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## Case Reports:

# Subcutaneous Erythropoietin Reverses Optic Neuropathy Induced by Methanol Poisoning: Three Case Reports

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## ABSTRACT

**Background:** Methanol is a highly toxic alcohol and causes such severe side effects as CNS depression, blindness, acute renal failure and even death.

**Methods:** Patients were three male referrals (aged 29-56 years) to the poisoning center at Taleghani Hospital, Urmia, Iran, in 2020. They had unknowingly ingested methanol. Their chief problems were bilateral blindness and metabolic acidosis. Upon taking medical history and physical examinations, they were assessed by an ophthalmologist, while testing the arterial blood gases and standard laboratory tests. They were given standard treatments and antidotes 3-4 days, which did not reverse the blindness. Subsequently, each patient was injected with five doses of subcutaneous erythropoietin every second day. The visual acuity progress was monitored daily until their discharge from the hospital.

**Results:** Following 3-4 days of ineffective standard treatments, patients were injected with low doses of subcutaneous erythropoietin, which gradually reversed the visual acuity to normal level over the next 7 to 9 days. The patients were discharged from the hospital 10-12 days post admission, with normal visual acuity and without having any side effects.

**Conclusion:** The subcutaneous erythropoietin effectively relieved the acute optic neuropathy and reversed the blindness to normal vision. This study is the first to investigate the therapeutic effects of subcutaneous erythropoietin in the treatment of optic neuropathy secondary to methanol intoxication.

**Keywords:** Methanol; Blindness; Optic neuropathy; Subcutaneous erythropoietin

## Introduction

Methanol or methyl alcohol is a highly toxic compound [1]. Methanol is metabolized to formate (formic acid), which is responsible for visual impairment, blurred vision, impaired visual field and ultimately blindness. Other complications and adverse effects of methanol poisoning include: metabolic acidosis, coma, multi-organ failure and even death [2-6]. Because of high prevalence and mortality in Iran due to methanol intoxication, early diagnosis and effective treatment is of clinical significance [7].

Ethanol, fomepizole (Antizol) and hemodialysis are effective in the management of methanol poisoning [8]. Furthermore, autologous bone marrow stem cells, vitamins B1, B6 and B12 (Neurobion), folic acid, sodium bicarbonate, methyl prednisolone and erythropoietin

are recommended for the treatment of methanol poisoning [9-15]. Erythropoietin has neuro-protective, neuro-regenerative, anti-inflammatory and antioxidant effects. Although the mechanism of action is not fully understood, it is believed to inhibit the apoptosis and facilitate the repair process of damaged neurons [16]. Further, erythropoietin (Eprex) has been used in the treatment of chronic neurodegenerative complications, such as ALS, Parkinson and Alzheimer diseases, and stroke [17].

Although intravenous erythropoietin is relatively effective in the management of optic neuropathy and blindness, it has severe side effects, such as cardiovascular complications, hypertension, thrombosis and acute pulmonary embolism [18, 19]. This study aimed to investigate the therapeutic effect of subcutaneous erythropoietin in the management of optic neuropathy due to methanol intoxication.

## Materials and Methods

Three patients with accidental methanol ingestion (100-150 ml) were referred to the poisoning center at Taleghani Hospital in Urmia, Iran, early in 2020. Table 1 represents the patients' characteristics, the amount of methanol ingested, and the number of days after methanol intoxication for their admission into and discharge from the hospital. Their chief complaint was bilateral blindness. The patients' visual acuity was assessed immediately by an ophthalmologist. After taking the medical history and physical examinations, arterial blood gases analysis and blood chemistry tests were ordered, and the patients were admitted to the hospital (Table 2). At this point, they were provided with antidotes, hemodialysis and the standard anti-methanol poisoning treatments (Table 3). Since the patients' vision was not restored after three to four days of providing the treatment protocol, they were scheduled for subcutaneous erythropoietin injections every second day for a total of five doses. The patients' visual acuity was regularly examined by the same ophthalmologist and clinical toxicologists until they regained full visual acuity, allowing their safe discharge from the hospital. Details of the treatment protocol from admission to discharge are shown in Table 3.

