Research article

The role of a combination of N-acetylcysteine and magnesium sulfate as adjuvants to standard therapy in acute organophosphate poisoning: A randomized controlled trial

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ABSTRACT

Background: Mortality in acute organophosphate (OP) poisoning remains high despite current standard therapy with atropine and oximes. Due to dose-limiting side effects of atropine, novel therapies are targeting other putative mechanisms of injury, including oxidative damage, to reduce atropine dosage.
Objectives: N-acetylcysteine (NAC) and magnesium sulfate ($MgSO_4$) have different mechanisms of actions and should act synergistically in OP poisoning. In this study, we wanted to evaluate whether this novel combination, used as an adjuvant to standard care, could improve clinical outcomes.
Methods: The study was conducted in the Emergency Department and ICU of AIIMS Bhubaneswar (a tertiary care center and government teaching institute) between July 2019 and July 2021. Eighty-eight adult patients with history and clinical features of acute OP poisoning were randomly allocated (1:1) into two groups. The Study group received 600 mg NAC via nasogastric tube thrice daily for 3 days plus a single dose of 4 g Inj. $MgSO_4$ IV on first day and the Control group received suitably matched placebo (double-blinding) – in addition to standard care in both the groups. The primary outcome measure was to compare the total dose of Inj. Atropine required (cumulative over the entire treatment duration) between the control group and the study group receiving NAC and $MgSO_4$. The secondary outcome measures were lengths of ICU and hospital stays, need and duration of mechanical ventilation, the differences in BuChE activity, oxidative stress biomarkers – MDA and GSH levels, the incidences of adverse effects including delayed sequalae like intermediate syndrome and OPIDN, and comparison of mortality between the two groups.
Results: Data from 43 patients in Control and 42 patients in Study group was finally analyzed. The baseline parameters were comparable. Total atropine requirements were lower in the Study group [175.33 ± 81.25 mg (150.01–200.65)] compared to the Control [210.63 ± 102.29 mg (179.15–242.11)] [Mean ± SD (95% CI)], but was not statistically significant. No significant differences in any of the other clinical or biochemical parameters were noted.

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Conclusion: The N-acetylcysteine and MgSO$_4$ combination as adjuvants failed to significantly reduce atropine requirements, ICU/hospital stay, mechanical ventilatory requirements, mortality and did not offer protection against oxidative damage.

1. Introduction

Due to easy access and widespread use in agriculture, organophosphorus pesticide poisoning has been a major public health concern, particularly in the developing nations [1]. In India, for example, pesticides accounted for 16.8% of all suicidal and about 1% of accidental deaths in the year 2020 [2]. The case fatality rate is approximately 15–30% despite the current standards of treatment with atropine, oximes and supportive care [3,4].

Esterases, like acetylcholine esterase (AChE) and butyrylcholine esterase (BuChE, also known as pseudocholinesterase), form the predominant mechanism of termination of cholinergic signaling by degradation of acetylcholine at the synapses and in the plasma, respectively. Organophosphates (OP) inhibit these esterases resulting in unopposed cholinergic action mediated via the muscarinic and nicotinic receptors, both centrally and peripherally, and give rise to the plethora of characteristic signs and symptoms of OP poisoning [5].

Current treatment employs atropine (a muscarinic receptor antagonist) to counter the muscarinic side effects and oximes (e.g., pralidoxime) for regenerating AChE enzyme [4,6]. However, the treatment requires very high doses of atropine, often resulting in delirium, hyperpyrexia, tachycardia – which may be dose-limiting and undesirable [7]. Oximes, on the other hand, are not universally useful – their effectiveness differ across the class of OP compound used – and many current evidences have questioned the rationale of their use [8,9]. Hence, adjunctive and novel therapies exploiting various other putative targets in the treatment of OP poisoning are being actively researched with the aim of reducing atropine requirements and improving clinical outcomes, particularly preventing the delayed sequalae like intermediate syndrome and organophosphorus-induced delayed neuropathy (OPIDN) [10,11]. Two such novel approaches are the use of N-acetyl cysteine (NAC) and magnesium sulfate (MgSO$_4$). Magnesium is a membrane stabilizer, behaving like a calcium antagonist, preventing release of acetylcholine from the presynaptic terminals and has been also postulated to reduce the delayed neuronal toxicities due to OP poisoning [12,13]. NAC is a reactive oxygen species (ROS) scavenger and protects against the oxidative stress mediated secondary damages following unopposed cholinergic activation by OP poisoning [14]. Thus, these two drugs act by complementary mechanisms both pre- and post-synaptically to mitigate the effects of continuous cholinergic transmission – and appear to be mechanistically synergistic.

