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Therapeutic Effect of Adding Magnesium Sulfate in Treatment of Organophosphorus Poisoning

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Abstract

BACKGROUND: In recent years, the prevalence of poisoning has increased dramatically due to population growth and access to drugs and toxins. Today poisoning is one of the important reasons for visiting hospitals.

AIM: The present study aimed to investigate the effect of magnesium sulfate on organophosphorous toxicity.

METHODS: Patients who had inclusion criteria in the study were randomly assigned to one of two groups (control group or case group) by an emergency medicine specialist. Patients' data including age, sex, ECG, vital signs, arterial oxygen saturation were recorded for patients. Patients in the case group (40 subjects) received 2 mg magnesium sulfate 50%, while the control group (40 subjects) received 100 cc normal saline (as placebo) as an intravenous infusion

RESULTS: The distribution of gender in the two groups of patients was the same. Also, the mean age, Stature and weight of patients were similar in both groups. In the group receiving magnesium sulfate, diastolic blood pressure was lower when compared with another group, at 0 and 2 hours after intervention. Moreover, the mean of systolic blood pressure in both groups was determined to be the same at all hours. Furthermore, the heart rate in the group receiving sulfate was lower as compared to the control group for 8 hours, 16 and 24 hours after intervention.

CONCLUSION: The use of magnesium sulfate in organophosphate poisoning reduces therapeutic costs an average hospital length of stay and mortality compared to those who did not receive magnesium sulfate.

Introduction

In recent years, the prevalence of poisoning has increased dramatically due to the growth of societies and the ease of access to drugs and toxins [1]. In Iran, over 50 various pesticide combinations are utilised for agriculture, and today in Iran there are over 40 organophosphorus chemicals (OPs), with acute and subacute toxicity, as well as OPs, are applied in agronomy, homes, gardens and veterinary practice. [2]. Usually, the severity of poisoning in adolescents and adults is often acute, due to excessive consumption of oral medications or the misuse of some medications, environmental, industrial, and available agricultural products deliberately or accidentally [3] [4].

In general, the incidence of poisoning is quite different in each region and each country due to the geographical distribution of each particular region and the type of toxic substance [5] [6]. Many of the poisonings are drug-related, and the rest are classified as non-drug poisoning. Generally, common causes of poisoning include drugs, hydrocarbons, organophosphorus pesticides (OPPs), natural anticholinergic or chemical compounds, rodenticide, opiate, carbon monoxide, alcohol, fungi, insect and animal bites, *acid and basic material*s [5] [7]. Pesticides, especially organophosphorus, are distributed in many areas, to fight pest infestations. Because of their ease of access, poisoning from them

has become more prevalent. Organophosphate poisoning is one of the main clinical problems in the world, especially in developing countries, where is associated with high mortality [5] [8] [9]. About 28.4% of the agricultural pesticides used in Iran are organophosphorus [10]. Insecticides are organophosphorus compounds that lead to toxicity in humans by inhibiting the acetylcholinesterase enzyme [11]. As other studies indicated, the mortality rate from organophosphate poisoning has been reported by 3 to 25% [12]. The most common cause of death in this poisoning is respiratory failure due to respiratory depression, resulting from respiratory muscle weakness, central nervous system suppression, bronchus, bronchospasm and bradycardia [13]. Although poisoning and contamination with this toxin occur in all countries, in third world countries due to the low level of industrial and health care, the annual incidence of organophosphate poisoning and mortality is higher [14]. In Iran, organophosphate is widely used as an insecticide poison in the agricultural industry. According to a study conducted in Isfahan, this substance was the fourth most common poisoning and the second leading cause of death in patients referring to the poisoning department of the Noor Medical Center [15]. Magnesium sulfate is an inorganic salt containing magnesium, sulfur and oxygen, with the formula $MgSO_4$. The mechanism of magnesium effect is not well known but affects the Na + K + ATPase pump in sodium, potassium and calcium channels. It also reduces the release of acetylcholine at the site of the nerve-muscle.

