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Study Of Effectiveness Of Fresh Frozen Plasma Transfusion In Preventing Intermediate Syndrome In Organophosphorus Poisoning Patients With Raised CPK Levels

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Abstract
Background : *Acute Organophosphorus poisoning is a medical emergency and is a preventable and treatable cause of mortality in Emergency department. Acute organophosphate insecticide poisoning can manifest 3 different phases of toxic effects, namely, acute cholinergic crisis, intermediate syndrome (IMS), and delayed neuropathy. Among them, IMS has been considered as a major contributing factor of organophosphate-related morbidity and mortality because of its frequent occurrence and probable consequence of respiratory failure. Hence, in the present study, we intended to evaluate the efficacy of FFP transfusion in prevention of IMS following OP poisoning.*
Method : *This prospective observational study was conducted at Department of Emergency Medicine, J. J. M. Medical College, Davangere, Karnataka from August 2021 to October 2021. A total of 40 patients with the history of acute OP poisoning fulfilling the inclusion and exclusion criterion were enrolled. The 40 patients were randomly divided into two groups viz. Control (n=20) and Cases (n=20). Patients in control group were treated with the traditional management protocol of OP. Patients in cases were treated with the traditional management protocol of OP as control group plus FFP. Assessment parameters viz. measuring CPK level on day 1, 2 and 3 of admission and day 6 and 7, need of ventilator support, duration of ICU stays and mortality.*
Results : *Revealed that statistically significant (p-0.000) decrease in mean CPK levels was observed in study subjects transfused with FFP along with standard OP poisoning treatment. Furthermore, none of the subjects required ventilator support following transfusion of study subjects with FFP along with standard OP poisoning treatment.We found direct correlation between initial & final CPK value and duration of ICU stay, ventilator support requirements & mortality. Moreover, the correlation was found to be statistically significant ($p < 0.001$) in each case.*
Conclusion treatment of IMS cases following OP poisoning with FFP was proved effective, and therefore FFP transfusion could be recommended for early management of IMS following OP poisoning since it can improve the clinical outcome through decreasing mortality, duration ICU stay and the need of ventilator support.
Keywords: *Intermediate syndrome (IMS), Organophosphate poisoning (OP), Fresh frozen plasma, (FFP), ICU stays, Ventilator support, Mortality*

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I. Introduction

Pesticide poisonings remain a serious public health problem worldwide. According to the World Health Organization's estimate, 3 million cases of pesticide poisoning occur every year, resulting in more than 250,000 deaths.[1] This number also accounts for a substantial fraction of the almost 900,000 people worldwide who die by suicide every year.[18] Among the numerous pesticides that can result in death, organophosphate insecticides are the most common culprit agents because of their high toxicity.Deliberate self poisoning has reached epidemic proportions in developing world where highly toxic poisons and less facilities ensure high fatality.[17]Organophosphate (OP) pesticides are used widely for agriculture and domestic purposes. OP poisoning

is an increasing worldwide problem, particularly in the tropics more than in the industrialized world.[2] OP is an important reason for hospitals and intensive care units' admission in the developing countries.[3] Moreover, it is responsible for more than 200,000 deaths each year in those countries.[4] The main factors responsible for the widespreadOP poisoning are its easy availability and unawareness of the poorly educated farmers in those countries.[5]

Acute organophosphate insecticide poisoning can manifest 3 different phases of toxic effects, namely, acute cholinergic crisis, intermediate syndrome (IMS), and delayed polyneuropathy. Among them, IMS has been considered as a major contributing factor of organophosphate-related morbidity and mortality because of its frequent occurrence and probable consequence of respiratory failure. Incidence of IMS has been reported to be as high as 80%.[6]

There are emerging options for new cheaper and/or easily quantifiable biochemical markers in relation to OP poisoning like creatine phosphokinase (CPK), lactate dehydrogenase (LDH), serum immunoglobulins (IgG, IgA), circulating complements (C3, C4), etc…[7] But immunoglobulin assays, apart from being costly and difficult to perform in most laboratories, are often unreliable. Several animal model studies on rat liver and fresh-water snails indicate the association between OP poisoning and CPK levels.[8] In a study reported by Agarwal SB et al proposed that serum level of CPK is often found to be elevated in OP poisoning and may be used as a biomarker.[7]

OP poisonings are classically treated with atropine and oximes. However, these methods are sometimes shown to be of limited benefit.[9,10] Therefore, continuous search for other methods has been attempted. A study conducted in Turkey concluded that fresh frozen plasma (FFP) is an efficient method of management of patients with OP poisonings.[3] With this scenario, present study was designed with the main aim to evaluate the efficacy of FFP transfusion in prevention of IMS following OP poisoning.

