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EFFECTIVENESS OF CONTINUOUS PRALIDOXIME (PAM) INFUSION COMPARED WITH REPEATED BOLUS INJECTION IN ORGANOPHOSPHORUS (OP) POISONING

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ABSTRACT

The poisoning due to pesticides is a worldwide problem. More so in the areas of developing countries due to easy availability of these compounds for agriculture, which most of the people in these countries depend upon for their livelihood. The patients with the history of pesticide consumption are treated effectively in the hospitals after diagnosis by the use of muscarinic antagonists (atropine) and the oximes (pralidoxime). Pralidoxime is often used with atropine to help reduce the parasympathetic effects of organophosphate poisoning.

The use ofoxime is debatable due to its unclear fact about its effectiveness that the compound prevents mortality and morbidity. Even the route of its administration and the dosage are contentious while treating such patients.

In the present study, the effectiveness of continuous Pralidoxime (PAM) infusion was compared with repeated bolus injection in Organophosphorus (OP) poisoning. It was found that the continuous infusion of PAM has better clinical improvement and less mortality.

Keywords: Pesticides, Atropine, Oximes, Bolus Injection, Continuous Infusion

INTRODUCTION

Pesticide poisoning is not only a major clinical problem of rural areas of the developing world, but also is a problem in industrialized countries of the world. It probably kills about 300,000 people every year. The deaths due to self-poisoning account for a significant proportion of the deaths from pesticide poisoning **[1]**.

The organophosphorus pesticides are used widely for agriculture, vector control, and domestic purposes **[2]**. These insecticides act by inhibition of acetylcholinesterase. The resulting build-up of acetylcholine causes overstimulation of cholinergic synapses in the autonomic nervous system, central nervous system and neuromuscular junction, producing the acute cholinergic crisis. Patients die from respiratory failure during this crisis, or from a delayed respiratory failure called the intermediate syndrome **[3]**.

The initial management of acute exposures to organophosphorus is immediate assessment and management of disturbances in airway, breathing, and circulation. The three most widely used classes of antidotes are muscarinic antagonists (usually atropine), oximes (usually pralidoxime or obidoxime), and benzodiazepines. Glycopyrrolate also help in decreasing secretion without causing toxic delirium **[4]**.

The current standard treatment for acute Organophosphorus compound poisoning comprises of the administration of intravenous atropine and oximes to counter acetylcholinesterase inhibition at the synapse. But the usefulness of oximes has been confronted over the past many years by clinicians around the world.

This study looks into the clinical profile of OP poisoning and compares the effectiveness of continuous pralidoxime (PAM) infusion with repeated bolus injection in OP poisoning.

MATERIALS AND METHODS

This prospective cross-sectional open-labeled observational study study was conducted in the emergency wards, Intensive care units and wards of Medicine department of Kasturba Medical College Hospital, Manipal, South India. During the study period of two years from November 2007-November 2009, 94 cases of organophosphorus compound poisoned patients were studied.All patients with history, symptoms & clinical signs of OP poisoning who present within 48 hours of consumption or din serum pseudocholinesterase level were included in the study. The patients with more than 8 hours history of consumption of organophosphorus poison, history of Carbamate poisoning, Double poisoning

with opiods, barbiturates, known cases of Systemic diseases like malignancies, COPD, cardiac disease, neuromuscular diseases, renal failure, Diabetes mellitus and hypertension were excluded from the study.

Patients who present with OP poisoning were selected based on the history of consumption of OP compound and clinical symptoms of OP poisoning. Patients were observed for the laboratory investigation and treatment aspect in terms of atropine and oximes.

Patients were divided into 3 groups based on the PAM they received. One group received no PAM at all (**No PAM regimen**). The second group received 1 g i.v.bolus dose followed by intermittent dose of 1 g i.v. 8^{th} hourly doses (**Intermittent regimen**). The third group received PAM infusion 1 g iv bolus dose followed by 250-500 mg/hour infusion (**Infusion regimen**).

The efficacy of two regimens of PAM Infusion versus Intermittent regimen were also assessed in terms of the total dose of atropine required, the incidence of Intermediate syndrome, the number of days of ventilator requirement, number of days required to recover from poison in hospital. PAM was given for a period of 4-5 days on an average. However in some of the cases it was shorter or slightly longer depending on treating physicians' choice.

