Original Research Article

Comparison of continuous infusion versus repeated bolus dose of Pralidoxime for the treatment of Organophosphate Pesticide poisoning

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Abstract:

Background

The present study compared the continuous infusion versus repeated bolus dose of pralidoxime for the management of organophosphate pesticide poisoning in terms of death(%), recovery (%), sequelae(%), mean atropine dose in 24hrs, mean ventilator days, total ICU stay, total hospital days, pneumonia, intermediate syndrome and its complications.

Material and Methods

This was a randomized control study. Carried out on 64 patients of either sex 15-65 years who presented in emergency medicine ward at Rajindra Hospital, Patiala. The patients who gave consent for the trial were given 2 gm of loading dose of pralidoxime over 30 mins and then randomized into two groups by simple random method:- Group I (n=32)– After loading dose, patients were given continuous infusion of pralidoxime 1gram/ hour for 48 hours. Group II (n=32) – After loading dose, patients were given repeated bolus dose of pralidoxime 1 gram/ hour every 4hourly for 48 hours.Thereafter, pralidoxime was continued at a rate of 1 gram/ hour every 4hourly till the patient was on ventilatory support.

Result

The mean atropine dose in group I was 32.7812± 7.17853 and in group II was 41.2812 ± 10.02974. The difference between them was statistically highly significant (p value <0.001). The mean ventilation days in group I was 5.2222 ± 2.97856 and in group II was 7.7037± 4.89753. The difference between them was statistically significant. (p value is 0.029). The mean hospital days in group I was 8.2188± 3.73937and in group II was 11.0938 ± 6.41248. The difference between them was statistically significant. (p value is 0.032).

Conclusion

With this study we concluded that, the infusion dose of pralidoxime was better than repeated bolus dose of pralidoxime in terms of mean atropine dose required mean ventilator days and total hospital stay.

Background:

Since organophosphorus pesticides kill hundreds of thousands of people in rural Asia every year, it is essential to establish an effective regimen for treatment of such cases of poisoning. Randomised controlled trials during the 1990s compared a 12 gm infusion of pralidoxime over 3-4 days with a 1 gm bolus dose and with placebo.[1'2] The investigators reported no benefit from pralidoxime, and increased mortality in those receiving the infusion.[1'2] They concluded that pralidoxime should not be given to organophosphorus-poisoned patients.[3]

Treatment with oximes might have been rendered ineffective because either the dose or the duration of therapy was not sufficient. Further, many patients in the trials presented late and had taken dimethyl pesticides.[1'2] If treatment with oximes is delayed, the phosphate bound to the inhibited acetylcholinesterase loses an alkyl group and becomes resistant to pralidoxime therapy. The loss of an alkyl group occurs more quickly for dimethyl organophosphorus pesticides such as dimethoate than for diethyl organophosphorus pesticides such as chlorpyrifos.[4,5]

On the basis of tests in vitro and in animal studies , the minimum concentration of pralidoxime in plasma at which this treatment is effective was thought to be 4 mg/ L.[6] Thus a bolus-loading infusion followed by a maintenance infusion might be the best regimen.[7] On this basis, the World Health

Organization has proposed that patients be given about 30 mg/ kg pralidoxime salt as a loading dose, followed by an infusion of at least 8 mg/ kg/ hr (in a 50 kg south Asian patient this is roughly equivalent to 1–2 gm bolus followed by 0.5 gm/ hr).[4,8,9]

Reports of outstanding effectiveness of pralidoxime have been countered by studies showing disappointing results. Currently, there is a wide disparity in the dosage of pralidoxime administered. The low dose regimen of 1 gm/ day to 46 gm/ day is the most widely used (and is also called standard regimen).[10] In addition, a very high dose regimen of pralidoxime (1g/ h infusion) has also been recommended in a randomized controlled trial conducted in India.[11]

Therefore, with controversies regarding use of PAM and its dosage regimen we aimed to take up the present study where we conducted this prospective, randomized, controlled study to compare continuous pralidoxime infusion with repeated bolus injection to treat organophosphorus poisoning.