II. Materials and Methodology

Study design : This prospective observational study was conducted at Department of Emergency Medicine, J. J. M Medical College, Davangere, Karnataka from August 2021 to October 2021. The study was approved by the institutional ethics committee of J. J. M Medical College. The study aim was explained to patients and informed written consent was obtained from all the participants.

Study subjects:A total of 40 patients with the history of acute OP poisoning admitted to the emergency medicine department fulfilling the following inclusion and exclusion criterion were enrolled.

Inclusion criteria:

- Patients who are above 18 years of age.
- Admission to hospital on day 1 of OP poison consumption.
- Elevated CPK levels
- Patients or relatives who have given written informed consent

Exclusion criteria :

- Patients with age less than 18 years
- Patients who consumed mixed poison
- Patients who had aspiration on admission and who developed VAP on ventilator
- Patients who had alcoholic intoxication, history of myopathies, seizure disorders, malignancies, kidney disease and patients taking medications like statins, fibrates and dexamethasone.
- Very much agitated patients who require sedatives to control agitation
- Patients not fully atropinised

Methodology :

The 40 patients were randomly divided into two groups viz. Control (n=20) and Cases (n=20). Patients in control group were treated with the traditional management protocol of OP. Patients in cases were treated with

the traditional management protocol of OP as control group plus FFP. Both groups underwent the traditional management protocol of OP in the form of supportive measures, cutaneous decontamination (removing contaminated clothes and washing with copious amount of water), gastric decontamination (gastric lavage & 1 g/kg activated charcoal), antidotal therapy (atropine & oximes). Atropine: 3mg iv bolus, assessed for signs of atropinization (three point check list - dry mouth, clear chest, tachycardia & dilated pupils) after 5 mins, if yes last dose is repeated. If not, double of the previous repeated until atropinization is achieved. Atropine infusion started at 20% of the total dose of atropine required for atropinization. Tapering done by 20% every 8 hours using three point check list once patient is stable. Oximes : 30mg/kg bolus in 100 ml NS followed by infusion at 10mg/kg/hr. The FFP group received 4 units of FFP on day 4 and 3 units on day 5. Clinical data was collected in a pre-designed data sheet for each patient; it included the following: Socio-demographic data: age, gender,

assessment parameters viz. measuring CPK level on day 1, 2 and 3 and day 6 and 7, type of poison, time since consumption, pseudocholinesterase levels, need of ventilator support, duration of ICU stay and mortality.

Statistical analysis

The collected data was analysed using statistical package for social sciences (SPSS) IBM, version 20. For the description of data, mean values, percentages and standard deviations were used. Student's t-test and Pearson's Correlation coefficient were used for the assessment of statistical significance. P value <0.005 was considered statistically significant.

III. Results

Majority of the study subjects i.e., 50% each were in the age group of 21-30 years in Control and Cases groups. The mean age of study subjects in Control and Case groups was found to be 34.75 ± 15.28 and 36.65 ± 19.34 respectively (Table 1). Male predominance (60%) was observed in control group as compared to females (40%). Whereas in cases group, equal distribution of males (50%) and females (50%) was observed (Figure 1).

Table 1: Distribution of study subjects based on age

Variables	Control		Cases	
	N	%	N	%
10 – 20 years	1	5.0	1	5.0
21 – 30 years	10	50.0	10	50.0
31 – 40 years	2	10.0	2	10.0
41 – 50 years	4	20.0	2	10.0
51 – 60 years	1	5.0	3	15.0
61 – 70 years	1	5.0	1	5.0
71 – 80 years	1	5.0	1	5.0
81 – 90 years	-	-	1	5.0
Mean ± S.D	34.75 ± 15.28		36.65 ± 19.34	
Minimum	20		19	
Maximum	75		85	