## Results

In this study, three male patients were admitted to the hospital with bilateral blindness due to methanol intoxication. The average age of the patients was 40 years old with a history of alcohol abuse as noted in their past medical records. Table 1 presents the patients' characteristics, and the duration of hospital stay and discharge. The significant finding upon the initial clinical examination was hypertension present in two of the patients. Other clinical features, such as pulse rate, respiration, axillary temperature and oxygen saturation were reasonably within normal ranges. Data representing the blood chemistry analyses indicated metabolic acidosis and abnormal renal function. The results of standard clinical exami-

**Table 1.** Patients' characteristics, hospital admission and discharge.

| Characteristics | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Age (year) & gender | 35, male | 29, male | 56, male |
| Amount of methanol ingested (ml) | 150 | 100 | 100 |
| Admission time post intoxication (days) | 4 | 4 | 3 |
| Discharge from the hospital (days) | 12 | 10 | 10 |

**Table 2.** Results of the clinical exam and blood chemistry analyses upon hospital admission

| Case | Clinical Exam Findings | | | | | Blood Chemistry Data | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PB | P | RR | Temp | O2% | pH | $HCO_3$ | $pCO_2$ | BE | CPK | BUN | Cr. | Na+ | K+ |
| 1 | 150/100 | 78 | 18 | 36.5 | 92 | 7.2 | 9.4 | 23.9 | -16.3 | 137 | 33 | 2.15 | 135 | 3.4 |
| 2 | 120/80 | 86 | 20 | 37 | 93 | 7.3 | 20 | 42 | -6 | 166 | 38 | 1 | 141 | 3.7 |
| 3 | 150/90 | 84 | 14 | 36.5 | 95 | 7.2 | 7.9 | 18.8 | -16.9 | 187 | 65 | 3.7 | 137 | 5.1 |

BP: Blood pressure (mmHg); P: Pulse rate (per min.); RR: Respiratory rate (per min.); Temp: Temperature (°C); $O_2$: Oxygen saturation (%); BE: Base excess (mmol/l). Cr.: Creatinin; Normal $HCO_3$ range: 22-26 mEq/l

**Table 3.** Treatment protocol and the patients' clinical outcomes since hospital admission.

| Treatment Protocol | Patients | | |
|---|---|---|---|
| | Case 1 | Case 2 | Case 3 |
| Hemodialysis | 3hr/day × 2 days | 3hr/day × 2 days | 3 hr/day × 2 days |
| Diluted ethanol, oral * | 80 ml Ω → 50 ml/4hr × 3 days | 50 ml Ω → 50 ml/6hr × 4 days | 50 ml Ω→ 50 ml/6 hr × 3 days |
| Folic acid, oral | 20 mg/4hr × 5 days | 20 mg/4hr × 5 days | 20 mg/4hr × 5 days |
| Prednisolone, oral | 30 mg/D × 3 days | 20 mg/8hr × 5 days | 10 mg/8hr × 3 days |
| Neurobion, IM | 1 injection/D × 5 days | 1 injection/D × 3 days | 1 injection/D × 3 days |
| Na+HCO3 (8.4%), IV | 100 ml → 50 ml/8hr × 2 days | 100 ml → 25 ml/8hr × 2 days | 100 ml → 100 ml/8 hr × 3 days |
| Erythropoietin, IU, SC | 20.000 → 4.000 × 4 dose¶ | 10.000 → 4.000 × 4 dose¶ | 4.000 → 4.000 × 4 dose¶ |
| Clinical Progress & Outcome | | | |
| Light perception | 5 days | 6 days | 6 days |
| Finger counts | 7 days | 7 days | 8 days |
| Full vision recovery | 12 days | 10 days | 10 days |