While previously randomized controlled trials (RCTs) have individually evaluated the effects of NAC and MgSO$_4$, to the best of our knowledge, a combination of the two and their possible synergism have never been tested as an adjuvant in OP poisoning [15,16]. Hence, we studied the combination, with the null hypothesis being – in patients of acute OP poisoning, the combination of MgSO$_4$ and NAC as an adjuvant to standard therapy does not offer any benefits in terms of reducing atropine requirements, length of hospital/ICU stay, ventilator requirements or preventing delayed neurological complications. We also simultaneously evaluated for the known adverse effects of these individual therapies in our study population.

2. Materials and methods

2.1. Study design and study population

The study was in accordance to the Declaration of Helsinki (following medical ethics of human experimentation) and was duly granted clearance by the Institute Ethical Committee at AIIMS Bhubaneswar (Registration Number: ECR/534/Int/OD/2014/RR-17) and the approval number is T/IM-F/18-19/03. The trial was also registered with the Clinical Trials Registry of India (CTRI/2019/07/019970, registered on: July 01, 2019).

The study was designed as a single-center, randomized, placebo-controlled, double-blinded (patient and outcome-accessor), two parallel-group trial with 1:1 allocation ratio conducted in the Emergency Department and ICU between July 2019 and July 2021.

Adult patients of either sex (age >18 years and <80 years) presenting to the Emergency Department during the study period with history and clinical features of acute OP poisoning were considered eligible for inclusion into this study. Patients who received any prior treatment for the OP poisoning, history of concomitant poisoning with other agents, pregnant or lactating patients, patients with known coronary artery disease, seizure disorders, post cardiac arrest status and history of diabetes mellitus, and chronic respiratory, renal or hepatic dysfunction were excluded from this study. Written informed consent in the native language was obtained from the patients or their attending relatives (if the patient was delirious or unconscious). Refusal of consent was also noted and led to exclusion from the study.

2.2. Randomization, allocation concealment and blinding

The study participants were randomized using a computer-generated randomization sequence into two groups with 1:1 allocation as follows.

- **Study group** – Patients in this group, in addition to the standard treatment for OP poisoning as per institutional protocol, received:

   o 600 mg NAC tablet, dissolved in 20 ml water, administered through a nasogastric tube every 8th hour for the first 3 days [15] and
   o 4 g MgSO$_4$ injection diluted in 50 ml normal saline and infused slowly over 30 min only on the first day [13].
- **Control group** – Patients in this group, in addition to the standard care received the following placebo for blinding –
   o 5 g sugar tablet dissolved in 20 ml water through nasogastric tube every 8th hourly for the first 3 days and
   o 50 ml of normal saline infused slowly over 30 min only on day 1.

The computer-generated randomization codes were sealed into serially numbered opaque envelopes which were serially allocated to each successive patient by the Emergency Department physician on duty, who noted the code on the patient file. The allocation sequence was kept safe with the principal investigator, who took no part in the execution of the study. Upon allocation, the treating physician informed the code to the principal investigator, who ordered a staff nurse on duty over phone, to prepare the intervention or placebo drugs according to the allocation sequence and label them as "study drugs". Thus, both the patient and the treating physician (the outcome accessor) were blinded to the allocation.

2.3. The standard treatment

On arrival to the Emergency Department, the patients of suspected OP poisoning received standard care as per institutional protocol. This includes initial resuscitation with maintenance of airway patency, breathing, circulation and decontamination, with or without gastric lavage depending on the time of presentation from exposure (gastric lavage with activated charcoal was considered for patients presenting within 1 h of ingestion). Simultaneously, history was taken regarding mode of poisoning, evidence of the consumed poison in the form of the container (if available), previous co-morbidities, and treatments received. Complete physical examination was performed, including vitals charting, the presenting signs and symptoms of cholinergic over-activity were noted in the study proforma and the patient was classified into mild, moderate or severe category as per the following [17].

