ejpmr, 2020,7(5), 421-430

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

EFFECT OF MAGNESIUM SULPHATE IN ACUTE ORGANOPHOSPHORUS POISONING – A COMPARATIVE INTERVENTIONAL STUDY

***Dr. Rumaisa Ahmed, Dr. B. N. Raghavendra Prasad and Dr. Tameem Imran**

Post Graduate Medicine, Kuvempunagar Kolar Karnataka India 563101.

***Corresponding Author: Dr. Rumaisa Ahmed**

Post Graduate Medicine, Kuvempunagar Kolar Karnataka India 563101.

Article Received on 09/03/2020 **Article Revised on 29/03/2020** **Article Accepted on 18/04/2020**

INTRODUCTION

Organophosphorus compounds are used as commercial insecticides, chemical warfare as nerve gas and are also applied as aerosols or dusts.

Organophosphorus poisoning (OP) is the most common poisoning in India due to its easy availability. Acute OP pesticides poisoning is the most important cause of severe toxicity and death worldwide despite treatment. More than 3 million people worldwide are exposed to organophosphates each year, with an estimate of 3 lakh deaths.[1] The organophosphate accounts for > 80% of pesticide-related hospitalizations.

Unintentional and intentional OP poisonings continues to be a significant cause of mortality and morbidity in India.

OPC irreversibly binds to acetylcholinesterase which results in classical cholinergic symptoms.[2] The standard management is to reduce the OPCs absorption by gastric lavage and decontamination of skin along with administration of atropine and oximes.[3]

Atropine competitively binds to muscarinic and nicotinic receptors and inhibits acetylcholine accumulation. Oximes remove the phosphoryl group on acetylcholinesterase and regenerates cholinesterase activity that was inhibited by an organophosphate compound previously.

The role of oximes is not well defined as efficacy or safety of oximes in these settings is not established.[4,5] Oximes are relatively expensive and ineffective once acetylcholinesterase has aged.

Magnesium blocks ligand-gated calcium channels, resulting in reduced Ach release from the presynaptic nerve terminal. Thus improving function at NMJ and reduced activation.

Most of the studies have taken Magnesium sulfate at a dose of 4 g/day IV, administered only within the first 24 hours after admission. The mortality rate and hospitalization days of patients who received MgSO4 treatment were significantly lower than those who had not received MgSO4.[6]

Only one study, a phase 2 trial used 4g, 8g, 12g, and 16g and showed benefit as the dose of mgso4 increased.[7] As it was a phase 2 study the results could not be generalized. Further studies are required to see the efficacy and safety of mgso4 with increasing dose.

Thus an alternative or an adjunctive treatment that may alter acetylcholine release or protect the neuromuscular junction needs to be explored.

Hence we have taken up this study to see the effect of mgso4 both of 4 grams and 8 grams in Acute OP poisoning based on severity of OP poisoning.

OBJECTIVES

- To establish the severity of acute organophosphorus poisoning.
- To Administer MgSO4 in intermittent bolus given according to clinical severity when presented within 24hrs of consumption.
- To look at morbidity and mortality pattern in patients receiving MgSO4.
- To compare the morbidity and mortality with patients not receiving MgSO4.

4. MATERIAL AND METHODS

The study included 80 patients with alleged history of OPC consumption who presented to RLJ Hospital Kolar attached to SDUAHER during February 2018 - June 2019.

Patients above 18 years with history of OP compound poisoning within 24 hours of consumption and classified as moderste/severe op according to POP scale were included.

Contraindications for $MgSo_4$ therapy like heart block, Pregnant women, with other comorbidities like renal, cardiac and pulmonary dysfunction and mild Organophosphorus poisoning and mixed compounds were excluded.

4.4 Methods

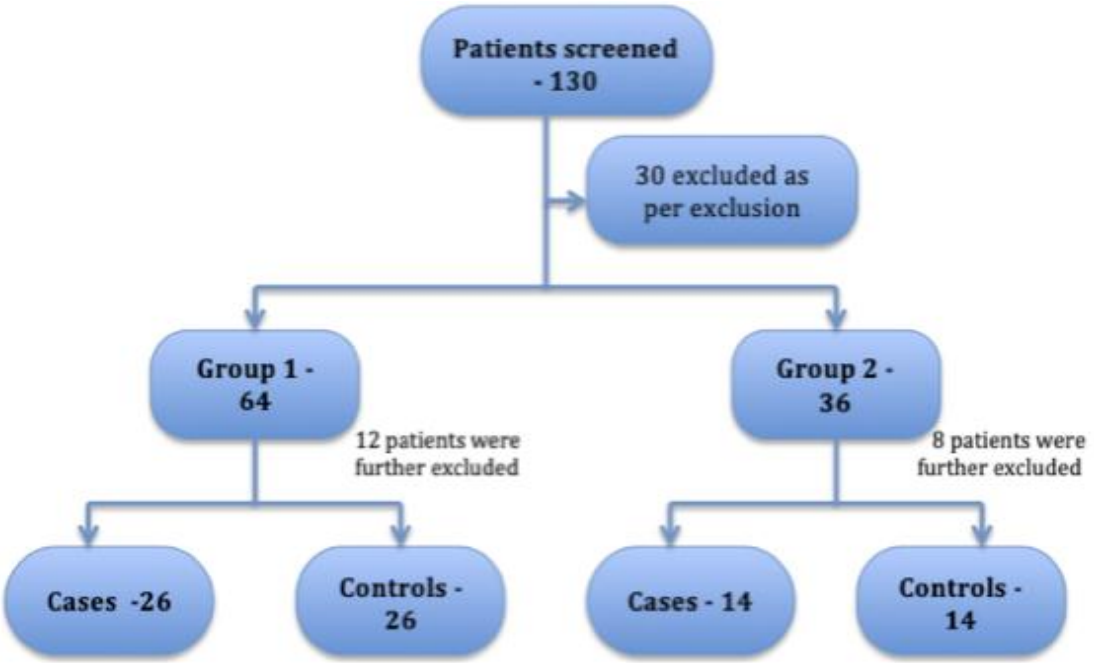
- Decontamination of skin and gastrointestinal tract was done as per standard institutional protocol.
- Injection Atropine intravenous (IV) was given as 2 mg boluses, till signs of atropinization was achieved (heart rate more than 80 beats/min, systolic blood pressure more than 80 mm of Hg, drying of oral, and tracheobronchial secretions) followed by a titrated infusion to maintain heart rate of 80–100 beats/min.
- Inj pralidoxime IV 30 mg/kg as loading dose, followed by 8–10 mg/kg/h infusion over 48 h was also given.
- Patients who developed acute respiratory failure and neuromuscular weakness were intubated and mechanically ventilated.