Ventilator support was considered in patients with apnoea or obvious hypoventilation, persistent cyanosis, persistent tachypnoea, deranged arterial blood gases.

Patients were also graded on the scale of 0-3 based on the classification by **Bardin, *et al.*, [5]**.

Grade 0 : Positive history
No signs of OP poisoning
Grade 1 : Mild secretions Few fasciculation
Normal level of sensorium
Grade 2 : Copious secretions
Altered consciousness
Generalized fasciculations
Rhonchi, crepitations or hypotension (systolic BP ≤ 90 mm Hg)
Grade 3 : Stupor
PaO2 < 10 KPa (<75 mm of Hg)
Abnormal chest X ray

Two or more criteria were needed for a specific grade. According to **[5]** grade 3 also included patients with attempted suicide. Since most of our patients who were admitted with OP poisoning had attempted suicide; this was not taken into consideration.

The cholinesterase estimation was done with standard Kit manufactured by **Boehringer Mannheim**. This method was based on photometry. The normal values suggested by the manufactures of the kit (at 37ºC) are the following:

1) Children, men and women over 40 years: 5300-12900 U/L
2) Women (18-40 years)- pregnant or taking oral contraceptive pills: 3700-9300 U/L

3) Women (18-40 years)- not pregnant, not taking oral contraceptive pills: 4300-11500 U/L

Serum cholinesterase levels were divided based on the degree of inhibition.

1) *Latent poisoning*: serum cholinesterase activity > 50% of lower limit of normal value (i.e. > 2650 U/L)
2) *Mild poisoning*: serum cholinesterase activity 20-50% of lower limit of normal value (i.e. 1060 – 2650 U/L)
3) *Moderate poisoning*: serum cholinesterase activity 10-20% of lower limit of normal value (i.e. 530 – 1059 U/L)
4) *Severe poisoning*: serum cholinesterase activity < 10% of lower limit of normal value (i.e. < 530 U/L)

The outcome measures of this observational study were assessed in terms of the percentage of recovery, related morbidity and mortality. The dose of atropine required, type of pralidoxime dosing, development of Intermediate syndrome, need for ventilator support and duration of recovery in hospital were also assessed. The data analysis was carried out by using SPSS 11 and chi-square test.

RESULTS

Total of 94 patients who reached the hospital within 48 hours of organo-phosphorus (OP) poisoning were included in the study as per the inclusion criteria, of which 89% of cases reached the hospital in 24 hours and the rest 11% reached within 24-48 hours **(Figure 1)**.

It was observed that 66 patients were males (69.5%) and 28 were females (29.5%) **(Figure 2)** with age ranging between 17-70 years. The majority are between the age groups 21-40 years (n= 57, 60.6%) **(Figure 3)**.

Severity Scale

As per the Glasgow Coma Scale (GCS) there were 52 patients in the minor category (GCS≥13), 32 patients in moderate category (GCS 9-12) and 10 patients in severe group (GCS≤8) **(Table 1)**.

Cholinesterase levels were measured and was classified as per levels mentioned in **[6]**. Three values of cholinesterase were taken and the lowest of them was considered for calculation. For easier tabulation we divided into three groups – normal, low normal (which included levels in latent poisoning) and very low (which included levels in mild, moderate and severe poisoning). There were 17 cases in normal group, 18 cases in low normal group and 59 cases in very low group as shown in **Figure 4**.

There were 5 patients with deranged LFT all of them were attributed to the chronic alcohol abuse. There was mild rise in ALT/AST levels with low Albumin levels. Only 1 patient developed severe renal failure.

All patients were given gastric lavage irrespective of gastric lavage given from outside. All patients received bolus doses of atropine till signs of atropinisation like pupillary mydriasis, dry mucosa and heart rate more than 100/min followed by atropine maintenance dose through infusion (0.6mg/ml). This was supplemented by giving additional doses of atropine to regain quick control of secretions or severe bradycardia when indicated. Patients with severe poisoning received larger doses of atropine. Glycopyrrolate are used alone or in combination with atropine in reducing secretions.

Pam Dose and Outcome

Continuous infusion pralidoxime regimen Vs Intermittent pralidoxime regimen was studied. There were 26 patients who received the infusion regimen and 54 cases received intermittent regimen.

