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Albuterol as an Adjuvant Therapy in Acute Anticholinesterase Pesticides Poisoning: A Randomized Clinical Trial

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Abstract: Background: Acute anticholinesterase pesticides poisoning is a major problem in developing countries. Although atropine and oximes are known antidotes, novel therapeutic regimens are needed to improve patients' outcome. Albuterol is a selective bet 2 adrenergic agonist that can improve oxygenation. **Objective:** The aim of this study was to evaluate safety and efficacy of aerosolized albuterol as an adjuvant in the management of patients with acute anticholinesterase pesticide poisoning. **Methods:** This was a randomized, controlled, parallel-group study performed between May 2017 and August 2018 on 60 patients with acute anticholinesterase poisoning who were admitted to the Tanta University Emergency Hospital Poison Control Center. The patients were randomized into 3 equal groups (20 patients each). Group I participants received the standard treatment. In addition, each participant in groups II and III received a single dose (2.5 mg and 5 mg) of aerosolized albuterol respectively. Oxygenation, mortality, total dose of atropine administered, hospital stay period and the need for ICU admission and/or mechanical ventilation were the outcome measures included. **Results:** There were a total of 89 patients examined and 60 patients randomized. We found no statistically substantial differences in patient demographics among the groups studied, exposure characteristics, clinical manifestations or routine laboratory investigations on admission. The duration of hospital stay in patients treated with albuterol was substantially lower. However, the use of aerosolized albuterol as an added treatment could not improve oxygenation. **Conclusion:** Aerosolized albuterol was seemingly safe, and in patients with acute anticholinesterase pesticide poisoning, hospital stays were decreased.
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1. Introduction

Anticholinesterase pesticides include organophosphates (OP) and carbamates (CM). They include large group of chemicals and represent more than 50 % of all pesticides used worldwide **(Rathishet al., 2018).**

Acute anticholinesterase pesticides poisoning is a severe clinical problem in rural regions and developing countries. Reaching a physician or a hospital on time is difficult. In addition, hospitals are not sufficiently staffed or prepared to cope with patients who are severely poisoned. There is a shortage of intensive care beds and ventilators, and even unconscious patients are treated in open wards. Moreover, little clinical research had been performed to determine best management **(Eddleston et al., 2008).**

OP or CM pesticides inhibit cholinesterase activity, resulting in accumulation of acetylcholine (ACh) at muscarinic and nicotinic receptors with initial stimulation and then exhaustion of cholinergic synapses. Acute cholinergic crisis occurs immediately or within 12 hours from exposure. It has muscarinic, nicotinic and CNS effects. It rapidly progresses to respiratory failure or even death. Excessive airway secretion, airway obstruction, muscle weakness and central apnea are the main manifestations. In addition, cardiac disturbance and multi-organ failure are considered possible causes of death **(Lutovac et al., 2017; Ohbe et al., 2018; Slavica et al., 2018).**

Diagnosis is based on clinical suspicion, odor of pesticides, characteristic clinical signs and decreased acetylcholinesterase or butyrylcholinesterase activity in the blood **(Eddleston et al., 2008).**

Rapid and effective stabilization of patients can reduce the number of early deaths and improve short and long-term complications. Initial treatment of acute cholinergic crises involves maintenance of airway, breathing and circulation and administration of antidotes (atropine and oximes) **(Abedin et al., 2012; Eddleston, 2018).** Atropine at muscarinic receptors

competes with acetylcholine and inhibits cholinergic activation. It dries mucous membranes of respiratory tract especially excessive secretion. However, it only stops production of secretion and does not remove the already formed secretions from the lungs **(Takemura et al., 2013).** Usually, large doses of atropine are needed for quicker stabilization and reduction of anticholinesterase poisoning mortality **(Abedin et al., 2012).** Oximes are cholinesterase enzyme reactivators. Use of oximes in CM poisoning is unnecessary because of its reversible cholinesterase inhibition. Furthermore, oximes might worsen CM toxicity **(Vale & Lotti, 2015).** To date, sufficient evidence regarding benefit or harm of oximes is lacking. Therefore, new drugs that could improve outcome of these cases are urgently needed **(Buckley et al., 2011; Blumenberg et al., 2018).**

