The Potential Role of Intravenous Magnesium Sulfate Administration on the Outcome of Acute Organophosphorus Toxicity. A prospective study in Poison Control Center Ain Shams University

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Abstract

Background: Organophosphate compounds (OP) have been used as pesticides and chemical warfare nerve agents worldwide. They are readily available because of inadequate regulations controlling their sale. The easy availability of these compounds has resulted in a gradual increase in accidental and suicidal poisoning. It also has resulted in many deaths that occur within hours of the ingestion. The efficacy of the traditional treatment of OP which includes atropine and oximes still an issue of debate.

Aim of the Work: Assessing the potential role of intravenous MgSO4 administration on the outcome of acutely OP intoxicated patients via a prospective single-blind randomized controlled trial in the Poison Control Center of Ain Shams University Hospitals (PCC ASUH).

Patients and Methods: The study assesses the potential role of intravenous MgSO4 administration on the outcome of 40 acutely OP intoxicated patients within the period from 8-11-2016 to 18-1-2018. The study is prospective single-blinded randomized controlled trial that was carried out on patients admitted to (PCC-ASUH) with acute OP toxicity. Patients were divided according severity into moderate and severe groups then each group was subdivided into two subgroups; one received MgSO4 and the other didn't receive it. MgSO4 treated patients received 4g/d for only the first 24 hours after admission. Patients were observed for outcomes such as; mortality, total duration of hospital stay, need for ICU admission and its duration and intermediate syndrome and CVS toxicity occurrence.

Results: There was no significant difference in duration of ICU stay, total duration of hospital stay and need for mechanical ventilation between MgSO4 treated and non-treated patients. MgSO4 administration may have decreased mortality, intermediate syndrome and CVS toxicity, but the difference was statistically insignificant between MgSO4 treated and non-treated patients.

Conclusion: Our study found that intravenous MgSO4 administration didn’t modify the total dose of atropine and oximes given to OP intoxicated patients during their hospital stay, also MgSO4 didn’t modify the need for mechanical ventilation. Although MgSO4 had reduced the number of patients who developed intermediate syndrome and CVS toxicity, duration of ICU stay, total duration of hospital stay and mortality, but unfortunately this reduction was statistically insignificant.

Keywords | Intravenous Magnesium Sulfate, Acute Organophosphorus Toxicity.

Introduction

Organophosphorus (OP) compounds are largely used as pesticides worldwide. The easy availability of these compounds and lack of knowledge about the serious consequences resulting in increase in accidental and suicidal poisoning. According to the World Health Organization (WHO) three million cases of pesticide poisoning (mainly OP compounds) occur every year, resulting in an excess of 250,000 deaths, OP was also responsible for 40% of deaths among cases admitted to Poison Control Center Ain Shams University (PCCASU) through year 2013 (Tawfik and ElHelaly, 2015).

OP insecticides are irreversible inhibitors of acetyl cholinesterase (AchE) enzyme. The clinical manifestations are due to excess acetylcholine (Ach) at muscarinic and nicotinic receptors with initial stimulation and then exhaustion of cholinergic synapses. There are three phases in acute OP poisoning: Acute cholinergic crises (first 48 hours), intermediate syndrome (IMS) (24-96 hours after
poisoning) and OP induced delayed polyneuropathy (OPIDN) (Abdollahi and Karami-Mohajeri, 2012).

Atropine and oximes are traditionally used in the management of OP toxicity, but their efficacy is an issue of debate, some findings in animals suggest lack of efficacy of oximes in OP toxicity, other findings indicate no advantage of using oximes with atropine compared with atropine alone, so other agents that could improve the outcome should be studied (Pajoumand et al, 2004).

Magnesium sulfate (MgSO₄) was found to decrease Ach release in the central nervous system and at peripheral sympathetic and parasympathetic synapses by blocking calcium channels and also reduces CNS overstimulation. Also hypomagnesaemia caused by OP due to vomiting and diarrhoea may be a contributory factor in severity and outcome, so intravenous MgSO₄ administration is suggested by some authors to reduce hospitalization, morbidity and mortality of OP toxicity and its safety has been evaluated via some studies that concluded that intermittent injection of MgSO₄ is safe (up to 16 gram) (Basher et al., 2013; Andrews et al., 2014).

Magnesium sulfate is inexpensive comparing to oximes which is expensive and ineffective after aging of acetyl cholinesterase and it is also familiar to doctors as it is widely used in different diseases like pre-eclampsia and bronchial asthma (Basher et al., 2013).

**Aim of the work**

*The present study aims at:*

Assessing the potential role of intravenous MgSO₄ administration on the outcome of acutely OP intoxicated patients via a prospective single-blind randomized controlled trial in the Poison Control Center of Ain Shams University Hospitals (PCC-ASUH).

