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Effect of Magnesium Sulphate on Short Term Mortality and Intermediate Syndrome in Patients Suffering from Organophosphate Compound Poisoning in ICU

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ABSTRACT
Background:*Organophosphate compounds (OPC) are one of the major causes of poisoning worldwide. In Bangladesh, it remains as an important health problem along with a poor prognosis. The standard treatment of OPC (Atropine and Pralidoxime) is not enough to reduce the mortality and morbidity burden.****Objectives:****The objective of this study was to determine the effect of magnesium sulphate on short term mortality and intermediate syndrome in patients suffering from organophosphate compound poisoning in ICU.****Methods:****This randomized clinical trial was conducted in Dhaka Medical College at the Department of Anaesthesia, Pain & Intensive Care Medicine from September 2020 to August 2021. A total of 62 ICU admitted patients with a history and clinical syndrome of OPC poisoning presenting within 24 hours of intoxication were included in this study according to the selection criteria. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).****Results:****In this study, the age distribution of the study population was found to be 48.4% for patients aged 18-30 years, 45.5% for 31-40 years, 6.5% for 41-50 years, and 0% for 51-60 years in group M. In group C, there were 54.8% of people aged 18 to 30, 32.3% of people aged 31 to 40, 9.7% of people aged 41 to 50, and 2.8% of people aged 51 to 60. The study population's sex distribution was 58.1% male and 41.9% female. Endotracheal intubation was observed in 11% of the patients in group M and 17% in group C.* ***Conclusion:****This study demonstrated improvement of the patients who received MgSO4 along with standard treatment. Consequently, this can be expected that future studies conducted on a larger scale might help to establish the beneficial effect of MgSO4 as a complementary treatment for the management of OPC poisoning.*
Keywords:*Organophosphate compounds (OPC), MgSO4, Mortality and Morbidity,*

I. INTRODUCTION

Organophosphate compounds (OPC) poisoning is a public health burden worldwide. In low and middle-income countries, it is a major cause of suicide as well as accidental poisoning. [1] According to World Health Organization (WHO), organophosphate pesticide poisoning kills an estimated 2,00,000 people every year mainly in the Asia Pacific region. [2]

In Bangladesh, most rural people are dependent on agriculture for their living. OPC is a popular pesticide and available in village shops. The frequency of occurrences of OPC poisoning is 89.8% among the poisoning cases which comprises 7.1% of total hospital admissions in Bangladesh. [3] OPC poisoning is associated with acute cholinergic crisis, intermediate syndrome (IMS), and delayed polyneuropathy. After initial recovery from the acute cholinergic crisis, some patients develop weakness of extraocular, facial, proximal limb, and respiratory muscles. This is regarded as intermediate syndrome. IMS is a noteworthy factor that contributes to OPC-induced mortality and morbidity. [4] In the clinical course of OPC poisoning, patients who require admission in an intensive care unit (ICU) need a longer length of stay, longer duration of antidote therapy, and ventilator support. It increases the risk of complications and additional costs. Early recognition and treatment are necessary to avoid such disastrous events.

The primary mechanism of action of organophosphate pesticides is irreversible inhibition of carboxyl ester hydrolases, particularly acetylcholinesterase (AChE). Due to AChE inhibition, acetylcholine (Ach) accumulates in presynaptic nerve terminals. This leads to overstimulation and disruption of neurotransmission. [5] Atropine, Oximes are essential drugs for OPC poisoning. But newer drugs are being tried along with conventional therapies. Magnesium sulphate (MgSO4), calcium channel blockers, benzodiazepines, sodium bicarbonate, clonidine, nicotinic receptor antagonist drugs, beta-adrenergic agonists, and lipid emulsions are some examples of drugs which are studied recently. Treatment guideline for OPC poisoning has not changed much since 1955, with Atropine and Oximes being the mainstay. [6] There is still controversy about the dosing of the drugs, when to give them, and how they can reduce intermediate syndrome. Atropine and Pralidoxime are included in the National Guidelines for Bangladesh fifth edition. But several studies have doubted the use of Pralidoxime for the treatment of OPC poisoning. [7] Many recent studies and analyses have questioned the effectiveness, dosing, and timing of Pralidoxime administration. [8] But there is no evidence against using them. The clinical trials which have been performed to see the effect of MgSO4, all of them were small in size, risk of bias was increased. The results from those studies stated that MgSO4 may have useful effect in the management of OPC poisoning. [9] Larger trials are needed to comment regarding the usefulness of MgSO4. Ongoing studies are assessing new modalities of treatment to prevent or improve organophosphate-induced toxicity.

