Taylor & Francis
Taylor & Francis Group

NEURO-OPHTHALMOLOGY
An International Journal of Neuro-Ophthalmology

Neuro-Ophthalmology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ioph20

Erythropoietin for the Treatment of Methanol Toxic Optic Neuropathy: Does It Really Work? A Case Series

Nooran O. Badeeb, Shaima Alharazi, Asmaa Mohammedsaleh, Hasan Hijazi, Nihal M. Sadaga & Manal Hadrawi

To cite this article: Nooran O. Badeeb, Shaima Alharazi, Asmaa Mohammedsaleh, Hasan Hijazi, Nihal M. Sadaga & Manal Hadrawi (19 Aug 2024): Erythropoietin for the Treatment of Methanol Toxic Optic Neuropathy: Does It Really Work? A Case Series, Neuro-Ophthalmology, DOI: 10.1080/01658107.2024.2391436

To link to this article: https://doi.org/10.1080/01658107.2024.2391436

NEURO-OPHTHALMOLOGY
https://doi.org/10.1080/01658107.2024.2391436

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Erythropoietin for the Treatment of Methanol Toxic Optic Neuropathy: Does It Really Work? A Case Series

Nooran O. Badeeb[a,b], Shaima Alharazi[c], Asmaa Mohammedsaleh[d], Hasan Hijazi[b], Nihal M. Sadaga[e], and Manal Hadrawi[b]

[a]Department of Ophthalmology, University of Jeddah, Jeddah, Saudi Arabia; [b]Department Ophthalmology, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia; [c]Department of Ophthalmology, King Abdullah Specialist Hospital, Makkah, Saudi Arabia; [d]Department Ophthalmology, King Abdulaziz University Hospital, Jeddah, Saudi Arabia; [e]Department of Medicine, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia

ABSTRACT

Erythropoietin (EPO) has demonstrated neuroprotective properties and has been used in small case series to treat methanol optic neuropathy. This study aims to evaluate the effectiveness of EPO. This retrospective case series included data from patients diagnosed with methanol optic neuropathy between November 2022 and December 2023 from two centers in Jeddah, Saudi Arabia. Demographic information, time of consumption of methanol to EPO treatment, and other treatments administered were collected. Vision assessment was performed before and after EPO treatment. A total of 8 male patients were included, with an average age of 38.25 ± 7.15 years. The median duration of the follow-up was 66 days, ranging from 13 to 660 days. The means of vision in the logMAR of both eyes before EPO treatment was 1.98 ± 1.08, which changed to 1.87 ± 0.89 after EPO treatment. Patient's presenting vision before EPO treatment is a significant positive predictor for the vision after treatment with coefficient = 0.782 and 95% CI = 0.349, 0.936. Time to EPO treatment was not statistically significant in defining end vision. Treating methanol optic neuropathy is challenging and time sensitive. In this case series, EPO and adjuvant steroids showed variable effects on visual improvement. Although the vision improved after the treatment, these differences were not statistically significant. Repeat EPO did not give better outcomes. Long-term follow-up is needed to determine the overall impact of EPO treatment.

ARTICLE HISTORY
Received 2 June 2024
Revised 4 August 2024
Accepted 8 August 2024

KEYWORDS
Methanol; optic neuropathy; blindness; toxic optic neuropathy; optic atrophy; alcohol

Introduction

Methyl alcohol (methanol) is a clear, colorless, and flammable liquid produced by the reaction of hydrogen with carbon monoxide or carbon dioxide. Methanol is metabolized in the body to formaldehyde by alcohol dehydrogenase, following which formaldehyde is rapidly converted to formic acid, a metabolite that causes most of the toxicity associated with methanol. The accumulation of formic acid results in metabolic acidosis and inhibition of mitochondrial cytochrome C oxidase (enzyme in the aerobic respiration pathway) and depletion of adenosine triphosphate, leading to axonal cell death.[1,2] Methanol is highly toxic for humans if ingested. Ingestion of as little as 10 mL can result in complete and permanent visual loss from bilateral optic neuropathy, and 30 mL can be fatal, although the fatal dose is typically 100–125 mL.[3] Toxicity usually occurs from accidental ingestion. For example, in some countries, alcoholic beverages are legally and religiously prohibited, and homemade or smuggled alcoholic drinks containing methanol are the source of toxicity.

