ORIGINAL RESEARCH PAPER

Anaesthesiology

TWO DOSE REGIME OF OXIME THERAPY 'WHO RECOMMENDED' VS 'TRADITIONAL' IN MANAGEMENT OF ORGANOPHOSPHATE POISONING [PROSPECTIVE, RANDOMIZED AND DOUBLE BLINDED]

KEY WORDS: OPC, Pralidoxime, Sucidal

Dr. Balwinder Kaur Professor, Department Of Anaesthesia, GMC, Patiala.

Dr. Tripat Kaur Professor, Department Of Anaesthesia, GMC, Patiala.

Dr. Anjali Gupta* Senior Resident, Department Of Anaesthesia, GMC, Patiala. *Corresponding Author

ABSTRACT

Introduction: Acute organic insecticide poisoning is a major global health problem and organophosphorous compounds (OPC) are the most common suicidal poisons. The dosage of pralidoxime in the treatment of OPC poisoning is an unresolved issue. **Aim:** Comparison of 'Two Doses Regime' of oxime therapy 'WHO Recommended' vs 'Traditional' in management of organophosphate poisoning. **Material and Methods:** The present randomized, double blind clinical study was conducted on 70 patients of either sex aged 16-80 years admitted at Rajindra Hospital Patiala, Punjab from November 2020-2022 with history of organophosphate poisoning. The patients were allocated into two groups: Group W (WHO) and Group T (Traditional) on the basis of pralidoxime dose regime. Patients from group W received 30 mg/kg pralidoxime bolus followed by 8mg/kg/hr infusion and group T received 2 g pralidoxime bolus and 1 g every 6 hourly. The oxime was continued until atropine had not been needed for 12-24 hr or the patient has been extubated. **Results:** Total 70 patients admitted in emergency room were enrolled for study from Nov. 2020-22 after taking written and informed consent, 35 patient were randomised in both groups. The recovery rate was same in both the groups (77.1%). Mean duration on mechanical ventilation in the W group was significantly lower than T group (5.04(1.66) vs. 6.20(1.75)) days; P=0.024. Mean dose of atropine administered was significantly lower in W group compare to T group (25.914(3.807) vs. 29.457(3.320)mg; P=0.001. Mean hospital days were significantly lower in group W as compared to group T (6.571(2.693) vs. (8.429(2.923)). Mean total ICU stay was significantly lower in group W than group T (5.629(2.462) vs. 6.057(2.879)) **Conclusion:** A dose regimen of pralidoxime consisting of 30 mg/kg pralidoxime bolus followed by 8mg/kg/h infusion reduces the mean ventilator days, total ICU stay, mean hospital days and atropine dose requirement. The WHO dose regimen had significantly better outcomes compared to the traditional dose regimen.

INTRODUCTION

Organophosphate (OP) pesticide poisoning is a significant clinical issue on a global scale, resulting in an estimated 200,000 fatalities annually because of its accessibility, affordability, and lack of strict norms and regulations around sales [1,7] For the past 40 years, intentional consumption of organophosphorus insecticides has been widespread. India has one of the highest prevalenceof OP poisoning in the world, mostly in rural areas [8]. Unfortunately, the majority of OPC poisoning victims are under 30 years old, the most productive age group, especially women, farmers, and those from poor socioeconomic status [11,3].

OPC works by preventing the acetylcholinesterase enzyme (ACE) from doing its job. Throughout the body, at all the muscarinic and nicotinic sites, acetylcholine is broken down by ACE, which prevents it from accumulating. The enzyme's molecule contains an anionic tryptophan site and an esteratic serine site. There is inactivation of the vital enzyme acetylcholine esterase, which plays a crucial role in neurotransmission, results in elevated levels of acetylcholine at synapses, which causes an acute cholinergic crisis [6].

Resuscitation, the delivery of atropine (muscarinic antagonist) and pralidoxime (ACE reactivator) and if required, mechanical ventilation are all components of treatment [2].

