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Research Paper

The Adverse Reactions of Erythropoietin in Methanol Toxicity: A Descriptive Study

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ABSTRACT

Background: Nowadays, erythropoietin is employed as a substitute therapy for eye ailments, particularly optic nerve damage induced by methanol toxicity. Despite its benefits, erythropoietin can have negative effects on blood factors. These effects may include thrombosis, stroke, seizures, and changes in hematological function. This study examined the adverse effects of erythropoietin on individuals suffering from optic neuropathy caused by methanol.

Methods: This study was a prospective descriptive study at Loghman Hakim Hospital, Tehran City, Iran, in 2022. The study involved individuals who suffered from methanol poisoning and were administered erythropoietin twice a day for three days, with a dosage of 10000 units each time. Patients were examined up to 6 weeks after discharge in terms of increased hemoglobin levels, seizures, central vascular thrombosis, and heart attack or stroke. The data was analyzed by SPSS software, version 18.

Results: The study comprised of 37 patients. No patient reported seizures, heart and cerebral strokes, and deep vein thrombosis except polycythemia. After being discharged from the hospital, the mean hemoglobin levels increased by 2.01% six weeks later compared to the levels measured during admission. Moreover, there was a 2.4% rise in hemoglobin levels six weeks after discharge when compared to the levels measured two weeks after being discharged.

Conclusion: Using erythropoietin to treat optic neuropathy can improve vision, but it also carries the risk of increasing hemoglobin levels, which must be monitored closely in treated patients.

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Introduction

Methanol poisoning can be a life-threatening condition and has a mortality rate that varies between 18 and 44%. Around 5000 cases are diagnosed annually in the US, with an incidence rate of 6.4 cases per one million hospitalizations. The majority of patients are male (70%) compared to female cases (30%). The mean age of patients is 38±18 years [1]. The Middle East is facing a significant issue with methanol poisoning, particularly in Iran where 84 deaths were reported during an outbreak in 2018. A study conducted in 2013 found that there were 44 cases of methanol poisoning resulting in death in Iran within a single year [2, 3].

Methanol poisoning and the resulting formic acid metabolism product experience toxic effects due to the ineffective metabolism of formic acid in primates, including humans [4]. The first report of methanol toxicity to the visual system dates back to 1855 [1], and methanol-induced optic neuropathy can cause long-term or irreversible visual impairment by damaging and impairing the optic nerve and other structures such as the retina, chiasms, and the optic tract [5]. Approximately 50% of methanol poisoning cases exhibit visual symptoms, but the exact dose that causes pathological changes in the human visual system is unknown and may depend on individual metabolic predisposition [6, 7].

The timely initiation of treatment for Me-ION is crucial for the recovery of visual function after survival, as stated by Tanrivermis Sayit et al. [8]. The systemic treatment of methanol poisoning aims to limit metabolic acidosis, inhibit the hepatic metabolism of methanol into toxic metabolites, and facilitate the elimination of these compounds from the body [9]. In recent years, erythropoietin (EPO) has been recognized as a promising therapeutic method for improving the visual acuity of patients with various types of optic neuropathies [10].

The primary function of the glycoprotein hormone Erythropoietin (EPO) is to regulate erythropoiesis by promoting the growth and development of hematopoietic stem cells, while also inhibiting apoptosis [11]. The normal growth of the human eye is dependent on EPO, which is expressed in higher concentrations in the retina and retinal pigment epithelium (RPE) compared to plasma [12, 13]. This hormone plays a crucial role in safeguarding the retina from hypoxic damage and excessive exposure to bright light. Studies have shown that EPO can prevent the death of photoreceptor cells caused by intense light by inhibiting caspase activity [14, 15]. According to Pakravan and Sanjari, administering EPO through the veins along with corticosteroids, B-group vitamins, and folic acid resulted in a significant enhancement of visual acuity in two individuals who had methanol toxic optic neuropathy [16]. Further research has been carried out to evaluate the efficacy of erythropoietin in treating optic neuropathy resulting from methanol poisoning, and efforts are underway to advance its utilization [10, 17-21].

