Review Article

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Management of organophosphorus poisoning and the role of magnesium sulfate: A scoping review of literature

Running Head: Organophosphate poisoning & magnesium sulfate

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Abstract

Organophosphorus agents are easily absorbed via respiratory, gastrointestinal, and dermal routes, and inhibit the acetylcholine transferase enzyme (AChE), which is responsible for the majority of toxicity caused by organophosphates in the body. A comprehensive search was conducted across three prominent databases, namely Google Scholar, PubMed, and Science Direct, to identify relevant articles published. The search focused on the keywords "MgSO4" or "magnesium sulfate" in conjunction with "organophosphate" or "organophosphate poisoning."

Inhibition of AChE results in the accumulation of acetylcholine (ACh) in synapses and stimulation of cholinergic receptors. Considering that several studies have shown the use of magnesium sulfate (MgSO4) in inhibiting the release of ACh in the central and peripheral sympathetic and parasympathetic synapses, this study was conducted to review the role of MgSO4 in the treatment of OP. The intravenous administration of MgSO4 exhibits favorable tolerability and clinical efficacy in alleviating cardiac toxicity associated with OP exposure.

Key words: Organophosphate poisoning, Cholinergic receptors, Acetylcholine transferase, Magnesium sulfate

CAPSULE SUMMARY

(1) What is already known? Organophosphate poisoning

(2) What is new in the current study? Magnesium sulfate in the management of organophosphorus poisoning

1. Introduction

Organophosphorus agents continue to be extensively utilized as agricultural pesticides, and their potential detrimental effects on health remain a significant concern, particularly in relation to occupational exposure. However, it is important to note that intentional poisoning incidents involving these readily accessible pesticides have also been reported. Organophosphate poisoning (OP), in general, accounts for approximately 50% of hospital admissions related to poisoning, particularly in developing countries [1, 2]. Organophosphorus agents can be easily absorbed through multiple routes, including the respiratory, gastrointestinal, and dermal pathways, and they exert their effects by inhibiting various esterase enzymes. Among these enzymes, butyrylcholinesterase (BuCh) plays a role in the regulation of emotional behaviors [3]. Additionally, organophosphorus agents inhibit carboxylesterase (CE), which is involved in the metabolism of numerous drugs [4]. However, the primary mechanism responsible for the majority of organophosphate-induced toxicity in the body is the inhibition of the acetylcholine transferase (AChE) enzyme, leading to the impaired hydrolysis of acetylcholine (ACh). The structural similarity between organophosphates and ACh results in the formation of a covalent bond that inhibits the esteratic site of AChE [5]. The reactivation of the organophosphate-AChE complex, which is a potential treatment option in OP, is contingent upon the occurrence of the aging phenomenon. Aging refers to the stabilization of the organophosphate-AChE complex through dealkylation, rendering the complex resistant to hydrolysis (Figure 1). This phenomenon has significant implications for the effectiveness of oximes in reactivating the complex [6].

The inhibition of AChE leads to the accumulation of ACh in synapses, which in turn stimulates both nicotinic and muscarinic receptors. During the initial hours after exposure to OP compounds, cholinergic overstimulation becomes evident through various manifestations, including lacrimation, salivation, urinary and fecal incontinence, gastrointestinal (GI) cramping, vomiting, sweating, miosis, bradycardia or tachycardia, and hypotension. Subsequently, in less than half of the poisoned cases, an intermediate syndrome phase may develop within 24 to 96 hours. This phase is characterized by symptoms such as muscle fasciculations and weakness, pulmonary depression, and reduced deep tendon reflexes [7,8]. The

main research question in the current work is reviwing role of magnesium sulfate as key antidote in the management of organophosphorus pesticide poisoning.

2. Study design and search strategy

The heterogenicity of data regarding the role of MgSO4 in OP necessitated the selection of a scoping review methodology for this study. The scoping review adhered to the guidelines outlined by the Joanna Briggs Institute for conducting scoping reviews [9], and no systematic reviews were performed. A comprehensive search was conducted across three databases, namely Google Scholar, PubMed, and Science Direct, using the keywords "MgSO4" or "magnesium sulfate" in combination with "organophosphate" or "organophosphorus poisoning". The search was limited to articles published between 2010 and 2023, and inclusion criteria involved the presence of these keywords in the titles, abstracts, or keywords of the articles. The obtained articles were imported into EndNote and, after removing duplicates, the remaining articles were independently screened by two researchers based on predefined inclusion and exclusion criteria. If any uncertainty arose regarding specific articles, a third investigator would evaluate them. Data extraction, including author details, publication year, sample population characteristics, study design and setting (including dosage and duration of MgSO4 administration), initiation time of MgSO4 administration, and clinical outcomes, was conducted by the two independent investigators. The search process is illustrated in figure 1, providing an overview of the study search detail. Through the initial search using the specified keywords, a total of 176 articles were identified. Following the application of exclusion criteria, which involved removing three unrelated articles and three duplicate articles, a total of 47 papers were deemed relevant for further review. These 47 papers consisted of nine clinical trials, one case report, three animal studies, and 16 review articles. Additionally, the remaining 12 papers encompassed various other types of studies, including observational studies, theses, books, and editorials (as illustrated in figure 2).