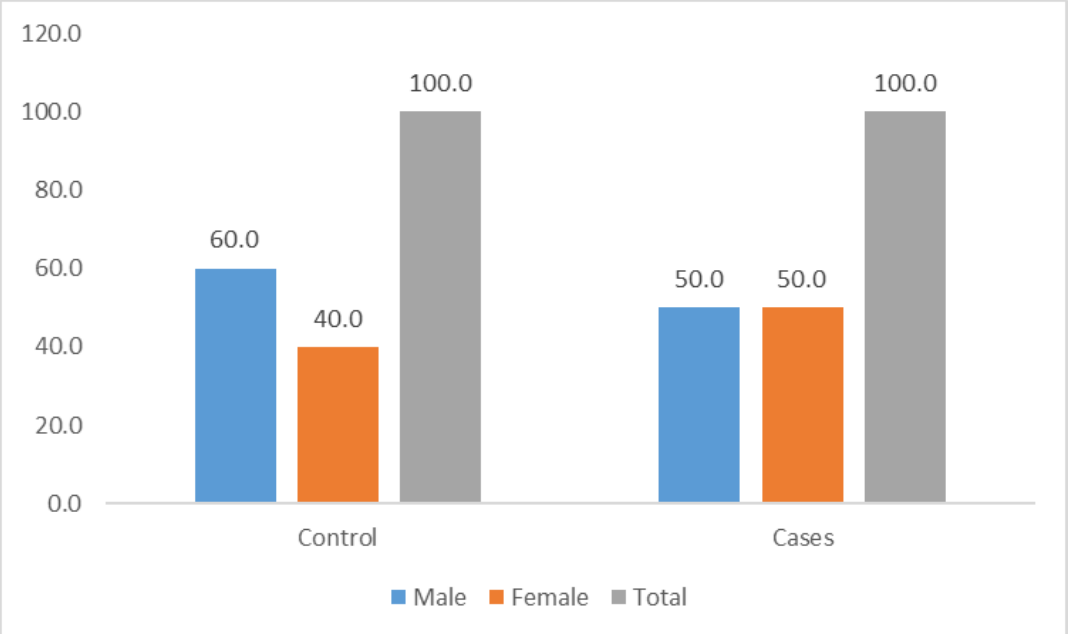

Figure 1: Distribution of study subjects based on gender

Majority of the study subjects in control (70%) and cases (75%) consumed chlorpyrifos type of poison followed by 25% of study subjects in both the groups consumed monocotrophos type poison (Table 2).

Table 2: Distribution of study subjects based on type of poison consumed

Variables	Control		Cases	
	N	%	N	%
Chlorpyrifos	14	70.0	15	75.0
Monocotrophos	5	25.0	5	25.0
Ethion	1	5.0	-	-

The mean CPK levels of study subjects in control and cases was represented in Table 3. Results depicted that there was a statistically significant (p-0.000) decrease in mean CPK levels was observed in study subjects of cases groups as compared to control group based on students t-test (Table 3).

Table 3: Comparision of CPK levels among study subjects

	Control	Cases
Initial CPK Levels		
Mean ± SD	2552.60 ± 4356.47	642.35 ± 116.11
Minimum	433	456
Maximum	16782	808
Final CPK Levels		
Mean ± SD	1480.35 ± 2921.54	333.85 ± 168.08
Minimum	110	86
Maximum	12500	756
p-value	0.068	0.000

The results of distribution of study subjects based on ventilatory support and mortality was represented in Table 4. These findings delineated that out of total 20 subjects in control group 3 subjects required ventilator support, Whereas, in cases group none of the subjects required ventilator support. There was no mortality observed in both control and cases groups.

Table 4: Distribution of study subjects based on ventilatory support and mortality

Variables	Control		Cases	
	N	%	N	%
Ventilator support requirement				
Yes	3	15.00	0	0.00
No	17	85.00	20	100.00
Mortality				
Yes	0	0.00	0	0.00
No	20	100.00	20	100.00

We found high degree of correlation between initial & final CPK value and duration of ICU stay, ventilator support requirements & mortality. The correlation was found to be statistically significant ($p < 0.001$) in each case (Table 5).