The drug is used for various purposes, such as eliminating magnesium deficiency, helping to treat lethal arrhythmias called torsade, and preventing *eclamptic seizure*, as well as treating severe asthma and preventing premature uterine contractions during pregnancy. This drug prevents seizures or control of these attacks by blocking neuromuscular transmission [16]. Poisoning with this drug is not common, but excessive use of this drug can cause flushing and sweating, low blood pressure and reduced tendon reflexes. Atropine and oximes are traditionally used in the management of poisoning, but their efficacy is a subject of debate [17] [18] [19] [20] [21]. Animal findings indicate the low efficacy of pralidoxime in organophosphate poisoning [22] [23]. On the other hand, evidence suggests that it does not affect human poisoning [17] [19] [24].

Therefore, any pharmacotherapeutic agent that contributes to preventing or improving the toxicity of OPPs can also be helpful in reducing the cost of treatment and the length of hospitalisation. Animal experiments and uncontrolled human experiments demonstrate the effect of $MgSO_4$ [25] and clonidine for reducing organophosphate toxicity. Given the evidence mentioned above, the present study was conducted to investigate the effect of magnesium sulfate on organophosphate toxicity.

Material and Methods

Ethical approval and patient consents

All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ethics Committee of Arak University of Medical Sciences. Patients who contacted us indicated their consent by signing a written consent form.

Study design and patient populations

This double-blind, randomised clinical trial was conducted on patients referred to the emergency department of Vali-e-Asr Hospital in Arak, Iran with symptoms of organophosphate poisoning. The diagnosis of this poisoning is based on a history of contact with these agents and specific clinical signs of poisoning, which are presented as follows: Defecation/Diarrhea, Urination, Muscle Weakness/ Miosis, Bradycardia/ Bronchorrhea/ Bronchospasm, Emesis, Tears Lacrimation, Salivation, which is called DUMBLE.

Patients in the case group (40 patients) received 2 g of magnesium sulfate 50% (4 cc) for intravenous infusion in a total volume of 100 cc, in half an hour. The same amount of drug (2 g) was successively injected 3 times every 2 hours. The drug was prepared by a nurse and under the supervision of a specialist in emergency medicine and was provided to the *corresponding person* who was not aware of the type of medication.

In the control group, 100 cc normal saline (as placebo) injected intravenously in half an hour for patients in the control group (40 patients). The same amount of drug (100 cc normal saline) was successively injected 3 times for half an hour. It should be noted that all patients in each of the two groups received the standard medicine, suggested in the reference books for organophosphate poisoning.

Standard treatment consists of gastric lavage, serum administration, oxygen intake, pulmonary and oral secretions suction, cardiopulmonary and respiratory monitoring, charcoal administration (1 g/kg), and washing of infected skin with water and soap, and intravenous injection of 0.5-5 mg atropine. The dosage of *Pralidoxime* is 20-40 mg/kg, which is administered intravenously throughout 10 to 5 minutes. Pralidoxime can be repeated every 6 to 24 hours, if necessary.

Keeping the airway open, oxygen was given and *fixation of hypertension* during treatment. Other factors were also evaluated, including electrolytes, fasting blood sugar, liver and kidney function tests,

arterial blood gases, pupil size, tendon reflexes, fasciculations intensity, respiratory crackles and *oral secretions*, and in the case of tracheal intubation. Also, if intubation was done, the secretion of the chip was checked, and the levels of atropine and *pralidoxime* were also recorded.

All data were analysed by SPSS software v.19. The variables were applied to measure the mean, standard deviation, standard error, percentage of frequency. Covariance analysis, Chi-square and Independent T-test or its nonparametric equation were also used to compare the variables.

The inclusion criteria included: 1. Age between 18-65 years; 2. Patients with acute OPPs toxicity who have not received advanced medical care at the other medical centre and less than two hours after the time of their poisoning; 3. Filling out the informed consent form of the patient.

Exclusionary *criteria* include 1. Unwilling to participate in the study; 2. The *concomitant use* of *other drugs* as a coincidence or suicide attempt; 3. History of severe complications or sensitisation due to magnesium sulfate; 4. History of the known cardiac block, *cardiovascular injury*, myocardial *injury* due to previous MI, severe renal failure, hepatitis, Addison's disease.