- <u>Mild</u>: fatigue, headache, blurred vision, dizziness, nausea, vomiting, excessive sweating, salivation, abdominal pain, and chest tightness.
- <u>Moderate</u>: symptoms of mild poisoning plus muscular fasciculation, weakness, inability to walk, chest crepitations, and miosis.
- <u>Severe</u>: symptoms of moderate poisoning plus unconsciousness, flaccid paralysis, respiratory distress, cyanosis, and marked miosis with loss of pupil reflexes.

Irrespective of the classification, all the patients received Inj. Atropine 1-3 mg IV bolus, assessed and the dose repeated every 5-10 min until there was drying of the oral and bronchial secretions and the heart rate was >80/min. Then, infusion of Inj. Atropine was started, titrated between 0.4 and 4 mg/h to achieve a heart rate of 80–100/min. Inj. Pralidoxime was administered as a loading dose of 30 mg/kg IV followed by an IV infusion of 5–10 mg/kg/hr over the first 48 h [13]. Intravenous fluids and vasopressors were administered as required to target a systolic blood pressure >90 mm Hg and oxygenation and ventilatory requirements were also individualized to each patient. Standard laboratory investigations on admission included an arterial blood gas analysis on NOVA sequential blood gas analyzer, USA. Venous blood for complete blood counts done on Sysmex; liver and renal function tests including serum electrolytes were performed on Beckman Coulter AU fully automated analyzers using kits from Beckman Coulter, Ireland; Serum Magnesium estimation was done in stored serum samples using a Magnesium Assay kit from Sigma Aldrich (MAK026), USA. Additional blood tests included assays for plasma pseudocholinesterase (BuChE) activity, markers for oxidative stress – total plasma malonaldehyde (MDA), representing lipid peroxidation, and reduced glutathione (GSH) in plasma, representing the reserve to counter oxidative stress [15], were performed by 96 well ELISA kits from Sincere Biotech, using fully automated ELISA washer and reader from Biotek, USA. These biochemical assays were performed once on admission and repeated after treatment completion on day 5 or before discharge from the hospital. All other supportive care and treatment were as per Institutional protocol.

2.4. Objectives and outcome measures

The primary outcome measure was to compare the total dose of Inj. Atropine required (cumulative over the entire treatment duration) between the control group and the study group receiving NAC and MgSO$_4$. The secondary outcome measures were lengths of ICU and hospital stays, need and duration of mechanical ventilation, development of delayed sequalae of OP poisoning like intermediate syndrome and OPIDN, and comparison of mortality between the two groups. We also report the differences in BuChE activity, MDA and GSH levels at the initiation and completion of the treatment and the incidences of adverse effects and toxicities including seizures, depressed tendon reflexes, cardiac arrhythmias, and reduced urine output between the two groups.

2.5. Sample size calculation and statistical analysis

We took the study done by Vijaykumar et al. [13] as our reference and using the mean difference in daily atropine requirement for sample size calculation with a *p*-value of 0.05, power of 80% and allocation ratio as 1:1. The required sample size in each arm was 44 and total participants required was 88. All the data was tabulated in an Excel master data-sheet. Baseline as well as outcome data of study participants has been represented in the form of mean ± S.D or median (with inter-quartile range) for continuous variables and in the form of relative frequency (percentages) for categorical variables. Normality testing for the continuous variables among the outcome parameters was done using Shapiro-Wilk and Kolmogorov-Smirnov tests. The tests of significance applied were the Students'

t-test or the Mann Whitney *U* test (based on satisfying the normal distribution assumption) for continuous data and Fisher's Exact test for categorical variables. The *p*-values of 0.05 or less was considered to be statistically significant. Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) for Windows (Released 2021. IBM SPSS Statistics for Windows, Version 28.0 (complementary trial). Armonk, NY: IBM Corp).

3. Results

A total of 88 patients were recruited and randomized into two equal groups and finally 42 patients in the Study Group and 43 patients in the Control group were analyzed (Fig. 1). The baseline characteristics of the two patient subsets were comparable (Table 1). All the patients presented as cases of suicidal OP poisoning. The time of reporting to the Emergency Department from the alleged time of poisoning was highly variable across the patient population – median delay being 6 h. The predominant mode of poisoning was ingestion (96%) and the primary compounds implicated was a combination of Chlorpyrifos with Cypermethrin (a commonly used formulation in the locality) in about 80% of the cases.

