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Research Paper

Evaluation of the Efficacy of Melatonin in Visual Disturbed Methanol-intoxicated Patients: A Randomized Clinical Trial

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ABSTRACT

Background: This study evaluates the role of oral melatonin in improving vision in methanol toxicity since vision disorders are one of the side effects related to methanol toxicity and assumes the potential effects of melatonin in protecting neurons and optic nerves. Meanwhile, little attention has been paid by researchers to the effect of melatonin in these patients.

Methods: A double-blind randomized controlled clinical trial study was conducted on 40 patients diagnosed with methanol toxicity who were referred to Khorshid Hospital of Isfahan City, Iran, from May 2022 to May 2023. These patients were randomly divided into two groups. In the first group (the intervention group), in addition to the usual treatment, the patients were prescribed orally 3 mg of melatonin every morning and 6 mg of melatonin every night for 10 days. In the second group (the control group), in addition to the usual treatment, a placebo was administered similar to the intervention group protocol. Then, the clinical and vision parameters of the patients were evaluated before, during, and after the intervention.

Results: The mean pH, PCO_2 and HCO_3 increased significantly after the intervention compared to the pre-intervention in both groups ($P<0.05$); however, no significant difference was found between the two groups in any of the two follow-up times ($P>0.05$). The most common visual complication caused by methadone toxicity was blurred vision with 71.4% and 90% in the melatonin and non-melatonin groups, respectively. Visual complications improved significantly after the intervention compared to the pre-intervention; accordingly, the complete improvement of vision complications in the melatonin group (76.2%) was significantly more than the non-melatonin group (53.3%) ($P=0.040$).

Conclusion: Melatonin improves blurred or snowfield vision in methanol poisoning. Therefore, the administration of melatonin plus routine treatment can be effective in improving vision disorders (blurred or snowfield vision) caused by methanol poisoning.

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Introduction

Methanol (methyl alcohol) is an alcohol with the chemical formula CH_3OH. It is the simplest type of alcohol and has other characteristics, such as being light, colorless, volatile, flammable, and easily soluble in water. Methanol becomes its toxic metabolite, which causes acidosis and inhibits cytochrome oxidases in the cell [1-3]. Methanol toxicity can lead to a decreased level of consciousness, if not treated early in the course of toxicity, and the liver will convert methanol into formaldehyde and formic acid. Formic acid accumulation can lead to metabolic acidosis, vision disturbances, seizures, end-organ toxicity, coma, and death [1].

The optic nerve, which is highly energy dependent, is vulnerable to mitochondrial dysfunction, including methanol poisoning. Adenosine triphosphate shortage leads to the interruption of axoplasmic flow and intra-axonal. The papillomacular bundle fibers, which are small caliber axons rich in mitochondria, are particularly involved. Therefore, methanol-induced optic neuropathy belongs to acquired mitochondrial optic neuropathy, although other mechanisms, including oxidative stress and proinflammatory cytokines, are also reported. Some studies have reported that magnetic resonance imaging abnormalities, like T1 enhancement and or long T2 in the retrobulbar segment of optic nerves, were found in methanol-induced optic neuropathy. Optical coherence tomography finding of ganglion cell layer loss, selectively involving the papillomacular bundle, was also reported [4]. Ma et al. also mentioned that inhalational methanol toxicity may lead to serious damage to the optic nerve in a process of chronic intoxication with acute attack and poor prognosis [5].

Proper management of the patient requires the administration of buffer, antidote, folic acid, and often hemodialysis [1, 2]; however, after treatment, visual disturbances may or may not improve until hospital discharge [6-9]. Currently, two available antidotes for methanol toxicity are ethanol and fomepizole. Ethanol has potential adverse effects and limited success in restoring vision [10]. Fomepizole is deemed safe but is expensive and unavailable in many undeveloped countries where methanol toxicity occurs commonly [11].

