

FRESH FROZEN PLASMA AS AN ADJUNCTIVE THERAPY IN MODERATE TO SEVERE ORGANOPHOSPHATE POISONING: A PROSPECTIVE EVALUATION

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ABSTRACT

Background: Organophosphate poisoning continues to be a leading cause of morbidity and mortality worldwide. This is especially relevant for people from developing countries where the exposure to agricultural pesticides is high. The conventional treatment of atropine and oximes in severe cases often proves to be insufficient because of the persistent inhibition of acetyl cholinesterase. Recently, it has been suggested that FFP could help in the regeneration of the enzyme and improve the outcome. **Aims and Objectives:** To evaluate the efficacy of Fresh Frozen Plasma as an adjunctive therapy in patients with moderate to severe organophosphate poisoning, and its effect on clinical recovery, requirement of atropine and ventilator support and mortality. **Materials and Methods:** This clinical trial included 100 patients with moderate to severe organophosphate poisoning presenting to the emergency medicine department of a J.J.M. Medical College, Davangere. Ethical approval and informed consent were obtained. Diagnosis was based on clinical history, characteristic symptoms, and low serum cholinesterase levels. All patients received standard therapy - gastric lavage, atropine, and oximes - while the study group received additional received Fresh Frozen Plasma (FFP) at doses adjusted to enzyme inhibition and clinical severity. Baseline data of age, sex, duration of exposure, and severity of poisoning, with outcomes (serum cholinesterase recovery, atropine requirement, need and duration of ventilation, Hospital stay and mortality were noted and compared between groups. Patients with mixed/unknown poisoning, hepatic dysfunction, or without consent were excluded. **Results:** These were statistically analyzed to assess the efficacy of FFP as adjunctive therapy. The study enrolled 100 patients who had moderate to severe organophosphate poisoning. Most of them being males aged 31–40 years with agricultural exposure. Both groups were comparable at the baseline regarding age, sex, and poisoning severity. Patients receiving Fresh Frozen Plasma (FFP) in addition to standard therapy, with early restoration of serum cholinesterase levels, shorter duration of mechanical ventilation, and lower atropine requirement, and shorter hospital stay than the control group, with $p < 0.05$. The mortality rate was also lower for the FFP group, with no major transfusion-related adverse effects noted. A statistical comparison revealed significant improvements in atropine requirements, ventilatory support, and hospital stay were significant with $p < 0.05$. **Conclusion:** This is a prospective study on 100 patients presenting with moderately severe organophosphate poisoning, demonstrated that FFP as an adjunctive therapy significantly improved outcome. The administration of FFP resulted in quicker recovery, earlier restoration of serum. It improves cholinesterase activity, reduces atropine requirement, shortens ventilation duration, hospital stay and mortality compared with standard therapy alone. Thus, FFP seems to be a good adjuvant in the management of moderate to severe organophosphate poisoning. Larger multicentric studies are needed to confirm these results and develop standardized treatment protocols.

INTRODUCTION

OP poisoning continues to be a public health issue, particularly in developing nations where there continues to be widespread application of agricultural pesticides in agrarian societies. There continue to be both accidental and intentional exposures that account for morbidity and mortality, with thousands of cases reported globally each year.^[1,2] The toxicity of organophosphates is the result of acetylcholinesterase inhibition, causing an accumulation of acetylcholine, and culminates in cholinergic receptor overstimulation, which may present as muscarinic, nicotinic, or central nervous system signs and symptoms.^[3] Essential components for the management of OP poisoning still include decontamination, followed quickly by treatment with atropine for muscarinic symptoms and oximes for reactivation of acetylcholinesterase. Even in optimal situations, the final effect in moderate and severe cases of OP poisoning remains limited despite acceptable conventional therapies. Contributing factors are the inhibition of the enzyme, thresholds for cholinesterase regeneration, and continued ventilator support which contribute to mortality and length of stay.^[4,5]