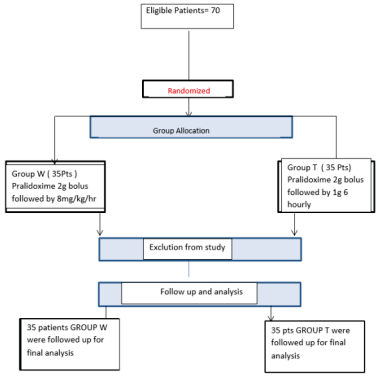
The World Health Organization has suggested that patients get a loading dose of 30 mg/kg pralidoxime, followed by an infusion dose of 8 mg/kg/hr [4]. Despite being used for many years, there is still debate regarding the efficacy and dosing of pralidoxime. However, in previous research, the WHO regimes had not been assessed in direct contrast to the conventional regime (2 g of pralidoxime bolus followed by 1 g every 6 hours) [12]. The present study aimed to compare the effectiveness of the WHO regime and the widely used traditional regime in the management of organophosphate poisoning in term of

Primary Outcome: Percentage of recovery, mean ventilator days, mean atropine dose requirement within 24 hours of admission.

Secondary Outcome: Percentage of intermediate syndrome, mean hospital days, total duration of ICU stay, pneumonia, adverse effects associated with pralidoxime therapy, percentage of fatalities.

MATERIALS AND METHODS

This was a randomized double blind study (patient and the observer) conducted on 70 patients of OPC poisoning from November 2020 to November 2022 (age 16 to 80 years) requiring admission in ICU at Rajindra Hospital, Government Medical College, Patiala, Punjab. After taking ethical committee clearance [IEC number: BFUHS/2K21p-TH/14758 dated 21/1/22]and written informed consent, these patients were randomized by simple random method into two groups of pralidoxime therapy WHO (W) recommended and Traditional (T). Group W: Received 30mg/kg pralidoxime bolus followed by infusion of 8mg/kg/hr. Group T: Received 2 grams pralidoxime bolus followed by 1 gram pralidoxime every 6 hourly. Pralidoxime was continued until atropine had not been needed for 12-24 hr or patient had been extubated.



Exclusion Criteria

Patient's refusal, Age <16 years or > 80 years, Pregnancy, Recipient of pralidoxime at a transferring hospital, Prior enrollment, patients admitted with an unidentified poisoning, patients with a history of chronic exposure to a particular poison, patients with a history of ingesting poisons other than organophosphorus compounds, patients with known medical conditions such as neuromuscular disorders and ailments known to affect biochemical parameters were all disqualified.

Data Collection

All patients admitted to Rajindra hospital, Patiala with acute organophosphorus pesticide poisoning were identified by the signs specific to OPC poisoning such as miosis, smell of poison from clothes or mouth, level of consiousness, thoroughly assessed and resuscitated in the emergency room with the help of doctor on duty and staff nurse. Once the patient is identified, the detailed relevant information pertaining to poison like history, type, nature, quantity of OPC consumed, pre-hospitalization duration, signs/symptoms of patient during the admission were taken. After admission to the ICU, vitals were recorded and oxygen supplementation given as patients requirement.Every patient was given atropine 18–30 mg on admission. Then once the patient vitals became stable, infusion of atropine was started by using a infusion pump, with an intermittent doses to achieve the control of secretions, pupils come back to normal size, and maintain the pulse rate between 80 and 100 beats per minute. Enrolled patients were then randomly assigned to group W and group T by consultant on duty in ICU and pralidoxime therapy started. The schedule remained concealed till the trial's completion.Primary Outcomes were percentage of recovery,mean ventilator days, mean atropine dose required in first 24 hours and secondary outcomes werepercentage of intermediate syndrome, pneumonia,mean hospitalization days, mean ICU stay,percentage of mortality.

Statistical Analysis

All data were analysed by descriptive statistics, which were presented as mean, standard deviation, and percentages. The proper statistical comparison tests were used. With the use of the Fisher Exact Test and the chi square test, categorical variables were examined. Where appropriate, the t test and Mann-Whitney U test were used to evaluate continuous data. The cutoff for statistical significance was set at 0.05. Microsoft Excel and SPSS version 22 were used to analyse the data.

RESULTS

In the current study 70 paients were enrolled, mean age group in Group W was 28.028(10.365) and in Group T was 30.200(9.449) years, of which 47 were males and 23 were females, 42 patients were married, 33 patients were involved in agricultural work, 40 patints of upper lower socioeconomic status, route of exposure and time since exposure was similar in both groups and statistically no significant difference was seen between two groups($p>0.05$). (Figure 1)After doing intragroup analyses on both groups, it was discovered that married men in the 21–30 age range (the society's youth) who are from upper lower class backgrounds experience OPC poisoning more frequently. OPC poisoning is more common in married men of upper lower class, which may be related to emotional liability, easy access to drugs, and debt.