Previous studies have shown benefits after using magnesium sulfate (MgSO4), as it reduces the requirement of Atropine, need for intubation, and decreases the length of stay in ICU. [10] Another study compared different doses of MgSO4 where all doses gave satisfactory results. [11] Although several studies are performed in western countries to evaluate the effectiveness of MgSO4 for organophosphate compound poisoning, limited studies were done in this country.

In Bangladesh, hospital-based studies show OPC poisoning is mostly encountered in the emergency department. [12] MgSO4 is a well-known drug. Although there are many studies on OPC poisoning they are based on recent situations, baseline surveys, and management. Additional effects of MgSO4 with the standard treatment are yet to be explored in the management of OPC poisoning.

This study was aimed to assess the effect of MgSO4 on short term mortality and development of intermediate syndrome in patients suffering from organophosphate compound poisoning in ICU when it was added with Atropine and Pralidoxime.

II. METHODOLOGY

This Randomized Clinical Trialstudy was carried out in the Intensive Care Unit (ICU) at the Department of Anaesthesia, Pain, Palliative & Intensive Care Medicine, Dhaka Medical College, Dhaka, duringSeptember 2020 to August 2021. 62 patients who were admitted with history of OPC poisoning who presented within 24 hours after intoxication were included in this study. Patients of both genders aged from 18-60 years with a history of OPC poisoning who were admitted within 24 hours after intoxication were primarily included in this study.All patients received proper management and follow-up according to the National Guidelines for Bangladesh fifth edition. All patients were followed up from the first to the fourthday, then weekly for four weeks from the day of ICU admission. Informed written consent was obtained from each patient's legal guardian before the study. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

III. RESULTS

Group M: patients getting MgSO4 along with standard treatment (Atropine and Pralidoxime)
Group C: patients getting standard treatment (Atropine and Pralidoxime) without MgSO4

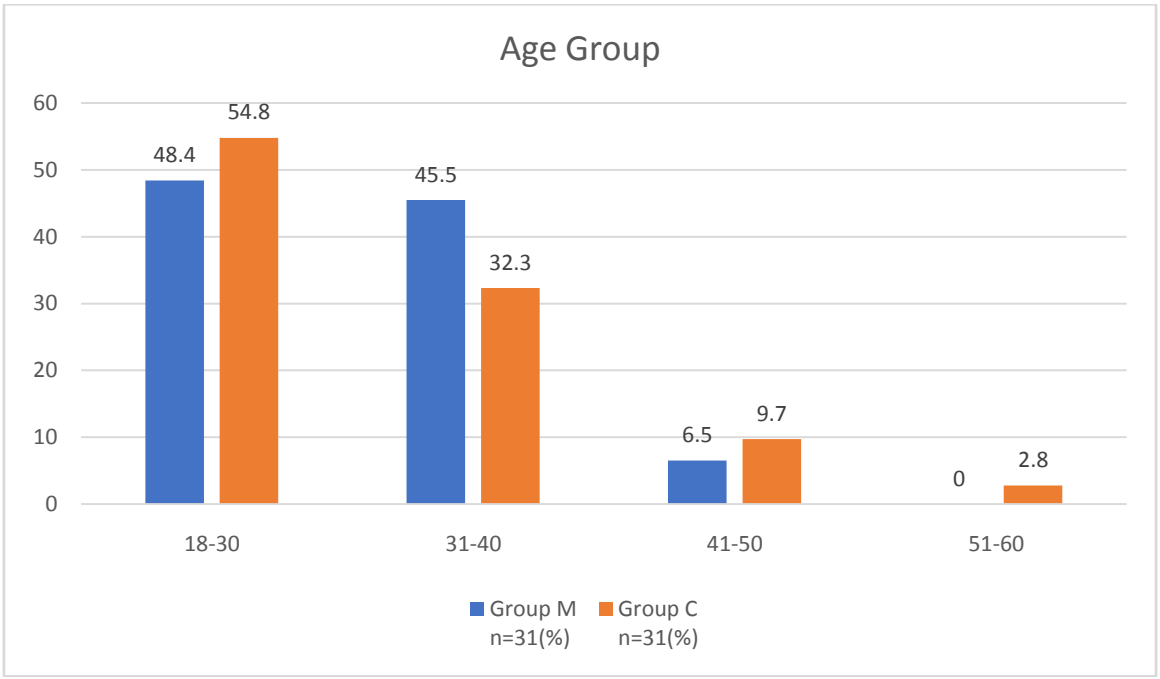

Figure-1: Distribution of the study groups according to age (n=62)