Erythropoietin given systemically can penetrate the blood retinal barrier (BRB) and achieve therapeutic levels in the eye [13]. However, long-term use of EPO can result in well-defined side effects such as polycythemia, thromboembolic events, hypertensive reactions, and pure red cell aplasia [22]. Short-term systemic administration of EPO has a favorable safety profile, though there have been cases of complications such as cerebral venous thrombosis reported after a brief course of intravenous EPO administration [23]. In addition, transient hypotension and a temporary increase in hemoglobin levels were observed after intravenous EPO treatment [24, 25].

Certain conditions make systemic and local administration unsuitable, such as elevated systemic blood pressure, polycythemia, previous thromboembolic events or epilepsy, proliferative diabetic retinopathy, and the presence of iris and retinal neovascularization [11]. In this study, we sought to identify the possible side effects of erythropoietin in the treatment of optic neuropathy in people poisoned with pure methanol.

Materials and Methods

This study was a prospective descriptive study. The studied population included patients suffering from methanol poisoning at Loghman Hakim Hospital in Tehran, who had received erythropoietin at a dose of 10000 units twice a day for three consecutive days. The study examined the adverse effects of administering erythropoietin, which include increased hemoglobin levels, seizures, central vascular thrombosis, and the occurrence of heart attack or stroke. All patients received a treatment protocol that involved the administration of intravenous methyl prednisolone every 6 hours for three days at a dose of 250 mg, as well as subcutaneous EPO every 12 hours for three days at a dose of 10000 units.

The inclusion criteria included people over 18 years of age, methanol poisoning, and visual complications due to poisoning. The exclusion criteria included people un-

der 18 years of age, taking other drugs along with methanol, not having visual complications due to poisoning, non-cooperation of the patient during the study, and death of the patient during the study.

Blood samples were collected at the beginning and end of treatment to check hemoglobin and venous gases. To detect stroke, neurological symptoms and a CT scan were evaluated, while heart issues were assessed through an electrocardiogram (ECG). After being discharged, the patients were examined for blood hemoglobin, occurrence of seizures, heart problems, deep vessel thrombosis (DVT), and functional neurological disorders (FND) at two-week and six-week intervals.

Patients with deep vein thrombosis may experience pain, tenderness, and swelling in one of their legs, typically in the calf or thigh. They may also feel a heavy ache in the affected area and notice warm, red skin around the clot, especially below the knee at the back of the leg. Patients were evaluated for significant FND symptoms such as limb weakness or paralysis, blackouts (known as dissociative or non-epileptic seizures/attacks), movement disorders like tremors, spasms, and jerky movements, speech issues such as whispering speech, slurred or stuttering speech, sensory disturbances like altered sensation on one side of the body, dizziness, and balance problems.

SPSS software, version 18 was utilized to analyze the data. Initially, frequency and descriptive indices were determined, followed by the evaluation of qualitative data using statistical tests such as chi-squared, Friedman, and Wilcoxon signed-rank tests. To ensure the normality of quantitative data distribution, the Kolmogorov-Smirnov test was employed. Similarly, in non-normal variables, the non-parametric tests mentioned earlier were performed while in normal variables, independent t-tests, paired t-tests, and repeated measures analysis of variance (ANOVA) were conducted. A significance level of $P<0.05$ was used, which indicates α error.

Results

During the study, 3 people were excluded from the study due to non-cooperation after discharge, one person died after discharge due to COVID-19 before a two-week follow-up and 4 people died before discharge. Table 1 displays the findings from the initial examinations. The study included 32 men (86.5%) and 5 women (13.5%). The mean age of the participants was 33.19±11.5 years (for males 34.22±11.8 and for females 26.6±7.13 years), with a minimum age of 18 and a maximum age of 64 years. The results of the independent t-tests showed that there was no significant difference in age between men and women (P=0.228). The medical history of the patients was examined and it was found that 33 patients (89.2%) had no previous record of suicide or substance abuse. However, 2 patients (5.4%) had a history of alcohol use and one patient (2.7%) had used methadone in the past. Additionally, one person (2.7%) had a history of attempting suicide. There was no record of seizures or myocardial infarction (MI) in any of the patient's medical histories. The mean time interval between alcohol consumption and referral to the hospital was 1.76±1.6 days.

When the patients were admitted to the hospital, it was noted that most of them (67.6%, 25 cases) had experienced blurred vision, which was statistically significant (P=0.001) according to the chi-squared test. Out of the total number of patients, 7 had light perception, 4 were blind, and one had hand movement perception. In the initial electrocardiogram (ECG), there were ST-T wave changes observed in one person, and in another person, the initial brain CT scan showed signs of atrophy.