The route of exposure in both the groups W and T were suicidal oral ingestion i.e. 33 vs. 34 patients respectively whereas only 2 patient in group W and 1 patient in group T had accidental inhalation route of OPC poisoning. All 35 patients of each group had additional exposure by dermal route. In both groups maximum number of patients presented to emergency department within time period 5.01-7.5 hrs of exposure to OPC. The probable reason for taking 5.01-7.5hrs by the patients for presenting to ICU is late detection by relatives,mostly patients who arrive are from villages who first visit to primary health centres, then to district hospitals from where they are finally referred to tertiary care centre resulting in delayed admission.

DISCUSSION

Poisoning by organophosphates is a significant issue for global public health. Pralidoxime has been used to treat OPC poisoning or as an adjunct to atropine. Pralidoxime is advised by the WHO, however research on it hasn't been able to determine whether it's useful, dangerous, or helpful. In order to compare the WHO (infusion) with TRADITIONAL (bolus) dose of pralidoxime in treatment of organophosphate poisoning, the current prospective, randomised, double-blind trial was done.

In current study, most common route for poisoning was oral. The Pawar et al study also had oral route of poisoning as the predominant way of OPC poisoning [9]. Percentage of recovery is equal in both groups Group W and Group T, i.e. 27(77.1%).The difference between Group W and Group T was statistically not significant ($p>0.05$). The results of our study are in concordance with the study conducted by SN Chugh which have mentioned that pralidoxime does not influence the mortality [13]. In a study conducted by Pawar et althe infusion group had a survival rate of 99%, whereas the bolus group had a survival rate of 92%. The better recovery rates in Pawar's study was due to the reason that it took place in a facility with expertise in treating individuals who had consumed OPC andthe average time between hospital admission and the beginning of pralidoxime was less than 2 hours [12]. Study done by Eddelston et al had survival percentage of 75.2% in pralidoxime infusion group which is similar to present study result (77.1%) and 84.2% in placebo group. The less recovery percentage in infusion dose as compared to placebo is explained by the baseline difference in GCS score i.e. lower GCS in pralidoxime infusion group compared to placebo group on admission [10]. Also in study conducted by Mahadevaiah Mahesh et al had survival percentage of 89.2% in infusion group which is more than present study (77.1%). The possible reason behind better recovery in study Mahadevaiah Mahesh et al in infusion group was exclusion of very severepoisoning i.e. patients required intubation on admission or within two hours post admission were not enrolled and survival percentage of 77.8% in bolus group which is similar to present study (77.1%) [5]. The study by S Singh et al reported 87.5% recovery in infusion dose as compared to present study (77.1%). The better outcome in Singh study could be because of arrival to hospital within 6 hours of ingestion compared to present study in which patient arrived till 20 hours [14].

In our study, the mean ventilator days in Group W was 5.044± 1.665 and in Group T was 6.200±1.756 which was statistically significant ($p<0.05$). The study conducted by Pawar et al study had 5 mean ventilator days in patients in infusion group which corresponds to present study and 10 mean ventilator days in patient in bolus group suggesting that pralidoxime should not be given by repeated boluses as it leads to rapid re-inhibition of reactivated AChE whenever plasma concentration of oxime falls and recurrence of muscle weakness and other symptoms [12]. Similar results were present in Mahadevaiah Mahesh et al study in which mean ventilator days in infusion group were 4.1 days and bolus group were 6.6 days.This is emphasizing the use of infusion of pralidoxime than bolus dose. In S.Singh et al study shows similar result, mean duration on mechanical ventilation 5.458±8.985 days [5]. A study by S.N. Chugh et al showed mean ventilator days in Group 1 (atropine alone) was 5.60 ± 4.27days and in Group 2 (atropine +pralidoxime) was 4.80±2.78 days. Less number of ventilator days in Group 2 shows role of pralidoxime in replenishing AChE enzyme [13].

The mean atropine dose (first 24hrs) in Group W was 25.914±3.807 mg and in group T was 29.457±3.320 mg which was highly significant ($p<0.01$). The findings of present study

were similar with the study Pawar et al in which median atropine dose in first 24hrs was 30 mg in bolus dose vs 6mg in infusion group [12]. The results of Mahadevaiah Mahesh et at study in which total atropine dose in study group was 345.0mg and in control group was 933.1mg was different probably caused by the fact that we only calculated the atropine dose for the first 24 hours and ignored the atropine dose that had already been administered in the emergency room and after 24 hours [5].

The number of patients with intermediate syndrome in Group W and T were 1(2.9%) and 2(5.7%) respectively which is statistically non-significant (p>0.05). In Mahadevaiah Mahesh et al study the incidence of intermediate syndrome in infusion group was 0% and in bolus group was 33.3% which supports that WHO group (infusion) is superior in terms of prevention of intermediate syndrome [5].