"Peradeniya Organophosphorus Poisoning Scale" was calculated. Based on which patients with a score of 0 to 3 were considered as mild poisoning, 4 to 7 as moderate poisoning and 8 to 11 as severe poisoning.

2 groups were divided based on PoP scale.
Group 1 (Moderate poisoning were allotted to this group) - cases received 4g of MgSO4 controls did not receive MgSO4.
Group 2 (Severe poisoning were allotted to this group) - cases received 8g of MgSO4 controls did not receive MgSO4.
Cases and controls were matched according to the severity of poisoning.

Primary outcomes that were measured were atropine requirement per day, number of patients requiring intubation and mechanical ventilation, day of intubation, duration of mechanical ventilation, ICU stay, and mortality.

It is a Comparative interventional study in which 80 patients were included.



Sample size is estimated based on the mortality observed in MgSO4 treated (15.9) and not treated (31.25) in acute OP poisoning in a study by Philomena J et al. considering confidence interval of 95%, 80% power with an effect size of 60% reduction in mortality in MgSO% treated group. The sample size is 80.

MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS

Table 11: MgSo4 treatment distribution among study subjects.

		Count	Percentage
MgSo4 given	4mg	26	32.5%
	8mg	14	17.5%
	Not given	40	50.0%

In the given study 26 (32.5%) of the study subjects received 4mg of MgSo4 and 14(17.5%) of them received 8mg of MgSo4.

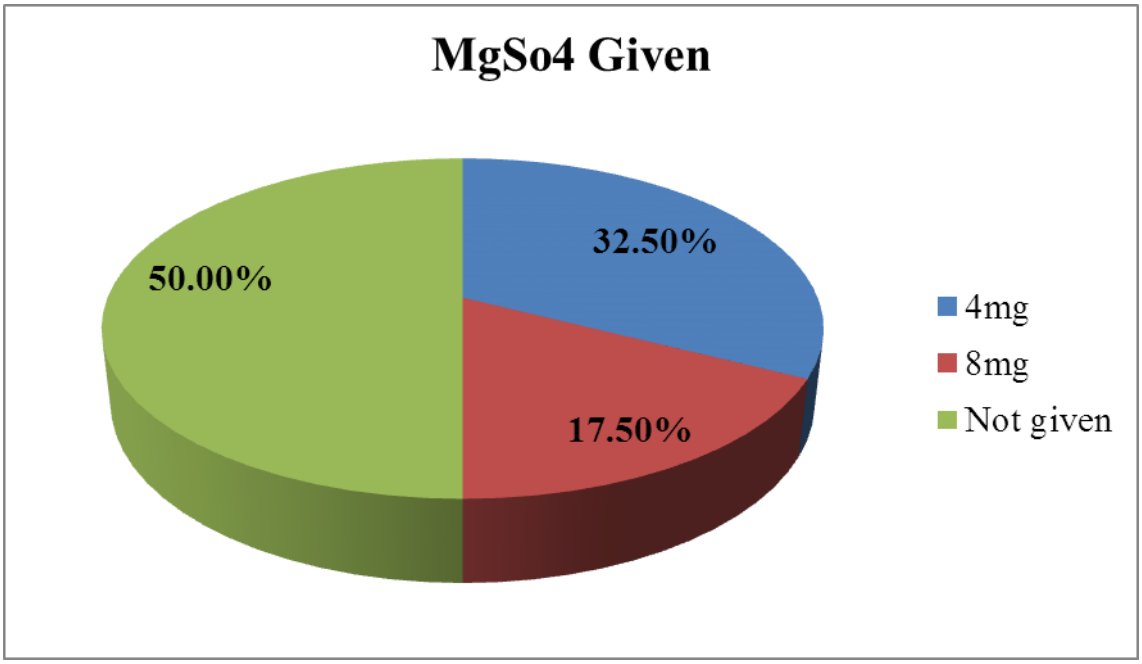


Figure 1: Pie chart showing MgSo4 treatment distribution among study subjects.