3. Management of acute poisoning

The first and most crucial step in successful management is to right and timely diagnosis of OP. According to clinical guidelines, OP management can be categorized into two main steps; immediate administration of effective antidotes and supportive treatments. Both strategies are discussed below.

3.1. Supportive therapy

The initial step involves the assessment of the airway, breathing, and circulation. In-hospital poisoned patients should be admitted to the intensive care unit (ICU) and receive emergency medical support. High-flow oxygen supply and fluid replacement should be considered. Following the establishment of intravenous (IV) access, volume resuscitation using 0.9% sodium chloride is initiated to maintain a urine output of 0.5 mL/kg/hour and a systolic blood pressure above 80 mmHg [10]. Close monitoring of physiological indicators, including blood pressure, pupil size, pulse rate, sweating, and auscultatory findings, is crucial to identify signs and symptoms resulting from cholinergic over-stimulation [11]. In cases where the tidal volume falls below 5 mL/kg or the vital capacity is below 15 mL/kg, or if the PaO2 level is below 60 mmHg, intubation of the poisoned patient becomes necessary.

An important issue to prevent further or delayed complications is to decontaminate the patient. In cases where the poisoning route is through ingestion, gastric decontamination should be contemplated once the patient is completely stabilized. The optimal time window for maximum effectiveness of gastric decontamination is within 1-2 hours following ingestion. However, in situations where hospital admission is delayed, it can still be beneficial up to 12 hours [7]. It is equally important to perform dermal decontamination to remove any residual organophosphate. Washing the affected area with water and soap is a suitable approach for this purpose [10, 12].

3.2. Effective Antidotes

Known specific antidotes including atropine and pyralidoxime have been used for many years in OP. However, research is still ongoing to find other effective options in the management of OP. The most famous class of drugs used in selected cases of poisoning are benzodiazepines (diazepam), which are effective in reducing CNS complications of OP. Acute intoxication with organophosphate cholinesterase inhibitors often leads to seizures, rapidly progressing to a life-threatening condition known as status epilepticus. Diazepam has traditionally been regarded as the standard treatment for seizure management [13]. In addition to its anticonvulsant properties, diazepam has shown efficacy in attenuating the elevation of ACh and choline concentrations in various brain regions [14]. Although the precise mechanism of action

of diazepam in OP is not fully understood, it may be more effective than other anticonvulsants such as barbiturates.

Diazepam has shown to be an effective adjunctive antidote in severe cases of poisoning, and it may even help alleviate certain central nervous system (CNS) complications associated with atropine administration [15]. In the CNS, certain GABAergic pathways are secondary activated by ACh, and diazepam can act as an antagonist to these GABAergic systems. Animal studies [16,17] have also demonstrated that diazepam reduces cerebral morphological damage resulting from seizures induced by organophosphate compounds and helps prevent respiratory failure by attenuating the overstimulation of central respiratory centers, thereby preventing death. However, there is limited research on the use of diazepam in humans for these purposes [10]. Recently, attention has been paid to the possible role of magnesium sulfate in reducing the complications of poisoning with organophosphates. In the following, its effects will be discussed in detail. Due to the cheap price and proper availability of this compound in most medical centers, it can be included in the OP treatment protocols after proving its beneficial effects.

3.2.1. Atropine

According to numerous guidelines, atropine is the preferred treatment option for reversing the initial symptoms of OP through competitive antagonism at muscarinic receptors. In the hospital setting, IV administration is the preferred route for atropine. For adults affected by poisoning, the recommended initial dose is 2 mg. This dose can be repeated as necessary at intervals of 5-10 minutes until the process of atropinization begins. Atropinization is often recognized by a reduction in body secretions, indicating the desired therapeutic effect [18].

While atropine is considered the primary treatment for OP, its efficacy is primarily limited to muscarinic receptors and does not affect nicotinic receptors significantly. Furthermore, its impact on CNS muscarinic receptors is also limited. Despite these limitations, there is a consensus among medical professionals regarding the critical role of atropine in the acute management of OP. It remains an essential component in the treatment regimen due to its ability to counteract the cholinergic overstimulation and mitigate the potentially life-threatening symptoms associated with OP.