Other treatment regimens include the use of folic acid, sodium bicarbonate, hemodialysis, etc. [12, 13]. These cares mainly prevent the formation of formic acid and more toxicity; however, they do not affect the eye inflammation caused [12]. Some studies report the use of intravenous methylprednisolone leading to good visual outcomes [5, 13, 14]. However, so far, less attention has been paid to the therapeutic effect of melatonin on the optic nerve and pupil changes in this group of patients. The beneficial effects of melatonin on the optic nerve and retinal changes have been previously reported. For example, Aranda et al., in the study of the neuron protection effect of melatonin in laboratory optic neuritis in rats, showed that melatonin (20 mg, injected subcutaneously) improves visual function. In addition, the reduction of microglia/macrophage reaction, astrocytosis, reaction to myelin, and loss of axon and retinal ganglion cells have also been observed [15]. Melatonin is beneficial along with classic antioxidants, such as vitamin E and vitamin C [16]. Meanwhile, the protective effects of melatonin against various pesticides and metal poisoning have been reported [17, 18].

When considering the use of melatonin to treat visual disturbance in methanol toxicity, the safety of melatonin is of utmost significance. Many reviews previously showed that short-term use of melatonin is safe, even in high doses, and the reported adverse effects are limited to occasional dizziness, headache, nausea, and sleepiness. Melatonin's safety in humans is significantly high [19]. In clinical trials, doses of 3 mg, 6 mg, and 10 mg of melatonin oral intake by the intensive care unit patients showed satisfactory safety compared to placebo [20, 21]. Also, even when melatonin was given to humans at a dose of 1 g/day for a month, there were no adverse reports of the treatment [22]. While the safety of melatonin has been verified in many human studies, its effect when given to methanol-poisoned patients should be carefully monitored despite the very high safety. Given that little attention has been paid to the ongoing challenge of persistent visual disturbances after methanol poisoning, the present study investigates the role of oral melatonin administration in improving vision in methanol poisoning in patients.

Materials and Methods

A double-blind, randomized controlled clinical trial was performed. The study population included all methanol-intoxicated patients referring to the emergency department of Khurshid Educational Medical Hospital or Al-Zahra Hospital of Isfahan City, Iran from May 2022 to May 2023.

Since no similar study had been conducted to evaluate the effect of melatonin on the improvement of vision disorders in patients with any intoxication, in the cur-

rent study, considering the vision disorders' percentage (37.5%) recorded in Ma et al. [5], and 0.3% error level, the sample size was obtained 30 for each group at a 95% confidence level (CI) and test power of 80%.

The inclusion criteria consisted of the diagnosis of methanol intoxication (confirmed by the patient's history and the presence of metabolic acidosis), having no other intoxication (through the history and negative urine screening in terms of toxicology), having any type of blurred vision or visual impairment, being 15-60 years old, exposed to poisoning <72 h before arriving at the hospital, no cardiopulmonary resuscitation upon arrival, and including no comatose patient before entering the study (having consciousness). Meanwhile, the exclusion criteria consisted of contraindications to melatonin use (such as people with high or low blood pressure, diabetics, autoimmune diseases, epilepsy, and other convulsive disorders, organ transplants and taking immunosuppressive drugs, bleeding disorders such as hemophilia, depression and dementia, subjects who chronically use or have used drugs such as benzodiazepines, codeine, or barbiturates, having an allergic reaction to melatonin, decreased level of consciousness, having the severe chronic disease (such as liver cirrhosis with hypertension, congestive heart failure, chronic respiratory disease, end-stage renal disease, or a high-risk immune condition such as leukemia, lymphoma, or AIDS) and the lack of follow-up and cooperation in further referrals until the end of the study for any reason (non-compliance with medical orders in taking prescribed medications or the patient death).

After obtaining written consent from eligible patients to be included in the study, 60 patients were selected using a simple random method.

Then, they were divided into intervention and control groups. Then, random numbers were created by this software and were automatically divided into two groups (A and B). Running the software, the numbers of each group were recorded on the checklists, and the information of a patient was recorded in each checklist, and the person was placed in one of the two groups based on the checklist number.

The methanol poisoning diagnosis was based on alcohol consumption (handmade, smuggled, industrial), clinical manifestations, quantitative and qualitative test results, and metabolic acidosis along with an increase in the anion gap and serum methanol level.