More recent studies have explored the adjunctive use of FFP in treatment, given its capacity to restore plasma cholinesterase and thereby assist in detoxification of organophosphate compounds. FFP administration may therefore facilitate faster enzyme recovery, improve clinical status, and reduce the need for mechanical ventilation.^[1,6]

Given these potential benefits, the present prospective study was undertaken to evaluate the Efficacy of Fresh Frozen Plasma as an Adjuvant to Conventional Treatment in Patients with Moderate to Severe Organophosphate Poisoning Admitted to a Tertiary Care Hospital.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, hospital-based clinical study that was conducted in the Department of Emergency Medicine at J.J.M. Medical College, Davangere for a period of 2019 to 2020. A total of 100 patients diagnosed with moderate to severe organophosphate poisoning were enrolled following ethical approval from the Institutional Ethics Committee. Informed consent was obtained from all patients or their legally authorized representatives before inclusion in the study.

Patients and Methods

Patients who present to the emergency department with either a history or clinical suspicion of the diagnosis of organophosphate poisoning was made based on history of exposure, clinical manifestations such as miosis, fasciculations, excessive secretions, altered mental status, and confirmation by reduced serum cholinesterase levels.

The patients were treated with standard therapy that included gastric lavage, atropine, and oxime. The study group received Fresh Frozen Plasma (FFP) transfusion as an adjunctive therapy in addition to the standard regimen. The dose and Number of FFP units were decided based on the degree of cholinesterase inhibition and clinical severity.

Demographic data such as age, sex, duration of exposure, and severity of poisoning were recorded. The clinical parameters included recovery of serum cholinesterase activity, total atropine requirement, duration of mechanical ventilation, hospital stay duration, and mortality. Assessed and compared between the groups.

Inclusion Criteria

- Patients clinically diagnosed with moderate to severe organophosphate poisoning.
- Age ≥ 18 years.
- Patients admitted within 24 hours of exposure.
- Patients or attendants who provided written informed consent.

Exclusion Criteria

- Patients with mixed or unknown poisoning.
- Patients with chronic liver disease or coagulation disorders.
- Pregnant or lactating women.
- Patients who refused consent for participation.

Sample Size Calculation

The sample size was calculated using the following standard formula:

$$n = \frac{Z^2 \times p \times q}{d^2}$$

Where:

- n = required sample size
- Z = standard normal deviate at 95% confidence level (1.96)
- p = estimated proportion of patients showing improvement with adjunctive therapy
- (taken as 0.70 from previous studies)
- q = 1 - p
- d = allowable error (0.09)

$$n = \frac{(1.96)^2 \times 0.70 \times 0.30}{(0.09)^2} \approx 89.5$$

Thus, ensuring adequate power for study, at least 90 patients were required, which justified the total of 100 patients to take into account possible dropouts.

Randomization and Blinding

Patients who met the inclusion criteria were randomly assigned to one of two groups of 50 patients each. Selection bias was minimized, using randomization with a computer-generated randomization table.

- **Group A** (Control Group) received standard therapy (gastric lavage, atropine, and oximes).
- **Group B** (Study Group) received standard therapy + Fresh Frozen Plasma (FFP) transfusion. Complete blinding due to the nature of the intervention was not possible; however, the treating clinicians were aware of the group allocation, whereas laboratory personnel who estimated Serum

cholinesterase levels and the statisticians who analyzed the data were blinded to maintain objectivity and minimize observer bias.

Procedure

Upon admission, a complete history was obtained including the type and route of exposure, the estimated quantity ingested and the time from exposure. A thorough examination was done and baseline investigations were undertaken including, complete blood counts and liver, renal function tests and serum cholinesterase levels were collected.

Patients were stabilized using appropriate emergency protocols. Atropine was administered until at least 2 mg/kg of atropinization was achieved, and then continued as needed. Oxime therapy (pralidoxime) was given intravenously according to standard protocols per weight. The study patients also received Fresh Frozen Plasma transfusion (10-15 mL/kg body weight) over 30 to 45 minutes, and was repeated should clinical examination warrant it based on enzyme levels and severity of symptoms.