* From a 99% ethanol diluted 1/5 with fruit juice; Ω Stat dose; →Followed by; D: Day; ¶ Every 2nd day

IM: Intramuscular; IV: Intravenous; IU: International unit; SC: Subcutaneous

nations and blood chemistry analyses at admission are presented in Table 2. Subsequently, hemodialysis was performed to expedite the excretion of methanol and the metabolites. Other components of standard medical care administered were ethanol, vitamins B1, B6 and B12 (Neurobion), folic acid, sodium bicarbonate, and prednisolone, the details of which are presented in Table 3. The patients' visual acuity was not restored after three to four days of implementing the standard treatments against methanol poisoning. Therefore, a new treatment plan was proposed that were tailored to each patient's condition and response. The new treatment consisted of five doses of subcutaneous erythropoietin (Eprex) injections, the details of which are presented in Table 3 for each patient. The clinical findings and the erythropoietin treatment protocol for each case are presented below.

## Participants

Case 1 was a 35 years old male patient who had ingested 150 ml of methanol accidentally. He had no past history of neurological deficits, trauma and chronic alcoholism. However, he had a history of corticosteroids and anabolic steroids abuse dating back to five years. He was admitted five days after his methanol intoxication with the chief complaints being bilateral blindness, vomiting and gastrointestinal upset. On admission, the pupils showed bilateral mydriasis and were unresponsive to light. Upon examination of the fundus by an ophthalmologist bilateral optic disc edema was diagnosed. Other significant clinical findings upon admission were hypertension (150/100 mmHg) and metabolic acidosis (Table 2). The bilateral blindness did not improve after three days of standard treatments. Subsequently, treatment with subcutaneous erythropoietin (Eprex) was initiated at 20,000IU (10,000 × 2 daily) and continued at 4000IU every second day for a total of five injections (36,000 IU, total). The patient was discharged 12 days post hospital admission, having regained his normal vision without presenting any side effects.

Case 2, a 29 years old male, was admitted to the poisoning center due to ingestion of 100ml of unknown alcohols. He had a history of chronic alcoholism and smoking, as stated in his past medical records. Upon admission 3 days post intoxication, his chief complaints were bilateral blindness and headache. The pupils showed bilateral mydriasis with minimal response to light. Upon examination of the fundus by an ophthalmologist bilateral optic disc edema was diagnosed.

The only significant clinical finding upon admission was metabolic acidosis with normal blood pressure (Table 2). The bilateral blindness did not improve after three days of standard treatments. Subsequently, treatment with subcutaneous erythropoietin (Eprex) was initiated at 10,000IU and continued at 4000IU every second day for a total of five injections (26,000 IU, total). The patient was discharged after 10 days of hospitalization, having regained his normal vision and without any evident side effects.

Case 3, a 56 years old male, was admitted to the poisoning center complaining of gradual and bilateral loss of vision two days after ingestion of 100 ml of a homemade alcohol. He was a heavy smoker and had been

diagnosed with chronic alcoholism and ischemic heart disease in his past medical records. On admission, the pupils showed bilateral mydriasis and were not responsive to light. Upon examination of the fundus by an ophthalmologist bilateral optic disc edema was diagnosed. Other significant clinical findings were hypertension (150/90 mmHg) and metabolic acidosis (Table 2). The bilateral blindness did not improve after three days of standard treatments. However, the subsequent treatment with subcutaneous erythropoietin (Eprex) was initiated at 4,000 IU and continued at the same dose every second day for a total of five injections (20,000 IU, total). The patient was discharged after 10 days since hospital admission, having regained his normal vision and without demonstrating any detectable side effects.