At the onset of the study, the demographic information of patients, including age, gender, the time interval between drug consumption and presence at the hospital, venous blood gas (VBG) parameters (such as HCO_3, PCO_2, and pH), blood tests (such as potassium, blood sugar, partial thromboplastin time, prothrombin time, international normalized ratio, sodium, liver enzymes [such as aspartate transferase, alanine transaminase, and alkaline phosphatase] and vision status [such as blurred vision, snowfield vision, diplopia, tunnel vision and no light perception]) were recorded [23].

Routine tests were done for all patients. In this hospital, routine treatment regimens included emergency hemodialysis for at least 6 h, erythropoietin 10 000 to 12 000 units from Eprex ampoules every 12 h slowly injected intravenously for 3 days, and 500 mg methylprednisolone injected intravenously (during an hour) every 12 h for 3 to 5 days.

In the first group (the intervention group), the patients were prescribed orally 3 mg of melatonin every morning and 6 mg of melatonin every night for 10 days (during hospitalization and after discharge) in addition to the usual treatment. In the second group (the control group), a placebo was administered similar to the intervention group protocol in addition to the usual treatment.

To comply with double-blindness conditions, two drugs, melatonin and placebo, were made by the same pharmacist coded with A and B labels, and provided to the researcher. Without knowing the type of intervention, the researcher administered the same prescription in two groups. Moreover, the patient and the person under statistical analysis did not know the type of intervention in the two groups until the end of the study. The placebo was prepared by the Faculty of Pharmacy of Isfahan University of Medical Sciences. Also, the outcome of the intervention was considered as any visual improvement based on the patient's statements and the physician's examination.

Statistical analysis

The collected data were analyzed using the SPSS software, version 26. Quantitative and qualitative data were represented as Mean±SD or number (%), respectively. To compare the mean of quantitative variables between the two groups, the independent sample t-test was used. The paired sample t-test was used to compare the mean of quantitative variables after the intervention compared to the pre-intervention in each of the two groups. Meanwhile, the chi-square test was used to compare the fre-

Table 1. Baseline demographic and clinical characteristics of the patients at baseline

Variables		Mean±SD/No. (%)		P
		Melatonin (n=21)	Without Melatonin (n=30)	
Gender	Male	19(90.5)	23(76.7)	0.075
	Female	2(9.5)	7(23.3)	
Age (y)		31.20±9.81	34.40±9.22	0.240
The time interval between consumption and referring to the hospital		14.22±1.90	15.17±1.79	0.075
pH (at admission)		7.21±0.21	7.15±0.08	0.141
PCO_2 (mm Hg)		25.26±10.97	25.72±7.98	0.863
HCO_3 (mmol/L)		10.69±6.75	9.49±4.43	0.567
Potassium (mg/dL)		4.23±0.87	3.91±0.94	0.221
Blood sugar (mg/dL)		135.90±57.51	128.94±39.90	0.608
AST (U/L)		40.17±15.0	33.41±13.37	0.100
ALT (U/L)		39.71±30.91	30.64±18.38	0.189
ALP (U/L)		259.28±80.42	229.26±66.33	0.155
PT (second)		13.11±2.00	12.82±1.70	0.575
PTT (second)		35.93±10.42	31.91±5.23	0.081
INR		1.31±0.12	1.11±0.11	0.064
Sodium (mEq/L)		140.55±1.80	139.42±3.60	0.177

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Abbreviations: AST: Aspartate transferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio.

quency distributions of qualitative variables. In all analyses, a significance level of <0.05 was considered.

Results

Out of 30 patients in the melatonin group, nine patients were excluded from the study due to stopping to participate in the study (n=5), lack of referral after being discharged from the hospital (n=3) and having end-stage renal disease (n=1). Therefore, the study was conducted in the melatonin group with 21 participants and the group without melatonin with 30 participants (Figure 1). In the melatonin group, 19 participants (90.5%) were male and two (9.5%) were female with an average age of 31.20±9.8 years. In the group without melatonin, 23 participants (76.7%) were male and seven (23.3%) were female with an average age of 34.40±9.2 years (P>0.05). Moreover, blood parameters, such as VBG, coagulation, and other parameters were not significantly different between the two groups at the beginning of the study (P>0.05) (Table 1).