Figure-1 shows age distribution of the study population, it was observed that patients were belonged to age 18-30 years were 48.4%, 31-40 years were 45.5%, 41-50 years were 6.5% and 51-60 years were 0% in group M. And 18-30 years were 54.8%, 31-40 years were 32.3%, 41-50 years were 9.7% and 51-60 years were 2.8% in group CAge was statistically similar across both groups of patients (p>0.05).

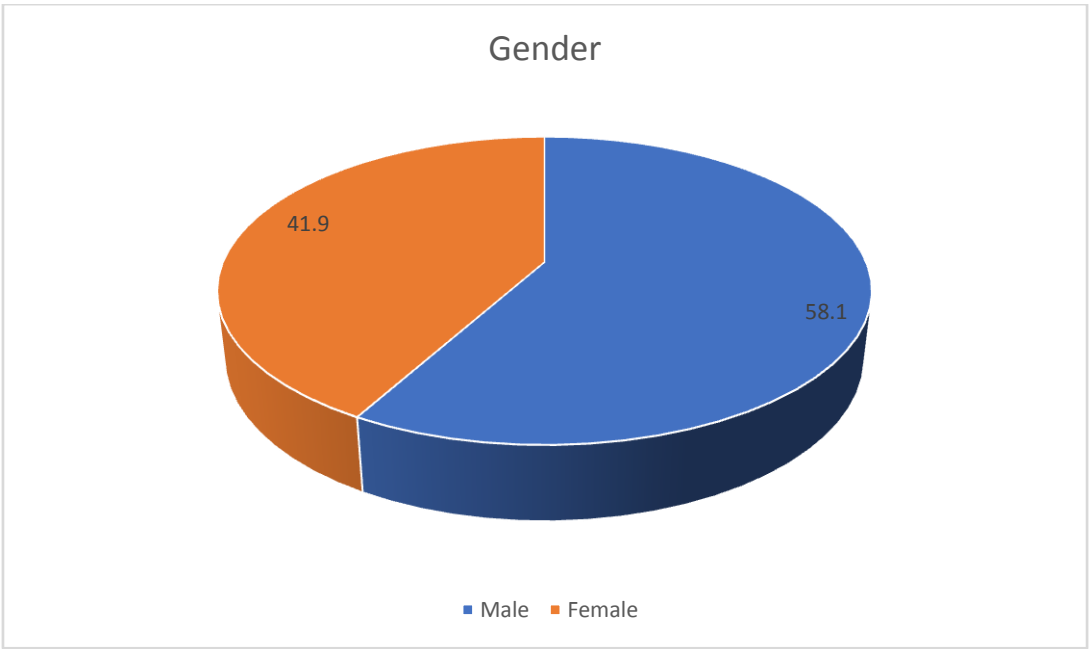

Figure-2: Distribution of the study groups according to age (n=62)

Figure 2 shows sex distribution of the study population, it was observed that 58.1% patients were male and 41.9% were female.

Table I: Initial clinical presentations of the study groups (n=62)

Clinical presentations	Group M n=31(%)	Group C n=31(%)	p value
Miosis	29(93.5)	27(87.1)	0.671
Respiratory difficulty	28(90.3)	25(80.6)	0.490
Bronchorrhea	25(80.6)	27(87.1)	0.473
Muscle fasciculation	12(38.7)	13(41.9)	0.796
Salivation	23(74.2)	21(67.7)	0.576
Vomiting	12(38.70	18(58.1)	0.127
Lacrimation	11(35.5)	14(45.2)	0.437
Abdominal cramps	9(29)	11(35.5)	0.587
Restlessness	20(64.5)	26(83.9)	0.082
Pulmonary edema	14(45.2)	10(32.3)	0.297
Loss of sphincter control	7(22.9)	6(19.4)	0.490
Dairrhoea	8(25.8)	5(16.1)	0.349
Sweating	15(48.4)	10(32.3)	0.196
Cyanosis	6(19.4)	7(22.9)	1.000

Table 1. shows Initial clinical presentations of the study groups, it was observed that 29(93.5%) patients were Miosis, 28(90.3) patients wereRespiratory difficulty, 25(80.6) patients wereBronchorrhea and 11(35.5) patients were Lacrimation in group M. And 27(87.1) patients were Miosis, 25(80.6) patients wereRespiratory difficulty, 27(87.1) patients wereBronchorrhea and 14(45.2) patients were Lacrimation in group C.