There were 14 cases who did not receive PAM (No PAM regimen). They received atropine as well as glycopyrrolate. All groups received atropine.

The outcome measures like total atropine requirement in each group, duration of ventilation, duration of recovery from poison effect and incidence of intermediate syndrome were studied. Duration of recovery from poison effect and duration of ventilation excluding pneumonia cases were also analysed.

Seventy four patients (78.7%) recovered completely from the poison effect. Nine of them (9.6%) had sequela in the form of non-resolving pneumonia with respiratory failure at time of discharge, there was 1 patient who developed blindness probably due to prolonged hypoxic ischemic encephalopathy, 3 others had features of hypoxic encephalopathy, 1 patient who had decubitus ulcer at time of discharge due to prolonged recumbency.

Eleven of them (11.7%) expired. The most common cause of death was severe pneumonia and sepsis. Three of them had sepsis and other 3 had severe pneumonia. One patient had ARDS. Refractory shock was seen in 1 person. Renal failure seen in 1 patient, rhabdomyolysis in 1 patient.

Severity of Poisoning

Similarly in GCS severity scale the patients of No PAM, intermittent and infusion groups were divided as per severity as mentioned in **Table 2**.

Primary Outcome

As shown in **Table 3**, in No PAM group 13 patients (92.9%) recovered, 1 patient expired (7.1%). In intermittent group 41

patients (75.9%) recovered, 6 patients had sequela (11.1%) and 7 expired (13%). In infusion group 20 of them recovered (76.9%), 3 had sequel (11.5%), 3 expired (11.5%). P value=0.07

According to severity as per **[5]**, patients were divided under each severity and outcome in each of these groups with PAM dosing was analysed.

In Grade 0 severity, patients in all the 3 groups had recovered. In grade 1, in No PAM group 5 out of 5 improved (100%), in intermittent group 13 out of 16 improved (81.3%) and 6 out of 6 (100%) improved in infusion group. As severity increase in grade 3, under No PAM group, 1 out of 1 recovered, 8 out of 15 (53.3%) recovered in intermittent group and in infusion 5 out of 8 (62.5%)recovered . 4 out of 15 patients expired in intermittent group whereas 1 out of 8 only expired in infusion group **(Table 4)**.

Secondary Outcome

Secondary outcome in terms of median dose of atropine requirement, mean days required for ventilation, mean days for recovery from effect of poison and percentage of intermediate syndrome was evaluated.

Secondary outcome was assessed in only those who recovered completely in all the groups.

Median Total Atropine Requirement

In the No PAM group the median requirement for atropine was 84 mg (Interquartile range from 9- 215 mg). In the intermittent group the median requirement for atropine was 333 mg (Interquartile range from 83- 1619 mg). In the infusion group the median requirement for atropine was 171 mg (Interquartile range from 71-484 mg). There was statistical significance with p value of 0.016 as shown in Table 5. It was observed that the median dosage for atropine was less in infusion group compared to the intermittent group. The No PAM group also required less, this was attributed to the fact that many of them received glycopyrrolate along with atropine, which reduced the requirement of atropine.

Mean Ventilatory Period

In infusion group out of 26 patients, 12 patients did not require ventilator. Similarly in Intermittent group out of 54 patients, 30 patients did not require ventilator.

The number of days required for ventilation, in all the grades of severity (as per **[5]**) in the infusion and intermittent groups, among those who recovered (without any sequela) were analysed.

In Infusion group in Grade 1, mean days required for ventilation was 4.5 days (range from 2-7 days).In grade 2 it was 9.5 days (range from 7-12 days) and in grade 3 it was 6.25 days (range from 2-9 days).

In Intermittent group in Grade 1, mean days required for ventilation was 8.3 days (range from 4-13 days). In grade 2, mean days required was 7.5 days (range 5-10 days) and in grade 3 it was 6.3 days (range from 1-10 days).

However when those patients who had pneumonia were excluded and the mean ventilator days were reassessed, In the infusion group ,in grade 1 mean days required was 2 days and in grade 3 it was 4.5 days. In the intermittent group in grade 1 it was 4 days and in grade 3 it was 6 days.

Mean Days of Recovery from Poison Effect

The number of days required for recovery from poison, in all the grades of severity (as per **[5]**) in the infusion and intermittent groups, among those who recovered (without any sequela) were analysed.

