BENEFITS OF ADDING NEBULIZED ATROPINE TO ATROPINE INFUSION IN TREATMENT OF ACUTE SEVERE ORGANOPHOSPHATE INSECTICIDE POISONING.

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Submit Date 20-09-2021
Revise Date 06-09-2022
Accept Date 30-11-2021

ABSTRACT

Background & objective: organophosphate (OP) insecticide poisoning is considered a major clinical problem, especially in developing countries with a 15–30% case fatality rate. These compounds act by inhibition of acetylcholinesterase enzymes, with clinical features of muscarinic overstimulation. Treatment mainly depends on muscarinic receptor antagonist, atropine, to relieve the symptoms of intoxication. This study aims to assess the benefits of adding nebulized atropine to infusion during the treatment of severe OP poisoning cases. **Patients & methods:** This cross-sectional observational study was conducted on 40 patients aged 18 to 58 years who were admitted with acute severe OP poisoning at the Poison Control Center of our university from September 2019 to August 2020. After first aid measures, the patients were divided randomly into two groups; the first group received atropine by infusion, while the second group was treated by nebulized and infused atropine. The following data were evaluated and compared between both groups; total atropine dose, oxime dose, heart rate, peak inspiratory pressure, plateau pressure, the number of endotracheal tubes used, development of pneumonia, total time of ventilation, and the number of survivors. **Results:** The results revealed that the cases who received atropine by the nebulizer and parenteral routes required a lesser dose of atropine for abolishing muscarinic symptoms, showed a significant decrease in plateau and peak inspiratory pressures, lower incidence of development of pneumonia, decreased need for chest tube insertion and better survival rate. **Conclusions:** nebulized atropine, besides infused one, would have many benefits with future considerations.

Keywords: organophosphorus compounds, insecticides, infusion atropine, nebulized atropine, treatment.

INTRODUCTION:

Organophosphorus compounds (OPC) have been used widely as pesticides for more than 70 years up till now. Poisoning by OPC may occur from intentional, accidental, and occupational exposure. World Health Organization (WHO) reported three million humans are exposed to OP per year, and nearly 300 000 deaths are recorded among them, leading to five million deaths over the last three decades **(Robb and Barker 2020).**

OPC block the action of acetylcholinesterase enzyme and consequently accumulation of acetylcholine at cholinergic synapses **(Peter et al., 2014)**. Acute respiratory failure is common in severe toxicity due to inhibition of the respiratory center, neuromuscular dysfunction, and bronchorrhea **(Hulse et al., 2014)**. Therefore, the management requires rapid resuscitation, oxygen administration, fluids, and atropine with respiratory support (**Balali-Mood & Saber, 2012).**

Atropine is the mainstay in the treatment of OP poisoning, being a competitive nonspecific antagonist at the muscarinic receptors with good central nervous system (CNS) penetration. It is preferable to administer it by continuous intravenous (IV) infusion as it reduces the time and total dose of atropine required to obtain full atropinization; thus, it has an effective role in reduced case fatality rate **(Eddleston and Chowdhury, 2016).**

Another alternative route is the respiratory route which offers rapid bioavailability; it also helps to obtain rapid therapeutic range and peak drug concentration in the blood within 30 minutes (min) close to the intravenous range **(Mittal et al., 2016)**. We investigate the value of adding nebulized atropine to atropine infusion in treating acute severe OPC poisoning.

PATIENTS & METHODS

This cross-sectional hospital-based observational study was conducted on 40 patients (14 males & 26 females) with severe OP poisoning, and their ages ranged from 18 to 58 years admitted at the Poison Control Center (PCC) of our university during the period from September 2019 to August 2020.

The patients were firstly diagnosed based on history, clinical examination, and laboratory using pseud-cholinesterase. Then, the patients were evaluated regarding the severity of OP poisoning according to Peradeniya organophosphorus poisoning scale (POP) **(Raveendra et al., 2020)** (table 1); the patients were assessed clinically for pupil size, respiratory rate, heart rate, seizures, and level of consciousness.