Table 1: Association between MgSo4 given and Outcome among those with moderate poisoning.

		MgSo4				P value
		4 mg MgSo4		MgSo4 Not given		
		Count	%	Count	%	
Recovery	Recovered	26	100.0%	26	100.0%	-
DAMA	DAMA	3	11.5%	2	7.7%	0.638
	No	23	88.5%	24	92.3%	
Death	No	26	100.0%	26	100.0%	-

In the study among those with moderate poisoning, there was no difference in outcome between those who received 4 MgSo4 and who did not receive MgSO4.

Table 2: Association between MgSo4 given and Outcome among those with severe poisoning.

		MgSo4				P value
		8 mg MgSo4		MgSo4 Not given		
		Count	%	Count	%	
Recovery	No	1	7.1%	0	0.0%	0.309
	Recovered	13	92.9%	14	100.0%	
DAMA	DAMA	0	0.0%	0	0.0%	-
	No	14	100.0%	14	100.0%	
Death	Death	1	7.1%	0	0.0%	0.309
	No	13	92.9%	14	100.0%	

In the study among those with severe poisoning, there was no significant difference in recovery among those who received 8 MgSo4, 92.9% recovered and 7.1% did not recover, among those who did not receive MgSo4, 100% recovered.

There was no significant difference in DAMA and death between those who received 8 MgSo4 and who did not received MgSo4.

Table 3: Duration of hospitalization, ICU stay and HDU stay with respect to MgSo4 given among those with moderate poisoning.

	MgSo4				P value
	4 mg MgSo4		MgSo4 Not given		
	Mean	SD	Mean	SD	
Says of hospitalization	5.92	1.26	8.88	3.64	<0.001*
Days of ICU Stay	1.50	.58	1.71	1.11	0.732
HDU stay	4.27	1.40	5.96	2.72	0.007*

In the study among those with moderate poisoning, there was significant difference in duration of stay in hospital and HDU stay between those who received MgSo4 and who did not received MgSo4.

Duration of stay and HDU stay was less among those who received 4 MgSo4 compared to those who did not receive MgSo4.

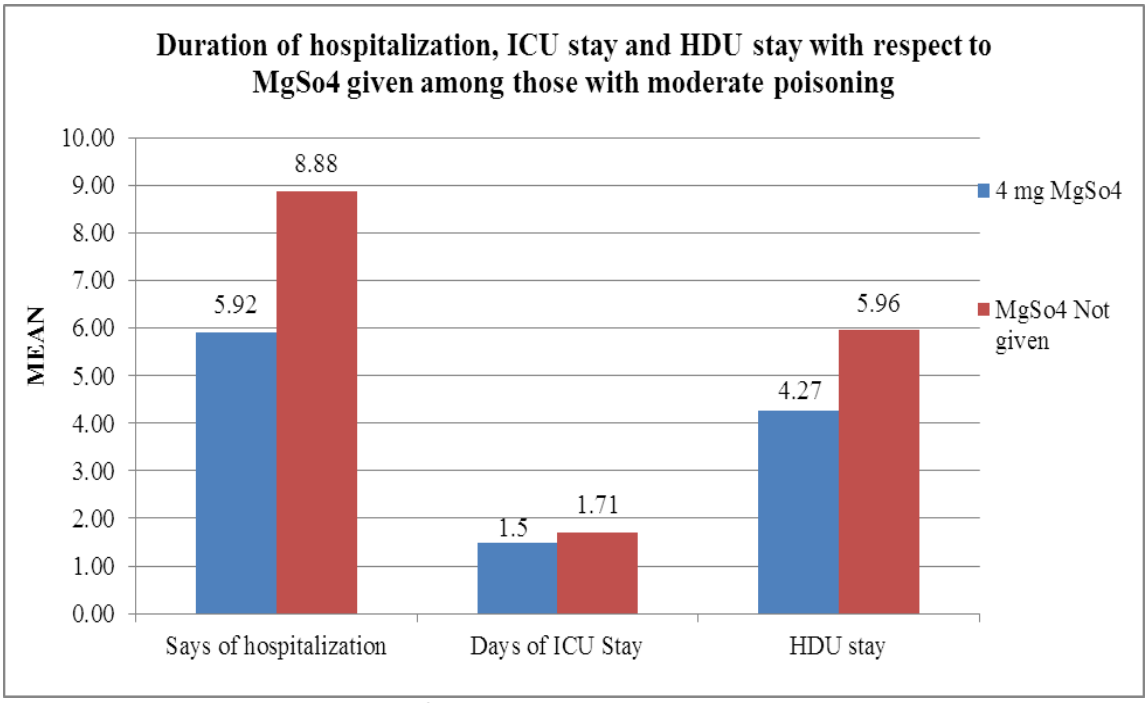


Figure 2: Bar diagram showing duration of hospitalization, ICU stay and HDU stay with respect to MgSo4 given among those with moderate poisoning in study subjects.

Table 4: Duration of hospitalization, ICU stay and HDU stay with respect to MgSo4 given among those with severe poisoning.

	MgSo4				P value
	8 mg MgSo4		MgSo4 Not given		
	Mean	SD	Mean	SD	
Says of hospitalization	9.21	4.06	8.36	2.10	0.489
Days of ICU Stay	2.11	1.05	1.36	0.67	0.07
HDU stay	6.21	2.49	5.00	1.47	0.128

In the study among those with severe poisoning, there was no significant difference in duration of stay in hospital, ICU stay and HDU stay between those who received MgSo4 and who did not received MgSo4.