In intermittent group 41 out of 54 recovered and in infusion group 20 out of 26 recovered completely without any sequela.

In intermittent group in grade 0 the mean days required for recovery from poison was 8 days (range from 2-20 days). In grade 1 it was 8.14 days (range from 2-22 days), in grade 2 it was 11 days (range from 5-22 days). In grade 3 it was 11.1 days (range from 5-18 days).

In the infusion group in grade 0 mean days required for recovery from poison was 6 days (range from 3-8 days). In grade 1 it was 5.6 days (range from 4-10 days), in grade 2 it was 9.4 days (range from 7-13 days), in grade 3 it was 9.6 days (range from 8-11 days).

Percentage of Intermediate Syndrome

The percentage of Intermediate syndrome in No PAM group was 7.1%, in intermittent group it was 22.2% and in infusion group it was 3.8% which was statistically significant with p value of 0.04 as shown in **Table 6**.

Cost of Treatment

(1 vial of PAM = Rs 180)

Continuous infusion regimen the cost was around 12000-14000 rupees and in Intermittent group the cost was around 5000-6000 rupees.

So in terms of cost, intermittent will be better as most of our patients are of low socioeconomic group, but in terms of recovery and mortality, infusion is better in moderately to severe cases and that is the primary outcome in this study on OP poisoning.

DISCUSSION

The acetylcholinesterase inhibited by oganophosphorus is reactivated by Oximes **[7]**. Some of these oximes are pralidoxime, obidoxime and trimedoxime. Among these pralidoxime remains the most widely used for the treatment of Organophosphorus poisoning. Despite of its vast use, the effectiveness of pralidoxime, has been much debated, with many Asian clinicians

considering it ineffective **[8-10]**. The randomised controlled clinical trial done in Vellore, India in the early 1990s showed the ineffectiveness of pralidoxime in the patients seen at this hospital and also showed the possibility of harmful effects caused by low-dose infusions of pralidoxime **[11-14]**. The Cochrane review based on two randomised controlled trials **[12-13]** reported no clear evidence of benefit or harm. The other meta-analyses combined non-randomised or historically controlled observational studies **[8, 15-19]** with randomised controlled trials **[11, 12, 20]** reducing confidence **[21, 22]** in their conclusion that oximes are harmful.

A randomised controlled trial in Baramati, India **[23]** studied the effect of very-high-dose pralidoxime iodide (2 g loading dose, then 1 g either every hour or every 4 h for 48 h, then 1 g every 4 h until recovery) in 200 patients with moderate organophosphorus poisoning. The high-dose regimen was associated with reduced case fatality, fewer cases of pneumonia, and reduced time on mechanical ventilation. However, this study suggests that large doses of pralidoxime could have benefit if patients are treated early and have good supportive care. But the study did not find a difference in benefit of high-dose pralidoxime in moderate dimethyl or diethyl organophosphorus poisoning.

Observational studies of pralidoxime and obidoxime suggest that the ability to reverse acetylcholinesterase inhibition with oximes varies with the pesticide ingested **[13, 24-26]**. Acetylcholinesterase inhibited by diethyl pesticides, such as parathion and quinalphos, seems to be effectively reactivated by oximes, but acetylcholinesterase inhibited by dimethyl organophosphorus, such as monocrotophos or oxydemeton-methyl, seems to respond poorly. Further studies are needed to establish whether this benefit remains for severe poisoning.

WHO recommends that oximes be given to all symptomatic patients who need atropine **[27-28]**. To ensure a therapeutic concentration, a loading dose of oxime is given, followed by a continuous infusion. The loading dose of oxime should not be given rapidly as a bolus as it causes vomiting (risking aspiration), tachycardia, and diastolic hypertension **[7]**.

In the present study, 80 patients received PAM but dose varied as some patients received infusion regimen and others the intermittent regimen. 14 patients did not receive PAM.

Baseline severity was assessed by using the clinical severity indices based on **[5]** and GCS severity scale. Primary outcome in terms of percentage of recovery, percentage of sequel or percentage of those expired

were compared with dosage regimen. In the No PAM group there were 92.9% recovery, 0% sequel and 7.1% expired. In the intermittent group there were 75.9% recovery with 11.1% sequel and 13% expired. In the infusion group 76.9% recovery, 11.5 % sequel and 11.5% expired. Compared to the intermittent group recovery was better with infusion group although sequela was more or less the same in the two groups. The percentage of patients expired was more in intermittent group (13%) compared to infusion group (11.5%). It was observed that in terms of primary outcome infusion regime was better than intermittent regimen. There was no statistical significance p value =0.07 (probably due to lesser number of cases).