This study included patients with severe poisoning; score 8-11, the patients presented within 1-2 hours from poisoning, and the ventilated patients only. While, mild and moderate cases, patients referred from other medical facilities or received prehospital treatment and those with comorbidities should be excluded for the possibility of alteration in measured parameters. Also, those 60 and above were excluded for the same reason.

The patients were managed according to the local protocol of our poison control center as follows: performing first aid measures, resuscitation, clearance of airway, and ensuring ventilation. Then, detailed history about the type of the agent and the route of toxicity were reviewed. Gastric lavage was performed to all patients. The patients were then transferred to the intensive care unit, where these investigations were done for all the patients: Electrocardiogram (ECG), complete blood count (CBC), urine chemistry, arterial blood gas, plasma choline esterase (ChE activity), and chest X-Ray.

Table (1): showing Peradeniya organophosphorus poisoning scale (POP)

parameter	Criteria	score
Pupil size	≥2m	0
	<2mm	1
	Pin point	2
Respiratory rate	<20/min	0
	.≥20/min	1
	.≥20/min with central cyanosis	2
Heart rate	>60/min	0
	41-60/min	1
	<40/min	2
fasciculation	None	0
	Present, generalized/continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal commands	1
	No response to verbal commands	2
seizures	absent	0
	present	1
0-3mild poisoning, 4-7 moderate poisoning, 8-11severe poisoning		

Atropine was started whenever muscarinic manifestations (chest crepitation, bradycardia, miosis, etc.) were evident. Pralidoxime was initially given to all patients in 250 mg IV bolus over 20 mins, then was repeated every 8hours (hrs.), and it was discontinued 12 hrs. after atropine cessation (**Ghonem et al., 2018).**

The forty patients were divided into two groups randomly, with 20 patients in each group, group I received atropine by infusion, while group II was treated by nebulized and infused atropine.

Atropine Infusion doses:

Atropine was started with a dose of 1.8–3.0 mg according to the severity, followed by gradually increasing doses every 5-15 mins till full atropinization was reached. Full atropinization is defined by these clinical features, including clear chest on auscultation, heart rate >80 beats per minute, systolic blood pressure >80 mmHg, which is adequate for tissue oxygenation **(Eddleston. 2019).**

Patients were then maintained on an infused atropine, using 10%-20% of the

atropine dose required to render the patient fully atropinized. Atropine infusion is maintained without permitting the reappearance of cholinergic manifestations or occurrence of atropine toxicity which is defined by confusion, hyperthermia, and absence of bowel sounds. Atropine infusion is maintained as long as the patient needs a mechanical ventilator and discontinued only after 24 hrs. Once all features of the cholinergic crisis had been resolved **(Bajracharya et al., 2016).**

Doses of nebulized atropine:

The dose of 2.5 mg / 6 hrs. was used in the current study is the conventional dose that is frequently recommended in the emergency room and is continued as long as infusion is maintained. Doses > 2.5 mg are not used as they may be associated with undesirable side effects due to increased systemic absorption **(Seale, 2003).**

The following data were evaluated for each group; the total infused atropine dose, oxime dose, mean heart rate, mean peak inspiratory pressure, mean plateau pressure (each parameter is recorded every two hrs. then totally divided by number of measure times per day), number of survivors, the incidence of pneumonia, total time of ventilation, total time to recovery, number of endotracheal tubes needed for each patient and chest tube insertion.

Ethical considerations:

This study was done after getting approval from the medical ethical committee of our university and obtaining informed written consent from the patients or their relatives.

STATISTICAL ANALYSIS:

All data were coded and tabulated, then calculated using SPSS program 26. The quantitative data were expressed as mean ± SD with minimum and maximum range, while qualitative data were presented as number &percentage. Qualitative data were analyzed by Chi-square test between groups or **Fisher's exact test**. Analyses were done between two groups for parametric quantitative data using **the Independent Samples T-test** and non-parametric quantitative data using the **Mann-Whitney test.** The difference was considered to be significant if P-value was found to be ≥ 0.05

RESULTS

Both groups were age and sex-matched, as summarized in (table 2). The mean age of patients was 32.5 ± 11.02 & 33 ± 11.1 in groups I & II, respectively, with insignificant differences between both groups. Seven patients (35%) were males while 13 were females (65%) in each group which was statistically insignificant.

