ORIGINAL ARTICLE

A Study on Comparative Evaluation of Add-on Pralidoxime Therapy over Atropine in the Management of Organophosphorus Poisoning in a Tertiary Care Hospital

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Abstract

Since its discovery in 1956, pralidoxime has been used in the management of organophosphorus poisoning (OP) in addition to atropine. While efficacy of atropine is proved beyond doubt, clinical experience with pralidoxime has led to widespread controversies about its efficacy in treatment of OP poisoning. In this study we compared the efficacy of add-on pralidoxime therapy over therapy with atropine alone in OP poisoning. In this open-label, parallel-group clinical study, patients of OP poisoning, presenting in emergency department of a tertiary care district hospital, were randomly allocated to receive either atropine or atropine plus pralidoxime. The parameters used for efficacy assessment were: mortality rate, requirement of ventilator and duration of stay in the hospital in either of the two treatment arms.The mortality rate, requirement of ventilator and duration of hospital stay in the two treatment arms failed to show any statistically significant difference. Add-on pralidoxime therapy over atropine monotherapy, does not offer any significant advantage in the management of OP poisoning.

Key Words

Organophosphorus, Pesticides, Poisoning, Pralidoxime, Atropine

Introduction

Poisoning with organophosphorus compounds (OP) is a common problem throughout the world particularly in developing countries. According to an estimate by World Health Organization (WHO), one million serious unintentional poisoning occur every year and an additional two million people are hospitalized for suicide attempts with pesticides (1). India is a predominantly agrarian country where pesticides are routinely used for farming. Data on the pattern of poisoning in North India accumulated at National Poison Information Center (NPIC) located in All India Institute of Medical Sciences, New Delhi suggest that suicidal poisoning with household agents (OPs, carbamates, pyrethrinoids etc) is the most common modality of poisoning (2). Recent data from National crime bureau of India shows suicide by consumption of pesticides account for 19.4% and 19.7% of all cases of suicidal poisoning in the year 2006 and 2007 respectively (3). OP compounds inhibit acetylcholinesterase resulting in accumulation of acetylcholine (Ach) and overstimulation of cholinergic synapses. Patients die mostly from respiratory failure and lung injury although there is variability in the clinical symptoms and signs depending on nature of compounds, amount consumed, severity, time gap between exposure and presentation in the hospital (4).Standard treatment involves resuscitation, administration of the anti-muscarinic

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agent atropine, an acetylcholinesterase reactivator such as pralidoxime, and assisted ventilation if necessary. 5 While the efficacy of atropine has been proved beyond doubt, clinical experience with pralidoxime has lead to widespread doubt about its efficacy in treatment of OP poisoning (6). Even Cochrane reviews concluded that current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute organophosphorus pesticide poisoning (7). The objective of present study was to evaluate the relative advantage of add-on pralidoxime therapy over treatment with parenteral atropine sulphate alone in OP poisoning.

Materials and Methods

Study Area: A tertiary care district hospital in West Bengal.*Study Period:*A period of 18 months commencing from January 2008.*Study Design:* Prospective, parallel-design, randomized, open-label clinical trial with two arms - one receiving atropine alone *(Group 1)* and the other, add-on pralidoxime therapy over atropine *(Group 2)*.

Inclusion and exclusion criteria: All consecutive patients, presenting in the emergency department of the hospital during the study period, with history and clinical evidence of OP poisoning were screened for eligibility for enrolment. Only those patients of age more than 12 years and of either sex, who presented within 24 hours following exposure to OP compounds, and had taken an OP compound other than a carbamate, were considered eligible for the study. Besides, patients with pregnancy were not randomized as follow up of such patients were difficult as they received care in different in-patients ward under the Obstetric Unit. All eligible patients were put to a severity scoring scale - Peradeniya Organophosphorus Poisoning (POP) scale (8) , the details of which is given below. They were randomized to either group irrespective of their severity grades (*Fig-1*).