3.2.2. Oximes

Reactivating AChE with oximes can help alleviate further effects of overstimulation. Pralidoxime, the most commonly used oxime, facilitates AChE reactivation by accepting a phosphoryl group from AChE itself, thereby preventing its aging [19]. It is important to note that phosphoryl oximes themselves can inhibit AChE; however, their instability in aqueous environments generally results in a short duration of effect. Although initial exacerbation of the cholinergic crisis, which is sometimes observed during oxime therapy, is primarily due to AChE inhibition by the oxime, it should be kept in mind that if treatment with atropine is not accompanied, inhibition of the enzyme by phosphorylated oxime products is also possible [20]. Phosphorylated oximes can inhibit AChE more stronger than organophosphates which leads to more toxicity instead of cure [21]. Accordingly, oximes should not be used alone in the treatment of OP.

Pralidoxime is typically administered with a loading dose of 2 grams (or 30 mg/kg) IV over a period of 30 minutes, followed by a maintenance dose of 500 mg/hour (or 8-10 mg/kg/hour). If muscle weakness persists, the loading dose may be repeated after 1 to 2 hours, and subsequent repeat doses may be administered every 4-6 hours as necessary [22]. Studies have indicated that continuous infusion of oxime agents after the loading dose may be more effective in mitigating the adverse effects of OP [23]. However, certain limitations still exist regarding the optimal timing of initial administration, the appropriate dose, treatment duration, and the ability to penetrate the CNS [24]. Some investigations have also suggested that the addition of oximes to the treatment of OP may yield little benefit, which could be attributed to under-dosing of the oxime agents [15].

4. Role of magnesium sulfate in OP

Numerous studies have demonstrated that magnesium sulfate (MgSO4) possesses inhibitory effects on the release of ACh at both CNS and peripheral sympathetic and parasympathetic synapses. This interference

with calcium channels in presynaptic nerve terminals, which are responsible for the release of ACh, leads to increased hydrolysis of certain pesticides. The administration of MgSO4 has shown efficacy in reducing arrhythmias associated with organophosphates and atropine, mitigating hyperstimulation of organophosphates in the CNS, and acting on N-methyl-D-aspartate receptors to reverse neuromuscular syncope in the peripheral nervous system [25]. Based on these mechanisms and the findings from animal and human studies, the present study aims to review the role of MgSO4 in the treatment of OP.

4.1. Animal studies

A specific animal study conducted on rats aimed to compare the anticonvulsant effects of MgSO4 with midazolam and caramiphen in the context of sarin poisoning. The study found that all three agents were effective in resolving the induced tonic-clonic seizures. However, upon closer examination, it was revealed that only midazolam and caramiphen were able to completely halt cortical convulsive activities, while MgSO4 was not able to achieve the same level of cessation. Additionally, after one week of sarin exposure, the MgSO4 group exhibited a significant increase in brain damage markers, which mirrored the pattern observed in the group treated solely with atropine. Furthermore, rats in the MgSO4 group displayed weight loss, restlessness, and reduced motor activity, indicating the persistence of subtle seizures in the CNS despite the control of overt seizures. Consequently, this study concluded that the use of MgSO4 for treating seizures induced by organophosphates such as sarin may not be a reliable option for mitigating subsequent cognitive impairment [26].

In addition to the previously mentioned animal study, two additional animal studies focused on the cardiac effects of using MgSO4 in OP poisoning, yielding similar findings. Hoda Shafiee et al. conducted a study to evaluate the preventive effect of magnetic magnesium-carrying nanoparticles on rat cardiac cells' mitochondrial energy depletion and free radical damage induced by malathion exposure [27]. The study revealed that this particular formulation exhibited superior efficacy in reducing cardiac cell lipid peroxidation (c-LPO) and reactive oxygen species, improving the ADP/ATP ratio, and increasing intracellular magnesium levels compared to MgSO4. These results suggest that the magnetic magnesium-

carrying nanoparticles may be more effective in mitigating cardiac damage caused by OP poisoning when compared to conventional MgSO4 treatment.

In a separate study conducted by Mohammadi et al., it was demonstrated that the administration of magnetic magnesium in rats poisoned with malathion resulted in improvements in blood pressure, heart rate, and arrhythmia, while also reducing cardiac cell lipid peroxidation (c-LPO) [28]. Furthermore, this study indicated that magnetic magnesium exhibited greater efficacy than both MgSO4 and atropine in restoring AChE activity. Moreover, in the context of the neuromuscular junction, it was found that this particular magnesium isotope outperformed MgSO4 in inhibiting the release of ACh, and it appeared to be more effective than MgSO4 under hypoxic conditions.