The number of patients with pneumonia in Group W and T were 5 (14.3%) and 6 (17.1%) respectively which is statistically non- significant (p>0.05). A study by Pawar et al had 8% patients with pneumonia in bolus group and 35% in infusion group [9]. Since the majority of aspirations would have happened prior to hospital admission and hence prior to treatment, the pronounced association between the pralidoxime regimen and avoidance of aspiration pneumonia was unexpected. The mean hospital days in Group W was 6.571±2.693 and in group T was 8.429±2.923 days,which was statistically non- significant(p>0.05). Our study results were different from the study conducted by Banerjee et al in which number of hospital days were 7.02 in oxime group and 5.68 in non-oxime group [9].

The total ICU stay in Group W was 5.629±2.462 days and in group T was 6.057±2.879 days,which was statistically non-significant (p>0.05).The study by S.N. Chugh et al showed total ICU stay 7.83±4.95 and 7.57±4.35 days in group 1 (atropine alone) and group 2 (atropine+pralidoxime) respectively.[10]

In the present study the percentage of mortality was 22.9% in both groups. Out of 70 patients, 8 died in group W and 8 died in group T,which was statistically non- significant (p>0.05). In Eddelston et al study mortality percentage of 24.8% in pralidoxime infusion group having the similar results as in present study i.e. 22.9%.[11]The study conducted by Mahadevaiah Mahesh et al had mortality percentage as 10.8 % in infusion group vs 22.2% in bolus group showing infusion regimen has better outcome [12]. A study by Pawar et al had mortality percentage as 1% in infusion group and 8% in bolus group. The molecular structure of the OP substance was unknown, which could explain why there was decreased mortality. The phosphate linked to the inhibited acetylcholinesterase loses an alkyl group and becomes resistant to pralidoxime therapy if treatment with oximes is delayed. Dimethyl organophosphorus pesticides lose an alkyl group more quickly than diethyl organophosphorus pesticides. Many of the patients could have been poisoned by dimethyl OP, and late presentation and delayed treatment could have resulted in higher death rate.

Limitations

The following considerations reduced the value of the study's findings. It was impossible to determine the specific OPC type (dimethyl or diethyl) in several cases. As a result, no subgroup analysis of OP medications could be performed to establish which of them reacts best to pralidoxime therapy. Due to a lack of facilities, it was not possible to evaluate the serum concentration of the OP compound, the serum levels of pralidoxime, or the activity of the enzyme AChE, even though the results of these parameters would have improved the assessment of the effectiveness of pralidoxime.

Conclusion

The present study concluded that, the use of infusion dose of pralidoxime is safe and more effective in organophosphate poisoning patients than its bolus dose in terms of lesser ventilator days, mean hospital days, total ICU stay, mean atropine dose, intermediate syndrome and pneumonia. However, the mortality and survival are similar in both groups.

[Table/Fig-1]: Demographic Parameters

S.NO	Author and Year of study	IV: Pralidoxime dose Used	Primary Outcome		
			Recovery (%)	Mean ventilator days	Mean atropine dose (mg in 24 hours)
1.	Pawar et al 2006	Loading dose 2g over 30mins.Followed by infusion(1g/hr) vs bolus(1g/hr*4hrly)dos e of pralidoxime for 48hrs.Followed by 1g*4hrly till patient is on ventilator.	The recovery percentage in infusion(99%) and bolus (92%) group.	10 days (bolus) 5 days (infusi on)	30mg(bolus) 6mg(in fusion
2.	Eddelston et al (2009	2g loading dose of pralidoxime over 20 mins followed by constant infusion of 0.5g/h for upto 7 days vs saline.	The recovery percentage in pralidoxime group(75.2%) and saline group(84.2%)		
3.	S Singh et al 2015	2 g loading dose of pralidoxime followed by 7.5 mg/kg/hr	87.5% recovery in infusion dose.	, mean duration on mechanical ventilation 131±95.65 hour.	
4.	Present study	2g loading dose of pralidoxime followed by constant infusion of 8mg/kg/h (WHO)vs bolus 1g*6hrly (Traditional).	In Group W, out of 35 patients, 27(77.1%) patients were recovered and in Group T out of 35 patients, , 27(77.1%) patients were recovered .	The mean ventilator days in Group W was 5.044± 1.665 and in Group T was 6.200±1.756.	The mean atropine dose (first 24hrs) in Group W was 25.914±3.807 and in group T was 29.457±3.320.