Table II: Vital signs of the respondent (n=62)

Vital parameters	Group M n=31(%)	Group C n=31(%)	p value
Temperature	37.32 ± 1.03	37.49± 0.76	0.535
Heart rate (beats/min)	89.33± 2.71	109.96 ±3.05	0.001
Systolic blood pressure	117±15	121±15	0.281
	Median=120	Median=123	
Diastolic blood pressure	74±10	75±10	0.620
	Median=70	Median=75	
	20.97±4.48	22.3±3.07	0.151
ABG parameters			
PH	7.40±.0.07	7.38±0.11	0.870
PaCO2(mmHg)	39.99±5.94	41.64±8.66	0.468
PO2(mmHg)	94.16±5.85	88.46±8.3	0.347
HCO3	25.24±3.39	25.47±5.06Respiratory rate	0.833

Table 2. shows Initial clinical presentations of the study groups, it was observed that in group M patients had 37.32 ± 1.03 Temperature, 89.33± 2.71 Heart rate and 20.97±4.48 Diastolic blood pressure. And in group C patients had 37.49± 0.76 Temperature, 109.96 ±3.05 Heart rate and 20.97±4.48 Diastolic blood pressure.

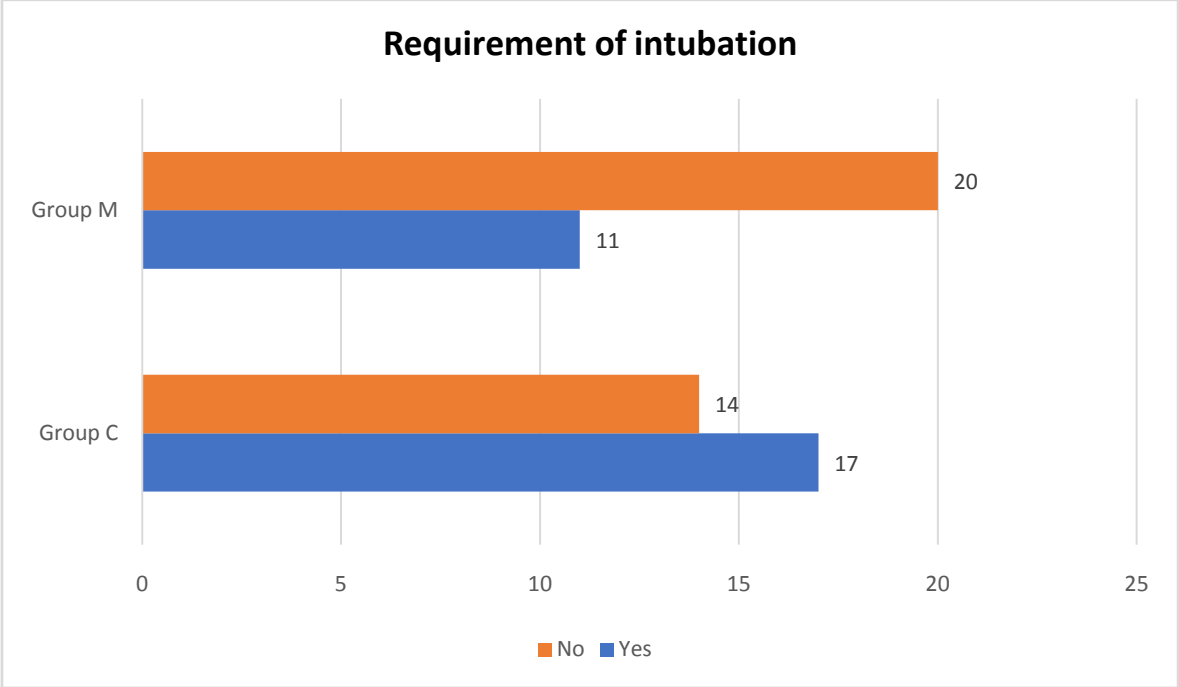

Figure-3: Distribution of the study subjects according to endotracheal intubation (n=62)

Figure 3 shows the study subjects according to endotracheal intubation, it was observed that 11% patients had endotracheal intubation in group M and 17% patients had endotracheal intubation in group C.