Albuterol is a short acting β_2 adrenergic agonist. It is recommended for treating exacerbations of asthma and other chronic obstructive airway diseases **(Kondili et al., 2011; Condella et al., 2018)**. Also, it is used for acute lung injuries and acute respiratory distress syndrome **(Folkesson and Matthay, 2006; Berthiaume and Matthay, 2007**). It produces smooth muscles relaxation from trachea to terminal bronchioles and increases the rate of fluid clearance through trans-epithelial sodium and chloride transport. These actions could reduce airway resistance, facilitate mucous drainage and increase vital capacity **(Kersten et al., 2017).** Thereby, it is reasonable to expect that albuterol could play roles supplementary to atropine to enhance respiratory function in anticholinesterase pesticides poisoning **(Eddleston and Chowdhury, 2016; Eddleston, 2018).**

Methods

The research was accepted by the Faculty of Medicine's Research Ethics Committee, Tanta University (Approval code: 31453/03/17). An informed written consent (if unable to take part in the consent process) has been obtained from each patient or his / her guardians. By having a code number for each patient, data confidentiality was retained. The trial was registered at the Pan African Clinical Trials Registry (PACTR201810624534118).

Participants:

The study recruited patients presenting with acute anticholinesterase pesticides poisoning to Tanta University Poison Control Center between May 2017 and August 2018. Patients (male or female, 12 years of age or older) with symptomatic acute poisoning with anticholinesterase (accidental or deliberate) were included in the study. Diagnosis was based on the following diagnostic criteria **(Karki et al., 2004)**:

1. History of exposure to an OP or CM agent.
2. Characteristic clinical manifestations of OP or CM poisoning.
3. Improvement of signs and symptoms after administration of atropine.
4. Low serum pseudocholinesterase activity.

A total of 89 patients were examined, 29 of whom were excluded due to non-compliance with the eligibility criteria (9 hepatic, 6 unreported treatments, 5 asthmatics, 4 late presenters, 3 cardiac, 1 pregnant and 1 patient ingested zinc phosphide with the anticholinesterase pesticide).

Randomization and allocation concealment:

The study was a single-blind, parallel group, placebo-controlled, randomized trial. Sixty patients were randomly divided into three equal groups I (conventional therapy plus saline), II (conventional therapy plus 2.5 mg albuterol) and III (conventional therapy plus 5 mg albuterol). A researcher who was not affiliated with the treatment or evaluation of the patients did randomization and sequence generation independently. Allocation of patients was concealed using sequentially numbered, opaque sealed envelopes method **(Doig et al., 2005).** The envelopes were impermeable to extreme light and the allocation sequence was hidden from the physician enrolling and evaluating the patients. The name and the participant's hospital admission number were written on the envelope to avoid subversion of the allocation sequence. Carbon paper transmitted the information inside the envelope onto the allocation card. Corresponding envelopes were only opened after all baseline evaluations were completed by the enrolled participants and it was time for the intervention to be allocated. Participants in the research and data analysts remained blind to the allocation.

Interventions:

All participants were administered saline or albuterol in addition to the conventional treatment according to the allocation sequence. Albuterol (Farcolin: each 20 ml contains 0.121 gm salbutamol sulphate, respirator solution, PHARCO Egypt) was used.

Group I (Control group) received 2 ml of normal saline (0.9 % sodium chloride) once by a face mask nebulizer for 10 minutes. It was given after patient resuscitation. All or some of the following is listed as traditional treatment: patient resuscitation, decontamination and antidote administration (atropine and/or obidoxime). Patient resuscitation including oxygen administration (3 L/min) via face mask, airway suctioning, insertion of oropharyngeal airway device and endotracheal intubation were indicated in some patients. Gastric lavage and a single (50 gm) dose of activated charcoal were performed in patients who presented within 2 hours after ingestion of anticholinesterase. Any contaminated material was discarded, and, if possible, dermal decontamination

using soap and water was carried out. Atropine (1 ampoule containing 1 mg of atropine per 1 ml) was administered as an intravenous (IV) bolus dose of 2 to 5 mg, repeated every 10 to 15 minutes until bronchial secretion was dry. Then, patients were given atropine injections intermittently as needed. Atropinization was maintained for 24 to 48 hours. Obidoxime (Toxogonin®; 1 ampoule containing 250 mg of 1 ml of obidoxime chloride manufactured by Merck, Darmstadt, Germany) was administered as a 250 mg loading dose of bolus IV, followed by 750 mg every 24 hours until at least 12 hours were no longer needed for atropine. **(Roberts and Aaron, 2007).**