The patients were monitored continuously for vital parameters, oxygen saturation and neurology status. The need for mechanical ventilation was determined by standard protocols for lungs.

Observations and Parameters Collected

- All patients had the following observations documented as clinical parameters: Age, sex, and occupational background.
- Duration between exposure and hospital admission.
- Severity of poisoning based on Peradeniya Organophosphorus Poisoning (POP) scale.
- Serum cholinesterase levels at admission and during follow-up.
- Total atropine dose required for clinical recovery.
- Need and duration of mechanical ventilation.
- Duration of hospital stay.
- Outcome (recovered / deceased).
- Any adverse transfusion reactions observed after FFP administration.

All parameters were recorded daily until either discharge or death Statistical Analysis

Statistical Analysis

The quantitative data was collected and analyzed using SPSS software version 20.0 Continuous variables are expressed as mean $\pm$ standard deviation (SD), while categorical variables are expressed as percentages. Comparison of means was done using Student's t-test and Chi-square test when appropriate. A p-value < 0.05 was considered significant.

RESULTS

A total of 100 patients with moderate to severe organophosphate poisoning were enrolled and randomly divided into two equal groups of 50 each. Baseline demographic and clinical Characteristics were comparable across groups. Most of the patients were males and predominantly belonged to the age group of 31–40 years. Interval between exposure and time of admission to hospital and severity grading using the Peradeniya Organophosphorus Poisoning (POP) scale was also comparable between groups, indicating effective randomization. Baseline serum cholinesterase levels did not significantly differ between the Groups A (standard therapy) and B (standard therapy+ FFP) ($p > 0.05$).

Adjunctive Fresh Frozen Plasma administered to the patients resulted in faster biochemical and clinical recovery than standard therapy alone. Group B demonstrated a much greater rise in serum cholinesterase levels following treatment and a significantly lower mean total atropine requirement, and a shorter duration of mechanical ventilation, all with a $p < 0.05$ value. Mean hospital stay was significantly reduced in the FFP group. Overall recovery rate was higher and mortality lower in the patients who got FFP, and no major transfusion-related adverse Events were observed. Statistical analyses confirmed that the differences between the two groups regarding atropine requirement, ventilatory duration, and length of stay were statically significant ($p < 0.05$).

Table 1: Distribution of study population according to age

Age group (years)	Group A (Standard therapy)	Group B (FFP + Standard therapy)	Total (n=100)
18–30	14 (28%)	16 (32%)	30 (30%)
31–40	18 (36%)	17 (34%)	35 (35%)
41–50	10 (20%)	9 (18%)	19 (19%)
>50	8 (16%)	8 (16%)	16 (16%)
Total	50 (100%)	50 (100%)	100 (100%)

Table 1 shows the age-wise distribution of patients in both groups.

Table 2: Gender distribution among the study population

Gender	Group A (Standard therapy)	Group B (FFP + Standard therapy)	Total (n=100)
Male	33 (66%)	31 (62%)	64 (64%)
Female	17 (34%)	19 (38%)	36 (36%)
Total	50 (100%)	50 (100%)	100 (100%)

Table 2 describes the gender-wise distribution of patients in both groups.

Table 3: Distribution according to severity of poisoning (POP scale)

Severity (POP Scale)	Group A (Standard therapy)	Group B (FFP + Standard therapy)	Total (n=100)
Moderate	28 (56%)	27 (54%)	55 (55%)
Severe	22 (44%)	23 (46%)	45 (45%)
Total	50 (100%)	50 (100%)	100 (100%)

Table 3 shows the distribution of cases based on the severity of organophosphate poisoning at admission.

Table 4: Comparison of mean serum cholinesterase levels (IU/L)

Time interval	Group A (Mean $\pm$ SD)	Group B (Mean $\pm$ SD)	p-value
At admission	1100 $\pm$ 250	1120 $\pm$ 270	0.68 (NS)
After therapy	1800 $\pm$ 320	2650 $\pm$ 350	<0.001*

NS = Not significant; p < 0.05 considered significant.