Table III: Length of ICU stay and duration of mechanical ventilation in both groups (n=62)

Parameter	Group M n=31(%)	Group C n=31(%)	p value
ICU stay (in days)	8.03± 3.11	12.29± 4.62	0.002
Mechanical ventilation duration (in days)	6.04 ± 3.17	9.76 ± 3.26	0.012

Table 3 shows length of ICU stay and duration of mechanical ventilation in both groups, it was observed that 8.03± 3.11 had ICU stay and 6.04 ± 3.17 had Mechanical ventilation duration in group M. And 12.29± 4.62 had ICU stay and 9.76 ± 3.26 had Mechanical ventilation duration in group C.

Table IV: Total dose of Atropine and Pralidoxime requirement in both groups (n=62)

Drug	Group M n=31(%)	Group C n=31(%)	p value
Atropine (mg)	128.74 ± 41.22	182.30 ± 60.27	0.002
Pralidoxime (mg)	2741.94 ± 228.82	3709.68± 416.8	0.001

Table 4 shows Total dose of Atropine and Pralidoxime requirement in both groups, it was observed that 128.74 ± 41.22 had Atropine and 2741.94 ± 228.82 had Pralidoxime in group M. And 182.30 ± 60.27 had Atropine and 3709.68± 416.8 had Pralidoxime in group C.

Table V: Categorization of study subjects according to intermediate syndrome (n=62)

Group	Intermediate syndrome		p value
	Yes	No	
Group-Mn=31(%)	6 (19.3)	25 (80.6)	0.054
Group-Cn=31(%)	13(41.9)	18(58.0)	

Table 5 shows Categorization of study subjects according to intermediate syndrome, it was observed that 6(19.3) had positiveIntermediate syndrome and 25 (80.6) had negativeIntermediate syndrome in group M. And 13(41.9) had positive Intermediate syndrome and 18(58.0) had negative Intermediate syndrome in group C.Pvalue 0.054.

Table VI:Categorization of study subjects according to short term mortality(n=62)

Group	Short term mortality		p value
	Yes	No	
Group-Mn=31(%)	5(16.1)	26(83.8)	0.046
Group-Cn=31(%)	12(38.7)	19(61.2)	

Table 6 shows Categorization of study subjects according to short term mortality, it was observed that 5(16.1) had short term mortality and 26(83.8) hadn't short term mortality in group M. And 12(38.7) had short term mortality and 19(61.2) hadn't short term mortality in group C. P value 0.046.

IV. DISCUSSION

Organophosphate compounds are widely used pesticide in Bangladesh. It is one of the most commonly found method of self-poisoning physicians have to treat in the medical wards. There is no proper universal guideline regarding the management of OPC poisoning. Atropine and Pralidoxime has been the mainstay of treatment for a very long time. This study was designed to observe the effect of MgSO4 on short term mortality and intermediate syndrome in the patients with OPC poisoning.

In this study, the majority were aged from 18-30 years. Male patients were higher in both groups. This finding was in agreement with the studies conducted by Sarkar and Khanum [1, 13] These two different studies were done in Bangladesh and both found majority of cases of OPC poisoning were from less than 40 years of age group with male predominance. In this study most of the cases were due to suicidal intension. The resemblance between Nazima and Ahmed was found in this regard. [14, 5] This trend states that in our country young adult males are most vulnerable to this type of intentional poisoning. More than half of the patients hailed from the rural area in both groups. OPC is more available in rural areas, so rural people have more access to OPC than the urban dwellers. Timsinha found most patients hailed from urban areas. [15] As it was conducted in Nepal and the study center was situated in an urban area.

In agreement with Banday et al.,in this study miosis was found more commonly. [16]Elbarranystated that, pupil can be dilated if nicotinic stimulation takes upper hand. OPC acts as a parasympathomimetic drug and causes constriction of constrictor pupillae muscle. [17] So miosis took place.