**Methodology**

The study assesses the potential role of intravenous MgSO₄ administration on the outcome of acutely OP intoxicated patients within the period from 8-11-2016 to 18-1-2018. The study is prospective single-blinded randomized controlled trial that was carried out on patients admitted to (PCC-ASUH) with acute OP toxicity.

**Patients**

Patients with acute OP toxicity of both sexes were included in the study; diagnosis was by history of exposure to OP compound, clinical manifestations and by measuring pseudocholinesterase enzyme level (Siva Prabodh et al., 2012).

The following patients were excluded from the study:

- Patients with co-ingestion of other drugs with OP
- Patients suffering from severe chronic systemic illness including liver failure, congestive heart failure, chronic respiratory disease and end stage renal disease (Basher et al., 2013 and Vijayakumar et al., 2017).
- Patients with any conditions that reduce pseudocholinesterase level like: parenchymal liver disease, malnutrition, inflammatory bowel disease, pregnant women with HELLP syndrome, myocardial infarction, AIDS (Lampón et al., 2012; Santarpia et al., 2013).
- Patients on medications that affect QT interval as Antipsychotics, tricyclic antidepressants and Class 1A, IC antidysrrhythmics (Yap and Camm, 2003).
- Patients who were presented to emergency department 24 hours after exposure to OP.

**Sample size**

The study included 40 patients with acute organophosphorus intoxication, sample size was calculated using stata program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. Results from a previous study (Benefits of magnesium sulfate in the management of acute human poisoning by organophosphorus insecticides) which was made by Pajoumand et al. (2004) were used to measure the sample size. The study showed that mean duration of hospitalization among treated group (Magnesium Sulfate group) was 2.97±2.18 days while in group B (non-treated group) it was 5± 1.9 days. Calculation according to these values produced a minimal sample size of 20 cases per each group.

**Reference for program**


**Ethical consideration:**

An informed consent has been obtained from each patient or from his/her caregiver before inclusion in the study for obtaining medical history, clinical examination, electro-cardiogram (ECG), taking blood samples for laboratory investigations and for permission to give MgSO₄, approval of PCC-ASUH director and ethical committee also was obtained.

Patients were classified according to the severity of intoxication as guided by Palaniappen, 2013 into:

- **Group I:** Moderate toxicity characterized by:
  - Miosis, bradycardia, tachycardia, hypotension, hypertension, muscle twitching, fasciculation, bronchorrhea, bronchospasm.
- **Group II:** Severe toxicity characterized by:
  - Convulsions, respiratory failure, pulmonary edema, flaccid paralysis, involuntary micturition/defecation, cyanosis, deep coma by using a simple randomization method, every other patient was chosen to receive MgSO₄ treatment, so group I was subdivided into:
    - **Group Ia:** received the traditional treatment (decontamination, atropine and oximes) according to patient's needs plus placebo (saline)
    - **Group Ib:** received the traditional treatment plus intravenous MgSO₄

**Group II was also subdivided into:**

- **Group IIa:** received the traditional treatment (decontamination, atropine and oximes) according to patient's needs plus placebo (saline)
- **Group IIb:** received the traditional treatment plus intravenous MgSO₄

Patients who received intravenous MgSO₄ were given 4g/d for only the first 24 hours after admission with monitoring its level as
recommended by Pajoumand et al; 2004 and Andrews et al., 2014.

**Laboratory data**

Two samples, 1 milliliter arterial blood for blood gas analysis and three milliliters venous blood for biochemical and toxicological analysis, were collected from each patient.

**Blood samples will be collected**

- On admission after initial stabilization
- Second sample after 24 hours for determination of serum magnesium level

The following investigations were done as a part of routine management of acutely intoxicated patients:
Arterial blood gases analysis, serum electrolytes (Na, K, Mg), blood urea, serum creatinine, blood glucose level, plasma cholinesterase (pseudo-cholinesterase) and electrocardiogram (ECG).

**Treatment and hospital admission:**

Recording the treatment measures received during hospital stay including decontamination methods, atropine, oximes and any other symptomatic treatment needed according to the patient condition according to the protocol of management in PCCASU.

**Outcome:** All the patients were observed for short-term outcomes; that were either complete recovery or death and total duration of hospital stay.

**Complications:** All patients observed for the complications developed during hospital stay e.g. intermediate syndrome, need for ICU admission, duration of ICU stay, need for mechanical ventilation, CVS toxicity.