## Discussion

Optic neuropathy and blindness are critical and disabling complications of methanol poisoning [5]. In recent years, intravenous injection of erythropoietin has been used to treat the optic neuropathy and blindness due to methanol intoxication [9, 12]. Despite its relative success, this approach has been associated with severe cardiovascular complications, hypertension, thrombosis and acute pulmonary embolism [18, 19]. This study was; therefore, planned to investigate the subcutaneous injection of erythropoietin as an alternative therapeutic approach to the treatment of optic neuropathy and blindness secondary to methanol poisoning. The current study demonstrated that five subcutaneous injections of erythropoietin every second day successfully resulted in the recovery of vision and the associated optic nerve neuropathy due to methanol intoxication.

In general, the results of this study are consistent with those reported by a previous study conducted in 2017 by Pakravan et al. [20] on 11 patients with optic neuropathy due to methanol poisoning. The latter study had some differences in the methodology compared to those used in the current study. That study used intravenous erythropoietin (10,000 IU) twice daily for 3 days plus intravenous methyl prednisolone (500 mg) twice daily for five days followed by oral prednisolone (1 mg/kg) for two weeks. However, their clinical outcomes were successful [20] as those documented in the current case reports.

A number of studies have successfully used erythropoietin in the management of optic neuropathy due to methanol poisoning [11-16] at such doses, ranging from 2000 IU (intravitreal) to 10000 IU (intravenous) twice daily for three days [15, 21]. Conversely, in most previous studies, erythropoietin were injected (intravenous or intravitreal) with or without corticosteroid in the management of optic neuropathy due to methanol poisoning and also, erythropoietin were injected at high dosages but in fewer repeats [17, 20].

Recommendations: To prevent the cardiopulmonary complications, hypertension and thrombo-embolism [18, 19], clinicians who prescribe erythropoietin for the management of methanol poisoning are advised to monitor the patients' blood pressure regularly and use antihypertensive and anticoagulant drugs as appropriate preventive measures.

Directions for Future Studies: The following concepts are promising topics for future research and to advance the current clinical knowledge about the effects of erythropoietin in the management of methanol intoxication and its side effects:

To establish the expected action of erythropoietin and to predict potential clotting in the cardiopulmonary vasculature, the patient's RBC, WBC, platelets should be counted upon admission, and at the start, during and end of the subcutaneous erythropoietin treatment.

To explore whether erythropoietin might facilitate the methanol metabolism, the blood methanol levels should be measured systematically prior, at the beginning, during and at the end of subcutaneous erythropoietin treatment. To explore the potential mechanism of action of erythropoietin in the inhibition of optic neuropathy and recovery of the eye sight.

Also, follow-up studies are recommended to investigate the lasting effect of erythropoietin on the recovery of visual acuity, and development of cardiopulmonary and renal complications. Study Limitations: The main limitation of this study was limited laboratory facilities and personnel to measure the blood methanol levels. As a result, hemodialysis was performed to facilitate the elimination of methanol from the blood and to corroborate the clinical findings and arterial blood gas analyses.

## Conclusions

In this study, the three cases of methanol poisoning recovered their sight successfully after treatment with low doses of subcutaneous erythropoietin without suffering any side effects, enabling their discharge from the hospital within 10 to 12 days post treatment. This study serves as a starting point in the investigation of the efficacy and safety of subcutaneous erythropoietin at low doses versus methanol intoxication. However, elucidation of

other benefits and mechanism of action of erythropoietin in the management of optic neuropathy and reversing the blindness due to methanol poisoning awaits future research.

## Ethical Considerations

### Compliance with ethical guidelines

This article was written after obtaining informed consent from the patients and their families, whose identities remained strictly confidential. All authors met the criteria of authorship based on the recommendations of the international committee of medical journal editors.

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### Author's contributions

Conceptualized the research questions and methodology, and supervised the study: Mohammad Majidi; Recruited the patients, provided the treatments and conducted the study: Solmaz Nekoueifard, Mohammad Majidi; Wrote the initial draft of the manuscript and assisted: Solmaz Nekoueifard; Preparation of the final draft of the submission: Mohammad Majidi.

### Conflict of interest

All authors were equally contributed in preparing this article.

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