The sample size was calculated based on α = 0.05, and *generalising* the *prevalence* to a country (0.062), [26]. Finally, 40 subjects were assigned to each group, where the total sample size was estimated as 80 based on the formula below.

$$\alpha = 0.05$$
$$p_1 = 0.062$$
$$p2 = 0.5$$
$$\beta = 0.2$$

$$n_1 = n_2 = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \left[P_1(1-P_1) + P_2(1-P_2)\right]}{(P_1 - P_2)^2} = 4$$

All data were analysed by SPSS software v.19. The variables were applied to measure the mean, standard deviation, standard error, percentage of frequency. Covariance analysis, Chi-square and Independent T-test or its nonparametric equation were also used to compare the variables.

Results

This double-blind, randomised clinical trial was conducted on patients with organophosphate poisoning symptoms. Therefore, 90 patients were enrolled in the study and 10 were excluded from the study, of which 3 patients died before 24 hours, and 3 subjects used carbamate insecticide that was discharged from the hospital after 18 hours of admission and a relative improvement. Furthermore, one case of advanced liver cancer was excluded.

With regard to gender, the case group consisted of 25 (62.5%) males and 15 (37.5%) women, while the control group consisted of 22 (55%) males and 18 (45%), there was no statistically significant difference between two groups in terms of gender and both groups were poisoned in the same ratio (P = 0.391).

The mean and standard deviation of age in control and case groups were determined to be 35.90 ± 10.53 and 29.90 ± 8.87 years, respectively, where there was no statistically significant difference between the two groups regarding age and both groups were matched regarding mean age (P = 0.059).

The mean and standard deviation of weight in groups with or *without* sulfate were estimated as 71.4 ± 11.43 kg and 72.90 ± 11.19 kg, respectively. There was no statistically significant difference between the two groups regarding weight (P = 0.677).

Furthermore, mean and standard deviation of stature in groups with or *without* sulfate were determined to be166.30 ± 11.07 and 168.60 ± 11.05 cm, respectively, no significant difference was found regarding stature in the two groups (P = 0.515).

The mean systolic blood pressure in both groups between *0* to 24 hours after the intervention was not statistically significant (Table 1).

Table 1: Mean systolic blood pressure in both groups

	Group	Mean	Standard Deviation	P value
SBP Zero hour	Without sulfate	135	13.95	0.615
	With sulfate	133	10.80	
SBP 2 hours later	Without sulfate	129	9.67	0.689
	With sulfate	130/50	13.56	
SBP 4 hours later	Without sulfate	129	9.67	0.657
	With sulfate	130/50	11.45	
SBP 6 hours later	Without sulfate	129/30	9.47	0.570
	With sulfate	131/25	11.90	
SBP 8 hours later	Without sulfate	133	9.23	0.885
	With sulfate	133/50	12.25	
SBP 16 hours later	Without sulfate	130/05	9.17	0.264
	With sulfate	133/95	12.32	
SBP 24 hours later	Without sulfate	132	9.51	0.210
	With sulfate	136/55	12.80	

The mean and standard deviation of diastolic blood pressure 0 and 2 hours after intervention in the two groups showed a statistically significant difference, indicating that the magnesium sulfate group had higher blood pressure in these time zones than the group without magnesium sulfate (P = 0.004; P = 0.004). However, our results didn't show (Table 2) significant statistical difference for *the remaining hours* (Table 2).

Table 2: Mean diastolic blood pressure in both groups

	Group	Mean	Standard Deviation	P value
DBP Zero hour	Without sulfate	79.75	7.77	0.004
	With sulfate	72.90	6.38	
DBP 2 hours later	Without sulfate	77.95	7.18	0.004
	With sulfate	71.65	5.81	
DBP 4 hours later	Without sulfate	77.30	7.56	0.769
	With sulfate	76.60	7.39	
DBP 6 hours later	Without sulfate	77.30	7.58	0.444
	With sulfate	75.55	6.70	
DBP 8 hours later	Without sulfate	75.80	6.86	0.413
	With sulfate	77.60	6.88	
DBP 16 hours later	Without sulfate	74.40	7.09	1.000
	With sulfate	75.40	7.09	
DBP 24 hours later	Without sulfate	74.60	7.02	0.321
	With sulfate	76.90	7.44	

As indicated in Table 3, the mean and standard deviation of heart rate 8, 16, and 24 hours after intervention in the two groups showed a statistically significant difference, indicating that at these times, patients receiving magnesium sulfate had a lower heart rate per minutes (P = 0.028; P = 0.001; P = 0.017).