Material and Methods:

Study Design

A prospective, comparative/ controlled, randomized study. After getting approval from the Institutional Ethical Committee, an informed consent was taken from each patient. This study was conducted on 64 patients aged between 15-65 years of either sex who presented to Rajendra Hospital, Patiala from November 2017 to November 2019.

Exclusive Criteria

Patient's refusal, age<15yrs ,pregnancy, patients who were already given pralidoxime at a transferring hospital, previous recruitment to this RCT, patients admitted with unknown poisoning, patient who had a history of chronic exposure for a specific poisoning, patients with history of other poison ingested with organophosphorus compounds.

Procedure:

- Group I (n=32)– After loading dose, patients were given continuous infusion of pralidoxime 1gram/ hour for 48 hours.
- Group II (n=32) – After loading dose, patients were given repeated bolus dose of pralidoxime 1 gram/ hour every 4hourly for 48 hours.

Thereafter, pralidoxime was continued at a rate of 1 gram/ hour every 4hourly till the patient was on ventilatory support. Patients were monitored continuously by non-invasive means to measure their blood pressure, heart rate, respiratory rate, and arterial oxygen saturation.

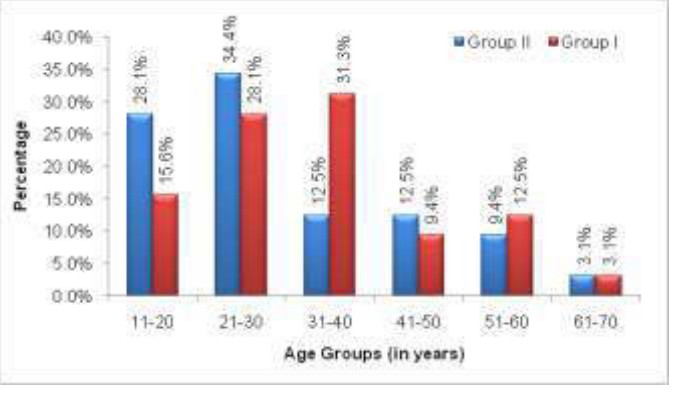
- Primary Outcomes were percentage of recovery, percentage of sequelae and percentage of fatalities.
- Secondary Outcomes were mean hospitalization days, percentage of intermediate syndrome, mean ventilator days, mean atropine days, pneumonia (aspiration or ventilator-associated), mean systolic and diastolic blood pressure in ?rst 24 hour and death.

Statistical Analysis:

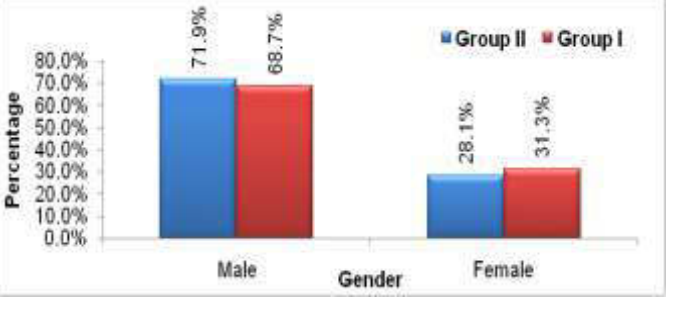
Analysis was conducted using IBMM SPSS statistics (version22.0). Numerical data was expressed as mean and standard deviation and statistically analysis was done using the independent t test to compare the two groups. For skewed data/ scores Mann -Whitney U-test was used. Gender was compared using Chi square test. The p value of <0.05 was considered as statistically significant and p value of <0.001 was considered as statistically highly significant.