POP Scale:

1. Pupil size: >2 mm (0), <2 mm (1), Pinpoint (2)
2. Respiratory rate: <20/ minute (0), >20/ minute (1), >20/ minute and central cyanosis (2)
3. Heart rate: >60/ minute (0), 41-60/ minute (1), <40/ minute (2)
4. Fasciculation: None (0), Present, generalized or continuous (1), Present, generalized & continuous (2)
5. Level of consciousness: Conscious and rationale (0), Impaired response to verbal commands (1), No response to verbal commands (2)
6. Seizures: Absent (0), Present (1)

Ethics: The study plan was duly approved by institutional ethics committee, (BMC/PG/541). Informed consent was obtained from eligible patients or the legally authorized representatives, if patient was unconscious.

Study Procedure: Patients on presentation were evaluated clinically, resuscitated for airway, breathing and circulation maintaining, and were randomized into one or the other study arms to receive either atropine alone or pralidoxime added-on atropine. The random allocation sequence was generated by computer under the supervision of the study statistician who had no role either in patient recruitment or treatment. The treating physician had no role in deciding which study arm a given patient was assigned to.

Group 1: Patients received atropine given in the dose of 2 mg i.v. stat and then 2 mg i.v. every 5-10 minutes till the signs of atropinization appeared (9). Criteria used for assessing adequate atropinization included: heart rate >80/

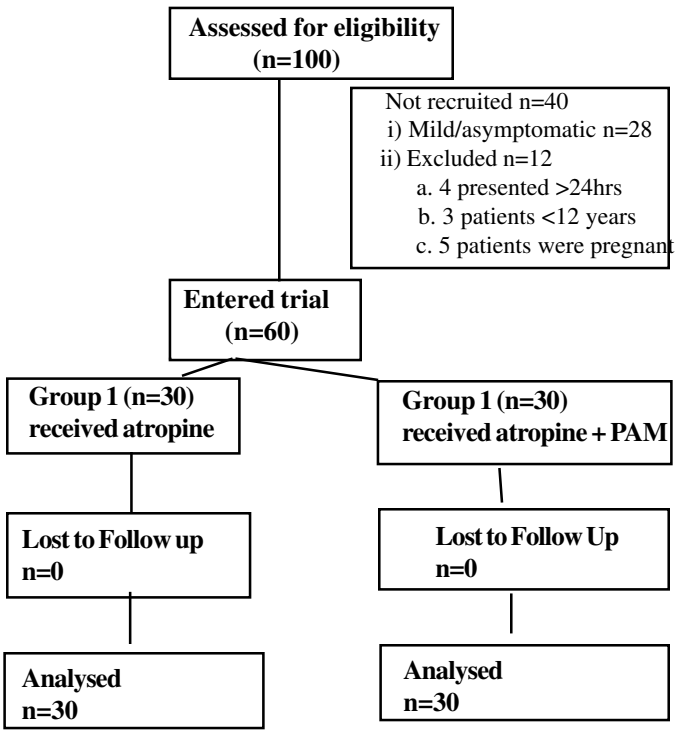

Fig1. Flow of Participants Through each Stage of the Trial

Table 1. Baseline Demographic Data and Clinical Characteristics of Enrolled Patients

Baseline characteristics	Subcategory	Group1 n=30	Group 2 n=30	p-Value
Age (in years)	12-20 yr	2	3	
	21-30 yr	8	7	**0.88***
	31-40yr	12	11	
	41-50yr	8	9	
	Mean± SD	**34.3±8.78**	**34.63±9.76**	
Sex	Male	11	14	
	Female	19	16	
Time of presentation since exposure(in hours)	<6 h	19	21	
	6-12 h	11	9	**0.65***
	>12 h	0	0	
	Mean± SD	**4.53±2.39**	**4.27±2.21**	
Severity of patients as per POP score	Mild(0-3)	8	6	
	Moderate(4-7)	12	14	**0.62***
	Severe(8-11)	10	10	
	Mean± SD	**5.77±2.91**	**6.13±2.71**	