The mean values of pH, PCO_2 and HCO_3 increased significantly post-intervention as compared to pre-intervention in both groups (P<0.05); however, no significant difference was found between the two groups in terms of VBG parameters before and after the intervention (P>0.05) (Table 2).

The frequency of blurred vision as the most common visual complication caused by poisoning before the intervention in the melatonin and non-melatonin groups was 71.4% and 90%, respectively. Other vision complications with an incidence rate of below 5% consist of blurred vision, snowfield vision, diplopia, tunnel vision, and no light perception. After the intervention,

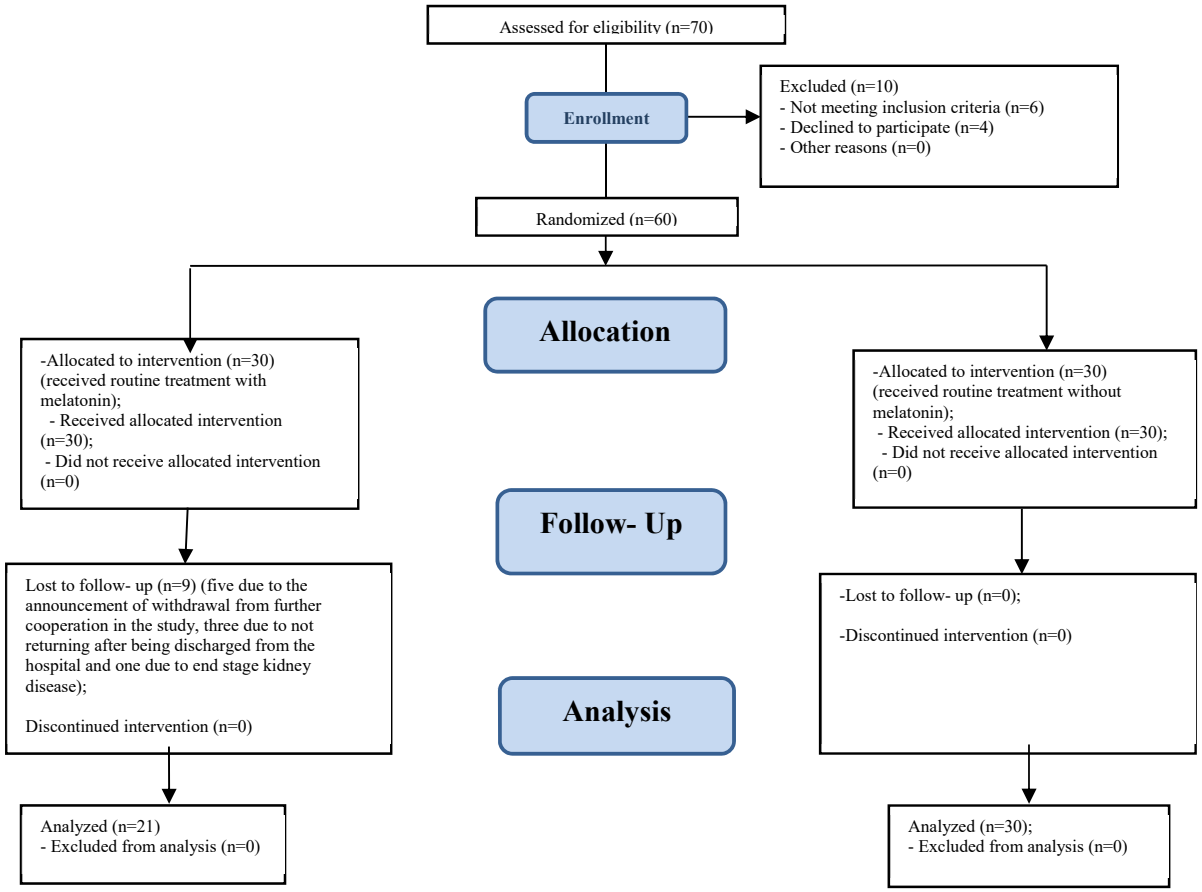

Figure 1. The consolidated standards of reporting trials flowchart of patients

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Table 2. Comparison of venous blood gas parameters of patients before and after the intervention in the two study groups