Results:

Graph 1

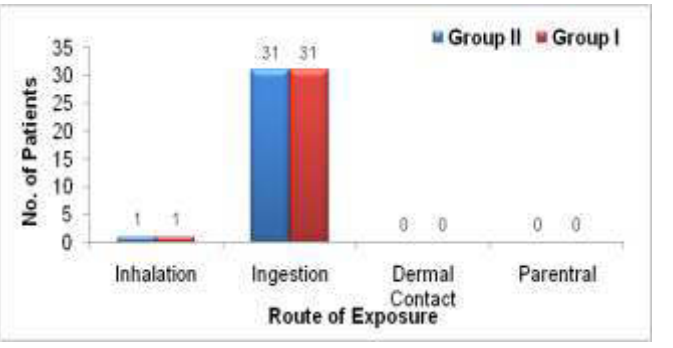


Graph 2

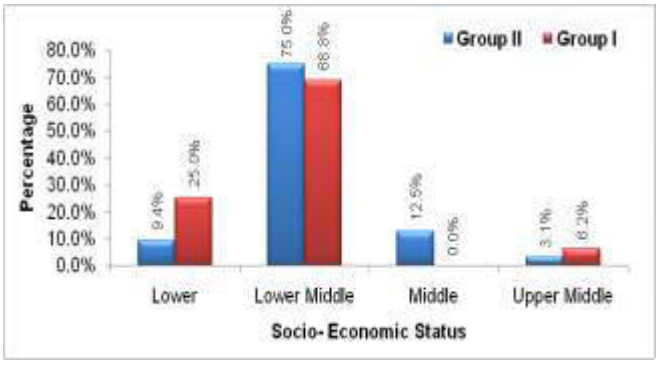


Graph 3

Graph 5



Graph 4



Graph 6

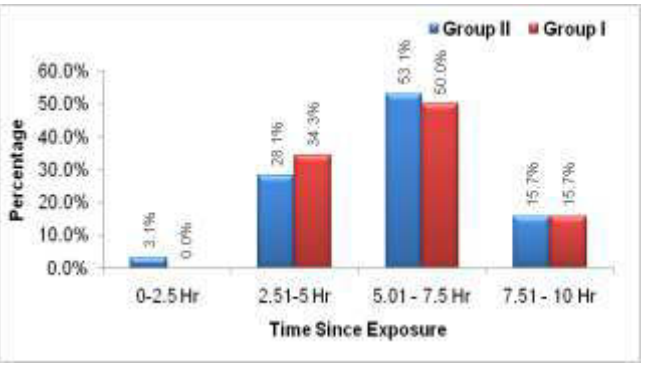


TABLE-1

GCS Score On Admission	Group II		Group I	
	No. of Patients	%age	No. of Patients	%age
≤10	19	59.4	21	65.6
>10	13	40.6	11	34.4
Total	32	100.0	32	100.0
Mean ± S.D	10.1250± 1.58114		10.0625± 1.66438	
Chi square	0.267			
P value	0.606			
Significance	NS			

The difference between Group I and Group II was statistically not significant. (p>0.05).

TABLE-2
SIGNS AND SYMPTOMS OF OPC POISONING

		Group II	Group I	Chi Square	P value	Significance
Meiosis	Yes	21	23	0.291	0.590	NS
	No	11	9			
Depressed Mental Status	Yes	26	26	-	-	-
	No	6	6			
Hypersalivation	Yes	24	18	2.494	0.114	NS
	No	8	14			
Agitation	Yes	13	9	1.108	0.292	NS
	No	19	23			
Fasciculation	Yes	9	10	0.533	0.465	NS
	No	23	22			
Nausea	Yes	3	4	0.160	0.689	NS
	No	29	28			
Bradycardia	Yes	22	26	1.333	0.248	NS
	No	10	6			
Muscle Weakness	Yes	29	28	0.160	0.689	NS
	No	3	4			
Vomiting	Yes	7	7	-	-	-
	No	25	25			
Diarrhea	Yes	20	21	0.068	0.794	NS
	No	12	11			
Mydriasis	Yes	11	9	0.291	0.590	NS
	No	21	23			

The difference between Group I and Group II was statistically not significant. ($p>0.05$).

Discussion

Demographic Parameters

In our study, as per graph 1-6 distribution of patients according to age, sex, marital status, socioeconomic status, route of exposure and time since exposure was similar in both groups and statistically no significant difference was seen between two groups($p>0.05$).