[Table/Fig-2]: Comparison of Outcomes in Two Groups (Group W and Group T)

PARAMETERS	GROUP W (n=35)	GROUP T (n= 35)	P VALUE
MEAN AGE(in years)	28.028 (10.365)	30.200 (9.449)	0.333
Gender (males)	24	23	0.799

(females)	11	12	
Marital Status			0.626
(married)	20	22	
(unmarried)	15	13	
Occupation			0.683
(agriculture)	18	15	
(labourer)	15	16	
(others)	2	4	
Socioeconomic Status			0.553
(lower)	1	4	
(upper lower)	22	18	
(lower middle)	11	12	
(upper middle)	1	1	
Time Since Exposure (in hours)			
<2.5	1	0	0.728
2.5-5.0	3	4	
5.0-7.5	12	18	
7.5-10.0	10	7	
10.0-12.5	4	1	
12.5-15.0	2	2	
15.0-17.5	2	2	
17.5-20.0	1	1	
Mean Gcs Score On Admission	9.057(3.343)	9.714 (3.659)	0.435
Route Of Exposure			
(inhalational)	2	1	0.998
(ingestion)	33	34	0.998
(dermal)	35	35	-

REFERENCES

1. Lorke DE, Petroianu GA. Treatment of organophosphate poisoning with experimental oximes: A review. Curr Org Chem. 2019;23(5):628-39.
2. Shaffo FC, Grodzki AC, Fryer AD, Lein PJ. Mechanisms of organophosphorus pesticide toxicity in the context of airway hyperreactivity and asthma. Am J Physiol Lung Cell Mol Physiol. 2018;315(4):L485-501.
3. Worek F, Thiermann H, Wille T. Oximes in organophosphate poisoning: 60 years of hope and despair. Chem Biol Interact. 2016;259:93-8.
4. Syed S, Gurcoo SA, Farooqui AK, Nisa W, Sofi K, Wani TM. Is the World Health Organization-recommended dose of pralidoxime effective in the treatment of organophosphorus poisoning? A randomized, double-blinded and placebo-controlled trial. Saudi J Anaesth. 2015;9(1):49.
5. Mahesh M, Gowdar M, Venkatesh CR. A study on two dose regimens of pralidoxime in the management of organophosphate poisoning. Asia Pac J Med Toxicol. 2013;2(4):121-5.
6. Worek F, Wille T, Koller M, Thiermann H. Reactivation kinetics of a series of related bispyridinium oximes with organophosphate-inhibited human acetylcholinesterase—Structure–activity relationships. Biochem Pharmacol. 2012 Jun 15;83(12):1700-6.
7. Jokanovic M. Structure-activity relationship and efficacy of pyridinium oximes in the treatment of poisoning with organophosphorus compounds: a review of recent data. Curr Top Med Chem. 2012;12(16):1775-89.
8. Nurulain SM. Efficacious oxime for organophosphorus poisoning: a minireview. Trop J Pharm Res. 2011;10(3):341-9.
9. Banerjee I, Tripathi SK, Sinha Roy A. A Study on Comparative Evaluation of Add-on Pralidoxime Therapy over Atropine in the Management of Organophosphorus Poisoning in a Tertiary Care Hospital. JK Sci. 2011;13(2).
10. Eddleston M, Eyer P, Worek F, Juszczak E, Alder N, Mohamed F, et al. Pralidoxime in acute organophosphorus insecticide poisoning—a randomised controlled trial. PLoS Med. 2009;6 (6):e1000104.
11. Bajgar J, Fusek J, Kuca K, Bartosova L, Jun D. Treatment of organophosphate intoxication using cholinesterase reactivators: facts and fiction. Mini Rev Med Chem. 2007;7(5):461-6.
12. Pawar KS, Bhoite RR, Pillay CP, Chavan SC, Malshikare DS, Garad SG. Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. The Lancet. 2006;368(9553):2136-41.
13. Chugh SN, Aggarwal N, Dabla S, Chhabra B. Comparative evaluation of atropine alone and atropine with pralidoxime (PAM) in the management of organophosphorus poisoning. J Indian Acad Clin Med. 2005;6 (1):33-7.
14. Singh S, Chaudhry D, Behera D, Gupta D, Jindal SK. Aggressive atropinisation and continuous pralidoxime (2-PAM) infusion in patients with severe organophosphate poisoning: experience of a northwest Indian hospital. Hum Exp Toxicol. 2001;20(1):15-8.