Assessment of secondary outcome like median total atropine dose required in mg, mean days required for ventilation, mean days of recovery from poison and percentage of intermediate syndrome was done. Atropine was given to all patients. The dosages of atropine requirement were significantly different in various grades of severity of poisoning. Atropine requirement increased with the severity of poisoning. These findings were similar to those of **[29]**. The median atropine requirement in infusion group was reduced significantly (p value=0.016). The incidence of intermediate syndrome was less in infusion group compared to intermittent group (p value=0.04). The mean days required for ventilation in the infusion group in grade 1 was 4.5 days(range from 2-7 days) and as severity increased to grade 3 it was 6.25 days (range from 2-9 days). In Intermittent group in Grade 1, mean days required for ventilation was 8.3 days (range from 4-13 days) and in grade 3 it was 6.3 days (range from 1-10 days). However when those patients who had pneumonia were excluded and the mean ventilator days were reassessed, In the infusion group ,in grade 1 mean days required was 2 days and in grade 3 it was 4.5 days. In the intermittent group in grade 1 it was 4 days and in grade 3 it was 6 days. Hence it was observed that in infusion group the mean days for ventilatory requirement was less compared to intermittent group, when the pneumonia cases were excluded, as the development of pneumonia also interfered with the ventilatory period.

The mean days required for recovering from poison effect was assessed. In intermittent group in grade 0 the mean days required for recovery from poison was 8 days (range from 2-20 days) whereas in grade 3 it was 11.1 days (range from 5-18 days). In the infusion group in grade 0, mean days required for recovery from poison was 6 days (range from 3-8 days) whereas in grade 3 it was 9.6 days (range from 8-11 days).

Hence mean days required to recover from poison was less in infusion group compared to intermittent group.

So here in infusion group median atropine requirement was reduced, percentage of intermediate syndrome was less, percentage of recovery was better and had less percentage of mortality. The mean days for ventilatory period excluding pneumonia cases showed that infusion group required lesser days and mean days to recover from poison was also lesser in infusion group.

There are few studies which support the benefit and risks of continuous infusion. A study carried out on OP poisoned patients by Pawar et al[23] compared 1 gm/hour infusion regimen with 1g/4th hourly bolus administration. A case series by Singh et al 201 showed that there was a decrease in mortality rate when continuous infusion of 7.5 mg/kg/h PAM was administered in moderate and severe OP poisoned patients. According to **[30]**, the four randomized clinical trials carried out on total 277 OP patients did not prove efficacy of PAM in OP poisoning. The major problem associated with these studies were that dose of PAM used was not sufficient to reactivate enzymes inhibited by OP compound. In other study by **[31]** showed that the treatment with PAM did not make any difference in moderate and severe OP poisoned patients.

In terms of cost, intermittent will be better as most of our patients of low socioeconomic group but in terms of recovery and mortality infusion is better in moderately to severe cases and that is the primary outcome in this study on OP poisoning.

CONCLUSION

It is evident from our study that PAM when administered as 500 mg/hour infusion there was better clinical improvement and less mortality. The incidence of intermediate syndrome was found to be less in infusion group and the median dose of atropine requirement was also less in this group. The mean ventilatory period (excluding pneumonia cases) was lesser for infusion group and the mean days to recover from poison was also less in infusion group. Furthermore multicenter studies are required to prove the benefits of pralidoxime continuous infusion.

REFERENCES

[1] Eddleston M, Early management after self-poisoning with an organophosphorus or carbamate pesticide – a treatment protocol for junior doctors, Crit. Care, 8 (6), 2004,391-397.

[2] Roberts MD and Aaron CK, Managing acute organophosphorus poisoning, Br. Med. J., 334, 2007, 629-635.

[3] Eddleston M, Pathophysiology of organophosphorus pesticide self-poisoning is not so simple, Netherlands J. Med., 66 (4), 2008, 146-148.

[4] Wadia RS, Treatment of organophosphorus poisoning, Indian J. Critical Care med., 7 (2), 2003, 85-87.