Table 5: Correlation between the initial and final CPK value (IU/L) and ICU stay (days), ventilator support requirement, and mortality

Correlation between	Pearson's co-efficient	p-value	Comments
Control Group			
Initial CPK value and ICU stay	1.000	SS	Direct correlation
Initial CPK value and ventilator support	0.711	SS	High degree correlation
Initial CPK value and Mortality	1.000	SS	Direct correlation
Final CPK value and ICU stay	1.000	SS	Direct correlation
Final CPK value and ventilator support	1.000	SS	Direct correlation

Final CPK value and Mortality	1.000	SS	Direct correlation
Cases Group			
Initial CPK value and ICU stay	1.000	SS	Direct correlation
Initial CPK value and ventilator support	1.000	SS	Direct correlation
Initial CPK value and Mortality	1.000	SS	Direct correlation
Final CPK value and ICU stay	1.000	SS	Direct correlation
Final CPK value and ventilator support	1.000	SS	Direct correlation
Final CPK value and Mortality	1.000	SS	Direct correlation

IV. Discussion

OP insecticides are arguably one of the commonest causes of morbidity and mortality due to poisoning worldwide, especially in developing countries like India. The morbidity and mortality outcome depends on time lag between exposure and the onset of management. With increase in use of OP compounds for agricultural and industrial purposes and due to easy access and low cost, they are becoming a major source of health hazard. So, it is cardinal to recognize the entire spectrum of the symptoms. Identification, risk stratification, early diagnosis and prompt treatment of OP poisoning victims are equally vital. OP poisoning cases are classically treated with atropine and oximes; but these methods are sometimes shown to be of limited benefit. Hence, in the present study we aimed to evaluate the efficacy of FFP transfusion in prevention of IMS following OP poisoning.

In our study, majority of the study subjects i.e., 50% each were in the age group of 21-30 years in control and cases groups. The mean age of study subjects in control and case groups was found to be 34.75 ± 15.28 and 36.65 ± 19.34 respectively. Male predominance (60%) was observed in control group as compared to females (40%). Whereas in cases group, equal distribution of males (50%) and females (50%) was observed. These findings were comparable with the previous studies reported in the literature.[12-14]

Raghavendra Mural et al reported that Chlorpyrifos (23.4%) was the most commonly used compound followed by Methyl parathion (21.9%) and Dichlorvos (18.8%).[13] These findings in concurrence with our study findings wherein we found more than 70% of study subjects consumed chlorpyrifos type of poison followed by monocotrophos type poison (25%).

In our study, there was a statistically significant (p value -0.000) decrease in mean CPK levels was observed in study subjects transfused with FFP along with standard OP poisoning treatment. Furthermore, none of the subjects required ventilator support following transfusion of study subjects with FFP along with standard OP poisoning. We found direct correlation between initial & final CPK value and duration of ICU stay, ventilator support requirements & mortality. Moreover, the correlation was found to be statistically significant (p value< 0.001) in each case. These findings were in accordance with Bhattacharyya et al., and Raghavendra Mural et al., wherein authors demonstrated high degree of correlation between CPK levels and the severity of poisoning.[12,13]

Guven et al., in their partially randomized controlled prospective study has two groups *viz.* FFP group and control group]. In FFP group (12 patients); 11 patients received both pralidoxime & atropine and one patient received atropine only. Plasma therapy was started after the 2nd day in 9 of 11 patients that received pralidoxime + atropine and the only patient that received atropine only, the remaining 2 patients were given FFP after developing intermediate syndrome (IMS). In the control group (21 patients); twenty patients received pralidoxime + atropine and one patient received atropine only. In FFP group, no cases of death or IMS developed in those given FFP before developing intermediate syndrome (0/9), while, the two patients who received FFP after developing intermediate syndrome and the one received FFP+atropine died. In the control group, 28.6% (6/21) developed intermediate syndrome, and 14.3% (3/21) patients died. Hence, Guven et al., concluded that FFP is effective for preventing mortality and improving the outcome from OP toxicity however it is not effective in the neuromuscular system.[3] These findings were further supported by various other researchers.[15,16]

V. Conclusion

In conclusion, it was demonstrated from our study that transfusion of FFP along with standard OP poisoning was effective in prevention of IMS following OP poisoning since there was significant reduction in CPK levels observed. Furthermore, none of the subjects suffering from IMS required ventilator support following transfusion of study subjects with FFP. Hence, treatment of IMS cases following OP poisoning with FFP was proved effective, and therefore FFP transfusion could be recommended for early management of IMS following OP poisoning since it can improve the clinical outcome through decreasing mortality, duration ICU stay and the need of ventilator support.

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