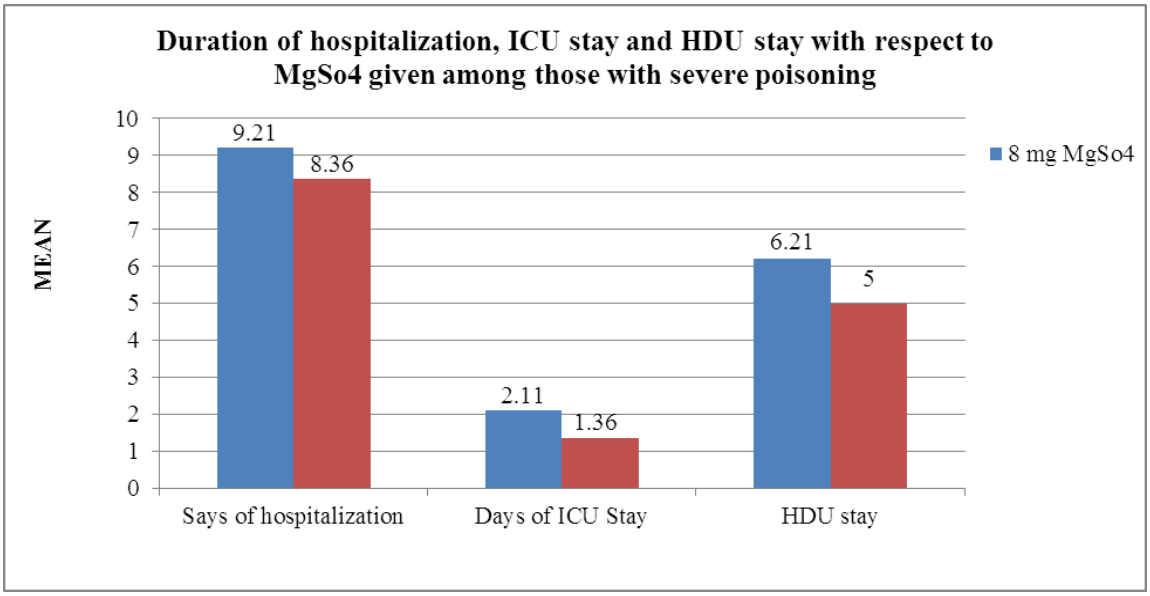


Figure 3: Bar diagram showing duration of hospitalization, ICU stay and HDU stay with respect to MgSo4 given among those with severe poisoning in subjects.

Table 16: Mechanical ventilation comparison between MgSo4 treated and not treated subjects.

		MgSo4			
		MgSo4 given		MgSo4 not given	
		Count	%	Count	%
Mechanical ventilation	No	35	87.5%	33	82.5%
	Yes	5	12.5%	7	17.5%

Z= -0.62, p = 0.528

In the study among those who received MgSo4 12.5% were intubated and mechnically ventilated and 17.5% were in intubated in patients who did not receive MgSo4. There was no difference in Mechanical ventilation.