According to the analysis of blood samples, it was found that 81.1% (30 individuals) of the patients had a condition known as acidosis, where the pH level was <7.35. Among these patients, 40.5% (15 individuals) had metabolic acidosis, where the HCO_3 level was <22 meq/lit. Additionally, 27% (10 individuals) had metabolic alkalosis, where the HCO_3 level was higher than 29 meq/lit. Furthermore, it was observed that 91.9% (34 individuals) of the patients had respiratory alkalosis, where the PCO_2 level was <35 mm Hg.

Results of the chi-squared test showed that there was no significant difference in the mentioned measures between males and females. The mean hemoglobin of patients in the first test was 16.4±2.4 g/dL, 43.2% (16 people) had hemoglobin above 17 and 4.5% (2 people) had hemoglobin below 12 g/dL. Significantly, all individuals with hemoglobin levels above 17 were male, and conversely, all those with hemoglobin levels below 12 were female (P=0.001) according to the chi-squared test results. The Spearman's correlation test showed that the time of methanol consumption did not show any significant correlation with visual symptoms, as indicated by a P of 0.378.

Patients stayed in the hospital for a mean of 2.89±1.2 days, with the longest stay lasting 6 days. Thirty-three people (89.2%) of the patients underwent dialysis, 87.9% underwent dialysis once, and 12.1% underwent

Table 1. Demographic information and initial examinations of patients

Variables		No. (%)/Mean±SD	P
Gender*	Male	32(86.5)	0.0001
	Female	5(13.5)	
Age (y)		33.19±11.5	
Visual symptoms on arrival*	Complete blindness	4(10.8)	0.0001
	Light perception	7(18.9)	
	Hand motion perception	1(2.7)	
	Blurred vision	25(67.6)	
pH		7.21±0.1	
HCO_3 concentration (meq/L)		23.44±10.7	
PCO_2 (mm Hg)		17.8±8.7	
Hemoglobin level (g/dL)		16.4±2.4	
ECG*	Normal	36(97.3)	0.0001
	ST-T change	1(2.7)	
Brain CT*	Normal	36(97.3)	0.0001
	Atrophy	1(2.7)	
Previous medical history*	No	33(89.2)	0.001
	Alcohol	2(5.4)	
	Methadone	1(2.7)	
	Suicide attempt	1(2.7)	
Time to use methanol (d)		1.76±1.6	

*Chi-squared test.

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dialysis twice. Ten patients (27%) were advised to see an ophthalmologist and undergo an ophthalmology consultation before being discharged from the hospital because they were still experiencing issues with their vision. Upon examination of the patients' visual symptoms during discharge, it was found that a majority of them (59.5%) had fully regained their vision, while two individuals remained blind (Table 2). At the time of discharge, the blood gas results revealed a significant difference in pH and PCO_2 compared to the time of admission to the hospital according to the paired t-test and Wilcoxon signed-rank test. Additionally, this test showed that there was a notable shift from acidosis and respiratory alkalosis to the normal range in patients. Although the concentration of HCO_3 in the blood improved at the time of discharge, it was not significant (P=0.392) according to the paired t-test (Table 2).

During two and six weeks after discharge, none of the patients were observed to have convulsions (seizure), functional neurological disorders, deep vein thrombosis, or heart problems (heart attack or stroke). After two weeks of being discharged, the mean hemoglobin level was found to be 16±2.3 g/dL, with 56.8% of individuals being within the normal range. Results of the paired t-test showed that there was no notable disparity in hemoglobin levels between admission to the hospital and two weeks after discharge. Out of the total number of people, 81.1% had regained their normal vision and only one person was still blind.

Table 2. Clinical information of patients upon discharge from the hospital

Variables		No. (%)/Mean±SD	P
Visual symptoms at the time of discharge*	Normal vision	22(59.5)	0.0001
	Complete blindness	2(5.4)	
	Light perception	1(2.7)	
	Hand motion perception	2(5.4)	
	Blurred vision	10(27)	
pH		7.43±0.07	
HCO_3 concentration (meq/L)		25.2±4.9	
PCO_2 (mm Hg)		36.8±9.1	
Duration of hospitalization (d)		2.89±1.2	
Referral to an ophthalmologist*	Yes	10(27)	0.005
	No	27(73)	
Number of dialysis sessions*	0	4(10.8)	0.0001
	1	29(78.4)	
	2	4(10.8)	

*Chi-squared test.