The treatment of methanol optic neuropathy involves the use of various substances, including B-group vitamins and systemic steroids,[4] ethanol, and fomepizole.[5] However, despite attempts with these treatments, the success in improving the final visual acuity of patients is limited. Typically, patients with this condition only achieve a final visual acuity of counting fingers or worse.[6,7]

Erythropoietin (EPO) is a glycoprotein that was experimentally used in studies to improve vision in methanol optic neuropathy patients. Several small case series have documented improvement in vision.[7,8]

CONTACT Nooran O. Badeeb nooran.badeeb@gmail.com Department of Ophthalmology, University of Jeddah, Hamzah Ibn Al Qasim St, Al Sharafeyah, Jeddah 23218, Saudi Arabia

Supplemental data for this article can be accessed online at https://doi.org/10.1080/01658107.2024.2391436.

Here we present our experience with EPO along with the conventional treatment, in cases presenting with methanol optic neuropathy.

Methods

This is a retrospective case series that examined patients with the diagnosis of methanol optic neuropathy from the period of November 2022 to December 2023 from two centers in Jeddah, Saudi Arabia.

Methanol-induced optic neuropathy was defined as a painless progressive reduction of vision with evidence of recent methanol ingestion and negative ocular history of other causes of vision loss. The data collected included patient characteristics such as age at diagnosis and gender. All ophthalmological examinations were done and documented by a single neuro-ophthalmologist. The initial and final ophthalmological examinations consisted of the best-corrected visual acuity (BCVA), color vision test, pupillary reaction, anterior segment, and funduscopic examination.

Data about therapeutic interventions were obtained, along with the time to treatment with EPO. All patients initially received systemic therapy including metabolic stabilization and detoxification. All of the patients received 20,000 IU of intravenous EPO (human recombinant) for 3 consecutive days except for 1 patient who received subcutaneous 500 u Darbepoetin alfa weekly doses for 4 weeks. All patients underwent renal dialysis in the acute phase. Intravenous methylprednisolone 1 gram daily was given to all patients as an adjunct therapy ranging from 3 to 10 doses. Patients were observed for EPO side effects by a specialized nephrologist. Patients who met the inclusion criteria are those with history of acute vision loss after the ingestion of methanol, received any form of erythropoietin treatment, and have visual acuity documentation before and after the treatment. The exclusion criteria included patients with systemic comorbidities, history of hypertension, ocular disease that might alter the visual acuity results, disorder of hemoglobin, and history of thrombosis.

For the purpose of comparison, the Snellen acuity chart was converted to the logarithm of the minimum angle of resolution (LogMAR) with the values of 1.9, 2.3, 2.7, and 3.0 considered for visual analog scale of counting fingers (CF), hand motion (HM), light perception (LP), and no LP (NLP), respectively. The study was conducted after obtaining approval from the institutional review boards of the research ethics committees of the King Fahad Armed Forced Hospital in Jeddah reference number (REC 588). All data were maintained confidential without using identifiers, and subjects' privacy and confidentiality were assured.

Data analysis

Data entry and analysis were performed using Statistical Package for the Social Sciences (SPSS) software version 25. Number of EPO treatment repeats was described as frequency and percentage. However, quantitative variables as age, time to start EPO, duration of follow up in days, vision logMAR before and after erythropoietin were described by mean and standard deviation or median and range. The normality of quantitative data was tested using the Shapiro-wilk test. Paired samples t test was used to assess difference before and after EPO for normally distributed data. However, Related-Samples Wilcoxon Signed Rank Test was used for not normally distributed data. The correlation between vision before and after EPO was expressed in the form of scatter plot. Spearman correlation was used to examine associations. Simple linear regression was also used to predict vision after EPO from vision before the treatment. Statistical significance was set at $p < .05$.

Results

There was a total of 8 male patients (16 eyes). The average age at the time of presentation was 38.25 ± 7.15 years, which ranged from 25 to 49 years. The time taken to start EPO was 36 ± 51.38 days, ranged from 2 to 160 days with median of 20.5 days. With regards to repeating EPO treatment, 5 patients (62.5%) received EPO treatment once, 2 patients (25%) received it twice, and only 1 patient (12.5%) received the EPO treatment 3 times. The median duration of the follow up was 66 days, ranging from 13 to 660 day (Table 1).

The standard dose of 3 cycles of 20,000 IU of intravenous EPO was administered to 7 patients. The remaining patient received subcutaneous 500 u

Table 1. Characteristics of included patients ($n = 8$).