4.2. Human studies

The clinical studies evaluated in this research, spanning from 2013 to 2019, consistently indicated the efficacy of MgSO4 in the acute management of OP. These studies revealed several benefits associated with the use of MgSO4 in the acute setting of OP. These benefits included a reduction in hospitalization duration, shorter ICU stays, decreased reliance on mechanical ventilation, and a lower requirement for total doses of atropine and oxime, which are known antidotes for OP toxicity. Additionally, MgSO4 demonstrated a reduction in mortality rates in OP cases. One trial conducted by Naguib M et al. specifically investigated the effects of MgSO4 in a dose of 4 grams per day, administered concurrently with conventional therapy, in individuals poisoned with OP substances. The findings of this trial highlighted the beneficial impact of MgSO4 in terms of reducing hospitalization duration and decreasing the mortality rate [29].

Basher et al. conducted a study that reported magnesium to be well tolerated in patients, with no observed adverse effects attributed to intermittent bolus injections of magnesium doses, even at doses as high as 16 grams [30]. Furthermore, a case study suggested that MgSO4 can effectively reduce the intensity of contractions in women experiencing hypertonic uterine contractions. The occurrence of acute organophosphorus pesticide poisoning-induced uterine contractions is a rare complication that may result in abortion. However, the precise mechanisms by which MgSO4 inhibits uterine contractility induced by OP are not yet fully understood [31].

In the clinical trial conducted by Jamshidi et al., the administration of MgSO4 was found to be beneficial in the treatment of acute organophosphate toxicity, resulting in a decrease in hospitalization duration. The protocol involved the intravenous infusion of 2 grams of MgSO4 50% (4 mL) in a total volume of 100 mL over half an hour, followed by three successive injections of 2 grams of MgSO4 at two-hour intervals. The treatment group receiving MgSO4 exhibited lower diastolic blood pressure and heart rate compared to the placebo group, as documented in the study [32]. The specific data from this clinical trial, along with other relevant clinical trials, are presented in Table 1.

4.3. Expert opinion

The review articles obtained in this research consistently highlighted that while MgSO4 has been considered as a potential adjuvant therapy for OP, its effectiveness has not been firmly established. These review articles acknowledged MgSO4 as a non-regular antidote, indicating that its role in the treatment of OP is still being investigated. Although MgSO4 has shown potential benefits in various studies, the review articles emphasized the need for further evidence to support its use [33].

In a systematic review conducted by Eddleston et al., an extensive search was performed across preclinical and clinical studies to evaluate the role of MgSO4 in the context of OP. The collected data indicated that administration of MgSO4 subsequent to organophosphorus insecticide poisoning effectively mitigates tachycardia and hypertension by diminishing cholinergic stimulation. Additionally, it was found to enhance skeletal muscle ATPase activity. It is important to note that in one rat study, MgSO4 was found to additionally suppress mean serum butyrylcholinesterase activity. Among the eight clinical studies included, a meta-analysis revealed pooled odds ratios for MgSO4 compared to placebo for mortality and the need for intubation and ventilation as 0.55 (95% confidence interval [CI] 0.32–0.94) and 0.52 (95% CI 0.34–0.79), respectively. However, there was no evidence of a dose-effect relationship across the studies. Nonetheless, a small dose-escalation study suggested a potential benefit from higher doses of MgSO4. A Phase II dose-response study, which involved groups of 10 patients poisoned with organophosphorus insecticides, compared 4 g, 8 g, 12 g, and 16 g of MgSO4 with placebo. All doses of MgSO4 were well tolerated, and there was a trend toward reduced mortality with larger doses [34-36]. The diverse outcomes obtained from

these studies can be attributed to several factors, including the risk of bias, lack of randomization, inadequate MgSO4 dosage, small sample sizes, and variations in the timing of drug administration following exposure. The authors conducted a risk of bias analysis to address these issues [1].

Another review highlighted that MgSO4, acting as a ligand-gated calcium channel blocker, can alleviate the release of ACh from pre-synaptic terminals. Additionally, it has been observed to mitigate CNS overstimulation mediated through NMDA receptor activation. However, caution should be exercised in its administration due to the presence of ambiguous outcomes resulting from inadequately conducted studies regarding the dosage of MgSO4 and other methodological aspects. Nevertheless, a trial demonstrated a reduction in the mortality rate when MgSO4 was administered to individuals poisoned with organophosphorus compounds [10].

Narang, Udit et al. conducted another review, which recommended the inclusion of MgSO4, along with antioxidants and other standard therapies, in the management of OP. However, the review acknowledged the inability to establish the efficacy of MgSO4 due to the limited availability of evidence-based data [37]. MgSO4 has been suggested to potentially alleviate the risk of ventricular tachycardia in patients experiencing tachycardias caused by nicotinic stimulation. Furthermore, it has shown promise in improving neuromuscular function [34]. Additionally, adjunctive use of MgSO4 has been demonstrated to decrease the required dosage of atropine for intubation, leading to reduced overall time spent in the ICU and associated mortality rates [7]. The specific data from this review articles, along with other relevant review articles, are presented in the Table 2.

