Research Article

Comparison of Efficacy and safety of Atropine and Glycopyrrolate in the Treatment of Acute Organophosphorus Poisoning in Minia Poison Control Center.

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Abstract
Objectives: To evaluate and compare the effectiveness of atropine alone and the combined therapy of atropine and glycopyrrolate in treatment of patients with acute organophosphate poisoning (OP). **Patients and methods:** Forty patients with history of OP poisoning were included in the study within the period from 1st of March 2017 to 28th of February 2018. The study is a prospective randomized controlled trial that was carried out on patients admitted to Poison Control Center of Minia University Hospital. These patients were divided in to two groups of 20 patients each. Group I was treated with atropine alone while group II was treated with atropine in combination with glycopyrrolate. **Results:** The majority of the patients were females (55%). The outcomes of these two groups were analyzed and compared including percentage of mortality, percentage of recovery, duration of hospital stay, need for mechanical ventilation, incidence of intermediate syndrome and percentage of adverse reactions.The percentage of recovery and percentage of mortality were the same between the 2 groups with p=1. However, there was reduction in hospitalization days and incidence of adverse drug reactions of the used drugs in (group II) when compared to (group I) . **Conclusion:** The study suggests that treatment with combined therapy of atropine and glycopyrrolate was more effective than therapy with atropine alone regarding the reduction in the duration of hospital stay and incidence of adverse reactions of the used drugs.

Key words: organophosphorus poisoning, atropine, glycopyrrolate.

Introduction
Organophosphorus (OP) compounds are largely used as pesticides worldwide. Their easy availability and lack of knowledge about their seriousness resulting increase in accidental and suicidal poisoning. According to a World Health Organization (WHO) report, every year three million cases of poisonings with insecticides occur worldwide resulting in approximately 200,000 deaths.(1)

OP insecticides are irreversible acetyl cholinesterase (AchE) enzyme inhibitors. The clinical manifestations are caused by excess acetylcholine (Ach) at the muscarinic receptors, nicotinic receptors and in CNS. Manifestations of OP poisoning occur in three phases: Acute cholinergic crisis (first 48 hours), intermediate syndrome (IMS) (24-96 hours after poisoning) and OP induced delayed polyneuropathy. (2)

Anticholinergics are competitive antagonist to Ach and reverse all muscarinic effects both in CNS and peripheral nervous system. Glycopyrrolate is a synthetic quaternary amine with peripheral effects similar to those of atropine. It is longer acting drug and doesn't cross the blood brain barrier and therefore, it has lesser effect on CNS. (3)

Aim of the work
The aim of this study is to evaluate and compare the effectiveness of atropine alone and the combined therapy of atropine and glycolpyrrolate in treatment of patients with acute organophosphate poisoning (OP).

Patients and method
The study is a prospective randomized controlled trial that was carried out on patients admitted to Poison Control Center of Minia University Hospital. Forty patients were collected within the period from 1st of March 2017 to 28th of February 2018. Written informed consent was obtained from relatives of all patients.

Patients

Forty patients with acute OP toxicity of both sexes aging from 20 to 60 years were included in the study. Diagnosis was made by history of exposure to OP compound, clinical manifesttations and by measuring pseudocholinesterase enzyme level. These patients were divided in to two groups of 20 patients each. Group I was treated with atropine alone while group II was treated with atropine in combination with glycopyrrolate.

The cases included in the study were chosen as they have no history of previous diseases including hepatic, renal, cardiovascular, respiratory or CNS illness. Patients were excluded from the study if they had concomitant ingestion of other drugs in a suicidal attempt. Patients with trauma, patients with drug or alcohol abuse and patients presented to emergency department 24 hours after OP exposure were also excluded.

Atropine was given either as a continuous infusion or intermittent dosing (the end-point of atropinisation was drying of secretions, flushing, tachycardia and mydriasis). Continuous infusion was started as 0.02-0.08 mg/kg per hour and intermittent dosing was performed using atropine in the doses of 2 mg IV and then 2 mg after every 5-10 minutes till the signs of atropinisation appeared. After achieving atropinisation, the interval between the doses was increased so as to maintain adequate atropinisation. Atropine was then slowly withdrawn over a period of 3-5 days.
Glycopyrrolate was given at a dose of 7.5 mg infused in 200 ml saline till the desired effects of dry mucous membranes. It has also been given at a dose of 0.2mg IM and repeated every 6 hours if required.

Outcome

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

Complications

All patients observed for the complications developed during hospital stay e.g intermediate syndrome, respiratory tract infection, need for mechanical ventilation, CNS toxicity and other adverse effects.

Statistical analysis

Statistical analysis was performed using the SPSS software for Windows v. 20 (SPSS Inc., Chicago, IL). For comparing quantitative data, Kruskal Wallis test and Mann Whitney tests were performed. For comparing qualitative data, Fisher exact test was performed. A probability value ($p=0.05$) was considered statistically significant.

Results

During one year study forty patients with acute OP poisoning were evaluated. The majority of the patients were females (55%). Group I consisted of 20 patients with the mean age of 25.3±6.2 mostly from rural areas (80%). Group II also consisted of 20 patients having mean age of 34.3±13.6 and most of them belonged to rural areas (70%). There was no significant difference in demographic data and time of arrival between the 2 groups. As regard percentage of recovery and percentage of mortality there was no significant difference in patients treated with atropine alone and patients treated with a combined therapy of atropine and glycopyrrolate ($P=1$) However, there was reduction in hospitalization days in group II when compared to group I (Table I).