**Statistical analysis:** The obtained data were revised, coded and organized for statistical analysis using SPSS (Statistical package for Social Science) version (18) software (SPSS Inc, USA). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

**Results**

Table (1): t-test analysis of amount of atropine and oximes given to groups a (MgSO4 treated) and b (MgSO4 non-treated):

<table>
<thead>
<tr>
<th>Classification</th>
<th>Amount of atropine</th>
<th>MgSO4</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>MgSO4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 - 100</td>
<td>Yes (b)</td>
<td>2.128</td>
<td>0.040*</td>
</tr>
<tr>
<td></td>
<td>10 - 100</td>
<td>No (a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>74.600 ± 33.049</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51.150 ± 36.553</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (2): Chi-Square analysis of deaths among groups Ia, Ib, IIa and IIb:

<table>
<thead>
<tr>
<th>Classification</th>
<th>MgSO4</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (b)</td>
<td>No (a)</td>
</tr>
<tr>
<td>Moderate (I)</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>100.00</td>
</tr>
<tr>
<td>Severe (II)</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>25.00</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>75.00</td>
</tr>
</tbody>
</table>

X2 Chi-square statistical analysis test, N: number, P >0.05: non significant, P <0.05: significant, P <0.01: highly significant

Table (3): t-test statistical analysis of total duration of hospital stay of groups Ia, Ib, IIa and IIb:

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total duration of hospital stay (day)</th>
<th>MgSO4</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>MgSO4</td>
<td></td>
</tr>
<tr>
<td>Moderate (I)</td>
<td>0.5 - 7</td>
<td>Yes (b)</td>
<td>0.331</td>
</tr>
<tr>
<td></td>
<td>1 - 5.5</td>
<td>No (a)</td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>2.350 ± 1.973</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.063 ± 1.635</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (II)</td>
<td>Range</td>
<td>MgSO4</td>
<td></td>
</tr>
<tr>
<td>Total duration of hospital stay (day)</td>
<td>1 - 9</td>
<td>Yes (b)</td>
<td>-0.098</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>3.313 ± 1.981</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.438 ± 3.029</td>
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</tbody>
</table>

- SD: standard deviation, P >0.05: non-significant, P <0.05: significant, P <0.01: highly significant.
The efficacy of the traditional antidotes of organophosphates is limited, and thus alternative or adjunctive treatments need to be considered. Oximes should be given as soon as possible after exposure. Unfortunately, these agents do not favorably affect the outcome, based on several parameters including total atropine requirement and duration of complex aging, which is still a major issue of debate, despite the great developments in the intensive care management, ingestion of OP compounds is still a greatly contributing agent of poisoning with mortality rates reaching up to 10-20%. So early diagnosis and appropriate treatment is often lifesaving (Chowdhary et al., 2014).

Discussion
Organophosphates are one of the most common causes of poisoning, especially in developing countries, and despite the great developments in the intensive care management, ingestion of OP compounds is still a greatly contributing agent of poisoning with mortality rates reaching up to 10-20%. So early diagnosis and appropriate treatment is often lifesaving (Chowdhary et al., 2014).

Classic management of OP toxicity includes giving atropine to reverse the muscarinic effects and giving oximes to break up the OP/AChE complex to restore cholinesterase activity and neutralize muscarinic and nicotinic manifestations (Indu et al., 2016).

Oximes should be given as soon as possible after complex aging takes place, it is reported that there is a beneficial response as long as 24 hours after exposure. Unfortunately, these agents do not favorably affect the outcome, based on several parameters including total atropine requirement and duration of hospitalization (Sungur and Guven, 2001).

The efficacy of the traditional antidotes of organophosphorus remains a major issue of debate, thus alternative or adjunctive treatments need to be considered.
explore and one of the proposed agents is MgSO₄ (Syed et al., 2015).

The present study was prospective single-blinded randomized controlled trial that was carried out on patients admitted to (PCC-ASUH) with acute OP toxicity who were selected according to predetermined criteria. This work aimed to assess the potential role of intravenous MgSO₄ administration on the outcome of patients with acute OP intoxication which included mortality, total duration of hospital stay, need for ICU admission and its duration, morbidity during hospitalization including development of intermediate syndrome, need for mechanical ventilation and CVS toxicity. Patients in our study were classified as regard the severity of intoxication into moderate and severe groups guided by Palanipappan, (2013), and each group was subdivided into two subgroups; one received MgSO₄ (50%) and another subgroup that didn’t receive MgSO₄ (50%).

In the current study, there was no significant difference in total dose of atropine and oximes between MgSO₄-treated and non-treated patients, this was in agreement with Pajoumand et al., 2004.

Since there are numerous variations in the optimal dosing regimen of atropine (Abedin et al., 2012) and the lack of dose–response studies that aim to identify its ideal dosage regimen (Eddleston and Chowdhury, 2016) so it is difficult to compare between results of different poison control centers as regards the effect of intravenous MgSO₄ administration on modifying the dose of atropine in OP poisoning.