*SD: Standard deviation *A p-value<0.05 is considered as statistically significant*

Table 2. Intergroup Differences in Outcome Parameters

OUTCOME	GROUP 1	GROUP 2	P-VALUE
Mortality	1 (3.33%)	2 (6.67%)	1.0*
Requirement of ventilator	2 (6.67%)	6 (20%)	0.25*
Duration of stay in hospital (in days) ***Mean ± SD***	5.067±1.596	5.4±1.499	0.407*

A p-value<0.05 is considered as statistically significant

Table 3. Status of the Present Study with Respect to Previous Studies

Study	Study Design (No. of patients)	Interventions	Results
Duval (1991) (13)	Retrospective comparison (N = 62)	Pralidoxime (1200 mg/24 hr) vs. standard treatment with atropine	No statistical difference in the risk of death or the need for ventilation between the treatment groups.
De Silva (1992) (8)	Historical comparison (N = 45)	Pralidoxime (4 g over first 24 hr then 1 g/day) vs. historical control	No statistical difference in the risk of death, the need for ventilation or the rate of intermediate syndrome between the treatment groups.
Samuel (1997) (14)	RCT (N = 110)	Pralidoxime (12 g infusion over 3 days) vs. placebo (and standard care with atropine)	Pralidoxime was associated with a significantly higher risk of death, need for ventilation and rate of intermediate syndrome.
Balali-Mood (1998) (15)	Prospective comparison (N = 72)	Pralidoxime (14 $\pm$ 7.4 g), obidoxime (60.6 + 24.3 g) vs. standard treatment with atropine	Pralidoxime and obidoxime were associated with more respiratory complications. No deaths were observed in the pralidoxime arm. Deaths were observed in the obidoxime and standard care arms.
Chugh (2005) (17)	Prospective comparison (N = 30)	Pralidoxime (1 g/6 hrs) vs. standard treatment with atropine	No statistical difference in the risk of death or the need for ventilation between the treatment groups.
Cherian (2005) (16)	RCT (N = 21)	Pralidoxime (12 g/day (severe) or 4 g/day (moderate) over 3 days) vs. placebo (and standard care with atropine)	No statistical difference in the risk of death or the need for ventilation between the treatment groups.
Present study	RCT (N=60)	Pralidoxime (1g/every 6 hours) and atropine Vs standard treatment with atropine.	No statistical difference in mortality rate, the need for ventilation and duration of stay in the hospital between the two treatment groups

min, dilated pupils, systolic blood pressure >80 mm Hg, clear chest with absence of wheeze (10). After achieving atropinization, the interval between the doses was so increased as to just maintain adequate atropinization. Atropine was slowly withdrawn over a period of 3-5 days.

Group 2: Atropine was used in the same manner as in Group 1 and pralidoxime chloride was given in a dose of 0.5-1 g i. v. every 6 hours (11). The dose of pralidoxime was titrated by the treating physicians based on the clinical response of the patient.

Patients showing the early evidences of respiratory failure were urgently shifted to the intensive care unit (ICU). They were closely monitored and assessed for need of ventilator support. Those requiring mechanical ventilation were put on ventilator and the support was continued till the patients fulfilled the criteria of weaning. Patients who did not require mechanical ventilation however were put under close observation treated with oxygen supplementation and other routine care until stabilized.Parameters to be studied: Efficacy outcome in either arm was analyzed through finding out: mortality, need for ventilatory support and the duration of stay in hospital (in days).

Statistical Analysis

Fisher's exact test was done to compare the efficacy parameters between the two groups. Interval data have been expressed as Mean± SD (standard deviation). A p-value<0.05 has been considered as statistically significant. Statistical software used is Statistical Package for Social Sciences (SPSS) version 10.