The route of poisoning was oral in all patients. The types ingested of pesticides included malathion and dimethoate; class II according to WHO classification **(World Health Organization & International Programme on Chemical Safety,** (2010, with insignificant difference between both groups (Table 2).

Table (2): showed age, sex and type of pesticide distribution between both groups.

		Group (I) 20 cases	Group (II) 20 cases	P value
Age		32.5 ±11.02	33 ±11.1	0.887
Sex	Male	7 (35%)	7 (35%)	1
	female	13 (65%)	13 (65%)	
Type of pesticide	malathion	14 (70%)	17 (85%)	0.256
	dimethoate	6 (30%)	3 (15%)	

Heart rate measurements revealed an insignificant difference between the means of both groups all through the total period of atropine administration (chart 1). However, plateau pressure (chart 2) and peak inspiratory pressure (chart 3) measurements showed a significant decrease in the means of group **II** than group **I.**

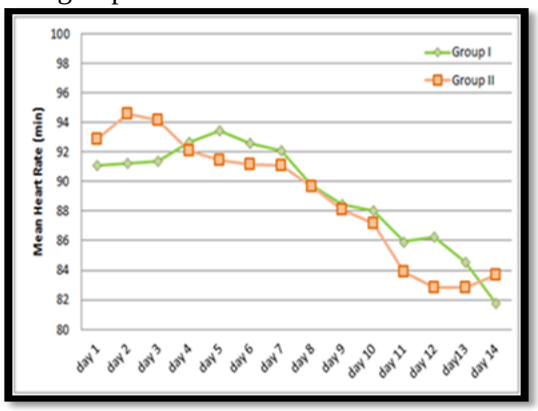

Chart (1): showing difference in mean of heart rate between both groups.

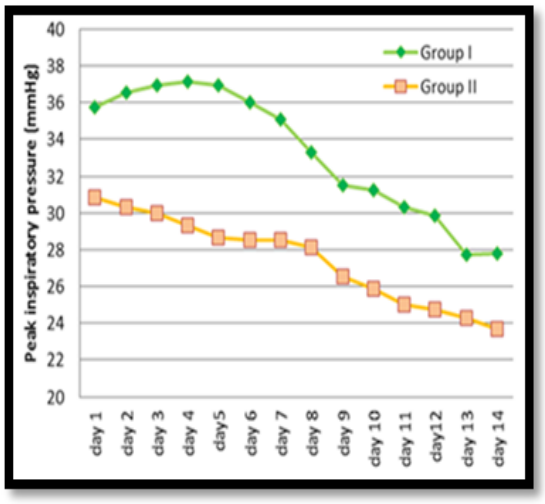

Chart (2): Showing difference in means of plateau pressure between both groups.

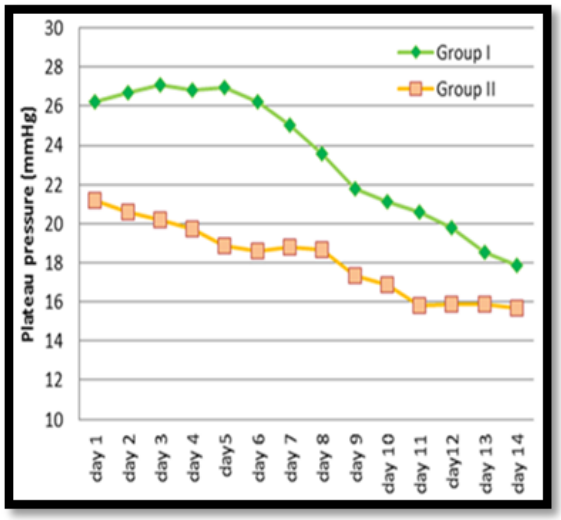

Chart (3): showing difference in means of peak inspiratory pressure between both groups.

The mean infused atropine dose required for full atropinization was 401.75 ± 66.4 & 307 ± 32.9 in groups (I) & (II), respectively. It was significantly decreased in group (II) than group (I) ($p < 0.001$), while the mean oxime dose was 10.8 ± 0.26 in group (I) & 10.21± 0.301 in group (II) with an insignificant difference between both groups (Table 3).