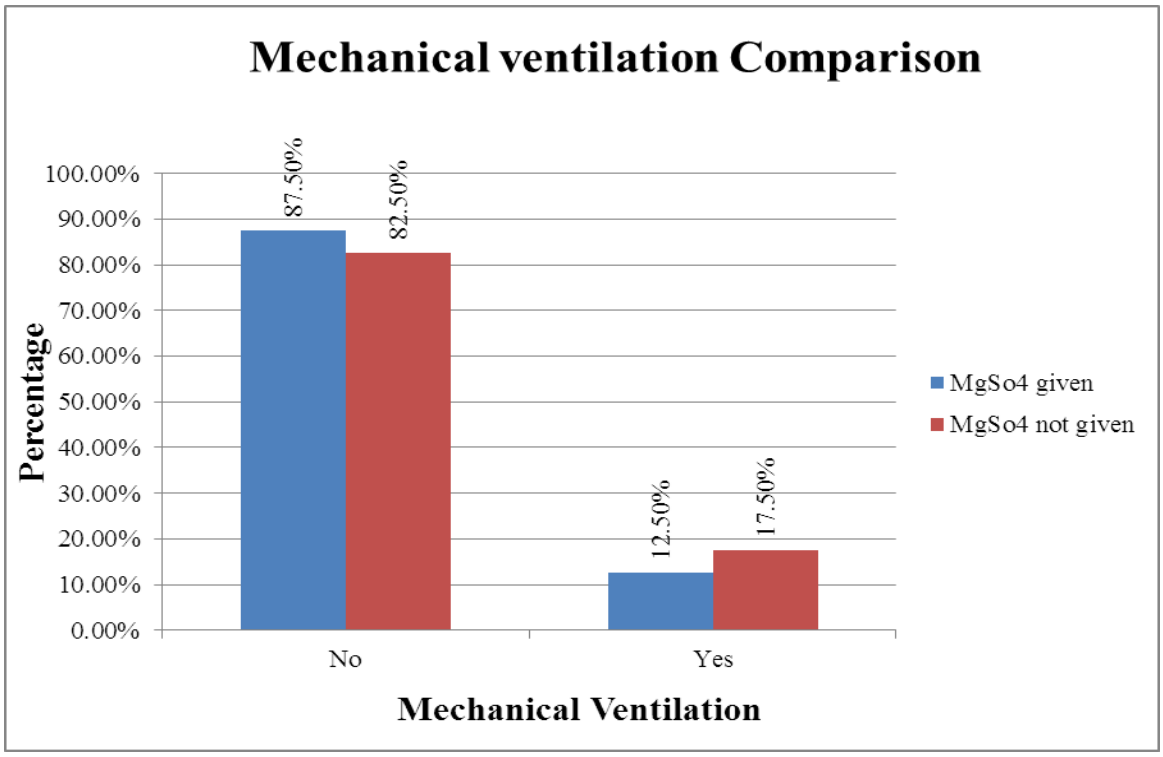


Figure 4: Bar diagram showing Mechanical ventilation comparison between MgSo4 treated and not treated subjects.

Table 7: Atropine dose levels comparison between with respect to MgSo4 given among those with moderate poisoning.

	MgSo4				P value
	4 mg MgSo4		MgSo4 Not given		
	Mean	SD	Mean	SD	
Day 1	12.12	5.98	22.58	14.48	0.001*
Day 2	18.77	6.85	37.54	14.43	<0.001*
Day 3	12.35	5.77	20.54	7.67	<0.001*
Day 4	10.27	4.99	17.85	7.30	<0.001*
Day 5	5.54	4.61	12.19	4.37	<0.001*
Day 6	2.42	3.07	8.00	4.06	<0.001*
Day 7	0.65	1.60	3.81	4.22	0.001*

In the study among those with moderate poisoning, there was significant difference in Atropine dose levels between those who received 4mg MgSo4 and who did not received MgSo4 from Day 1 to Day 7.

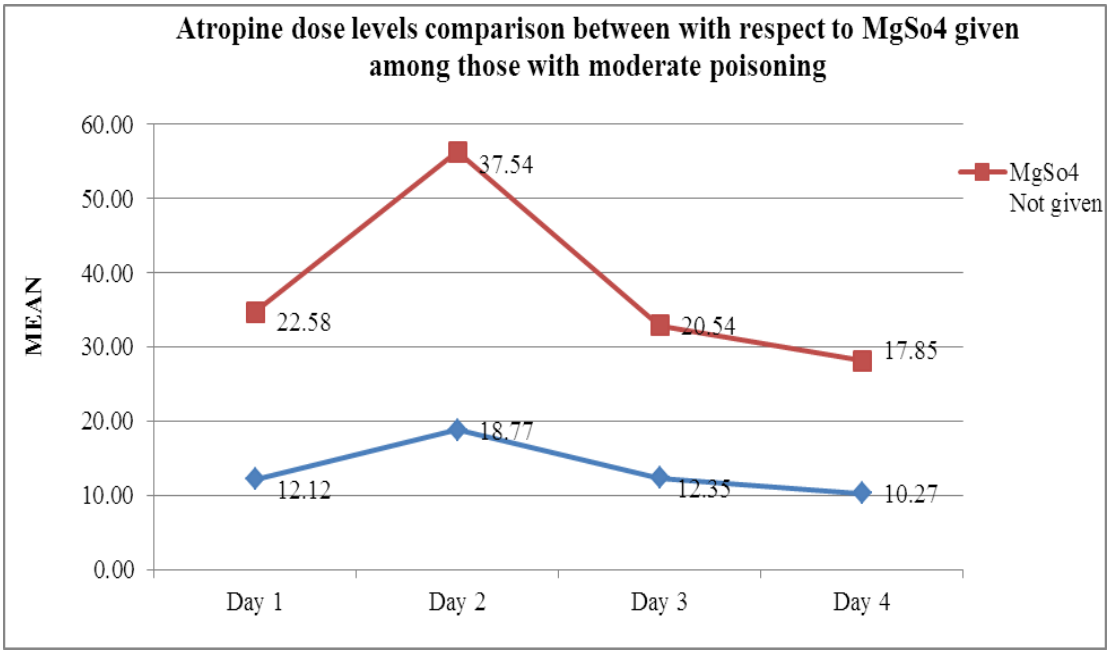


Figure 5: Bar diagram showing atropine dose levels comparison between with respect to MgSo4 given among those with moderate poisoning in study subjects.