Table 3: Average heart rate (Pr) in both groups

Group		Mean	Standard Deviation	P value
Pr Zero hour	Without sulfate	57.90	5.37	0.139
	With sulfate	55.70	3.65	
Pr 2 hours later	Without sulfate	107.15	11.37	0.757
	With sulfate	108.20	9.91	
Pr 4 hours later	Without sulfate	105.85	10.00	0.252
	With sulfate	109.55	10.10	
Pr 6 hours later	Without sulfate	104.90	10.32	0.608
	With sulfate	106.50	9.21	
Pr 8 hours later	Without sulfate	104.55	9.43	0.028
	With sulfate	98.90	5.75	
Pr 16 hours later	Without sulfate	101.00	6.27	0.001
	With sulfate	92.25	3.94	
Pr 24 hours later	Without sulfate	95.20	6.27	0/017
	With sulfate	90.85	4.67	

There was no significant difference between the two groups in the number of breaths per minute at 0, 2, 4, 6, 8, 16, 24 hours after intervention. Moreover, No significant difference was found in the mean of arterial oxygen in the two groups at 0, 2, 4, 6, 8, 16, 24 hours after intervention.

Distribution of intubation frequency at 0, 2, 4, 6, 8, 16, 24 hours after intervention showed no statistically significant difference between the two groups regarding the need for intubation (Figure 1).

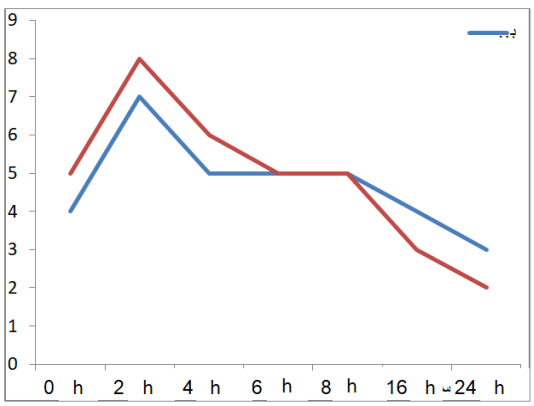

Figure 1: Frequency distribution of patients who were intubated at 0, 2, 4, 6, 8, 16, and 24 hours, based on the group

The frequency of pulmonary secretions at 0, 2, 4, 6, 8, 16, 24 hours after the intervention was not significantly different between the two groups and the lung secretions in both groups were approximately equal to one.

Moreover, the mean and standard deviation of admission hours showed that the use of magnesium sulfate in organophosphate poisoning reduced the number of admission hours (P = 0.006), (Table 4).

Table 4: Average hospitalization hours in both groups

Group		Mean	Standard Deviation	P value
Hospitali-zation	Without sulfate	58.05	12.17	0.006

Furthermore, the mean and standard deviation of atropine did not show a significant difference in the mean of atropine consumption (P = 67.9), (Table 5).

Table 5: Average atropine consumed in patients in both groups

	Group	Mean(mg)	Standard Deviation	P value
atropine	Without sulfate	1070	10	0.679
	With sulfate	1088	15	

Additionally, the mean and standard deviation of consumed *Pralidoxime* exhibited no significant difference (P = 0.232), (Table 6).

Table 6: The mean of consumed *Pralidoxime* at the end of 24 hours in patients in both groups

	Group	Mean(g)	Standard Deviation	P value
Pralidoxime	Without sulfate	344	26	0.232
	With sulfate	352	22	

On the other hand, the distribution of pupil diameter in both groups at 0, 2, 4, 6, 8, 16, 24 hours after intervention suggested no statistically significant difference (Table 7).