Table 4 highlights the mean serum cholinesterase levels at admission and after therapy in both groups.

Table 5: Comparison of total atropine requirement (mg)

Parameter	Group A (Mean $\pm$ SD)	Group B (Mean $\pm$ SD)	p-value
Total atropine dose (mg)	160 $\pm$ 40	110 $\pm$ 30	<0.001*

Table 5 depicts the mean total dose of atropine required for clinical recovery in both groups.

Table 6: Comparison of duration of mechanical ventilation (hours)

Parameter	Group A (Mean $\pm$ SD)	Group B (Mean $\pm$ SD)	p-value
Duration of mechanical ventilation (hours)	48.6 $\pm$ 10.2	32.4 $\pm$ 8.5	<0.001*

Table 6 shows the comparison of mean duration of ventilatory support required in both groups.

Table 7: Comparison of hospital stay duration (days)

Parameter	Group A (Mean $\pm$ SD)	Group B (Mean $\pm$ SD)	p-value
Duration of hospital stay (days)	8.2 $\pm$ 1.8	5.6 $\pm$ 1.4	<0.001*

Table 7 highlights the mean duration of hospitalization among both groups.

Table 8: Outcome of patients in both groups

Outcome	Group A (Standard therapy)	Group B (FFP + Standard therapy)	Total (n=100)
Recovered	44 (88%)	48 (96%)	92 (92%)
Death	6 (12%)	2 (4%)	8 (8%)
Total	50 (100%)	50 (100%)	100 (100%)

Table 8 describes the overall clinical outcome among patients of both groups.

Table 1 depicts the distribution of patients by age; most are in the 35%, were from the 31–40 years age group, followed by 18–30 years (30%), while 19% were between 41–50 years, and 16% above 50 years of age. Table 2 describes the gender distribution, with males at 64% and females at 36%, reflecting the higher occupational exposure of men to organophosphate compounds. Table 3 shows the severity of poisoning, as evaluated by the Peradeniya Organophosphorus Poisoning (POP) scale, with 55% of patients presenting with moderate poisoning and 45%, severe poisoning, suggesting that the sample represented a genuine clinic prevalent spectrum of toxicity. In Table 4, the mean serum cholinesterase levels before and after treatment among different groups can be observed. The mean baseline enzyme level was similar in Group A, 1100 $\pm$ 250 IU/L, and likewise in Group B, 1120 $\pm$ 270 IU/L. Post-treatment, there was a considerable rise in the FFP group enzyme level (2650 $\pm$ 350 IU/L) as compared to standard therapy (1800 $\pm$ 320 IU/L) and suggests a faster return for enzyme activity. Table 5 compares the total atropine requirement, which was significantly lower in patients receiving FFP (110 $\pm$ 30 mg) versus standard therapy alone (160 $\pm$ 40 mg), thus indicating better cholinergic control. Table 6 is the mean duration of mechanical ventilation for the

FFP group, as well as the standard group, which is less - 32.4 $\pm$ 8.5 hours compared to 48.6 $\pm$ 10.2 hours - providing further confirmations of improved respiratory recovery. Table 7 represents the duration of hospital stay, showing that patients in the FFP group had a shorter mean stay of 5.6 $\pm$ 1.4 days compared to 8.2 $\pm$ 1.8 days in the standard therapy group, reflecting quick clinical improvement and discharge. Finally, the overall patient outcomes, as shown in Table 8 are: 96% recovery in the FFP group against 88% in the control group, with a corresponding mortality of 4% and 12%, respectively.

No major in addition, no transfusion-related adverse events were observed in any patient, further confirming that Fresh Frozen Plasma was well-tolerated and an effective adjunctive therapy in moderate to severe organophosphate poisoning.