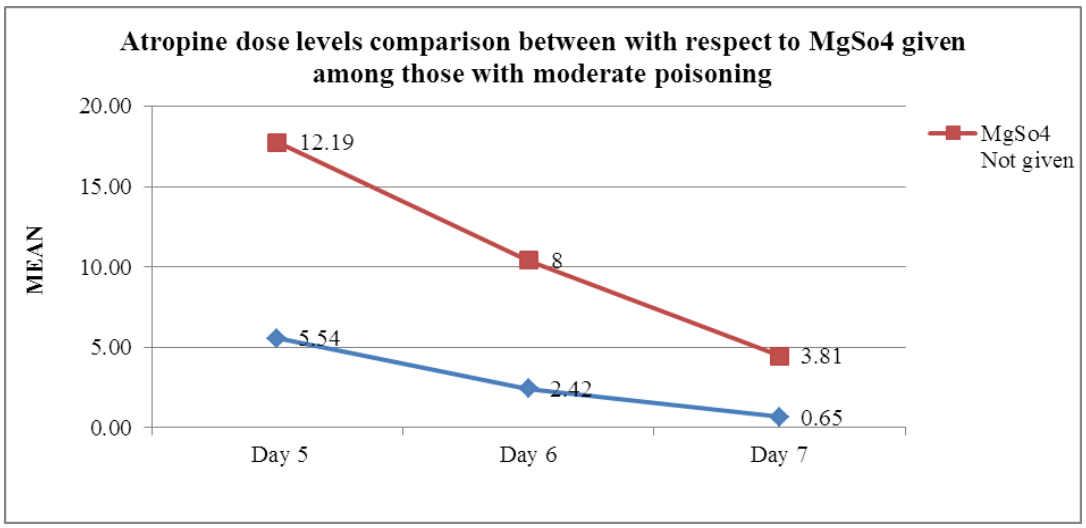


Figure 6: Bar diagram showing atropine dose levels comparison between with respect to MgSo4 given among those with moderate poisoning in study subjects.

Table 8: Atropine dose levels comparison between with respect to MgSo4 given among those with severe poisoning.

	MgSo4				P value
	8 mg MgSo4		MgSo4 Not given		
	Mean	SD	Mean	SD	
Day 1	24.21	10.74	14.64	10.24	0.023*
Day 2	36.79	11.83	31.71	10.92	0.249
Day 3	19.71	8.81	16.86	5.20	0.306
Day 4	15.64	8.44	13.93	3.56	0.490
Day 5	13.07	12.45	11.21	3.07	0.592
Day 6	6.29	3.87	6.21	3.53	0.960
Day 7	3.50	2.65	3.36	2.21	0.878

In the study among those with severe poisoning, there was significant difference in Atropine dose levels between those who received 8mg MgSo4 and who did not received MgSo4 Day 1 n day 1. And on other days there was no significant difference in Atropine dose requirement between two groups.

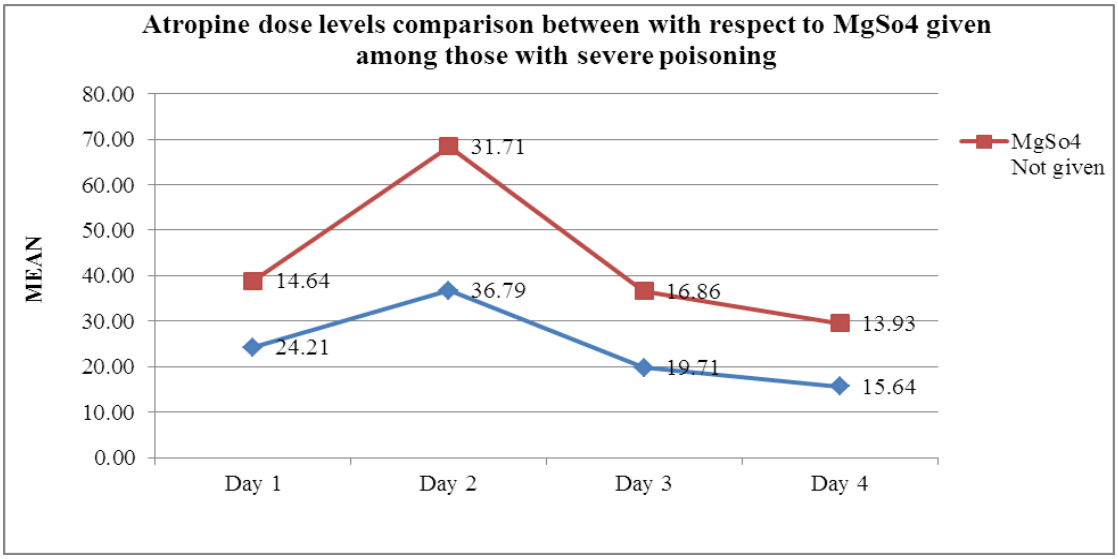


Figure 7: Bar diagram showing atropine dose levels comparison between with respect to MgSo4 given among those with severe poisoning in study subjects.