On doing intragroup analysis in both groups it has been found that the OPC poisoning is more common in married males of age group 21-40yrs (youth of the society) belonging to lower middle class. The prevalence of OPC poisoning in married males of lower middle class may be due to marital discord, emotional liability, easy availability of drug and financial debts.

The route of exposure in both the groups were predominantly suicidal oral ingestion in 30 patients in each group whereas only 1 patient in each group had accidental inhalation route of OPC poisoning. The Pawar et al(2006)[11] study also had oral route of poisoning as the predominant way of OPC poisoning.

In both groups maximum number of patients presented to Rajindra Hospital ICU between the time periods 5.01-7.5 hrs. The likely reason for taking 5.01-7.5hrs presentation to ICU is that mostly patients who come to Rajindra Hospital are from rural areas who first go to primary health centres, then to district hospitals from where they are finally referred to Rajindra Hospital, Patiala.

Poisoning Severity

In our study, distribution of patients according to GCS and signs and symptoms of poisoning was similar in both groups and statistically no significant difference was seen between two groups ($p>0.05$)(Table no. 1)

The crucial time elapsed in referring and

transportation of patient led to further decrease in GCS and leads to progress in signs and symptoms of OPC poisoning.

The diagnosis of OPC poisoning was based on clinical features observed in table no.2. We did not use serum AChE enzyme activity, serum concentration of OP compound and serum pralidoxime levels.

Haemodynamic Monitoring

Vital Parameters

After admission to ICU baseline vitals HR, SBP, DBP, MAP, SPO2, RR, recorded and thereafter monitored continuously and charted after every 10 min for 8 hrs and then half hourly till 48hrs.

Heart Rate

On comparing the mean heart rate between two groups, it was found that there was statistically no significant difference between the two groups. ($p>0.05$)

SPO2

Oxygen saturation in spontaneously breathing patients was maintained with oxygen via venturi mask in propped up position.

The patients on mechanical ventilatory support were managed to have maximum oxygenation with minimum oxygen. The patients were initially put on ventilator and then weaned off according to weaning protocol of mechanical ventilation.

On comparing the mean oxygen saturation between two groups, it was found that there was statistically no significant difference between the two groups. ($p>0.05$).

Blood Pressure

The patients' blood pressure was maintained with MAP above 65mmHg. In case of signs of hypotension, vasopressors or ionotropes were started.

The results of our study found that patients remained normotensive largely. On comparing the mean SBP/ DBP/ MAP between two groups it was found that there was statistically no significant difference between the groups.

Primary Outcome

Recovery (%)

In group I the percentage of recovery was 68.75% and in group II was 71.85% (table no. 3). The apparent better outcome (22vs.23) in bolus patients in terms of recovery was due to the fact that one patient in group I died of fatal arrhythmias.

Similar study conducted by Pawar et al[11] had survival percentage as 99% in infusion group and 92% in bolus group. The lower mortality rates in this study was attributed to the fact that it was carried out in a professional centre exclusively dealing with OP poisoned patients and mean interval between admission to hospital and commencement of pralidoxime was considerably short less than 2hrs. Whereas in our present study the mean time of admission to ICU was 5.01-7.5hrs . Moreover, they included less severe cases than the ones in our study. Eddelston et al[12] in their study had survival percentage as 75.2% in pralidoxime group which was in concordance with our study.

Mahesh M et al[13] had survival percentage as 89.2% in infusion group vs 77.8% in bolus group which was similar to our study.

The study conducted by Lin et al[14] had survival percentage as 70.83% in control group and 95.45% in the study group.

Our study had dissimilar results when we compared with Cherian et al[15] and Banerjee et al[16]. Cherian et al in his study had survival percentage as 73.7% in high dose group, 86.2% in single dose group and 94.6% in placebo group. Banerjee et al in his study had survival percentage as 96.67% in atropine alone group and 93.3% in pralidoxime and atropine group.