Numerous studies have been conducted to explore alternative effective options in the management of OP, despite the longstanding use of atropine and oximes as the primary known antidotes. Among these options is MgSO4, which is utilized as a non-standard therapy and non-regular antidote for OP poisoning. In the aforementioned studies, it has been consistently recommended to administer an infusion of 4 g of MgSO4 on the first day of hospital presentation, followed by a daily dose of 2 g as needed. The administration of this drug has shown various benefits, such as a decrease in hospitalization duration, shorter stays in the ICU, reduced mortality rates, decreased reliance on mechanical ventilation, and a lower requirement for

total doses of atropine and oxime. Consequently, the outcomes of the patients in these studies did not significantly differ.

5. Conclusion

The outcomes of clinical trials investigating the effectiveness of MgSO4 in OP have exhibited inconsistency. Presently, there is insufficient evidence to establish MgSO4 as a robust and effective antidote for OP management. However, it demonstrates satisfactory tolerability and clinical efficacy in mitigating the cardiac toxicity associated with OP when administered intravenously. Moreover, it has shown effectiveness in reducing hospital stays, the need for critical care, and invasive mechanical ventilation support. The utilization of a magnetic MgSO4 formulation has also proven effective in mitigating mitochondrial energy depletion caused by OP-induced free radical damage in cardiac cells. Furthermore, it has demonstrated the ability to reduce blood pressure, heart rate, and OP-related arrhythmias. The review of research data from 2010 to 2023 highlights the necessity for the design of a clinical trial that addresses the optimal timing and dosage of MgSO4 in the context of OP.

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AUTHOR CONTRIBUTION

ZZ, ZN, and HTB are involved in the interpretation and collecting of data, writing, and editing of the manuscript. ZZ, HA, and MM were involved in editing and preparing the final version of the manuscript. ZZ submitted of the manuscript. All authors reviewed the paper and approved the final version of the manuscript**.**

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DATA AVAILABILITY S TATEMENT

The data is available to the correspondent author and can be obtained upon request.

ETHICAL APPROVAL

This study was approved by the Mazandaran University of Medical Science Ethics Committee (No: IR.MAZUMS.REC.1399.7850) and was carried out in accordance with the Helsinki Declaration Principles.

CONSENT FOR PUBLICATION

Not Applicable.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Table 1. Clinical trials of intravenous $MgSO_4$ for acute OP

Author Year	Patients	Intervention	Start intervention	Outcomes and comments
Basher et al. 2013 [30].	12–60 y. old adult	**1**. Atropinization **2**. 4 groups: daily $MgSO_4$ (doses: 4, 8, 12 or 16 gr) **3**. intermittent bolus IV (4 gr/over 10–15 min for 4 h)	First 24 h	Cholinergic crisis, IMS, Median atropine requirement, (NS) Median of subsequent post atropine loading infusion doses (NS), Intubation, Death Mean serum Mg concentration before intervention, (NS) Mean serum Mg concentration 24 h after intervention, (NS) 24 h Mean Urine Mg concentration (P=0.019) (Cholinergic crisis, death, intubation were lower with $MgSO_4$)
Sriharsha et al. 2016 [38].	Acutely adult	4 gr $MgSO_4$ over 4 h	First 24 h	Atropine load (p=0.01), Total atropine dose (p<0.001), Number of days of ventilation (p=0.04), Days of ICU stay (p<0.001), Mortality rate, (P<0.05) Hospitalization days (P<0.05) ($MgSO_4$, in a dose of 4 gm concurrent to conventional therapy, in OP acute human poisoning is beneficial by reducing the hospitalization days and rate of mortality)
Afify et al. 2016 [39].	Acutely adult	**Group I** (50 patients treated with atropine and oximes): $MgSO_4$ 1g/6 h for 24 h **Group II** (50 patients only treated with atropine and oximes)	Acutely poisoned ND	Amount of atropine (p<0.001) Amount of oxime (p=0.038) ($MgSO_4$ decreases atropine and oxime use in acute OP)
Jamshidi et al. 2018 [32].	Patients	**Case group**: 2 g $MgSO_4$ 50% (4 cc) in 0.5 h and 2 g over 2 h for 3 times **Control group**: 100 cc normal in the same manner	ND	SBP in both groups during the first 24 h of intervention, (NS) DBP in 0 and 2 h after intervention was higher in $MgSO_4$ group (p=0.004) and insignificant statistical difference for the remaining hours Heart rate in 8, 16, and 24 h after intervention was lower in $MgSO_4$ group, (P=0.028; P=0.001; P=0.017) Respiratory rate during the first 24 h of intervention, (NS) Arterial oxygen during the first 24 h of intervention, (NS) Intubation frequency during the first 24 h of intervention, (NS) Lung secretions during the first 24 h of intervention, (NS) Admission hours (p=0.006) The amount of consumed Pralidoxime (NS)