Concerning the number of endotracheal tubes used, the mean was 2.87 ± 0.52 in group I while 2.26 ± 0.66 in group II with a significant difference between both groups ($p = 0.008$). Eight (40%) cases needed chest tube insertion in group I, while 1 (5%) case only in group II needed fixation of a chest tube. Pneumonia developed in 11 cases in group (I), while in 4 cases only in group II (table 3)

The total time of ventilation ranged between 7-12 days in the survived patients. At the same time, the total time to recovery ranged between 10-14 days, with an insignificant difference between both groups. Five patients (25%) did not survive in group I, while 1 case did not survive in group II with an insignificant difference (table 3).

Table (3): showing descriptive statistics between group (I) & group (II).

		Group (I) 20 cases	Group (II)20 cases	P value
Atropine dose		401.75± 66.428	307.00± 32.983	0.000*
Oxime dose		10.8 ± 0.26	10.21± 0.301	0.264
Pneumonia	No	9 (45%)	16 (80%)	0.022*
	yes	11(55%)	4 (20%)	
Endotracheal tube number		2.87±0.516	2.26±0.653	0.008*
Chest tube	No	12 (60%)	19 (95%)	0.02*
	yes	8 (40%)	1 (5%)	
Total time of ventilation (d)		9.80±1.014	9.21±1.316	0.264
Total time of recovery (d)		13.20±1.146	12.37±1.571	0.089
Survival	No	5 (25%)	1 (5%)	0.182
	yes	15 (75%)	19 (95%)	

DISCUSSION:

Organophosphates are considered the most common poisoning agents in developing countries, including Egypt, and cause a significant health problem because of their easy availability, wide usage in agriculture, and low cost **(Abdel Baseer et al., 2021).** Also, **El-Maddah 2012** reported that OP poisoning was the second most common of total acute poisoning with incidence (30.4%) in Egypt.

Acute respiratory failure is the primary cause of death in these cases, attributed to respiratory center depression as a central mechanism and peripheral mechanisms as bronchospasm, bronchorrhea, pneumonia, and aspiration pneumonia. Moreover, the occurrence of delayed intermediate syndrome requires prolonged ventilation with consequently increased burden of those patients due to increased risk of ventilator-associated pneumonia, ventilator-associated lung injury, and pneumothorax (**Hulse et al., 2014).**

Atropine sulfate is a belladonna alkaloid, the antidote of choice in clinical guidelines; it has muscarinic receptor antagonist properties. Oximes are also used clinically to reverse AChE inhibition by hydrolysis of the bond created with OP act as enzyme reactivators **(Alozi & Rawas-Qalaji, 2020).**

Nebulized atropine has many advantages, like the instantaneous absorption of the drug into the blood and aversion of hepatic first-pass loss. Also, the application of the drug at the desired site of action is helpful in the case of pulmonary disease. For example, drugs can be given in this manner for the treatment of bronchial asthma **(Stein & Thiel, 2017)**.

So, this study aimed to evaluate the alternate respiratory route of atropine administration if added benefits to IV infusion in cases of severe OP poisoning management.

These results revealed that adding nebulized atropine to the infusion route showed a significant decrease in total atropine dose in those patients, while oxime dose had insignificant difference also it showed insignificant difference regarding heart rate among both groups.

Peak inspiratory and plateau pressure were used to evaluate resistance to airflow and pulmonary compliance, consequently, to early detect complications which may occur in ventilated patients in our study as increase both parameters have a high risk of pneumothorax. In this study, both showed a significant decrease in patients treated with nebulized atropine; this effect may be attributed to the bronchodilation effect of atropine which made it useful in the treatment of bronchial asthma as reported by Newman **2018.**

Patients given added nebulized atropine to atropine infusion showed a decrease in the number of chest tube insertions needed (1 patient only) and decrease in patients who developed pneumonia 4 in group II while 11 in group **I**; this could be explained by blocking mucus hypersecretion, which is triggered by M3 muscarinic receptors stimulation **(Alharbi et al., 2021).**

Moreover, nebulized atropine causes a decrease in the number of EET used, which is attributed to a decrease in bronchial mucous production, which is noticed soon after inhaled atropine that did not need recurrent change EETs **(Rubin, 2015).**

The total time of recovery was 10-14 days, with an insignificant difference between both groups. The survival rate was better in group II with an insignificant difference between both groups. Although the difference between both groups is insignificant but decrease deaths of OP poisoning is a great goal in patients' management.