In this study vital parameters and ABG parameters difference was nonsignificant except for heart rate. Heart rate reduced significantly in the MgSO4 treated group. Jamshidi et al. and Philomena et al.found reduction of heart rate in the MgSO4 treated group. [18, 19] MgSO4 acts as a bronchodilator. Decreases work of breathing. When oxygen consumption reduced by the respiratory muscle, myocardial perfusion increases and reduces heart rate.

Vijayakumar and Basher found the requirement of intubation was significantly 30% less in MgSO4 treated group. [10, 12] MgSO4 increases the catabolism of OPC, decreases the release of acetylcholine. Thus, less intubation was needed. In this study, more patients came with respiratory distress. For securing the airway and maintenance of oxygen saturation intubation was done early. So, the result came out non-significant.

In this study, there was a significant reduction in the need for mechanical ventilation in MgSO4 treated group highlighting the beneficial effect of magnesium sulphate. Vijayakumar found reduction in the need for mechanical ventilator. [10] Loss of consciousness and loss of airway control increase the risk of aspiration followed by chemical pneumonitis. These worsen oxygenation and can progress to respiratory failure. MgSO4inhibits the release of histamine from must cells, and decreases mucus production, relaxes the bronchial muscle, and expands the airway. When given with Atropine and Pralidoxime, it influenced to reduce the need and duration of mechanical ventilator.

Reduction of intubation and duration of mechanical ventilation had reduced the need for staying in the hospital in the patients receiving MgSO4 significantly in this study. This finding further supports the beneficial role of MgSO4 in the management of OPC poisoning.Pajoumand Vijayakumar found similar results. [10, 11]

This study showed that total dose requirement of Atropine and Pralidoxime was reduced significantly in MgSO4treated group. Elbarrany showed that MgSO4 significantly reduced Atropine and Pralidoxime requirements. [11] Atropine causes bronchodilatation and reduction of secretion by acting with the muscarinic receptors of the respiratory smooth muscles. Pralidoxime reactivates acetylcholinesterase. MgSO4 dilates pulmonary artery, and reduces pulmonary resistance. When given with standard treatment, MgSO4 could work synergistically to improve outcomes. Pajoumand did not find any significant difference in a total dose of Atropine and Pralidoxime between MgSO4treated and non-treated group. [11] That study compared the daily dose of these drugs, so the result could not be compared with this study. Basher stated that loading dose of Atropine was less needed in magnesium treated group. [12] But median total Atropine dose had no statistical significance. Vijayakumar did find a significant reduction in Atropine requirement in MgSO4 treated group. [10] Dosing guidelines of Atropine and Pralidoxime differ from one institute to another. As there is no optimal

dosing regimen to follow, it is difficult to compare between those institutes whether MgSO4 can help to reduce the total dose of Atropine and Pralidoxime requirement

In agreement with Eddleston, Philomena and Jamshidi significantly less mortality in MgSO4 treated group was observed in this study. [6, 18, 20] Basher showed reduced mortality but with increasing doses of MgSO4. [12] Magnesium sulphate inhibits the release of acetylcholine from the central and peripheral nervous systems. It reduces myocardial oxygen consumption, increases oxygenation, causes bronchodilatation, and improves the patient's general condition. The result of this study was in contrast with Vijayakumar who found that mortality was reduced but not significant. That study was not powered enough to comment on mortality. [10]

Regarding this study, the capacity to measure repeated magnesium levels was limited by funding. The level of acetylcholinesterase was not measured.

There are few clinical unicentered small clinical trials are available about the effects of giving intravenous MgSO4 in OPC poisoning. The results are also conflicting. Very few studies are available about the effects of MgSO4 in reducing intermediate syndrome. So, this study was taken to see if MgSO4 could reduce the mortality and intermediate syndrome when it was added with standard treatment.

Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

V. CONCLUSION

In this study, the effect of MgSO4 was observed when added with standard treatment (Atropine and Pralidoxime) in intensive care unit admitted patients with organophosphate compound poisoning. Reduction of length of ICU stay, the duration of mechanical ventilation, total dose requirement of Atropine, Pralidoxime, and short-term mortality was observed in patients who received MgSO4.

VI. RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

ACKNOWLEDGEMENTS

The wide range of disciplines involved in effect of magnesium sulphate on short term mortality and intermediate syndrome in patients suffering from organophosphate compound poisoning in ICU research means that editors need much assistance from referees in the evaluation of papers submitted for publication. I would also like to be grateful to my colleagues and family who supported me and offered deep insight into the study.

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