Table 7: Distribution of pupil diameter in both groups

P value	Group		Pupil diameter	
	With sulfate	Without sulfate		
-	20	20	Lower 3 mm	Zero hour
	0	0	Between 3 and 6 mm	
	0	0	Up to 6 mm	
0.824	1	2	Lower 3 mm	2 hours later
	9	10	Between 3 and 6 mm	
	9	9	Up to 6 mm	
1.000	0	0	Lower 3 mm	4 hours later
	3	4	Between 3 and 6 mm	
	17	16	Up to 6 mm	
1.000	0	0	Lower 3 mm	6 hours later
	3	4	Between 3 and 6 mm	
	17	16	Up to 6 mm	
0.301	0	0	Lower 3 mm	8 hours later
	8	4	Between 3 and 6 mm	
	12	16	Up to 6 mm	
0.748	0	0	Lower 3 mm	16 hours later
	11	13	Between 3 and 6 mm	
	9	7	Up to 6 mm	
0.501	0	0	Lower 3 mm	4 hours later
	12	15	Between 3 and 6 mm	
	8	5	Up to 6 mm	

Discussion

This study aimed to investigate the effect of magnesium sulfate on organophosphate poisoning. Organophosphate poisoning is one of the main clinical problems in the world with thousands of victims per year [27]. By inhibiting acetylcholinesterase activity, these compounds cause acetylcholine to accumulate in some brain synapses and neuromuscular synapses. Organophosphate poisoning is defined by various disorders such as the four clinical syndromes, *cholinergic crisis*, interstitial syndrome, organophosphate-induced *delayed polyneuropathy* (OPIDP), and organophosphate-induced chronic neuromuscular disorders. Each of these syndromes has its symptoms and symptoms [28]. Patients who receive first *auxiliary treatment* and emergency medical treatment have a better chance of recovery. However, the presence of arrhythmia and respiratory failure associated with poor prognosis. Ultimately, early diagnosis and proper treatment of complications can potentially reduce mortality.

Based on results presented in this study, the frequency of gender distribution was similar in both groups of patients and also the mean age, stature and weight of patients in both groups were determined to be similar. In the group receiving magnesium sulfate, diastolic blood pressure was found to be lower 0 and 2 hours after intervention as competed to patients who did not receive sulfate. The mean of systolic blood pressure in both groups was the same at all hours. The heart rate per minute in 8, 16 and 24 hours after the intervention was lower in the magnesium sulfate group than patients *without receiving* magnesium sulfate. Also, the number of hospital days in the group receiving magnesium sulfate was lower than that of other patients.

$MgSO_4$ inhibits acetylcholine release in the central nervous system, peripheral sympathetic and parasympathetic synapses. This prevents calcium channels in presynaptic nerve terminals, which release acetylcholine and increases the hydrolysis of some pesticides. It reduces arrhythmias associated with organophosphorus compounds and atropine, in the central nervous system decreases overstimulation by organophosphorus compounds, acting on the N-methyl-D-aspartate receptor, and reverses neuromuscular faint in the peripheral nervous system [29] [30] [31].

In the study of Pajoumand et al., The use of $MgSO_4$ at a dose of 4 g/day was considered useful in the treatment of acute human organophosphate toxicity, leading to a decrease in hospitalisation days and mortality rates that were consistent with the results of our study [32]. Our study also revealed that the number of hospital days in patients receiving magnesium sulfate was higher than those who did not receive magnesium sulfate, where reduces the cost of treatment. Basher in 2013 investigated the effect of magnesium sulfate on the toxicity of acute organophosphorus pesticides, and no adverse effects of magnesium were reported. In our study, no adverse effects were also found in patients receiving magnesium sulfate [33].

Recent advances in the treatment of organophosphate pesticide poisoning have shown that the alkalization of blood with sodium bicarbonate and magnesium sulfate can be *promising auxiliary treatment* [34], furthermore, Ahmed et al., in 2010, investigated the role of fresh plasma and magnesium sulfate in the treatment of acute toxicity of arganophosphamide insecticides, and showed that the addition of magnesium sulfate and fresh plasma to conventional treatments in organophosphate poisoning reduced the rate of hospitalization and death, where the results of this study were consistent with our findings [32].

In conclusion, the results of our study showed that the use of magnesium sulfate in organophosphate poisoning reduces therapeutic costs and the number of hospitalisation days and mortality compared to those who did not receive magnesium sulfate. Also, magnesium sulfate is also used to control tachycardia, ventricular arrhythmias, muscle fasciculations, where is therefore preferred to traditional therapies.

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