				Pupil diameter during the first 24 h of intervention, (NS) (The use of $MgSO_4$ in OP reduces therapeutic costs an average hospital length of stay and mortality)
Vijayakumar et al. 2017 [25].	18–60 y. old adult	**Case group**: 1. Atropine and pralidoxime 2. 4 g $MgSO_4$ 20% over 30 min **Control group**: normal saline in the same manner	Admitted to ICU within 24 h of ingestion	The need for intubation (NS) Requirement of atropine (P<0.001) Duration of mechanical ventilation (NS) Duration of ICU stay (P=0.026) , Effect on mortality (NS) (4 grams of $MgSO_4$ given to OPCP patients within 24 h of admission to ICU, decreases atropine requirement, need for intubation, and ICU stay)
Elbarrany et al. 2019 [40].	Adult patient	1. Atropinization and pralidoxime 2. Group I: nontreated patients Group II: 1 g $MgSO_4$ /6 h for 4 doses	ND	The hospitalization period (P=0.05) Cardiac arrhythmias (e.g., PVC, PAC, and VT) (P=0.001) Respiratory failure (P=0.001), Death (P=0.008) (The above items were significantly lower in Mg-treated patients)
Taftazany et al. 2019 [41].	Patients	**Group I**: Atropine and oximes + normal saline **Group II**: Atropine and oximes + 4g MgSO4 only the first 24 h	ND	Amount of atropine (P=0.040), Amount of oximes (P=0.374) Death (NS), Intermediate syndrome (NS) Duration of hospital stay (NS), Duration of ICU stay (NS) Need for MV (NS), CVS toxicity (NS) (Conflicting results: IV $MgSO_4$ didn't modify the total dose of atropine and oximes, and need for MV. Although $MgSO_4$ had reduced the number of patients who developed IMS and CVS toxicity, duration of ICU stay, total duration of hospital stay and mortality, but this reduction was statistically insignificant)
Kumar et al. 2022 [42].	18–60 y. old adult	**1**. Atropine **2**. **Group I**: 1 g $MgSO_4$ every 6 hours for 24 hours . **Group II**: 1 g $MgSO_4$ every 6 hours for at least 5 days **Group III** (controls group): not receive $MgSO_4$	ND	Inhospital mortality rate (P=0.261) Development of IMS (P=0.788) Requirement of MV (P=0.664), Duration of MV (P=0.621) , Length of hospital stay (P=0.247) (no benefit from the addition of IV $MgSO_4$ (either in the first 24 h of the admission or during the entire hospital stay, at a dose of 1

				g every 6 h) to the atropine and supportive care in the management of OPC poisoning)
Mitra et al. 2023 [43].	18–80 y. old adult	Case group, 600 mg NAC tab. every 8 hours for 3 days and 4 g $MgSO_4$ over 30 min only on day 1 Control group: 5 gr sugar tab. every 8 hours for 3 days and 50 ml of normal saline over 30 min only on day 1	On arrival to the Emergency Department	Biochemical parameters before and after treatment completion (ex:Plasma pseudocholinesterase, Plasma total Malonaldehyde, free redused glutathione level in plasma, Serum Magnesium levels (NS) Atropine requirements (NS), ICU stay (NS) Invasive MV (NS) Median duration of hospital stay (NS), Mortality (NS) Number of cases with neurological sequalae (NS) (The combination of N-acetyl cysteine and $MgSO_4$ as adjuvants to standard therapy in the treatment of acute OP failed to significantly improve the clinical outcomes with respect to atropine requirements, ICU stay, mechanical ventilatory requirements, and mortality and did not offer protection against oxidative damage)