TABLE -3

	Groups	YES	NO	P value	Chi Square	Significance
RECOVERY	Group II	23	9	0.784	0.075	NS
	Group I	22	10			

Sequelae (%)

In the present study, 2 patients had anoxia in each group I and B which developed when they were discharged from ICU to general ward. So these patients were again readmitted in ICU. 1 patient had fatal cardiac arrhythmias in group I. None patient had convulsions in both groups. Since no previous study

and literature documented sequelae quantitatively. So we couldnot compare it. (Table 4)

TABLE -4

	Groups	ANOXIA	CARDIAC ARRYTHMIAS	CONVULSIONS
SEQUELAE	Group II	1	NIL	NIL
	Group I	1	1	NIL

Mortality (%)

In the present study the percentage of mortality was 31.25% in group I and 28.12% in group II. Out of 64 patients, 10 died in group I and 9 died in group II(table -5)

Similar study conducted by Pawar et al[11] had mortality percentage as 1% in infusion group and 8% in bolus group. The probable reasons attributed to the higher mortality in our study were that the patients mostly presented quite late to our ICU (5.01-7.5hrs). In Pawar et al study patients presented within 2hrs. Majority of the patients in our study had GCS < 10 on late arrival and were aspirated leading to an extra complication of aspiration pneumonitis. Moreover, the chemical structure of the OP compound was not known. It is fact that if treatment with oximes is delayed, the phosphate bound to the inhibited acetylcholinesterase loses an alkyl group and becomes resistant to pralidoxime therapy. The loss of an alkyl group occurs more quickly for dimethyl organophosphorus pesticides than for diethyl organophosphorus pesticides. Many of the patients might have been of dimethyl OP poisoning and late presentation and treatment could have led o more mortality.

Eddelston et al[12] in their study had mortality percentage as 24.8% in pralidoxime group having the similar results.

The study conducted by Mahesh M et al[13] had mortality percentage as 10.8 % in infusion group vs 22.2% in bolus group showing infusion regimen has better outcome.

The study conducted by Lin et al[14] had mortality percentage as 29.17% in control(low dose) group and 4.55% in the study(high dose) group showing high dose regimen which is similar to our infusion group is better than low dose regimen.

Our study had dissimilar results when we compared with Cherian et al[15] and Banerjee et al[16]. Cherian et al in his study had mortality percentage as 26.3% in high dose group, 13.8% in single dose group and 5.4% in placebo group. It is likely that the 'high-dose' regimen of pralidoxime used in Vellore did not produce an effective plasma concentration, a loading dose of pralidoxime being required to reach an effective plasma concentration. This may be the reason for the observed mortality and lack of efficacy of the higher dose infusion (without the loading dose). An alternative interpretation of the lower mortality and lower need for ventilation in patients receiving the lower bolus dose of pralidoxime would therefore be that although a bolus dose when given alone, produces an effective concentration for a limited period of time, does achieve higher plasma concentrations[17]. Banerjee et al in his study had survival percentage as 3.33% in atropine alone group and 6.67% in pralidoxime and atropine group.

TABLE-5

	Groups	YES	NO	P value	Chi Square	Significance
MORTALITY	Group II	9	23	0.784	0.075	NS
	Group I	10	22			

Secondary Outcomes

Mean Ventilator Days

The mean ventilator days in Group I was 5.2222 ± 2.97856 and in Group II was 7.7037 ± 4.89753(table-6). This finding corresponds to Pawar et al study(2006)[11] which had 10 vs 5 median ventilator days in patient in control vs study group respectively.

Similar results were present in Mahesh M et al[13] study in which mean ventilator days in study group were 4.1days and in control group were 6.6days.

TABLE-6

	Groups	MEAN±SD	P value	Significance
MEAN VENTILATOR DAYS	Group II	7.7037±4.89	0.029	S
	Group I	5.2222±2.97		

Total ICU Stay

The total ICU stay in Group I was 7.0000 ± 3.57410 and in group II was 9.4375 ± 5.98890.

TABLE-7

	Groups	MEAN±SD	P value	Significance
TOTAL ICU STAY	Group II	9.4375±5.98890	0.052	NS
	Group I	7.0000±3.57410		

Mean Hospital Days

Our study (Table-8) had dissimilar results when compared with Banerjee et al[16] study in which number of hospital days were 7.02 in oxime group and 5.68 in non-oxime group.

