Original Paper

Combined Atropine and Glycopyrrolate in Organophosphate Poisoning: The Right Solution for an Old Problem?*

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ABSTRACT

Unintentional and intentional organophosphate (OP) poisonings continue to be a significant cause of morbidity and mortality in India. Conventional treatment with atropine may lead to CNS toxicity, although control of secretions may still be inadequate. The aim of this study was to assess the effectiveness of atropine along with glycopyrrolate in organophosphate poisonings.

A prospective randomized double-blinded, placebo-controlled trial was done in an emergency department of a university hospital. Patients who consumed OP compounds were included. Pregnant women, hypothermic adults, mixed poisonings, and concomitant alcoholic intoxications were excluded. The subjects received either atropine and glycopyrrolate, or atropine and a matching placebo as a bolus through a peripheral IV line. All other aspects of treatment were carried out as per standard procedure.

Seventy six victims were involved during a six month period, 38 belonging to the study group, and the remaining to the control group. There were no significant differences in demographic data, time of arrival, or time of starting treatment. Results revealed that the duration on ventilator was reduced in 60% of the study group as compared to the control group, reduction in the duration of ICU stay occurred in 20% of control group, while it was 72% of the study group. CNS toxicity occurred in 40% of control group, and 2% of study group. Intermediate syndrome developed in 8 of 38 subjects in the control group, and 1 of 38 in the study group. Development of respiratory tract infection was seen in 12 % of the control group, while it occurred in only 5% of the study group. Addition of glycopyrrolate appears to be a promising new intervention in the management of OP poisoning.

Key words: Organophosphate poisoning, Atropine, Glycopyrrolate

Introduction

Acute organophosphate (OP) poisoning is a significant cause of morbidity and mortality in developing countries including India. Although no exact estimates are available from India, hospital based studies suggest that it is the commonest poisoning in India with nearly half of the toxicologic admissions to the 'emergency room' being due to these compounds.

Most of these poisonings unfortunately result from suicidal intent.[1-5] According to the WHO, one million serious accidental, and two million suicidal poisonings due to insecticides occur worldwide, every year, of which 200,000 die, and most of these deaths occur in developing countries.[6]

The anticholinesterase organophosphate (OP) compounds are the organic derivatives of phosphorus containing acids. In India, they are freely available in shops, and are widely used as insecticides in agriculture, and in homes.

The death rate from OP poisoning has stabilized, and unfortunately not further decreased during the last few

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years in most countries around the world. Currently, atropine with oximes constitutes the mainstay of therapy in patients with acute OP poisoning. Conventional treatment with atropine often leads to CNS toxicity, while control of secretions may still be inadequate.

In a previous study,[10] we found that high-dose diphenhydramine, a CNS and peripherally-acting antihistamine and anticholinergic, protected against mortality from an otherwise lethal OP exposure. But it has a high frequency of side effects, and is thus not very suitable in routine practice. There is, therefore, a need for development of newer modalities of treatment.

A few studies are available on glycopyrrolate in organophosphate poisoning as a helpful agent to decrease morbidity and mortality.[12-14] However, to date, no detailed, controlled clinical study is available on the efficacy of glycopyrrolate in organophosphate poisoning, in spite of favourable evidence to this effect.

Materials and Methods

Study Design

A prospective, randomized, double-blinded placebo-controlled trial was done in the emergency department of a University hospital. The Institutional Ethics Committee of the University approved this study.

Eligibility Criteria

Patients between 4 to 60 years of age with acute OP poisoning who presented to the emergency department were included in the study. They were considered for the study only if they had been previously diagnosed or treated for OP poisoning, or the history and examination findings indicated OP exposure.

Pregnant women, hypothermic patients, mixed poisoning, OP poisoning in combination with alcohol, and patients who did not consent to the study were excluded.

Initial Management and Assessment

On arrival to the emergency room, the patients' airway, breathing and circulation problems were first addressed. A detailed history was then taken and clinical examination was performed to rule out any associated illness. Informed consent was obtained from the patients' relatives or attendants. Pulse, blood pressure, respiratory rate, oxygen saturation, and presence of fasciculations, loose stools and pupillary signs were recorded. Initial serum cholinesterase level was assayed as a diagnostic test.

Study Protocol

After enrolment, patients were randomly allocated to one of two groups. Random number tables were used for the randomizations. The individual random numbers were kept in separate envelopes so that secrecy could be maintained until the patient was included in the assigned group. The medications were prepared by a doctor who was not part of the study, and were labeled as **A** (combination of atropine and glycopyrrolate), or **B** (atropine only). Thus, the patients and investigators were blinded to the nature of the treatment given to a patient.

Patients with OP poisoning received either atropine and glycopyrrolate, or atropine and matching placebo as a bolus. All patients received multidose activated charcoal, and other decontamination procedures as per standard procedure.[16,17] The medications were constituted as follows:

- **Group A** - 3 ml solution consisting of 1 ml of atropine solution (1 mg) + 2 ml of glycopyrrolate (0.4 mg)
- **Group B** - 3 ml solution consisting of 1 ml of atropine solution (1 mg) + 2 ml of water

The drugs were administered through a peripheral IV line over a period of three to five minutes, and repeated until secretions diminished. As mentioned above, all the patients were also administered pralidoxime at a flow rate of 500mg/hr.[18,19]

Assessment of Response

All clinical parameters as well as decrease in secretions were recorded. The primary objective was to determine whether the decrease in secretions by the two interventions would be significantly different in the two study groups. Any side effects noted by the patient or physicians were recorded.

