received IVMP and EPO. The patients were between 17 and 43 years old (median: 32). Five patients were previously diagnosed cases of NMOSD of which one received azathioprine and the other four were on rituximab. No significant difference was seen between intervention and control groups, regarding gender, involved eye (right or left), and age. The staged eye score did not show a significant difference between the two groups at baseline ($P > 0.05$). At follow-up, only one ON case in the control group did not experience any level of improvement despite 7g IVMP and PLEX. However, the overall median improvement in staged eye score was 4 scores. It was 2 in the control and 5 in the intervention group. Using Moses test of extreme reactions, the difference was significant ($P < 0.001$).

In the myelitis group, two (28.6%) were men and five (71.4%) were women. All participants with myelitis were naive cases without any prior history of disease-modifying therapies (DMTs). Four patients were randomized to IVMP and NS group, while the other three received IVMP and EPO. Myelitis cases were between 29 and 56 years old (median: 42). No significant difference was seen between intervention and control groups, regarding gender and age. Baseline motor forces were not significantly different among the two groups ($P > 0.050$). Just one patient in the control group suffered severe weakness [Medical Research Council (MRC) Scale: 2/5] in lower extremities that did not respond to pulse therapy and even PLEX. Other participants' motor forces were at least 4/5 of MRC score (mild to moderate severity). None of the patients in the control group had improvement in motor forces at follow-up. All the patients in the intervention group showed substantial improvement with minimal or no remaining weakness.

The difference was statistically significant, regarding Fisher's exact test ($P = 0.029$) (Table 3).

Table 2. Basic characteristics of the patients

Optic neuritis group	**Intervention group**	**Control group**
Gender [n (%)]		
Men	3 (38.0)	1 (20.0)
Women	5 (62.0)	4 (80.0)
Age (year) [median (minimum-maximum)]	31.5 (21-43)	32.0 (17-34)
Side of involvement [n (%)]		
Right	4 (50.0)	4 (80.0)
Left	4 (50.0)	1 (20.0)
Myelitis group		
Gender [n (%)]		
Men	1 (33.0)	1 (25.0)
Women	2 (67.0)	3 (75.0)
Age (year) [median (minimum-maximum)]	42.0 (35-56)	37.0 (29-42)

Table 3. The outcome measures in each group

	Intervention arm	Control arm	P
Median improvement in staged eye score (optic neuritis group)	5	2	< 0.001*
Patients with substantial clinical improvement (myelitis group) (%)	100	0	0.029**

*Moses test of extreme reactions; **Fisher's exact test

No other clinical symptom or sign (significant sensory loss or sphincter problem) was found at any time. In all groups, no adverse event was reported by the patients nor found by the neurologist.

Discussion

The results show the possible benefit of adding EPO to the classic IVMP in treating the attacks of NMOSD in both visual and motor aspects. Regarding the aforementioned "Lazarus effect", this added benefit could result in notable changes in the patients' outcomes. No reported adverse event adds optimism.

Clinically, Najmi et al. showed the superiority of the combination of IVMP and EPO over IVMP alone in the treatment of relapses in patients with MS.[14] Previous to this study, a similar effect was seen in animal models.[19] The value of EPO has been shown even in progressive forms of MS.[21] On the other hand, in cases of unilateral acute ON of unknown or demyelinating origin, Shayegannejad et al. showed the benefit of adding EPO to IVMP on perimetric variables but not on optical coherence tomography. They concluded that more evidence was still needed in this regard.[22] In 2012, a phase 2 trial showed the positive effect of EPO on the retrobulbar diameter of the optic nerve and retinal nerve fiber layer (RNFL) thickness after 16 weeks of administration of EPO as an add-on therapy for treating acute ON.[23]

It is believed that the drug acts as an immune modulator.[15] Its production and role in the CNS have been of interest since 1994 when Masuda et al. found this novel site of EPO production.[24] There is evidence of its contribution to fetal CNS development.[25] Apoptosis prevention, decreasing inflammation, and neuronal repair promotion are some considered mechanisms of EPO neuromodulation.[17,26,27] Aside from protection against apoptosis as its key pathway of alteration in neurodegeneration, EPO could also enhance neurogenesis through the activation of brain-derived neurotrophic factors.[28] It also modulates cytokine release and oxidative stress reactions. More recent studies indicate that its epigenetic effects on microribonucleic acid (miRNAs) may have roles in mediating neurodegenerative pathways.[7] Considering the acute relapses, a study showed that EPO addition to the IVMP pulse therapy was of clinically significant benefit in acute relapses of animal models of MS.[19] Genc et al. believed that the effect of EPO on nitric oxide production and its protection of microglia against interferon-gamma and lipopolysaccharides (LPS) could predict its possible benefits in inflammatory diseases of CNS like MS.[29] Vittori et al. mentioned in their review that it seemed that EPO might not be a direct anti-inflammatory agent but it enhanced neuronal resistance against proinflammatory cytokines and was an aid in compensating for possible injuries.[30] We think that emerging data are in favor of the potential advantage of EPO in acute relapses of demyelinating diseases of the CNS besides the underlying neurodegenerative process.

One important limitation of our study is the limited number of cases. Furthermore, optic involvement would be better evaluated by more objective tools such as visual evoked potential or optic magnetic resonance imaging (MRI), not only by visual acuity. Larger studies with more detailed evaluations are essential to assess the advantages and disadvantages of this treatment option.

Conclusion

EPO could be a new adjuvant treatment for debilitating attacks of NMOSD. Future studies enrolling more patients are needed to study the potential benefit.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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