TABLE-8

	Groups	MEAN±SD	P value	Significance
MEAN HOSPITAL DAYS	Group II	11.0938±6.41248.	0.032	S
	Group I	8.2188±3.73937		

Given the expenses of one day in the ICU(thousands of rupees) and the benefit of infusion over bolus dose of pralidoxime in cutting short the duration of ICU and hospital stay, the inclusion of infusion dose in treatment of OP patients is worth the cost of pralidoxime that patients pay .

Mean Atropine Dose

The findings of our study (Table-9) were consistent with the study Pawar et al(2006)[11] in which median atropine dose in first 24hrs was 30vs.6mg in control and study group respectively.

The results of Mahesh M et al[13] study in which total atropine dose in study group was 345.0mg and in control group was 933.1mg was different probably because we calculated atropine dose only for first 24hrs and did not take into account the atropine dose given already in emergency department.

In Lin et al[14]study 5.5mg atropine was given in experimental group and 2mg atropine in control group.

TABLE-9

	Groups	Mean	S.D	P value	Significance
MEAN ATROPINE DOSE(mg in 24hrs)	Group II	41.2812	10.02974	<0.001	HS
	Group I	32.7812	7.17853		

Intermediate Syndrome

The number of patients with intermediate syndrome in Group I and II were 3(9%) and 5(15.6%) respectively(Table-10).

In Mahesh M et al[13] study there was 0% incidence of intermediate syndrome in study group and 33.3% in control group was present which supports the fact that infusion group is better in terms of prevention of intermediate syndrome.

Our study had dissimilar results when compared with Cherian et al[15] study in which 61.5% patients had intermediate syndrome with high dose, 36.1% with single dose and 13.8% with placebo. The results of Lin et al[14] study in which number of patients with intermediate syndrome were 8 in experimental group and 5 in control group were also conflicting.

TABLE-10

Secondary Outcomes		Group II		Group I		Chi Square	P value	Significance
		No.	%age	No.	%age			
Intermediate Syndrome	Yes	5	15.6%	3	9.37%	0.571	0.450	NS
	No	27		29				

Pneumonia

The number of patients with pneumonia in Group I and II were 5 and 6 respectively(table-11).

Similar study Pawar et al (2006)[11] study had 8% patients with pneumonia in group I and 35% in group II. We cannot compare the incidence of pneumonia with previous studies as the etiology of pneumonia depends upon many factors.

TABLE-11

Secondary Outcomes		Group II		Group I		Chi Square	P value	Significance
		No.	%age	No.	%age			
Pneumonia	Yes	6	18.75%	5	15.63%	0.110	0.740	NS
	No	26		27				

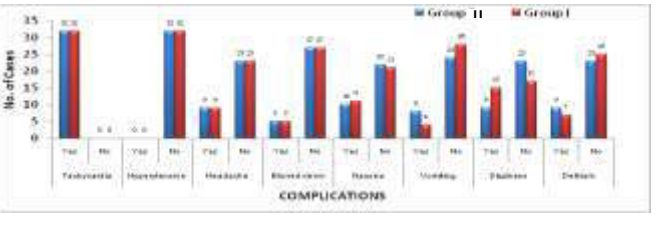
Complications

Graph-7 shows that complications in both groups were comparable and there was no statistically significant difference between both groups in terms of complications.

Atropine being a tertiary amine readily crosses the blood-brain barrier and is responsible for atropine toxicity with large doses of atropine causing agitation, blurring of vision, confusion, headache and tachycardia in both groups. The complications related with treatment were comparable to the complications in Eddelston et al (2009)[12] in which tachycardia(61) , headache(7), blurred vision(8), dizziness(9), nausea(13) and vomiting(21) was present in patients in pralidoxime group.[13]

The complications related with treatment compared in both groups I and B were tachycardia, hypertension, headache, blurred vision, nausea, vomiting, dizziness, and delirium.

Graph-7



Conflict of Interest : None

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