The cumulative total and daily average dose of Inj. Atropine received IV was higher in the Control group as compared to the Study group, but the differences were not statistically significant (Table 2). Similarly, duration of ICU stay, hospital stay and need for invasive mechanical ventilatory supports were lower in the Study Group, but failed to achieve statistical significance (Table 2). Plasma pseudocholinesterase levels were comparable between the two groups both at the start and after the completion of the intervention,
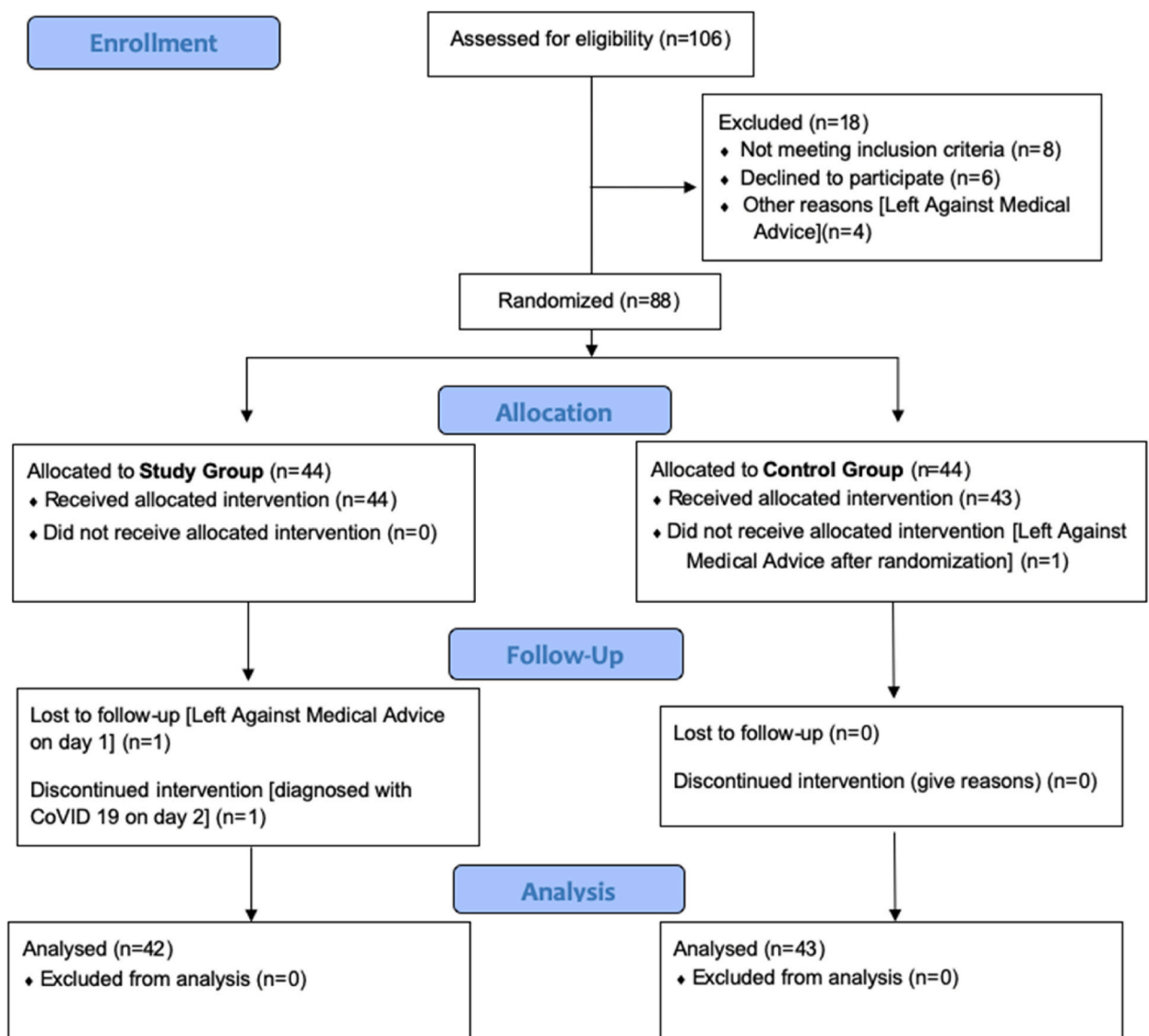

Fig. 1. CONSORT flow diagram.

Table 1

Baseline characteristics of the patients. Values are represented as Mean ± SD for continuous, normally distributed parameters and as Number of patients (represented as a percentage of the total) for categorical variables.