VBG	Time Follow-up	Mean±SD		P[1]
		Melatonin (n=21)	Without Melatonin (n=30)	
pH	Before intervention	7.21±0.21	7.15±0.08	0.159
	After intervention	7.40±0.06	7.41±0.04	0.478
	P[2]	0.001	0.001	
PCO_2	Before intervention	25.26±10.97	25.72±7.98	0.863
	After intervention	38.93±6.09	39.89±5.49	0.559
	P[2]	0.001	0.001	
HCO_3	Before intervention	10.69±6.75	9.49±4.43	0.567
	After intervention	27.09±6.29	25.84±4.08	0.393
	P[2]	0.001	0.001	

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[1]The significance level obtained from the independent t-test to compare the mean values of variables between the two groups in each follow-up time; [2]The significance level obtained from the paired t-test to compare the mean values of the variables post-intervention compared to pre-intervention in each of the two studied groups.

Table 3. Comparison of the visual status of patients before and after the intervention between the two study groups

Visual Status	Time of Follow-up	No. (%)		P*
		Melatonin (n=21)	Without Melatonin (n=30)	
Blurred vision	Before intervention	15(71.4)	27(90)	0.268
	After intervention	0	0	-
Snowfield vision	Before intervention	1(4.8)	1(3.3)	0.749
	After intervention	0	0	-
Diplopia	Before intervention	2(10.0)	1(3.3)	0.315
	After intervention	0	0	-
Tunnel vision	Before intervention	1(4.8)	1(3.3)	0.749
	After intervention	0	0	-
No light perception	Before intervention	1(4.8)	1(3.3)	0.749
	After intervention	1(4.8)	2(6.7)	0.829
Counting fingers	Before intervention	0	1(3.3)	-
	After intervention	1(4.8)	2(6.7)	0.749
Hand motion	Before intervention	1(4.8)	1(3.3)	0.749
	After intervention	1(4.8)	2(6.7)	0.829

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*The significance level obtained from the chi-square test to compare the frequency of the variables between the two groups in follow-ups.

counting fingers and hand motion complications were reported, which were few. No significant differences were observed regarding vision complications between the two groups before and after the intervention. However, visual complications improved significantly after the intervention, i.e. the complete improvement of vision complications in the melatonin group (76.2%) was significantly higher than in the non-melatonin group (53.3%) (P=0.040). However, the no light perception complication in the non-melatonin group increased in one case after the intervention though no significant difference was detected between the two groups (P>0.05) (Table 3).

Discussion

According to the results, the mean values of VBG parameters did not differ significantly between the two groups; however, the mean values of VBG parameters increased significantly post-intervention as compared to pre-intervention in both groups. Besides, blurred vision was identified as the most common complication among the vision complications caused by methadone poisoning so its incidence percentages pre-intervention in the melatonin and non-melatonin groups were 71.4% and 90%, respectively. No light perception as the most severe vision complication increased in one case after the intervention in the non-melatonin group. Its incidence was reported at 4.8% in the melatonin group and 6.75% in the non-melatonin group. Evaluating the patient's condition improvement and the removal of complications caused by methadone poisoning, it was manifested that the complete improvement of visual complications in the melatonin group (76.2%) was significantly higher than the non-melatonin group (53.3%).

In this regard, some previous studies have introduced melatonin as a promising candidate for optic neuritis treatment that has anti-inflammatory-neuroprotective effects [24-27]. Our findings are in line with them considering optic nerve pathology in this poisoning.

Moreover, Wei et al. revealed that melatonin therapy affects the apoptosis level of retinal ganglion cells after Traumatic optic neuropathy by alleviating the increased caspase-3 protein level. Its mechanism may be that it further up-regulates the autophagy level of retinal ganglion cells after Traumatic optic neuropathy, ultimately inhibiting the apoptosis of retinal ganglion cells after traumatic optic neuropathy and playing a neuroprotective role [28].