The mean hemoglobin level after six weeks of discharge was 16.62±2.17 g/dL, with 45.9% of individuals falling within the normal range. This value was significantly greater than levels observed in earlier stages (P=0.001)

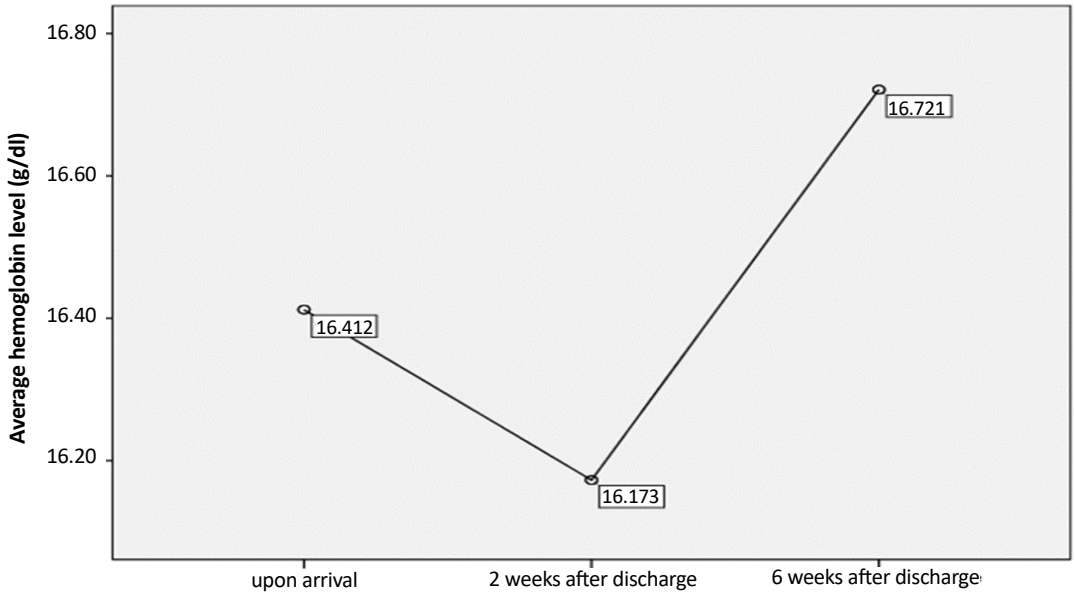

Figure 1. Mean hemoglobin of patients at hospital admission (ANOVA test)