In the present study, number of patients who developed intermediate syndrome was more in MgSO₄ non-treated patients, but the difference was insignificant. There was no difference in need for mechanical ventilation between MgSO₄ treated and non-treated patients, this was in contrast with a study done by Vijayakumar et al., 2017 who found that MgSO₄ had reduced the need for mechanical ventilation.

Cardiac manifestations are commonly observed in patients with OP toxicity. There are three stages of cardiac toxicity, first short period of sympathetic overstimulation followed by prolonged period of parasympathetic activity then QT prolongation followed by torsade de pointes ventricular tachycardia and then ventricular fibrillation (Balouch et al., 2012).

In the present study, number of patients who developed CVS toxicity was more in MgSO₄ non-treated patients than MgSO₄ treated patients, but the difference was insignificant. Studies that discuss the effect of intravenous magnesium in prevention of CVS toxicity are insufficient.

In contrast to Vijayakumar et al. (2017) who found that MgSO₄ had significantly reduced ICU stay duration, our study found that duration of ICU stay wasn’t modified by intravenous MgSO₄ administration. As regard total duration of hospital stay, our study found that there was no significant difference in total duration of hospital stay between MgSO₄ treated and non-treated patients. This was in contrast with Pajoumand et al. (2004).

Our study found that there was no significant difference in mortality between MgSO₄ treated and non-treated patients. This agreed with results of a study done by Gunay et al. (2010) and Vijayakumar et al. (2017) but it was in contrast with Pajoumand et al. (2004) who had found that MgSO₄ reduced the mortality significantly.

Conclusion
In conclusion, the present study found that intravenous MgSO₄ administration didn’t modify the total dose of atropine and oximes given to OP intoxicated patients during their hospital stay, also MgSO₄ didn’t modify the need for mechanical ventilation. Although MgSO₄ had reduced the number of patients who developed intermediate syndrome and CVS toxicity, duration of ICU stay, total duration of hospital stay and mortality, but unfortunately this reduction was statistically insignificant.

In fact, the studies suggesting beneficial effects from new treatments such as MgSO₄ are very small; they are carried out on a local basis, no multicentric studies are available, and finally, results are conflicting. Further studies related to the improvement of the management of poisoning with OP compounds are required.

References
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المختص العربي

الدور المحتمل للحقن الوريدي لسلفات الماغنيسيوم في نتيجة التسمم الحاد بالمركبات الفسفورية العضوية . دراسة مستقبلية في مركز علاج التسمم بمستشفيات جامعه عين شمس

ايناس التفاتاني و رباب نبيل حافظ و غادة محمد عبيد

الخلفية: استخدمت المركبات الفسفورية العضوية كمبيدات حشرية وعامل أصبحة حربية كيميائية في جميع أنحاء العالم، وهي متاحة بسهولة بسبب عدم كفاية الأنظمة التي تتحكم في بيعها. وقد أدى ذلك إلى زيادة التسمم بمركبات فسفورية العضوية، وهو الوضع الذي يحدث في غضون ساعات من الابتلاع، غير أن فعالية العلاج التقليدي للمركبات الفسفورية العضوية الذي يشمل الأتروبين والأوكسيرتامات لا تزال مسألة نقاش.

الهدف من الدراسة: تقييم الدور المحتمل للحقن الوريدي لسلفات الماغنيسيوم على النتيجة المترتبة على التسمم الحاد بالمركبات الفسفورية العضوية عن طريق تجربة مستقبلية ضابطة مفردة الاخفاء عشوائية في مركز علاج التسمم بمستشفيات جامعة عين شمس.

المرض والأساليب: تقييم الدراسة الدور المحتمل للحقن الوريدي لسلفات الماغنيسيوم على النتيجة المترتبة على التسمم الحاد بالمركبات الفسفورية العضوية لأربعين مريض. تم تقسيم المرضى إلى مجموعات حادة ومتوسطة التسمم ثم تقسيم المرضى إلى مجموعات عولجت وأخرى لم تعالج بسلفات الماغنيسيوم. تم تشكيل المرضى بطريقة مستقلة ضابطة مفردة الاخفاء عشوائية.

النتائج: لم يكن هناك اختلاف ذو دلالة إحصائية بين المرضى الذين عولجوا بسلفات الماغنيسيوم والمريض الذين لم يعالجوا. قد يكون الفرق في النتائج نتيجة للفرق في الجرعات المصرفية بين المرضى الذين عولجوا والمصابين بالمرض الذي لم يعالج.

الخلاصة: دراسة نشرت في المجلة الأكاديمية والإجبارية لقسم الطب الشرعي، وبدأت في المجلة الأكاديمية والإجبارية لقسم الطب الشرعي.