Variable	Mean ± SD	Median (range)
Age	38.25 ± 7.15	40.50 (25–49)
Time to start EPO	36 ± 51.38	20.5 (2–160)
Number of EPO treatment repeats		
Once No. (%)	5 (62.5)	
Twice No. (%)	2 (25.0)	
Triple No. (%)	1 (12.5)	
Duration of follow up in days	142.16 ± 215.71	66 (13–660)

EPO: Erythropoietin.

Darbepoetin alfa weekly doses for 4 weeks. All patients underwent renal dialysis in the acute phase. Intravenous methylprednisolone 1 gram daily was given to all patients as an adjunct therapy ranging from 3 to 10 doses. Patients number 5 and 7 underwent electrical therapy, and patient number 7 received stem cell therapy elsewhere during the chronic phase with no visual acuity improvement.

Table 2 shows the means of visual acuity before and after the treatment with EPO. The vision in the right eye, left eye, and both eyes before EPO treatment were 1.97 ± 1.22, 1.99 ± 1.02, and 1.98 ± 1.08, respectively, and changed to 1.90 ± 0.93, 1.85 ± 0.92, and 1.87 ± 0.89 after EPO treatment. Although the vision improved after the treatment, these differences were not statistically significant. Individual visual acuities before and after the treatment are listed in Table 3.

In addition, patient's vision before EPO treatment was the only significant positive predictor for the vision after treatment with coefficient = 0.782 and 95% CI = 0.349, 0.936 (Table 4).

By using Spearman correlation, Table 5 shows non-significant negative weak correlation between time taken to start EPO and vision after treatment (r = −0.164. $p = .726$)

All our patients received the erythropoietin treatment under the observation of nephrology and hematology experts, with no complications observed during and after the treatment duration

Discussion

Saudi Arabia has witnessed a significant increase in the occurrences of methanol toxicity across various regions in recent years. Insights into this matter were provided through the study conducted by Kabli et al.,[9] who shed light on this issue, focusing on a case series

Table 2. Vision log mar before and after EOP treatment ($n = 8$).

Vision log mar	Before EOP treatment, Mean ± SD	After EPO treatment, Mean ± SD	*p* value
Right eye	1.97 ± 1.22	1.90 ± 0.93	.461[a]
Left eye	1.99 ± 1.02	1.85 ± 0.92	.636[b]
Both eyes	1.98 ± 1.08	1.87 ± 0.89	.443[a]

[a]Related-Samples Wilcoxon Signed Rank Test, [b]Paired Samples t Test.

Table 3. Patients characteristics, time to EPO and visual acuities before and after EPO.

#	Age	Time to EPO	OD Pre Snellen (logMAR)	OS Pre Snellen (logMAR)	EPO repeats	OD post Snellen (logMAR)	OS post Snellen (logMAR)	Color vision	Fundus exam	Follow up duration	Doses of IVMP
1	25	12 d	NLP (3)	NLP (3)	2 (IV EPO)	NLP (3)	NLP (3)	0/16 OU	Pale disc OU	80 d	1
2	41	20 d	NLP (3)	HM (2.3)	2 (IV EPO)	CFNF (1.9)	CFNF (1.9)	0/16 OU	Diffuse disc swelling OU	34 d	1
3	37	7 d	NLP (3)	LP (2.7)	3 (IV EPO)	NLP (3)	NLP (3)	0/16 OU	Pale disc OU	28 d	3
4	40	2 d	20/40 (0.3)	CF 2M (1.9)	1 (IV EPO)	20/50 (0.48)	20/50 (0.48)	0/16 OU	Mild disc swelling OU	13 d	3
5	41	40 d	20/25 (0.1)	20/25 (0.1)	1 (IV EPO)	0.7 (20/100)	0.7 (20/100)	0/16 OU	Pale disc OU	180 d	10
6	41	160 d	CFNF (1.9)	CFNF (1.9)	1 (subcutaneous Darbepoetin)	CF (1.9)	CF (1.9)	0/16 OU	Pale disc OU		3
7	49	21 d	NLP (3)	NLP (3)	1 (IV EPO)	HM (2.3)	CF 50cm (1.9)	0/16 OU	Pale disc OU	660 d	6
8	32	30 d	20/400 (1.3)	20/200 (1.0)	1 (IV EPO)	CF (1.9)	CF (1.9)	0/16 OU	Pale disc OU	52 d	1

EPO: Erythropoietin, OD: ocular Dexter, OS: ocular Sinister, OU: Oculus Uterque, LogMAR: Logarithm of the Minimum Angle of Resolution, d: days, NLP: No light perception, LP: Light perception, HM: Hand Motion, CF: Counting fingers, CFNF: Counting fingers near face.