There was no significant difference in need for mechanical ventilation and incidence of intermediate syndrome between the 2 groups with $P=1$ (Table II). It was found that the combined treatment of atropine with glycolpyrrolate reduces dose of atropine with $P=0.278$ (Table III) with subsequent decrease in atropine adverse effects. Incidence of confusion, hallucinations and tachyarrythmias were significantly more in group I when compared with group II with $P<0.001$ (Table IV).

Table (I): Outcome data between the study groups.

		Group I	Group II	P value
		N=20	N=20	
Hospital stay	*Median* *IQR*	5 (4-6)	4 (3-5)	0.066
Outcome	*Recovery* *Died*	18(90%) 2(10%)	18(90%) 2(10%)	1

- ***IQR: interquartile range***
- ***Significant level at P value < 0.05***

Table (II): Complications between the study groups**.**

		Group I	Group II	P value
		N=20	N=20	
Ventilation Required	*No* *Yes*	16(80%) 4(20%)	16(80%) 4(20%)	1
intermediate Syndrome	*No* *Yes*	18(90%) 2(10%)	18(90%) 2(10%)	1
Respiratory tract infection	*No* *Yes*	14(70%) 6(30%)	16(80%) 4(20%)	0.465

****: Significant level at P value < 0.05.***

Table (III): Doses of atropine used in treatment between the study groups.

		Group I	Group II	P value
		N=20	N=20	
Atropine	*Median* *IQR*	55.5 (42-90)	49.5 (31-70)	*0.278*

- ***IQR: interquartile range***
- ***Significant level at P value < 0.05***

Table (IV): Adverse effects of the drugs between the study groups:

		Group I	Group II	P value
		N=20	N=20	
Confusion	No Yes	2(10%) 18(90%)	14(70%) 6(30%)	***<0.001****
Hallucinations	No Yes	2(10%) 18(90%)	14(70%) 6(30%)	***<0.001****
Tachyarrythmias	No Yes	0(0%) 20(100%)	10(50%) 10(50%)	***<0.001****
Fever	No Yes	6(30%) 14(70%)	12(60%) 8(40%)	***0.057***

****: Significant level at P value < 0.05***

Discussion

Organophosphates are one of the most common causes of poisoning especially in developing countries with mortality rates reaching up to 10-20%. So early diagnosis and appropriate treatment is often lifesaving.[4]

The antidotes of OP poisoning are anticholinergic drugs such as atropine and glycopyrrolate, atropine being the older of the two medications. Muscarinic effects of OP poisoning are reversed by these drugs. Conventional treatment with atropine may lead to CNS toxicity, although control of secretions may still be inadequate.[5]

Glycopyrrolate (glycopyrronium bromide) is a quaternary ammonium with anti-muscarinic activity and peripheral actions like to that of atropine, however glycopyrrolate is twice as potent as atropine for peripheral effects. It can be safely use during pregnancy as it doesn't cross the placental barrier. Glycopyrrolate can't pass through the BBB so it does not have any detectable central anti-cholinergic effects.[6]

Atropine is universally accepted antidote most frequently used for the patients of OP poisoning. Some of the previous studies revealed that atropine treatment is effective, however it often causes agitation, hallucinations and confusion. Other effects of atropine treatment are hyperthermia, bowel ileus, urine retention and tachycardia, however the use of combined therapy of atropine and glycopyrrolate improves tachycardia with no changes in body temperature and CNS stimulation hence glycopyrrolate can't pass through the BBB.[7] Out of all the forty patients included in the study confusion and hallucinations were seen in 24 (60%) cases and 18 cases of them were from Group I. Incidence of confusion and hallucinations is significantly more Group I when compared to group II with P<0.001.

So it was found that the combined treatment of atropine with glycopyrrolate reduces dose of atropine with P=0.278 and also reduces the central adverse effects associated with it improving the quality of treatment.

Other clinical manifestations seen were intermediate syndrome in 2 (10%) case in group I and 2 (10%) cases in group II. Respiratory infection was seen in 10 patients, 6 (30%) cases of them from group I explaining that combined therapy of atropine and glycopyrrolate provides better control on chest secretions. Out of 40 cases 36 patients recovered and 4 patients died. Incidence of mortality is not statistically significant between both groups.

Our study found that there was no significant difference in mortality between patients treated with atropine alone and patients received combined therapy of atropine and glycolpyrrolate, however there was reduction in the duration of hospital stay and incidence of adverse reactions especially CNS toxicity associated with atropine treatment. This agreed with results of a study done by Khalid et al.,. (2017) and Anju et al., (2011) whom study revealed that both the groups had the same efficacy but atropine showed a very distinct CNS toxicity, [3, 7] but it was in contrast with Arendse et al., (2009) who had found that the infusion of a combination of atropine and glycopyrrolate had a lower mortality rate but the occurrence of atropine toxicity was unchanged between the (**2 groups)**. [8]

Conclusion

The study suggests that treatment with combined therapy of atropine and glycopyrrolate was more effective than therapy with atropine alone regarding the reduction in the duration of hospital stay and incidence of adverse reactions of the used drugs.

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Conflict of Interest:- Nil.

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