Another study showed that blurred or snowfield vision in methanol poisoning resolved (with routine treatment) [3], while in our study this improvement was augmented with melatonin prescription.

Zhang et al. summarize the likely benefits of melatonin in the attenuation of COVID-19 based on its putative pathogenesis and review the evidence indicating that melatonin will have supportive adjuvant utility in treating COVID-19-induced pneumonia, acute lung injury, and acute respiratory distress syndrome [29]. This study is about the supportive utility of melatonin in treating methanol-induced visual disturbance.

Other studies showed that intravenous methylprednisolone could salvage vision in methyl alcohol poisoning, but corticosteroids have more adverse effects than melatonin and should be infused while melatonin is capsule; therefore, they prepare the situation to continue treatment after discharge [12, 13].

Also, Aranda et al. studied the neuronal protection effect of melatonin in laboratory optic neuritis in rats and demonstrated that melatonin (20 mg injected subcutaneously) improves visual function. Moreover, as visual functions are maintained, improved structural results have also been observed, such as reduction of microglia/macrophage reaction, astrocytosis, reaction to myelin, and loss of axon and retinal ganglion cells [15].

Another study also investigated the effect of oral melatonin on the cone response of the electroretinogram and the photopic luminance-response function of humans and revealed that the oral administration of melatonin significantly reduces cone maximum response and the total OPs (oscillatory potentials). Furthermore, the effect of melatonin on retinal function was very fast since it can be easily observed after 30 min and remains 50 min after consumption [30].

Emser et al. indicated that the oral administration of 10 mg of melatonin reduces electroretinogram cone response and decreases both scotopic and photopic b waves in humans [31].

Melatonin (as an amphiphilic molecule) crosses all morpho-physiological barriers and is found especially in mitochondria, potentially protecting it against oxidative stress [32, 33].

Paradies et al. investigated the effect of melatonin on mitochondrial dysfunction and related disorders and showed that this indoleamine is a free radical scavenger with good solubility in both aqueous and organic phases, maintaining a high capacity to modulate mitochondrial homeostasis [23].

Some reports also stated that melatonin can be potentially effective in neutralizing the basic mechanisms of cardiotoxicity caused by aluminum phosphide due to its antioxidant, anti-apoptotic, and anti-arrhythmic properties. It may also improve clinical symptoms following exposure to aluminum phosphide due to its pain relief and anti-anxiety properties [34].

Conclusion

The beneficial effects of melatonin as an adjuvant treatment in methanol toxicity as an anti-inflammatory and anti-oxidant in visually disturbed patients are significant. According to our findings, melatonin improves blurred or snowfield vision in methanol poisoning. In summary, evidence has shown that Melatonin has beneficial effects on visual disturbances in methanol poisoning.

Study limitations

This study's limitations include failure to investigate methadone properties, such as neutralizing the cardiotoxicity mechanisms, pain relief, anti-anxiety properties, and improving the clinical symptoms of patients. Furthermore, the small sample size, the lack of long-term follow-up of visual complications caused by methadone consumption, and the lack of examination of visual damage in patients with methods such as magnetic resonance imaging of the optic nerve can be considered as other limitations of the study. Meanwhile, the administration of methanol for the improvement of visual complications, including the complications caused by methadone poisoning, is considered the study strength as the first clinical trial study. Assuming limited related research studies, further similar studies are recommended, prescribing different doses of methanol and patient follow-ups at different times to obtain more reliable and generalizable results for society.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Code: IR.ARI.MUI.REC.1401.048) and Iranian Registry of Clinical Trials (Code: IRCT20220050704734N3). Written consent was obtained from participants.

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Authors' contributions

Conceptualization, study design, investigation and final approving: Shiva Samsamshariat and Shafeajafar Zoofaghari; Data collection, data analysis, review and editing: Rokhsareh Meamar, Negar Jalali and Asieh Maghmi Mehr.

Conflict of interest

The authors declared no conflict of interest.

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