Parameters		Study Group (n = 42)	Control Group (n = 43)	*p*-value
Age (years)		37.95 ± 15.86	34.49 ± 14.71	0.30
Sex	Male	27 (64.3%)	21 (48.8%)	0.19
	Female	15 (35.7%)	22 (51.2%)	
Body weight (kg)		55.29 ± 8.51	55.58 ± 7.20	0.86
Severity of Poisoning (Minton and Murray [17])	Mild	32 (76.2%)	33 (76.7%)	0.89
	Moderate	6 (14.3%)	7 (16.3%)	
	Severe	4 (9.5%)	3 (7.0%)	
Peripheral oxygen saturation on admission	≥90%	39 (90.7%)	39 (92.8%)	0.68
	80–89%	2 (4.8%)	4 (9.8%)	
	<80%	1 (2.4%)	0 (0%)	
GCS on admission	13–15	33 (78.6%)	39 (90.8%)	0.32
	9–12	5 (11.9%)	2 (4.6%)	
	≤8	4 (9.5%)	2 (4.6%)	

with values approaching normal reference ranges after treatment completion (Table 3). Total plasma MDA levels were not significantly different between the groups and did not show any significant reductions post intervention. Free fraction of reduced glutathione (GSH) in plasma increased after treatment but was not significantly different between the two groups. Serum Magnesium levels increased in the Study Group more than the controls after treatment, but remained within the reference normal ranges in both groups (Table 3).

There were two deaths in the Control group and one in the Study group. One patient in the Control group developed Intermediate syndrome. No complications – seizures, depressed tendon reflexes, cardiac arrhythmias, or acute kidney injury - attributable to the interventions were noted in either of the two groups.

4. Discussion

In this randomized controlled trial, we found that the requirement of Inj. Atropine (both total and mean daily), was lesser in the Study group as compared to the Control, but failed to reach statistical significance. Although there was a reduction of the median total hospitalization period in the Study group, the intervention did not show any significant difference in the duration and need for ICU stay and mechanical ventilation, mortality, or development of delayed neurological sequalae between the two groups. More importantly, the intervention failed to demonstrate any reduction in oxidative stress (using MDA and GSH levels as markers) between the two groups after treatment.

The role of NAC as an adjuvant in OP poisoning for reducing oxidative damage stems from multiple pre-clinical studies in murine models [23–25]. The two published RCTs reporting atropine dosage showed widely varying requirements of Inj. Atropine (from 5 mg cumulative to 9-24 mg/day) [15,26]. Of the two studies that reported oxidative stress markers, one used only NAC while the other used a combination of NAC and sodium bicarbonate as adjuvant [15,27]. Our study, however, failed to detect any trend (either increase or decrease) of MDA and GSH in either the Study or the Control groups. At this point, it remains purely speculative as to whether this is a result of the effect of concomitant administration of MgSO$_4$ [28].

MgSO$_4$ as an adjuvant in OP poisoning on the other hand has been studied in much greater details. A phase II trial demonstrated the relative safety of administration of even higher dosage (up to total 16 g) of MgSO$_4$ to be well tolerated in patients and suggested that

Table 2

The primary and secondary outcome measures obtained clinically. Values are represented as Mean ± SD (95% Confidence Interval) for parametric continuous data; as Median (Inter-quartile range) for non-parametric continuous data and as Number of patients (represented as a percentage of the total) for categorical variables.

Parameters		Study Group (n = 42)	Control Group (n = 43)	*p*-value
Atropine requirements (mg IV)	Cumulative total	175.33 ± 81.25 (150.01–200.65)	210.63 ± 102.29 (179.15–242.11)	0.08
	Per day (average for each patient across the treatment duration)	23.39 ± 10.82 (20.02–26.76)	28.11 ± 13.63 (23.87–32.35)	0.08
ICU stay	Number of patients requiring	6 (14.3%)	6 (14.0%)	0.96
	Median duration of ICU stay among those who required (days)	7 (5,10)	8 (5,9)	0.83
Invasive mechanical ventilation	Number of patients requiring	6 (14.3%)	6 (14.0%)	0.96
	Median duration of ventilation among those who required (days)	6 (5,7)	7 (6,7)	0.76
Median duration of hospital stay (days)		8 (5,10)	10 (5,12)	0.62
Number of deaths (mortality)		1 (2.4%)	2 (4.6%)	0.54
Number of cases with neurological sequalae		0 (0%)	1 (2.3%) [Intermediate syndrome]	0.31

Table 3

Biochemical parameters before and after treatment completion (measured at day 5 or discharge, whichever is earlier). Values are represented as Mean ± SD (95% Confidence Interval).