Table 2. Review articles of intravenous $MgSO_4$ for acute OP

Author Year	Outcomes and comments
Nurulain et al. 2013 [33].	• $MgSO_4$ as non-standard therapy and non-regular antidote • Its effectiveness has not yet been sufficiently established
Brvar et al. 2018 [35].	• The odds ratios for $MgSO_4$ for mortality : 0.55 (95% CI 0.32-0.94) • The odds ratios for $MgSO_4$ for the need for intubation and ventilation for all eight studies were 0.52 (95% CI 0.34-0.79) • There was no apparent evidence of a dose effect • The most common dose of $MgSO_4$ studied was 4 g • $MgSO_4$ doses such as 4 g every 4 h might offer greater benefit
Eddleston et al. 2008 [10].	• $MgSO_4$ reduced ACh release from pre-synaptic terminals • reduced mortality with magnesium sulphate (0/11 [0%] vs 5/34 [14·7%];(p<0·01)
Bajracharya et al. 2017 [44].	• The use of magnesium in acute OP in humans has been reported in three small studies. In the first study, IV administration of magnesium sulphate improved neuromuscular function. The second and third studies reported that magnesium decreased mortality compared with usual care.
Aman et al. 2021 [36].	• Preclinical studies of rodents suggested that $MgSO_4$ before or soon after OP exposure decreases mortality • $MgSO_4$ uses of managing cardiac dysrhythmias and hypertonic uterine contractions ($MgSO_4$) occurring in OP poisoned patients • A total of 8 clinical studies or trials have now been performed with $MgSO_4$ (239 patients receiving $MgSO_4$ doses of up to 26 g/d and 202 control patients). • The dose most commonly used was 4 g, which is also the standard dose for treating cardiac dysrhythmias and needs no intensive monitoring of magnesium concentrate • a small phase II study performed in Bangladesh that tested 4 escalating (4, 8, 12, and 16 g) doses of $MgSO_4$ demonstrated good tolerance
Eddleston. 2019 [1].	• Interruption of the calcium flow through channels by magnesium may be sufficient to reduce the synaptic concentration of ACh • Administration of magnesium to rodents before or soon after OP exposure, in addition to atropine and/or oxime, reduces mortality • A non-randomized Iranian clinical study of 4 g $MgSO_4$ in acute OP during 2003–2004 suggested that it was effective in reducing mortality and length of hospital stay
Narang et al. 2015 [37].	• $MgSO_4$ blocks calcium channels and thus reduces ACh release. • Given in a dose of 4 g on 1st day of admission, it has been shown to decrease hospitalization period and improve outcomes in patients with OP poisoning
Blain. 2011 [45].	• The administration of magnesium to animals poisoned with organophosphorus pesticides improves outcome, possibly owing to a favourable effect on neuromuscular junction block or increased hydrolysis of some pesticides • In one study, intravenous administration of magnesium sulphate 4 g to 4 people produced some improvement in neuromuscular function in two people. • Another non-randomised comparative study reported that magnesium decreased mortality compared with usual care (0/11 [0%] with magnesium v 5/34 [15%] with usual care

Husain et al. 2010 [46].	• Beneficial effect of $MgSO_4$ at a dose of 4g/day concurrent with standard therapy, in OP acute human poisoning has been reported
Eddleston et al. 2016 [34].	• Magnesium might also reduce the risk of ventricular tachycardia in patients presenting with tachycardias due to nicotinic stimulation • More recent Phase II dose–response study compared 4 g, 8 g, 12 g and 16 g of magnesium sulphate vs. placebo in groups of 10 OP insecticide-poisoned patients. Magnesium sulphate at all doses was well tolerated and there was a trend towards reduced mortality with larger doses.
Kaur et al. 2014 [16].	• It has been shown to be of benefit in animal models. • Intravenous $MgSO_4$ (4 g) given on the 1st day after admission have been shown to decrease hospitalization period, decreased mortality and improve outcomes in patients with OP • Magnesium may also provide protection by reducing the stimulatory effect of ACh on the muscle action potential and reversing the decrement in the force of contraction
Kumar et al. 2018 [47].	• In a study, IV MgSO4 (4 g) was administered to the patient on the first day after admission, and was found to reduce the hospital stay and improve the outcomes in patients with OP
Balali-Mood et al. 2012 [48].	• IV $MgSO_4$ (4 g) given in the first day after admission have been shown to decrease hospitalization period and improve outcomes in patients with OP
Alozi et al. 2020 [7].	• A phase II study confirmed the safety of $MgSO_4$ administration to OP poisoned patients, and several other trials recommended the infusion of 1 g of $MgSO_4$ every 6 h within the first 24 h of admission • Adjunctive $MgSO_4$ was also shown to reduce the dose of atropine needed for intubation and the overall time spent in the ICU and associated mortality rates were reduced as well
Asalu et al. 2019 [49].	• $MgSO_4$ has been shown to decrease hospitalization period and improve patients' outcomes in OP. • $MgSO_4$ is given in a dose of 4 g on day 1of presentation at the hospital and subsequently 2 g daily when necessary. • $MgSO_4$ acts by blocking calcium channels and thus reduces ACh release from the storage vesicles.
Rahimzadeh et al. 2010 [50].	• Recommended the infusion of 1 g of $MgSO_4$ every 6 h within the first 24 h of admission • Magnesium also reduce the risk of ventricular tachycardia in patients presenting with tachycardias