[5] Bardin PG, Vaneedan SF and Jonbest JR, Intensive care management of acute organophosphate poisoning, S. Afr. Med. J., 72, 1987, 593-7.

[6] Namba T, Carl T N, Jerald J and David G, Poisoning due to organophosphorus insecticide, acute and chronic manifestations, Am. J. Med., 50, 1971, 475-492.

[7] Eyer P, The role of oximes in the management of organophosphorus pesticide poisoning, Toxicol. Rev., 22, 2003, 165-190.

[8] De Silva HJ, Wijewickrema R and Senanayake N, Does pralidoxime affect outcome of management in acute organophosphate poisoning? Lancet, 339, 1992, 1136-1138.

[9] Singh S, Batra YK, Singh SM, Wig N and Sharma BK, Is atropine alone sufficient in acute severe organophosphate poisoning? Experience of a North West Indian hospital, Int. J. Clin. Pharmacol. Ther., 33, 1995, 628-630.

[10] Peter JV and Cherian AM, Organic insecticides, Anaesth. Intens. Care, 28, 2000, 11-21.

[11] Johnson S, Peter JV, Thomas K, Jeyaseelan L and Cherian AM, Evaluation of two treatment regimens of pralidoxime (1 gm single bolus dose *vs* 12 gm infusion) in the management of organophosphorus poisoning, J. Assoc. Physicians India, 1996, 44, 529-531.

[12] Cherian AM, Peter JV and Samuel J, Effectiveness of P2AM (PAM - pralidoxime) in the treatment of organophosphorus poisoning, A randomised, double blind placebo controlled trial, J. Assoc. Physicians India, 45, 1997, 22-24.

[13] Eddleston M, Szinicz L, Eyer P and Buckley N, Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials, Q J. Med., 95, 2002, 275-283.

[14] Peter JV and Moran JL, Role of oximes in human organophosphate poisoning—a critical look at the evidence, In: Nayyar V, editor. Critical Care Update 2004, Jaypee, New Delhi, 2004, 153-163.

[15] Duval G, Rakouer JM, Tillant D, Auffray JC, Nigond J and Deluvallee G, Intoxications aiguës par

insecticides à action anticholinestérasique. Evaluation de l'efficacité d'un réactivateur des cholinestérases, le pralidoxime, J. Toxicol. Clin. Exp., 11, 1991, 51-58.

[16] Abdollahi M, Jafari A, Jalali N, Balali-Mood M, Kebriaeezadeh A and Nikfar S, A new approach to the efficacy of oximes in the management of acute organophosphate poisoning, Iranian J. Med. Sci., 20, 1995, 105-109.

[17] Balali-Mood M and Shariat M, Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes, J. Physiol. (Paris) 92, 1998, 375-378.

[18] Sungur M and Guven M, Intensive care management of organophosphate insecticide poisoning, Crit. Care, 5, 2001, 211-215.

[19] Chugh SN, Aggarwal N, Dabla S and Chhabra B, Comparative evaluation of atropine alone and atropine with pralidoxime (PAM) in the management of organophosphorus poisoning, J. Indian Acad. Clin. Med., 6, 2005, 33-37.

[20] Cherian MA, Roshini C, Visalakshi J, Jeyaseelan L and Cherian AM, Biochemical and clinical profile after organophosphorus poisoning—a placebo-controlled trial using pralidoxime, J. Assoc. Physicians India, 53, 2005, 427-431.

[21] Grimes DA and Schulz KF, An overview of clinical research: the lay of the land, Lancet, 359, 2002, 57-61.

[22] Grimes DA and Schulz KF, Bias and causal associations in observational research, Lancet, 359, 2002, 248-252.

[23] Pawar KS, Bhoite RR, Pillay CP, Chavan SC, Malshikare DS and Garad SG, Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial, Lancet, 368, 2006, 2136-2141.

[24] Eddleston M, Eyer P and Worek F, Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study, Lancet, 366, 2005, 1452-1459.13.

[25] Eyer P, The role of oximes in the management of organophosphorus pesticide poisoning, Toxicol. Rev., 22, 2003, 165-190.

[26] Thiermann H, Szinicz L and Eyer F, Modern strategies in therapy of organophosphate poisoning, Toxicol. Lett., 107, 1999, 233-239.