Table 4. Predictor of vision after EPO treatment.

Predictor	Coefficient	95% CI of Coefficient	*p* value
Vision before EPO treatment	0.782	0.349, 0.936	.000*

EPO: Erythropoietin, CI: Confidence Interval, *: Significant *p*-value is less than 0.05.

observed in the emergency room in Jeddah, Saudi Arabia. The study revealed alarming levels of methanol in the blood, with an average concentration of 142 mg/dL (ranging from 13 to 155 mg/dL) during the period spanning from November 2022 to January 2023. These findings underscore the severity of methanol toxicity cases in the region during that particular timeframe. Another study by Alrobaian et al.[6] showed that a high mean level of methanol ingestion was 621 ± 16.86 ml.

Blindness from optic neuropathy is a devastating sequalae from methanol toxicity,[10] causing irreversible damage. With rise of EPO usage and discovery in treatment of optic neuropathy, a sense of optimism has emerged. Multiple studies showed efficacy of EPO in restoring vision in methanol optic neuropathy.[8,11,12] Our case series of 8 patients showed a trend of improved vision; however, it was not statistically significant. In adherence to our results, a nonrandomized interventional comparative study by Pakravan et al.[12] found that vision improvement in the group treated with adjuvant EPO along with steroids was not statistically significant than the group with steroids alone. In contrast, the results of the largest prospective study that used EPO along with IVMP for methanol optic neuropathy was done by Tabatabaei et al.,[11] who described 105 patients with improved vision after EPO. They suggested that using EPO within the first month of ingestion was a positive predictor value of vision improvement. Unlike our cohort, where time to EPO administration was not a predictor factor, the only positive predictor in our series was vision at presentation, with patients having favorable final visual acuity if their presenting vision was better. Another prospective study by Pakdel et al.[13] showed improved vision in their cohort who were treated with EPO with vision improvement from average LP (3.00 logMAR) pre EPO to 20/200 (1.00 logMAR) post EPO treatment.

Zamani et al.[4] reported a transient effect of EPO, with initial improvement and subsequent decline in vision after 2 months. In our data, only one patient showed initial improvement in vision to CF near the face, then declined to NLP again in both eyes. And an attempt of another cycle of EPO did not improve the vision afterward. By far, the only study that experienced the effect of a maintenance dose of EPO was by Tabatabaei et al.,[11] who showed that a monthly dose of EPO 10000IU BID and IVMP for 6 months had good results in terms of vision preservation.

Other modes of administration of EPO were tried; Alavijeh et al.[7] reported the first case of intravitreal treatment of EPO along with the standard dose of IV EPO in improving the vision from Poor LP in both eyes to 20/800. In addition, Nekoueifard and Majidi[10] reported successful treatment with subcutaneous injection of EPO, vision pretreatment being NLP (3.00 logMAR) to vision post treatment 20/200 (1.00 logMAR).

Known adverse effects from erythropoietin injections includes high blood pressure, pulmonary embolism, and thromboembolism,[14,15] However, no adverse events were reported in our study.

Limitations

This study had several limitations that should be considered. First, the level of methanol toxicity was not measured, which makes it difficult to assess the impact of methanol levels on the effectiveness of treatment. Second, the sample size was small, affecting the statistical power and generalizability of the findings. Additionally, the administration of Erythropoietin (EPO) along with steroids and supportive therapies makes it challenging to evaluate individual treatment effect of EPO.

Table 5. Correlation between time taken to start EPO and vision after treatment.

Correlation	Time to start EPO treatment, Correlation Coefficient	*P* value
Vision after EPO treatment	−0.164	.726

EPO: Erythropoietin.