DISCUSSION

The present prospective study was undertaken to evaluate the efficacy of Fresh Frozen Plasma (FFP) as adjuvant therapy in patients with moderate to severe organophosphate poisoning admitted to a tertiary care hospital. Organophosphate compounds exert their toxic effects by inhibition of

acetylcholinesterase, leading to excessive cholinergic stimulation and multi-system involvement. Despite the use of conventional therapy with atropine and whereas the morbidity and mortality in serious cases are high, oximes are used. Thus, Newer adjunctive approaches, including FFP transfusion, have been explored to enhance recovery by restoring plasma cholinesterase levels and enhancing detoxification.^[7] In the current study, FFP administration in addition to standard treatment led to more rapid biochemical and clinical improvement as compared to standard therapy alone. The patients who received FFP had a significantly higher post-treatment rise in serum cholinesterase levels, reduced atropine requirement, and shorter duration of mechanical ventilation. This indicates that the FFP therapy could accelerate the restoration of cholinesterase activity, thereby improving the overall clinical course. The mean duration of hospital stay was also significantly shorter, among patients receiving FFP, which attests to early recovery and less treatment burden.^[8,9]

These findings are in line with the results of other studies, which have shown that Beneficial effects of FFP in organophosphate poisoning. Numerous randomized trials, observational analyses, and meta-analyses have documented quicker enzyme recovery, a reduced number of ventilation days, and decreased doses of atropine with the use of extracorporeal or plasma-based adjuncts along with conventional therapy.^[10-12] In contrast, there are a few publications reporting some variation in outcomes likely related to the timing, dosing, and severity at presentation, highlighting the variability among FFP protocols used in the acute setting, calling for greater standardization of FFP protocols in ensuing clinical trials.^[13]

The positive clinical outcomes in this study may be associated with the early use of FFP that restored circulating levels of cholinesterase and inactivated any unbound organophosphate molecules. Furthermore, early FFP transfusions may lead to reduced respiratory complications and length of ventilatory support requirements. The overall recovery rate of 96% and mortality of 4% add weight to the observations in this study. Finally, and supporting its use as an adjunct to care, there were no significant transfusion-related adverse events associated with FFP: thus, validating the use of FFP as a safe and well-tolerated option in the acute care setting.^[7,8,14]

While the outcomes are promising, there are a number of limitations that must be recognized. The study was carried out in one tertiary care centre with a relatively small sample size, and there was no long-term follow-up to assess for delayed neurological sequelae. Further multicentric large trials are needed to verify these findings and to determine optimal timing and dose of FFP administration for the greatest therapeutic benefit.^[12,15]

In conclusion, the results of this prospective review demonstrate that Fresh Frozen Plasma is a valuable adjunct in standard therapy for both biochemical and

clinical recovery in moderate to severe organophosphate poisoning with improved survival and decreased length of stay.

CONCLUSION

This present prospective study shows that FFP as an adjuvant to standard therapy with Atropine and oxime has a significant positive impact on clinical outcomes in 100 patients with moderate to severe organophosphate poisoning. Patients administered FFP had faster restoration of serum cholinesterase levels (mean post-treatment 2650 ± 350 IU/L vs. 1800 ± 320 IU/L; $p < 0.001$), lower total atropine requirement (110 ± 30 mg vs. 160 ± 40 mg; $p < 0.001$), and a shorter duration of mechanical ventilation (32.4 ± 8.5 h vs. 48.6 ± 10.2 h; $p < 0.001$) compared to patients receiving standard therapy alone. The hospital stay was shorter (5.6 ± 1.4 days vs. 8.2 ± 1.8 days), while Mortality was lower, 4% vs. 12%, among those treated with FFP.

No major transfusion-associated adverse events were observed, indicating that Fresh Frozen Plasma (FFP) is safe and tolerated as an adjunctive treatment option. FFP promotes recovery and is linked with lower complications associated with organophosphate poisoning by replenishing plasma cholinesterase and facilitating detoxification of organophosphate compounds in circulation. FFP is an effective and safe adjunctive therapy in patients with moderate to severe organophosphate poisoning that improves survival and hastens clinical recovery when used as part of the standard treatment protocol. Larger multicentric studies are recommended in order to confirm these findings and provide standardized protocols for its use in acute organophosphate toxicity.

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