Group II received a single 2.5 mg dose of albuterol (according to manufacturer's pamphlet, 0.5 ml farcolin respirator solution, diluted to 2 ml with normal saline). After patient resuscitation, it was inhaled by face mask nebulizer for 10 minutes until aerosol generation ceases. Standard treatment was provided as previously described.

Group III received a single 5 mg dose of albuterol (according to manufacturer's pamphlet, 1 ml farcolin respirator solution diluted to 2 ml with normal saline). After patient resuscitation, it was inhaled by face mask nebulizer for 10 minutes until aerosol generation ceases. Standard treatment was provided as previously described.

Either albuterol or normal saline were administered before or just immediately after the first dose of atropine. The patients were monitored for any negative effects due to drug therapy with thorough documentation. All patients have been prospectively monitored with regular measurements of their vitals by qualified physicians. The physicians were instructed that if during the aerosolization, the starting heart rate increased by more than 30 beats per minute or the patient developed sustained atrial or ventricular arrhythmias the aerosol must be stopped, and cardiologic consultation should be done. Patients were followed up until discharge from the hospital or death.

Statistical Analysis:

Sorting and analysis of data were performed using Statistical Package for Social Sciences version 21. Qualitative data were described using number and percent. Chi-square and Monte Carlo exact tests were used for analysis as appropriate. Distributions of quantitative data were checked by the Kolmogorov-Smirnov and Shapiro-Wilk tests for normality. Mean and standard deviation (SD) were normally distributed data, and analysis was conducted using variance analysis (ANOVA) and paired sample t-test. Median and interquartile range (IQ) were presented as non-normally distributed data, and analysis was performed using Kruskal-Wallis H test. $P < 0.05$ was adopted as the level of significance.

3. Results

There were no statistically substantial differences among the three groups studied in terms of patient demographics, exposure characteristics, clinical characteristics or routine laboratory investigations on admission **(Table 1)**.

Table 1. Baseline demographic and clinical characteristics at presentation.

	Group I (n=20)		Group II (n=20)		Group III (n=20)	
Age (years), Median (IQR)	22 (18-45)		38.5 (21-55)		32.5 (20.5-51.5)	
Gender (male), n (%)	10	50.0	10	50.0	12	60.0
Mode of poisoning						
Accidental, n (%)	10	50.0	9	45.0	9	45.0
Suicidal, n (%)	10	50.0	11	55.0	11	55.0
Vomiting, n (%)	19	95.0	18	90.0	19	95.0
Abdominal colic, n (%)	18	90.0	19	95.0	15	75.0
Miosis, n (%)	16	80.0	16	80.0	17	85.0
Sweating, n (%)	11	55.0	12	60.0	9	45.0
Bronchospasm, n (%)	8	40.0	2	10.0	3	15.0
Crepitation, n (%)	8	40.0	2	10.0	2	10.0
Bradycardia, n (%)	1	5.0	1	5.0	0	0.0
Hypotonia and fasciculations, n (%)	11	55.0	7	35.0	5	25.0
Coma, n (%)	4	20.0	2	10.0	2	10.0
Severity, n (%)						
Mild	10	50.0	13	65.0	14	70.0
Moderate	6	30.0	5	25.0	3	15.0
Severe	9	15.0	4	20.0	2	10.0
Delay time (hours), Median (IQR)	2.75 (2-3.5)		2.5 (1.75-5)		4 (2-6.04)	

n: number; IQR: interquartile range.

On admission, the mean oxygen saturations by pulse oximeter were **92.10%, 94.10%** and **95.05%** in groups I, II and III respectively. Meanwhile, the mean values of oxygen saturation by arterial blood gas (ABG) analysis were **94.2%, 95.3%** and **97.2%** in groups I, II and III respectively. Before treatment, we found no significant differences between the studied groups regarding the mean oxygen saturation by pulse oximeter or ABG analysis **(Table 2)**.