Conclusion

In our study, the use of EPO did not show a statistically significant difference in vision improvement. The repeat of EPO did not show better visual prognosis. The only positive predictive factor for end visual acuity was the presenting vision. To validate the true magnitude of EPO in treating methanol-induced optic neuropathy, future studies with a larger number of patients are necessary. These studies should aim to assess the effectiveness of EPO alone and in conjunction with systemic therapy. Measuring the level of methanol toxicity at the acute stage can help understand the variability of vision improvement and whether it plays a role in response to treatment. By addressing these limitations and conducting more comprehensive research, a clearer understanding of EPO's role in managing methanol optic neuropathy can be achieved.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

References

1. Liesivuori J, Savolainen AH. Methanol and formic acid toxicity: biochemical mechanisms. Pharmacol Toxicol. 1991;69(3):157–163. doi:10.1111/j.1600-0773.1991.tb01290.x.
2. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA. American Academy of Clinical Toxicology ad Hoc Committee on the treatment guidelines for methanol poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol. 2002;40(4):415–446. doi:10.1081/clt-120006745.
3. Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. Med Toxicol. 1986;1(5):309–334. doi:10.1007/BF03259846.
4. Zamani N, Hassanian-Moghaddam H, Shojaei M, Rahimian S. Evaluation of the effect of erythropoietin + corticosteroid versus corticosteroid alone in methanol-induced optic nerve neuropathy. Cutan Ocul Toxicol. 2018;37(2):186–190. doi:10.1080/15569527.2017.1373121.
5. Abramson S, Singh AK. Treatment of the alcohol intoxications: ethylene glycol, methanol and isopropanol. Curr Opin Nephrol Hypertens. 2000;9(6):695–701. doi:10.1097/00041552-200011000-00017.
6. Alrobaian M, Alkhuraiji A, Almohanna R, Alshehri M, Alyahya B. Visual outcome of methanol toxic optic neuropathy after erythropoietin treatment in Riyadh, Saudi Arabia. Saudi J Ophthalmol. Published online 9000. https://journals.lww.com/sjop/fulltext/9000/visual_outcome_of_methanol_toxic_optic_neuropathy.99975.aspx.
7. Rashidi Alavijeh M, Mazaheri-Tehrani S, Saffari AS, Fazel M, Fazel F. Intravenous plus intravitreal erythropoietin for management of methanol toxicity optic neuropathy: a case report and brief review. Clin Case Rep. 2023;11(3):e7011. doi:10.1002/ccr3.7011.
8. Vafapour F, Jahangiri-Mehr S, Hassanzadeh S. Delayed reversal of methanol-induced blindness in an adult by a combination of erythropoietin and a high dose of methylprednisolone: a case report. J Med Case Rep. 2023;17(1):181. doi:10.1186/s13256-023-03899-w.
9. Kabli AO, Felemban AM, Nasri AK, Aljedani FA, Bedairi AM, Alghamdi MM, et al. Outcome of methanol toxicity outbreak in Saudi Arabia: case series study. Cureus. doi:10.7759/cureus.41108. Accessed June 28, 2023.
10. Nekoueifard S, Majidi M. Subcutaneous erythropoietin reverses optic neuropathy induced by methanol poisoning: three case reports. Iran J Toxicol. 2020;14(3):187–192. doi:10.32598/ijt.14.3.537.2.
11. Tabatabaei SA, Amini M, Haydar AA, Soleimani M, Cheraqpour K, Shahriari M, et al. Outbreak of methanol-induced optic neuropathy in early COVID-19 era; effectiveness of erythropoietin and methylprednisolone therapy. World J Clin Cases. 2023;11(15):3502–3510. doi:10.12998/wjcc.v11.i15.3502.
12. Pakravan M, Esfandiari H, Sanjari N, Ghahari E. Erythropoietin as an adjunctive treatment for methanol-induced toxic optic neuropathy. Am J Drug Alcohol Abuse. 2016;42(6):633–639. doi:10.1080/00952990.2016.1198800.
13. Pakdel F, Sanjari MS, Naderi A, Pirmarzdashti N, Haghighi A, Kashkouli MB. Erythropoietin in treatment of methanol optic neuropathy. J Neuroophthalmol. 2018;38(2):167–171. doi:10.1097/WNO.0000000000000614.
14. Cui X, Wan Z, Ma Z, Liu L, Yang Y. Occurrence of acute pulmonary embolism induced by recombinant erythropoietin during treatment of pure red cell aplasia associated with thymoma: a case report. Medicine (Baltimore). 2019;98(10):e14789. doi:10.1097/MD.0000000000014789.
15. Brunkhorst R, Nonnast-Daniel B, Koch KM, Frei V. Hypertension as a possible complication of recombinant human erythropoietin therapy. In: Gurland H, Moran J, Samtleben W, Scigalla P, Wieczorek L, eds. *Contributions to Nephrology*. Vol. 88. S. Karger AG; 1991:118–126. doi:10.1159/000419521.