To our knowledge, little literature studied the benefits of adding nebulized atropine to atropine infusion in treating severe OP poisoning.

These results coincide with **Shockley et al. 1989** who described a patient who had moderate to severe malathion poisoning and was treated with a combination of both intravenous and inhaled nebulized atropine successfully with the improvement of bronchorrhea, respiratory distress, and a rise in oxygen saturation, especially after adding nebulized atropine.

Özyurt et al. 2003 reported two cases of OP intoxication being treated with atropine aerosol spray (AAS) only and concluded that clinical improvement suggests significant systemic absorption of the drug occurring within 5 minutes of AAS application.

Also, **Ali et al. 2009** did a clinical trial using a nano–atropine sulfate dry powder inhaler in six healthy individuals and proved that using the respiratory route provides rapid and extended systemic absorption of the drug, making it a suitable treatment option, especially in emergency cases.

CONCLUSIONS

We concluded that using nebulized atropine in treating severe OP poisoning added benefits especially decreased atropine dose, improvement in respiratory function, increased survival.

RECOMMENDATIONS

Using atropine via the respiratory route in the treatment protocol of severe op poisoning besides infusion is recommended. Also, Future research about added nebulized β2-agonist to the standard therapy for evaluation of possible beneficial effects.

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الملخص العربي

فوائد اضافة الأتروبين المرذذ الي الأتروبين بالتسريب الوريدي في علاج حالات التسمم الحاد الشديد بالمبيدات الفسفورية العضوية .

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الملخص: يعتبر التسمم بمبيدات الفوسفات العضوي مشكلة سريرية رئيسية خاصة في البلدان النامية مع معدل وفاة للحالة يتراوح بين 15 و 30٪ . تعمل هذه المركبات عن طريق تثبيط إنزيمات أستيل كولين استريز ، مع وجود سمات إكلينيكية بسبب التحفيز المفرط لمستقبلات المسكارين. يعتمد العلاج بشكل أساسي على مضادات مستقبلات المسكارين(الأتروبين) للتخفيف من أعراض التسمم. الهدف من هذه الدراسة هو تقييم فوائد إضافة الأتروبين المرذاذ إلى الحقن الوريدي أثناء علاج حالات التسمم الشديدة بالمبيدات الفسفورية العضوية.

أجريت هذه الدراسة الرصدية المقطعية على 40 مريضًا تتراوح أعمارهم بين 18 و 58 عامًا تم قبولهم بتسمم بالمبيدات الفسفورية العضوية الحاد في مركز السموم في جامعتنا خلال الفترة من سبتمبر 2019 إلى أغسطس 2020. بعد إجراء الإسعافات الأولية ، تم تقسيم المرضى عشوائيا إلى مجموعتين ، المجموعة الأولى تلقت الأتروبين عن طريق التسريب الوريدي، بينما المجموعة الثانية تلقت الأتروبين المرذذ والمضغوط الي جانب التسريب الوريدي. تم تقييم ومقارنة كلا المجموعتين من حيث إجمالي جرعة الأتروبين ، جرعة الأوكسيم ، معدل ضربات القلب ، ذروة ضغط الشهيق ، ضغط البلاتوه ، عدد الأنابيب داخل القصبة الهوائية المستخدمة ، حدوث الالتهاب الرئوي ، إجمالي وقت التنفس الصناعي وعدد الناجين.

وقد وجد ان الأتروبين المرذذ إلى جانب التسريب الوريدي له فوائد عديدة مع اعتبارات مستقبلية.

الكلمات المفتاحية: مركبات فسفورية عضوية ، مبيدات حشرية ، تسريب أتروبين ، أتروبين مرذاذ ، علاج