After albuterol aerosolization, the mean values of oxygen saturation by pulse oximeter were **96.4%, 94.9%** and **95.5%** in groups I, II and III respectively, whereas those recorded by ABG analysis were **95.8%, 94.3%** and **96.5%** in groups I, II and III respectively **(Table 2)**. No significant differences in oxygen saturation by either pulse oximeter or ABG could be detected between the studied groups **(P > 0.05).**

In each of groups I and III, **10%** of patients died, while only **5%** of patients died in group II. Patients who required intubation were **20%, 5%** and **10%** in groups I, II and III respectively. Only in groups I and III, **10%** of patients were admitted to the ICU and required mechanical ventilation, but no patient in group II required ICU admission **(Table 3)**. We found no significant differences between the studied groups regarding mortality, intubation, or the need for ICU admission and mechanical ventilation **(P > 0.05)**.

The duration of hospital stay ranged from **6 to 360** hours, **4 to 72** hours and **6 to 144** hours in groups I, II and III respectively **(Table 3), with a statistically** significant reduction in groups II and III compared to the control group. The total dose of atropine ranged from **1 to 30 mg**, **0 to 10 mg** and **1 to 12 mg** in groups I, II and III respectively, with no substantial differences among the studied groups **(P > 0.05)**.

Table 2. Oxygen saturation by pulse oximeter and ABG analysis in the studied groups before and after albuterol aerosolization.

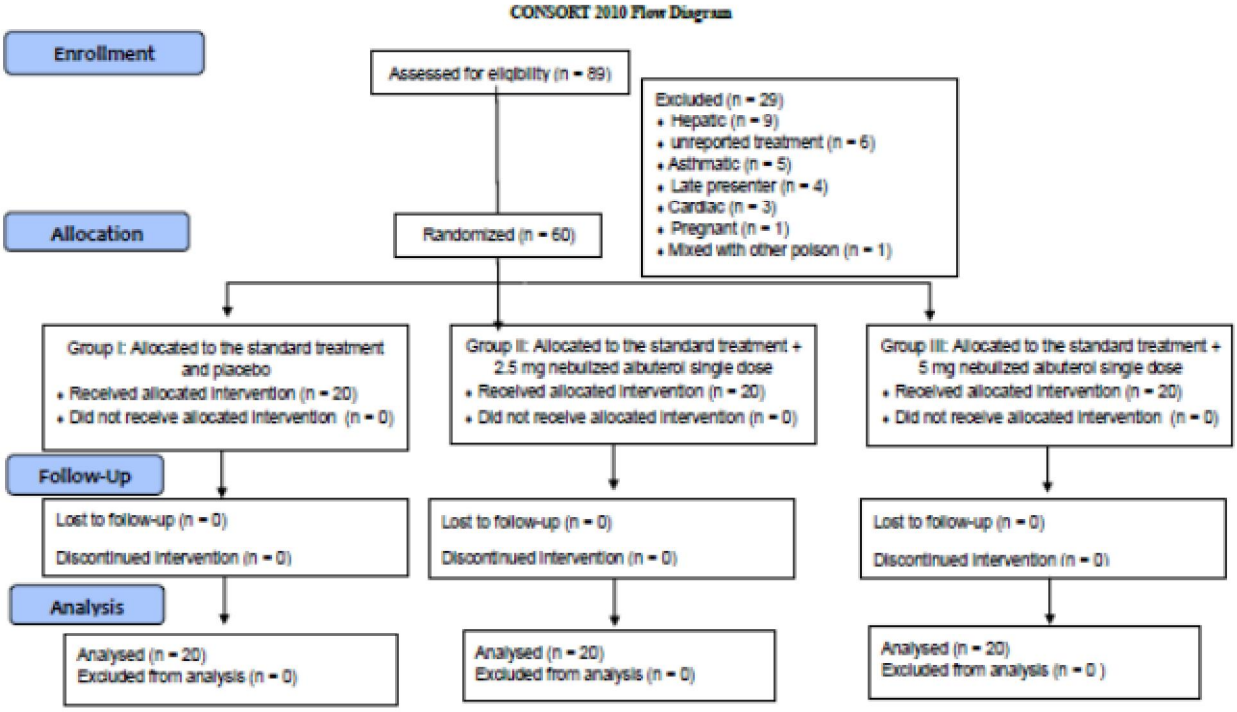
Parameters Before albuterol	Group I (n=20)	Group II (n=20)	Group III (n=20)	F	P value
Oxygen saturation (%) by pulse oximeter, Mean ± SD	92.10 ± 12.28	94.10 ± 12.15	95.05± 5.25	0.417	0.661
Oxygen saturation (%) By ABG analysis, Mean ± SD	94.2 ± 9.4	95.3 ± 6.5	97.2 ± 1.7	1.044	0.359
Parameters After albuterol	Group I (n=20)	Group II (n=20)	Group III (n=20)	F	P value
Oxygen saturation (%) by pulse oximeter, Mean ± SD	96.40 ± 6.67	94.90 ± 8.21	95.50 ± 6.40	0.224	0.800
Oxygen saturation (%) by ABG analysis, Mean ± SD	95.8 ± 9.8	94.3 ± 9.2	96.5 ± 2.2	0.401	0.671