Abrivations: OP: Organophosphate poisoning, ACh: Acetylcholine, MV: Mechanical ventilation, h: Hour, IV: Intravenously, IMS: Intermediate syndrome, ICU: Intensive care unite, NS: Not significant, ND: Not defined, PVC: Premature ventricular contraction, PAC: Premature atrial contraction, VT: Ventricular tachycardia, NAC: N-acetyl cysteine, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

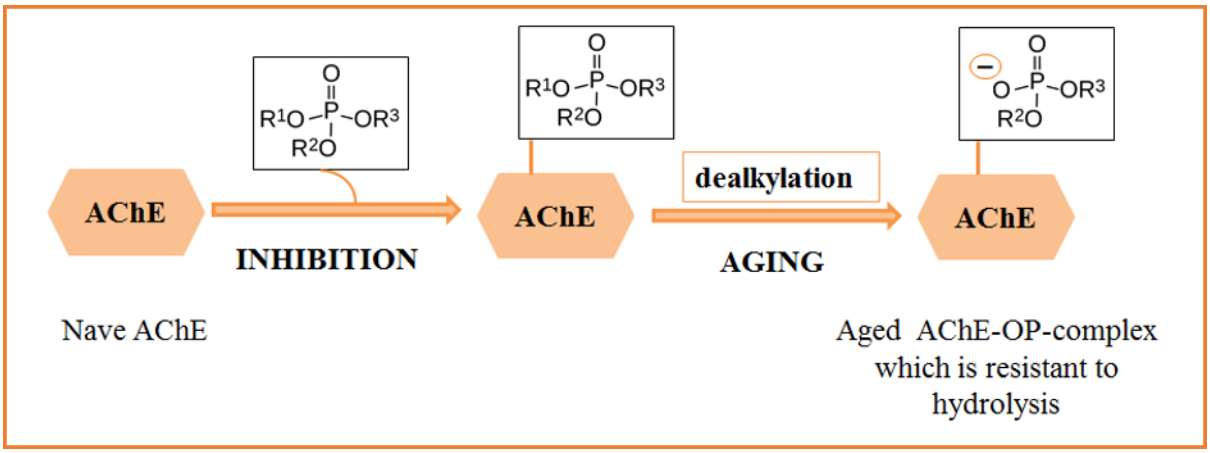

Figure 1. Inhibition of AChE by OP and Aging process

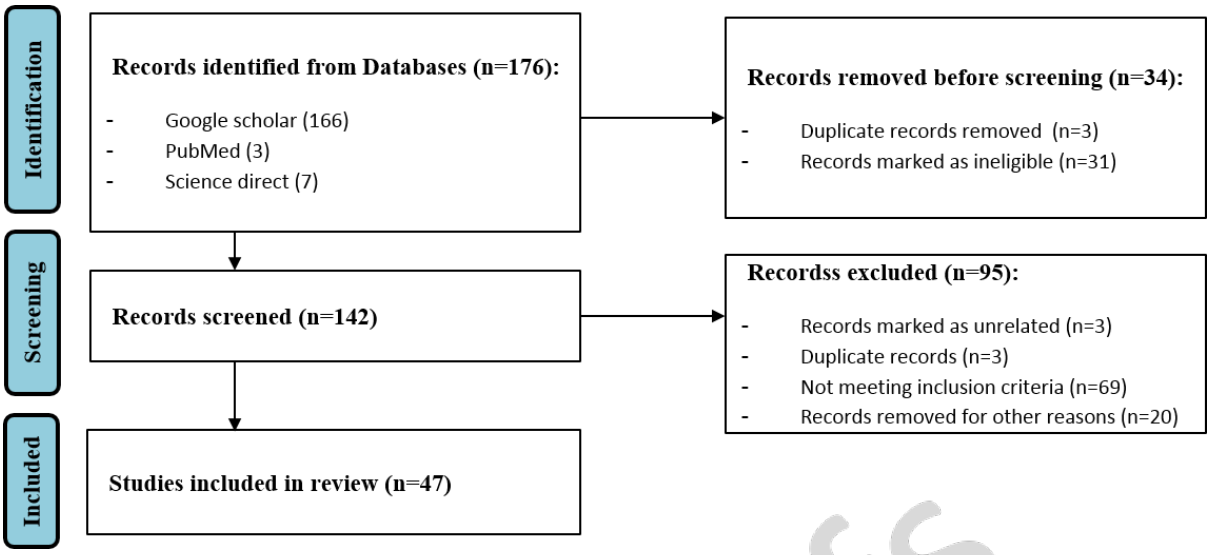

Figure 2. Flow diagram