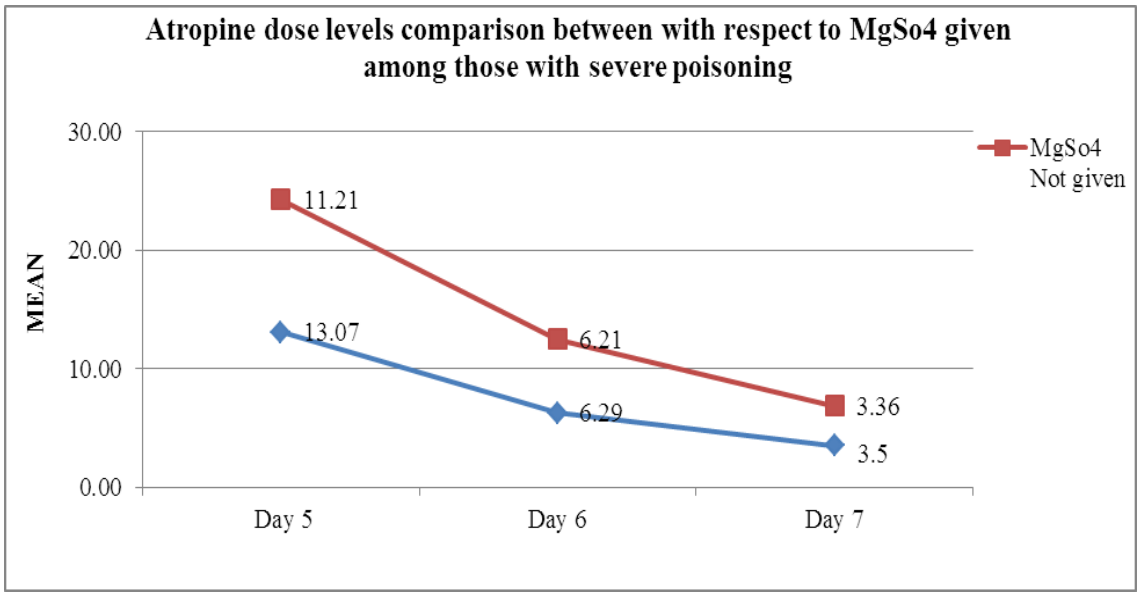


Figure 8: Bar diagram showing atropine dose levels comparison between with respect to MgSo4 given among those with severe poisoning in study subjects.

Table 9: Oximes levels comparison between with respect to MgSo4 given among those with moderate poisoning.

	MgSo4				P value
	4 mg MgSo4		MgSo4 Not given		
	Mean	SD	Mean	SD	
Oximes requirement	470.62	379.91	730.77	268.86	0.006*

In the study among those with moderate poisoning, there was significant difference in mean Oximes requirement among those who received 4 mg MgSo4 and who did not receive MgSo4. Oximes requirement was low among those who received 4 mg MgSo4 group.

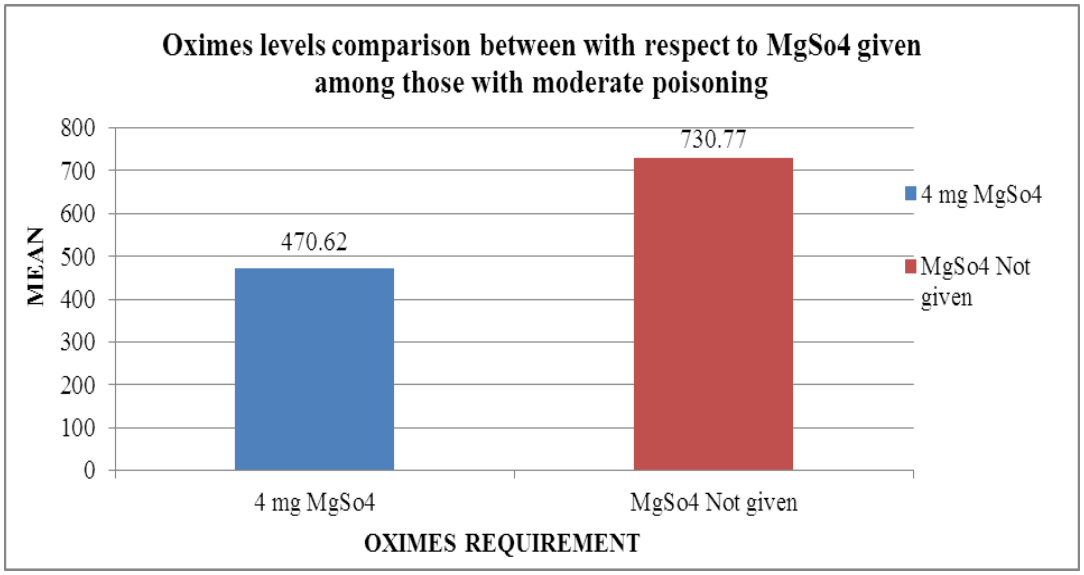


Figure 9: Bar diagram showing oximes levels comparison between with respect to MgSo4 given among those with moderate poisoning in study subjects.

Table 10: Oximes levels comparison between with respect to MgSo4 given among those with severe poisoning.

	MgSo4				P value
	8 mg MgSo4		MgSo4 Not given		
	Mean	SD	Mean	SD	
Oximes requirement	729.29	281.11	895.71	240.54	0.104

In the study among those with severe poisoning, there was no significant difference in mean Oximes requirement among those who received 8 mg MgSo4 and who did not receive MgSo4.