n: number; SD: standard deviation; ABG: arterial blood gas.

Table 3. Secondary outcome in the groups studied.

	Group I (n=20)		Group II (n=20)		Group III (n=20)		χ^2	P (MC)
	n	%	n	%	n	%		
Mortality	2	10.0	1	5.0	2	10.0	0.436	0.567
Intubation	4	20.0	1	5.0	2	10.0	2.264	0.317
ICU admission & mechanical ventilation	2	10.0	0	0.0	2	10.0	2.143	0.467
	Group I (n=20)		Group II (n=20)		Group III (n=20)		Kruskal-Wallis H	P
Atropine (mg), Median (IQR)	4 (2-13)		2 (2-4)		2 (2-5)		4.301	0.116
Hospital stay (hours), Median (IQR)	36 (12-48)		12 (7.5-22.5)		12 (8-12)		8.240	0.016*
Subgroups comparison by Mann Whitney	I & II 0.013*		I & III 0.018*		II & III 0.724			

n: number; ICU: intensive care unit; IQR: interquartile range. *Significant



4. Discussion

In the current study, there were no statistically substantial differences among the three groups studied in terms of patient demographics, exposure characteristics, clinical manifestations or routine laboratory investigations on admission, which could reflect faultless randomization performed in this study using the sequentially numbered opaque sealed envelopes method **(Doig et al., 2005).** The purpose of this research was to assess the safety of albuterol as an adjuvant in the treatment of patients with acute anticholinesterase pesticide poisoning. For the sake of safety, healthcare personnel were instructed to stop aerosolization and to consult the cardiologist when heart rate increased by more than 30 beats per minute or the patient developed sustained atrial or ventricular arrhythmias. None of the recruited patients required cessation of aerosolization or cardiology consultation. Although hypokalemia is one of the reported adverse effects of albuterol, serum potassium levels of our patients remain within normal ranges after aerosolized albuterol administration **(Sears, 2002; Sree and Rao, 2011).** Single dose of aerosolized albuterol was safe and shows no changes in heart rate or potassium level.

Another objective of this study was to evaluate efficacy of albuterol as an adjuvant therapy in acute anticholinesterase pesticide poisoning. For this goal, the mean peripheral blood oxygen saturations by pulse oximetry and ABG analysis were compared after albuterol aerosolization in the studied groups. Albuterol can give advantages over atropine by raising the rate of fluid removal from alveoli by activating epithelial sodium channel pumps and by treating bronchoconstriction **(Berthiaume and Matthay, 2007; Takemura et al., 2013).** Considering the former facts, it is prophesied for albuterol to improve hypoxia and oxygenation **(Cazzola et al., 2013)**. However, we found no significant differences between the studied groups regarding oxygen saturation by either pulse oximetry or ABG analysis after treatment. Likewise, a recent pilot study revealed no apparent evidence of benefit from administration of nebulized salbutamol **(Chowdhury et al., 2018).**

However, in an animal study, **Chávez and colleagues (2007)** reported an immediate benefit of intraperitoneal injection of salbutamol in guinea pigs with parathion poisoning.