[27] Johnson MK, Jacobsen D and Meredith TJ, Evaluation of antidotes for poisoning by organophosphorus

pesticides, Emerg. Med., 12, 2000, 22-37.

[28] WHO International Programme on Chemical Safety Poisons information monograph G001. Organophosphorus pesticides, World Health Organization, Geneva, 1999.

[29] Parvathy M and Vaidyanathan W, Organophosphorus poisoning, a clinical study, Antiseptic., 76, 1979, 517-520.

[30] Bairy KL, Vidyasagar S and Sharma A, Controversies in the management of organophosphate poisoning, Indian J. Pharmac., 139 (2), 2007, 71-74.

[31] CherianMA, Roshini C, Peter JV and Cherian AM, Oximes in organophosphorus poisoning, Indian J. Crit. Care Med., 9 (3), 2005, 155-163.

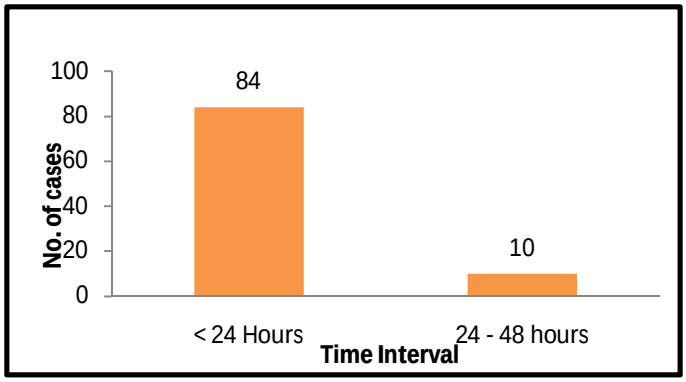

Figure 1: Interval Prior to Tertiary Centre Hospitalisation

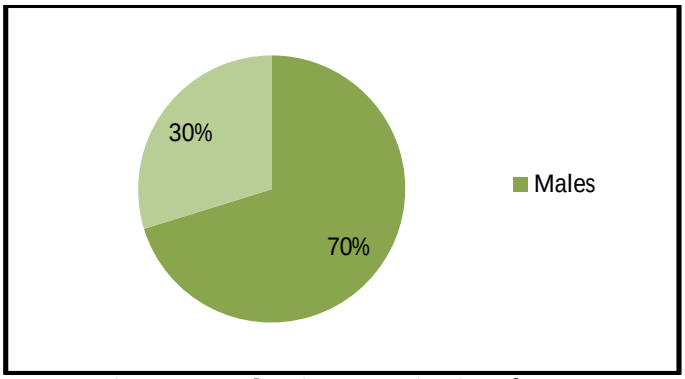

Figure 2: Genderwise Determination of Cases

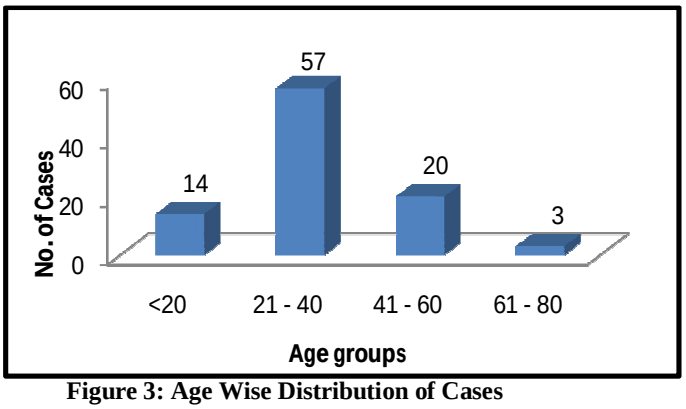

Figure 3: Age Wise Distribution of Cases

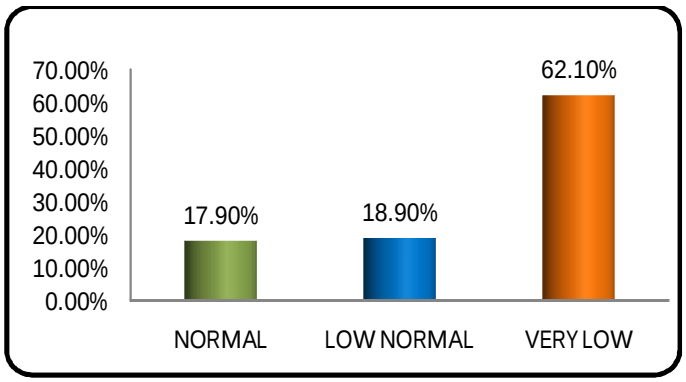

Figure 4: Level of Cholinesterase in the Patients

Table 1: Severity of Poisoning as Per Glasgow Coma Scale

Glasgow Coma Scale	Frequency	Valid Percent
Minor (≥ 13)	52	55.3
Moderate (9-12)	32	34.0
Severe (≤ 8)	10	10.6
Total	94	100.0

Table 2: Glasgow Coma Severity Scale

GCS Severity Scale		PAM DOSING			Total
		No PAM	Intermittent	Infusion	
Minor ≥13	Count	8	29	15	52
	% within PAM dosing	57.1%	53.7%	57.7%	55.3%
Moderate 9 - 12	Count	6	16	10	32
	% within PAM dosing	42.9%	29.6%	38.5%	34.0%
Severe ≤ 8	Count	0	9	1	10
	% within PAM dosing	.0%	16.7%	3.8%	10.6%
Total	Count	14	54	26	94
	% within PAM dosing	100.0%	100.0%	100.0%	100.0%

Table 3: Primary Outcome and PAM Dosing

Primary Outcome		PAM Dosing			Total
		No PAM	Intermittent	Infusion	
Recovered	Count	13	41	20	74