Parameters		Study Group (n = 42)	Control Group (n = 43)	p-value
Plasma pseudocholinesterase (expressed in kIU/L) [Normal: 8-18 kIU/L] [18]	At admission	2.74 ± 1.19 (2.37–3.11)	2.46 ± 1.07 (2.13–2.80)	0.26
	After treatment completion	7.27 ± 3.31 (6.24–8.30)	7.37 ± 2.94 (6.46–8.27)	0.89
Plasma total Malonaldehyde (MDA)	At admission	4.69 ± 4.91 (3.15–6.22)	4.56 ± 4.82 (3.08–6.05)	0.91
(expressed in μmol/L) [19,20]	After treatment completion	5.00 ± 5.94 (3.15–6.85)	4.31 ± 4.00 (3.08–5.55)	0.53
Free reduced Glutathione (GSH) level in plasma	At admission	3.47 ± 1.12 (3.12–3.81)	3.28 ± 1.15 (3.18–3.90)	0.75
(expressed in μmol/L) [Normal: 3.39 ± 1.04 μmol/L] [21]	After treatment completion	4.33 ± 1.52 (3.87–4.79)	4.04 ± 1.56 (3.55–4.52)	0.38
Serum Magnesium levels (expressed in mg/dL) [Normal: 1.8–2.29 mg/dL] [22]	At admission	1.64 ± 0.47 (1.50–1.78)	1.50 ± 0.61 (1.31–1.69)	0.32
	After treatment completion	3.34 ± 1.57 (2.88–3.81)	2.97 ± 1.57 (2.48–3.46)	0.27

mortality might improve with higher dosage [29]. However, in view of the need for less rigorous serum Mg level monitoring, we chose to design this study with the more widely used dose of 4 g [13,16,30]. In our study, the reported daily requirement of Inj. Atropine was much less in either group in comparison to previous published results [13], but not significantly different between the two groups. However, we make a note of the fact that the mean daily and cumulative atropine consumption were approximately 5 mg and 35 mg respectively, lower in the Study group as compared to Control and this may still be a clinically significant reduction. Also, there have been conflicting reports regarding the beneficial effects of 4 g $MgSO_4$ on reducing ventilatory requirements and ICU stay, hospitalization duration and mortality [13,16,30]. But in this study, we noted a statistically non-significant reduction of 2 days in median hospitalization duration, while the other parameters were similar between the two groups.

The commonly noted side effects of NAC are anaphylactoid reactions and vomiting [15], and those of $MgSO_4$ are neuromuscular weakness and cardiac arrhythmias – none of which were reported in our Study group. We did note one case of Intermediate Syndrome (delayed onset neuromuscular weakness) in the Control group, but whether $MgSO_4$ is protective against it remains to be defined.

The major strengths of our study were in its robust design and strict adherence to protocol with minimal loss to follow-up. We tested a novel combination of two safe and commonly used drugs as adjuvant therapies in OP poisoning with different mechanisms of action with the anticipation for synergistic action. Clinically relevant outcome parameters like atropine dosage, ICU stay and ventilatory requirements were reported along with biochemical profile for oxidative stress markers.

5. Limitations

Our study suffered from the limitations that due to constraints of monitoring and for ethical considerations of patient safety, higher and repeated dosage of $MgSO_4$ were not administered, nor was a therapeutic level monitoring done. Further, using MDA as a putative marker of oxidative stress has been questioned [28], but for the need of a better standardized marker, we still reported MDA levels.

6. Conclusion

The combination of N-acetyl cysteine and $MgSO_4$ as adjuvants to standard therapy in the treatment of acute organophosphate poisoning 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.

Author contribution statement

Jayanta Kumar Mitra: Conceived and designed the experiments; Analyzed and interpreted the data.
Upendra Hansda: Conceived and designed the experiments; Performed the experiments.
Debapriya Bandyopadhyay: Performed the experiments; Contributed reagents, materials, analysis tools or data.
Satyaki Sarkar: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Joshna Sahoo: Performed the experiments.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

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