Chowdhury et al., (2018) suggested that oxygen saturation did not rise because alveoli were filled with fluid in aerosolized albuterol, that no sufficient albuterol reach the epithelial cells of bronchioles and alveoli, but it was dissolved in fluid filling the lungs. It is likely that Albuterol may have treated bronchospasm effectively and that atropine has persisted for bronchorhea but there was no differentiation between bronchospasm and bronchorrhea in both current study and **Chowdhury et al., (2018).** So, it is supposed that injected albuterol might reach the bronchioles and alveoli through blood

and raise oxygen saturation but more expected adverse effect to occur.

Endotracheal intubations were indicated for four patients in group I. Two patients survived without mechanical ventilation. Two patients were admitted to ICU with mechanical ventilation then died (10%). One patient (5%) in group II was intubated and died during resuscitation before ICU admission. In group III, two intubated patients were admitted to ICU with mechanical ventilation then died (10%). No significant differences could be detected in the three studied groups regarding the need for intubation and mechanical ventilation or the mortality rate. Other researchers **(Elgazzar, 2012; Patil, 2016; El-Gendy et al., 2017; Jamal et al., 2017; Chuang et al., 2018)** reported comparable results; the study subjects required ICU admission and mechanical ventilation with more or less comparable mortality rate, which ranged from 12 to 27.6% in different studies **(Rabha et al., 2017).**

In the present study, the median dose of required atropine was 4 mg in group I and 2 mg in group II and III. Much higher doses were reported by **Chowdhury et al. (2018)** for full atropinization of the patients. This variation in atropine dose might be attributed to the difference in the end-point for atropinization in both studies. In the present research, there was no substantial difference among the groups studied with respect to the total dose of atropine administered, which coincides with the final conclusion of **Chowdhury et al., (2018).**

The median duration of hospital stay in albuterol-treated patients was significantly lower compared to the control group. This finding was parallel to data gathered by **Ghonem et al., (2015), King and Aaron (2015), Rajapakse (2017)** and **Brvar et al., (2018)**. They reported that most of the patients who stayed more than 5 days required respiratory support. Meanwhile, in the study herein; two patients in group I and III needed intubations and mechanical ventilation. There are many factors that could affect the duration of hospital stay after poisoning including the presence of accompanying diseases or complications (cardiovascular collapse, respiratory failure, aspiration pneumonia and septic shock) **(Baydin et al., 2014; Leão et al., 2015).** Moreover, **El-Naggar et al., (2009)**, **Banerjee et al., (2014)** and **Acikalin et al., (2017)** stated that the developmental levels of the country could affect the duration of hospitalization after poisoning. They reported that, the length of hospital stays varied from 2-7 days in developed countries to 3-12 days in developing countries. Furthermore, the longer hospital stay after poisoning was possibly due to the fact that most suicide attempts typically ingest large quantities of the pesticide and a high percentage of them need mechanical ventilation and due to the potential complications that may occur in badly poisoned patients treated in the ICUs **(Liang and Zhang, 2015; Ohbe et al., 2018).** On the basis of the current study findings, it could be concluded that albuterol could not improve resuscitation of patients with acute anticholinesterase pesticides poisoning.

In conclusion, as no serious adverse effects have been reported with its use, albuterol aerosolization can safely be used as an adjuvant to traditional treatment of acute anticholinesterase pesticides poisoning. Although it did not improve resuscitation of patients with acute anticholinesterase pesticides poisoning and it had no significant effect on atropine requirements, its use can provide an additional advantage by reducing the duration of hospitalization. There is a need for more studies on a greater number of patients before a conclusion can be drawn about their effectiveness in these patients.

This was a pilot study, and the findings of which, based on sample size estimation, and could pave the way for larger trials recruiting patients. Unfortunately, the recruited cases were mostly mild or moderate with normal baseline oxygenation during the period of the study, which could compromise assessment of the primary outcome, which was oxygenation that requires severe poisoning cases.

Potential Conflict of Interest:

The authors announce that they do not have a conflict of interest.

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