	% within PAM dosing	92.9%	75.9%	76.9%	78.7%
Sequela	Count	0	6	3	9
	% within PAM dosing	0%	11.1%	11.5%	9.6%
Expired	Count	1	7	3	11
	% within PAM dosing	7.1%	13.0%	11.5%	11.7%
Total	Count	14	54	26	94
	% within PAM dosing	100.0%	100.0%	100.0%	100.0%

Table 4: Outcome, PAM Dosing, Severity (Bardin et al) Cross Tabulation

Severity-Bardin et al	Outcome		PAM Dosing			Total
			No PAM	Intermittent	Infusion	
Grade 0	Recovered	Count	3	13	4	20
		% within PAM dosing	100.0%	100.0%	100.0%	100.0%
	Total	Count	3	13	4	20
		% within PAM dosing	100.0%	100.0%	100.0%	100.0%
Grade 1	Recovered	Count	5	13	6	24
		% within PAM dosing	100.0%	81.3%	100.0%	88.9%
	Sequela	Count	0	1	0	1
		% within PAM dosing	.0%	6.3%	.0%	3.7%
	Expired	Count	0	2	0	2
		% within PAM dosing	.0%	12.5%	.0%	7.4%
	Total	Count	5	16	6	27
		% within PAM dosing	100.0%	100.0%	100.0%	100.0%
Grade 2	Recovered	Count	4	7	5	16
		% within PAM dosing	80.0%	70.0%	62.5%	69.6%
	Sequela	Count	0	2	1	3
		% within PAM dosing	.0%	20.0%	12.5%	13.0%
	Expired	Count	1	1	2	4
		% within PAM dosing	20.0%	10.0%	25.0%	17.3%
	Total	Count	5	10	8	23
		% within PAM dosing	100.0%	100.0%	100.0%	100.0%
Grade 3	Recovered	Count	1	8	5	14
		% within PAM dosing	100.0%	53.3%	62.5%	58.3%
	Sequela	Count	0	3	2	5
		% within PAM dosing	.0%	20.0%	25.0%	20.8%
	Expired	Count	0	4	1	5
		% within PAM dosing	.0%	26.7%	12.5%	20.8%
	Total	Count	1	15	8	24
		% within PAM dosing	100.0%	100.0%	100.0%	100.0%

Table 5: Atropine Requirement in Different Groups

Dosage Regimen	Median Total Atropine Required (MG)
Intermittent	333 (83-1619)
Infusion	171 (71-484)
*P Value	0.016

*** chi square test**

Table 6: Intermediate Syndrome in Different Groups

Dosage Regimen	Percentage of Intermediate Syndrome
No PAM	7.1%
Intermittent	22.2%
Infusion	3.8%
*p Value	0.04

*** Chi Square Test**