Statistical Methods

At the time this study was being planned, only one published study could be located comparing the utility of atropine plus glycopyrrolate versus atropine alone. Hence, to derive meaningful and valid results, it was decided to include at least 100 patients in the study. No power calculation was performed before conducting the study.

Descriptive statistical parameters (mean and standard deviation) were calculated for each quantitative variable. Between different groups, comparisons of qualitative data were done using χ^2 tests (with Yates' correction). As

normality assumption and equality of variance were satisfied for most of the quantitative variables, in-group comparisons of means were done using unpaired *t* test/*z* test. Otherwise, wherever necessary, Wilcoxon's rank sum test was used. As a comparison of the baseline data of the two study groups did not reveal any significant difference ($p>0.05$), the results at a given point of time between two groups were also compared with the same methods to assess the comparative changes. For within-group comparison of quantitative data over time, the two-way analysis of variance (ANOVA) was done. In the case of significant results, Turkey's multiple range tests were used to identify the pairs of observations with significantly different results. The results were considered significant at the 5% level ($p<0.05$).

Results

Figure 1 shows the enrolment and allocation of the patients to the two study groups. Of 100 patients with acute OP poisoning, 24 patients were excluded. Thus, a total of 76 patients were recruited and randomly allocated to the two study groups, with 38 patients in each group. The groups did not differ significantly as regards their age, demographic data, time of arrival and time to start treatment (**Table 1**). The baseline pulse, blood pressure, respiratory rate, and SPO_2 of the two groups were not significantly different.

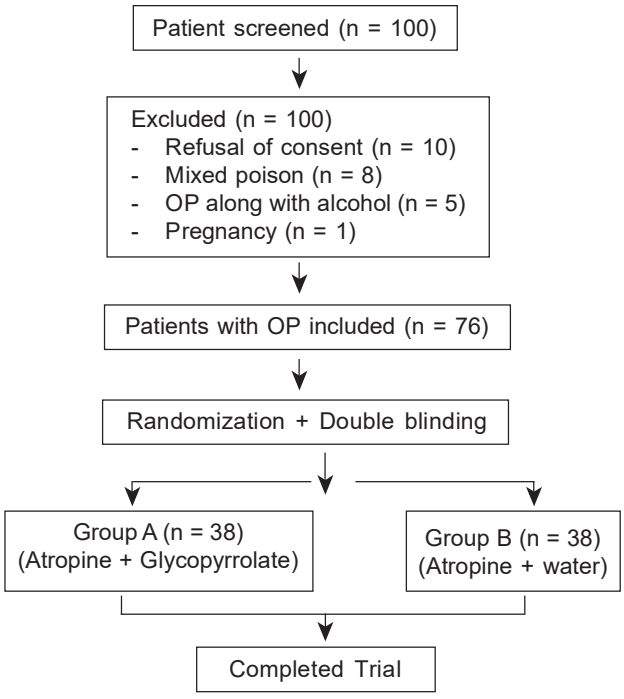

Fig. 1 Flow Chart of Random Allocation

Duration on ventilator was reduced in 70% (22 patients) of study group compared to control group. Mean duration of ICU stay was 4.5 days in study group compared to control group. CNS toxicity occurred in 40% of control group, and 2% of study group. Intermediate syndrome developed in 8 of 38 subjects in control group, and 1 of 38 in the study group. Development of respiratory tract problems occurred in 12% of control group, and 5 % of study group.

Discussion

Despite extensive agricultural use of these chemicals, and proliferation of research and production during wartime over the last 70 years, the exact mechanism by which they exert their ultimate lethality is subject to debate. However, three major theories have evolved over a period of time: 1) OP compounds primarily cause respiratory insufficiency through pulmonary cholinergic effects, specifically bronchoconstriction and copious bronchial secretions[3,4]; 2) Dominant nicotinic effects lead to respiratory muscle failure[5-7]; and 3) Central nervous system (CNS) cholinergic effects ultimately cause mortality by inhibiting central respiratory centers.[8,9]

The results of this study show that combination of atropine and glycopyrrolate has a more significant effect as compared to that of atropine alone. Although atropine injection remains the standard treatment for acute OP poisoning, other anticholinergic agents have also been suggested and used in this setting. Bardin and Eiden[11] found that glycopyrrolate, a highly polar quaternary ammonium compound that does not cross the blood-brain barrier, was equally effective in treating OP poisoning when compared with atropine, in patients brought to hospital.

Early death due to severe, acute OP poisoning appears to be, at least in part, due to a centrally mediated process. This is supported by the finding that pretreatment with atropine and diphenhydramine anticholinergic agents that cross the blood brain barrier were highly protective against dichlorvos poisoning.

Our study, the largest to date, showed significant benefit when glycopyrrolate was added to conventional treatment of OP poisoning. As the most important aspect of treatment of OP poisoning is to reduce the rate of hospitalization, future studies should be performed (with calculation of sample size) based on an event rate (hospitalization rate) in the control group of 20% and a power of 0.80. The reduction in the event rate in the treatment group

Table 1 Baseline Characteristics of the Patients in Two Study Groups

Parameters	Group A	Group B	p Value
1. Age (Years)	22.26	24.21	0.171
2. Men:Women	13.25	17:21	0.307
3. Time of arrival (min)	80.66	82.72	0.237
4. Time of starting treatment (min)	8.26	7.96	0.746
5. Received medication before arriving at hospital	8	10	0.110
6. Intubation	6	24	0.006

could be kept as 5% as this reduction will translate into a huge benefit. The large number of patients required warrants a multicentre study to unequivocally answer the question as to whether addition of glycopyrrolate is beneficial in patients with acute OP poisoning.

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