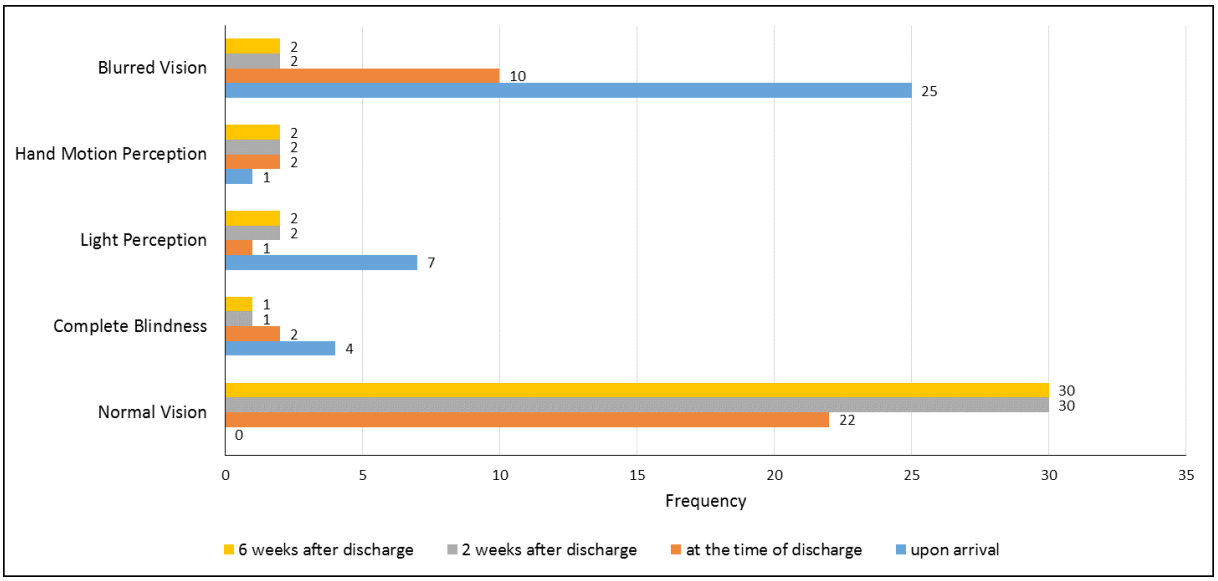

Figure 2. Changes in visual symptoms of patients (Friedman test)

according to the repeated measure ANOVA test (Figure 1). The hemoglobin levels showed an average increase of 2.01% six weeks after discharge compared to the levels recorded during hospital admission (mean of hemoglobin levels 16.72±2.17 gr/dL). Additionally, there was a 2.4% increase in hemoglobin levels six weeks after discharge compared to the levels recorded two weeks after discharge. Visual symptoms remained unchanged from 2 weeks after discharge (Figure 2) and people's vision had significantly improved according to the Friedman test.

Discussion

In this study, 37 patients suffering from methanol toxicity were treated with EPO in addition to the standard treatment. The patients' vision, hemoglobin levels, occurrence of seizures, as well as the incidence of heart and cerebral strokes and deep vein thrombosis were monitored for up to 6 weeks after they were discharged from the hospital. The study included 32 men (86.5%) and 5 women (13.5%) with a mean age of 33.19±11.5 years. The adverse drug reactions (ADR) reported by other authors like seizures, heart and cerebral strokes, and deep vein thrombosis were not reported by any patient during the present study. After being discharged from the hospital, the mean hemoglobin levels increased by 2.01% six weeks later compared to the levels measured during admission. Moreover, there was a 2.4% rise in hemoglobin levels six weeks after discharge compared to the levels measured two weeks after being discharged.

Methanol poisoning can result in severe and incapacitating optic neuropathy and blindness [1, 2, 26]. Erythropoietin has been utilized in the treatment of optic neuropathy and blindness caused by methanol poisoning recently [10, 16, 17, 19]. The utilization of erythropoietin was found to be beneficial in enhancing the eyesight of patients in our research. It resulted in three individuals regaining their vision after being completely blind and 81.1% of patients were able to restore their normal vision within two weeks of being discharged.

Although it was successful, systemic EPO can cause well-defined side effects such as polycythemia, thromboembolic events, hypertensive reactions, and pure red cell aplasia [22]. A case of cerebral venous thrombosis occurring 3 months after a brief period of receiving intravenous EPO administration (20000 U per day for 5 days) has been reported [23]. Grand mal seizures have been reported in dialysis patients since the initial use of recombinant human erythropoietin (rHuEpo), and this issue has been validated with a frequency ranging from 2 to 17% [27, 28]. During our study, we did not observe any instances of seizures, deep vein thrombosis, heart or cerebral strokes, or cardiovascular problems for up to six weeks following the discharge of the patients.

According to a report by Ricarda Diem and colleagues, administering intravenous EPO (33000 U per day) for 3 days led to a temporary rise in hemoglobin levels during the first week, which eventually returned to their original values after 4 weeks [25]. In their research, Berglund and Ekblom discovered that administering small amounts of

rhEpo resulted in a rise of over 10% in Hb levels and Hct within a span of 6 weeks [29]. According to our research, there was a 2.01% rise in the mean hemoglobin levels six weeks after admission compared to the levels recorded in admission. Additionally, the hemoglobin levels increased by 2.4% six weeks after being discharged when compared to the levels measured two weeks after leaving the hospital.

Conclusion

High hemoglobin levels could cause the body to produce an excessive amount of red blood cells, which thickens the blood and increases the risk of clots, heart attacks, and stroke. If left untreated, it can be a life-threatening condition. Using erythropoietin to treat optic neuropathy can improve vision, but it also carries the risk of increasing hemoglobin levels, which must be monitored closely in treated patients.

Ethical Considerations

Compliance with ethical guidelines

This article was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1400.859).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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