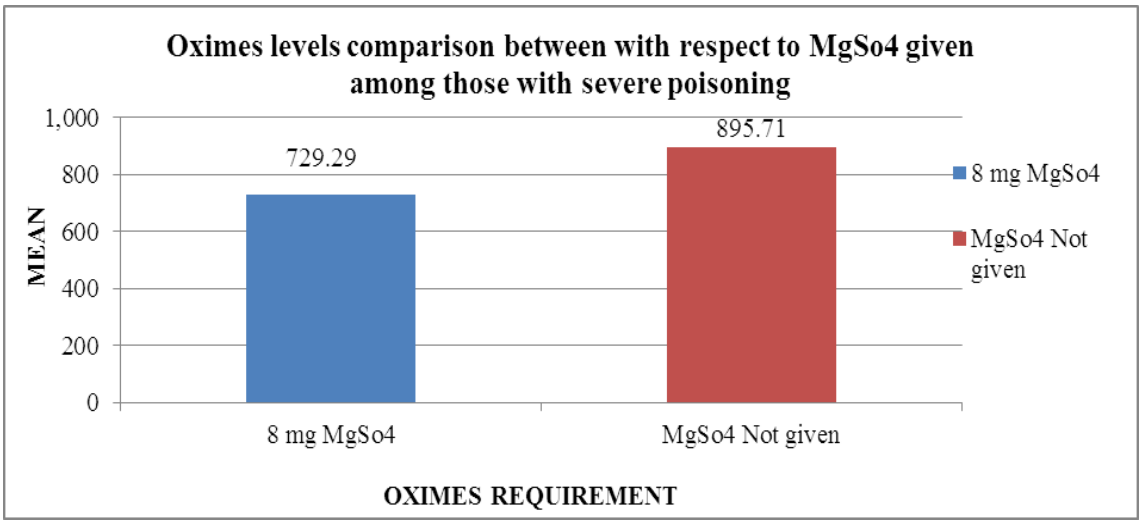


Figure 10: Bar diagram showing oximes levels comparison between with respect to MgSo4 given among those with severe poisoning in study subjects.

DISCUSSION

The causes of the high case fatality in OP poisoning are multifactorial and includes the high toxicity of domestically available poisons, late presentation to hospital, the scarcity of health care professionals compared with the large numbers of patients, the lack of facilities including ICU care, antidotes and trained personnel for the management of pesticide-poisoned patients.[8,9]

In this study about 51.2% patients belonged to age group of 21-30, which was comparable to other studies.[10-12] Generally non-fatal self poisoning is more common in females, but as we took moderate to severe poisoning, in our study males (76.2%) were commonly affected.

Group 1 had 52 patients of moderate OP poisoning. 26 cases and controls were divided and were matched equally. Patients of group 1 were given 4g of MgSO4 with in first hour of presentation. Group 2 had 28 patients of severe OP poisoning. 14 cases and controls were divided and were matched equally. Patients of group 2 were given 4g of MgSo4 with in first hour of presentation and another 4g were repeated after 6hrs.

MgSO4 of dose 4 g and 8g was selected for this study, for ease of administration and less intense monitoring of magnesium levels. Although an increase in serum magnesium levels was noted following the administration of $MgSO_4$, which was in normal range, and none of the patients had any side effects related to magnesium. The observations concur with that of other studies.[6,7]

Magnesium was well tolerated. No immediate adverse effects of diminished knee reflex or hypotension were observed following administration of magnesium sulfate.

Pseudo choline esterase was repeated on day 1,3, and 7. There was no significant difference in mean pseudo choline esterase in those who received MgSo4 and those who dint.

There is conflicting evidence regarding the effect of magnesium on atropine requirement.[6,7]

In our study we noted that Atropine requirement was lower in patients treated with 4mg MgSo4 in moderate poisoning on all the days compared to those who dint receive it. This was similar to studies conducted previously. In a study conducted in Bengaluru, Average atropine requirement per patient per day was higher in patients not treated with MgSo4 compared to patients who received MgSo4.

Where as the in severe poisoning the initial days atropine requirement only reduced and other days decrease was not significant.

Oximes requirement was low among those who received 4 mg MgSo4 group. However, there was no significant difference in mean Oximes requirement among those who received 8 mg MgSo4 and who did not receive MgSo4.

Average oximes requirement per patient during their complete stay differed in both groups as most of the patients were given for a fixed period of 48hrs or till atropine was given.

The need for intubation and mechanical ventilation varied depending on the severity of poisoning.[13] In our study, there was no statistical difference in the need for intubation and mechanical ventilation in magnesium group compared to control group. Most of the previous studies have shown significant reduction in the need for intubation and mechanical ventilation in Magnesium treated group. This may be due to decrease in acetylcholine release and facilitating, the metabolism of OPCP, which reduces the incidence of intermediate syndrome.[14] This may be the reason for the reduction in the need for intubation after initial 24 h in magnesium group.

The average duration of mechanical ventilation observed in this study is in agreement with observations of the previous studies;[15,16,17] there was no difference in the duration of mechanical ventilation in patients receiving magnesium compared to control. A single dose of $MgSO_4$ may not be enough to maintain a sustained therapeutic level that may influence the duration of mechanical ventilation.[7]

Reduction in the number of patients requiring intubation and mechanical ventilation has reduced the duration of hospital stay in patients receiving magnesium in this study, which further supports the beneficial role of magnesium in the management of OPCP.

There was no significant difference in mortality between groups in our study. Basher *et al*. noted reduced mortality with increasing doses of $MgSO_4$.[7]

In moderate poisoning, Duration of hospital stay and HDU stay was less among those who received 4mg MgSo4 compared to those who did not receive MgSo4. Whereas the ICU stay had no statistical difference.

In severe poisoning, there was no significant difference in duration of stay in hospital, ICU stay and HDU stay between those who received MgSo4 and who did not received MgSo4.

Comparison of primary outcomes to see the effect of increasing dose of magnesium couldn't be assessed in group 1 and 2 as 4g was used for moderate poisoning and 8g was used for severe poisoning.

Future multicentric studies with larger sample size with

daily and different dosing of magnesium are required.

CONCLUSION

Addition of MgSO4 to standard therapy has shown significant clinical improvement of moderate OPC poisoning by reducing the atropine requirement, oxime requirement and hospital stay with no adverse outcome. It does not influence need for intubation, ICU stay, the duration of mechanical ventilation and mortality.

In severe poisoning, however there was no influence of MgSo4 on atropine and oxime requirement, hospital stay, need for intubation and mechanical ventilation, ICU stay and mortality.

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