Results

During the specified study period, a total of 100 patients with history of OP consumption reported to the hospital emergency department seeking treatment, of whom in 28 patients features of OP poisoning were not evident. They were not admitted but were kept under observation in the day care observation unit for a few hours before released. Of the 72 patients who were diagnosed as OP poisoning were screened if they could be considered for randomization. A total of 12 patients were excluded - in 4 patients, more than 24 hours had elapsed when they attended the hospital; 3 patients of <12 years were accidentally exposed to OP compounds; the other 5 patients had pregnancy and were referred to the obstetric unit. Thus, 60 patients were considered eligible and consented into the trial. They were randomly allocated into either of the two groups. Thus each group had 30 patients. The intergroup variation with regard to baseline demographic and clinical characteristics of the patients recruited in the study (e.g., age, sex, time of presentation since exposure and severity of poisoning) were statistically not significant (*Table 1*). The details of the flow of participants through each stage of the trial are shown in Figure 1.

*Mortality:*Overall mortality in the present study was 3 out of 60 patients (5%). Case fatality was higher in Group 2 patients who received pralidoxime added-on atropine (2/30=6.67%) compared to those in Group 1, i.e. those receiving atropine alone (1/30=3.33%). But this difference was not statistical significance.

Need of ventilatory support: A total of 8 out of 60 patients (13.34%) were put on ventilator during treatment. In the Group 1, 2 out of 30 patients (6.67%) required ventilatory support while 6 out of 30 patients (20%) required it in Group 2. However, this difference in the two groups was not found to be statistically significant.

Duration of stay in hospital: Mean duration of hospital stay (in days) between Group 1 and Group 2 failed to show any statistically significant difference. The details of efficacy outcome data analysis are given in *table 2*.

*Adverse reactions:*There was no reported incidence of adverse drug reaction in either of the treatment arms.

Discussion

Since its discovery in 1956 by Wilson and his colleagues, pralidoxime has remained an integral part in management of organophosphorus poisoning (12). It was in the early nineties when researchers like Duval *et al* (13), De Silva *et al* (8) conducted clinical trials raising questions regarding the efficacy of pralidoxime in management of OP poisoning. This was followed by trials of Samuel *et al* (14), Balali- Mood *et al* (15), Cherian *et al* (16), Chabra *et al* (17) which were conducted with a similar intent. All these studies revealed that either add-on pralidoxime therapy did not offer any added benefit or is associated with worse outcome when compared to treatment with atropine. However, these studies mostly

considered two efficacy parameters - mortality rates and ventilator requirement. The duration of hospital stay may be another important efficacy end point which we considered in our study over and above mortality rates and ventilator requirement. Our study suggests that add-on pralidoxime therapy did not add any appreciable benefit in regard to mortality, duration of hospital stays and ventilator requirement, when compared with atropine monotherapy. Our study is in congruence with results observed in studies reported by Duval *et al* (1991) (13), De Silva *et al* (8) (1992), Chabra *et al* 17 (2005). However, it does not support that pralidoxime in combination with atropine is associated with a significantly higher risk of death and increased need for ventilatory support as observed by Samuel (14) (1997). The status of our study compared to previous studies conducted with similar intent is shown in *table 3*.

However our study was not without its limitations that are as follows.The study did not consider RBC cholinesterase level which has got significance in determining response to treatment with pralidoxime. Efficacy of pralidoxime in children of age <12 years were not considered in the study. Follow up after the patients were discharged from the hospital was beyond the scope of the present study.Any further work in the area should take into account the above issues that may help arriving at a more convincing answer to the controversy of add-on pralidoxime therapy over atropine alone in OP poisoning management.

Conclusion

The randomized clinical trial conducted by us suggests that add-on pralidoxime therapy did not offer any advantage over atropine monotherapy in management of OP poisoning. This study validates the questions raised by former studies regarding the justification for inclusion of pralidoxime in the management of OP poisoning.

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