ABSTRACT
Background: Organophosphate (OP) poisoning is an important reason for hospitals and intensive care units admission in the developing countries. OP poisonings are classically treated with atropine and oximes. These methods are sometimes shown to be of limited benefit. Objective: Assessment of the effectiveness of the management with fresh frozen plasma (FFP) in improving the outcome of patients with acute OP poisoning. Patient and Methods: A randomized clinical trial study was conducted upon 70 acute OP poisoning patients that were referred to the Emergency Department, Suez Canal University Hospital, Ismailia, Egypt. These patients were randomly divided into two groups (35 each); Control group: Treated with the traditional management protocol of OP (atropine and oximes). FFP group: Treated with the conventional management protocol of OP plus FFP. Results: No significant difference was found in cholinesterase level on admission between both groups, Serum cholinesterase level in the FFP group significantly increased after an hour of FFP infusion (2.48 iu/ml vs. 10.36 iu/ml p<0.0001). There is a significant difference between both groups regarding the duration of their hospital stay (2.43 ± 0.5 days for FFP group vs. 3.06 ± 1.4 days for control group; p<0.01) and intensive care unit admission (4 patients in FFP group vs. 12 patients in the control group; p<0.04). Conclusion Early management with FFP may be an effective method for the management of acute OP poisoning, as it can improve the clinical outcome through decreasing mortality, duration of hospital stay and the need for ICU admission.

KEYWORDS Forensic Sciences, Toxicology, Organophosphate poisoning, fresh frozen plasma, outcome.

Introduction
Organophosphorus pesticides are used widely for agriculture and domestic purposes. Organophosphate (OP) poisoning is an increasing worldwide problem, particularly in the tropics more than in the industrialized world [1]. OP is an important reason for hospitals and intensive care units admission in the developing countries [2]. Moreover, it is responsible for more than 200,000 deaths each year in those countries [3]. The main factors responsible for the widespread of OP are its easy availability and unawareness of the poorly educated farmers in that countries [4].

In 2005, analysis of intoxicated cases presented to Poison Control Center, Ain Shams University, Egypt revealed that insecticides intoxication represented 49% of the total number of chemical poisoning and that 55% (2201 cases) of those insecticide intoxication cases were due to OP poisoning. One-hundred and forty-four OP patients required intensive care unit admission, out of them 28 patients had died [5].

Organophosphorus compounds act by phosphorylation of...
were treated with the traditional management protocol of OP as with FFP [6]. Due to the contradictory results regarding the use of FFP for treating acute OP poisoning, this study was conducted to assess the effectiveness of the management with FFP in improving the outcome of patients with OP poisoning.

**Patients and methods**

This is a randomized clinical trial study. It was conducted upon seventy OP poisoned patients that were referred to the Emergency Department, Suez Canal University Hospital, Egypt. It received approval from the Institutional Review Board Ethical Committee of the Suez Canal University, Faculty of Medicine, Ismailia, Egypt. It was conducted by the guidelines of the Helsinki Declaration. The study participants were randomly chosen, any age and both genders were included, initial diagnosis of OP toxicity was based on history & clinical toxidrome (bronchорrhea, defecation, confusion, diarrhea, lacrimation, emesis, miosis, muscle fasciculations, salivation, urination, seizures, and weakness) [13] & Serum cholinesterase level less than 20% of normal value (<4 iu/mL). Patients suspected of having mixed exposure, pregnant/lactating females, and those who refused to participate in the study were excluded. Also, patients suffering from deep vein thrombosis, congestive heart failure, valvular heart diseases were excluded from the study, as these cases are contraindicated to take fresh frozen plasma. The 70 patients were randomly divided into two groups (35 each); Control group: Those who were treated with the traditional management protocol of OP. FFP group: Those who were treated with the traditional management protocol of OP as control group plus fresh frozen plasma (FFP). Both groups underwent the traditional management protocol of OP in the form of supportive measures (if necessary), 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: 2-4 mg IV (pediatric dose; 0.05 mg/kg) as a test dose. If there is no effect; the dose is doubled every 5 minutes until the endpoint of atropinization (clearance of chest secretions), once signs of adequate atropinization occur, the dose adjusted to maintain this effect for at least 24 hours [5]. Oximes: 1g IV (pediatric dose 25-50mg/kg) given in normal saline over 5 to 10 minutes, it is repeated every 6 to 12 hours for minimum 24 to 48 hours until signs resolve[14]. The FFP group received FFP in a dose of 20ml/kg after half an hour of hospitalization (time required for preparing the frozen FFP for intravenous administration and emergency management of the patient). The researcher collected the clinical data in a pre-designed data sheet for each patient; it included the following: Socio-demographic data: age, gender, residence, marital status and occupation. Data related to Poisoning: Mode of poisoning, route of poisoning, time of exposure and time of hospital arrival, Clinical evaluation: Regarding eye signs, skin, temperature, respiratory system, cardiovascular, gastrointestinal tract, central nervous system, musculoskeletal system and urinary system for signs of toxicity, Investigations: (complete blood count, random blood sugar, serum electrolytes, blood urea nitrogen, serum creatinine, creatine kinase MB, chest X-ray, electrocardiography ECG and arterial blood gases), Serum cholinesterase level: it was measured twice: at arrival time and after an hour of completing FFP infusion (by using chemical analyzer Cobase 411 apparatus, USA). The study was performed after approval from institutional research ethics committee.

**Statistical analysis**

Data were coded and analyzed by using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Qualitative data were expressed as frequency and percentages; quantitative data were expressed as the mean and standard deviation (SD). Independent t-test was used to test the significance of differences between means of the quantitative variables to compare between the two groups. Chi-square test was used for qualitative variables to test the significance of differences between the two groups. Fisher’s exact test was used to test the importance of the difference in the outcome of both study groups. P value of <0.05 is considered significant.

**Results**

The participant’s socio-demographic characteristics of both groups are summarized in Table 1; it shows that they are homogeneous regarding age, gender, residence, marital status and occupation (P>0.05). Table 2 shows that the most frequent route of exposure is inhalation in both groups, and the most frequent mode of intoxication is accidental poisoning in both groups. It also shows that both groups are also homogeneous regarding their circumstances of intoxication; their clinical presentation is provided in Table 3.

Both groups are also homogeneous regarding laboratory, radiological and ECG finding as shown in Table 4;

it also indicates that compensated metabolic acidosis is the prominent ABG finding of both groups. Regarding cholinesterase level, no significant difference was found in cholinesterase level on admission between both groups (2.48 IU/ml for FFP group vs. 2.24 IU/ml for control group; P>0.05) Table 4, Serum cholinesterase level in the FFP group significantly increased from 2.48 IU/ml on admission to 10.36 IU/ml after an hour of FFP infusion (p<0.0001). The current study demonstrated a significant difference between both groups regarding the duration of their hospital stay (2.43± 0.5 days for FFP group vs. 3.06 ± 1.4 days for control group; p<0.01) as in Table 5. Four patients were ICU admitted in FFP group vs. 12 patients in the control group; p<0.04, while 18 patients have discharged after observation in the Emergency Room in FFP group vs. 6 patients in the control group; p<0.005 table 5.

**Discussion:**

OP poisoning is a serious health problem in developing countries; it is associated with significant mortality and morbidity [15]. The mortality following OP ingestion ranges from 20 to 50% [16-17-18].

As traditional management protocol of OP toxicity that included atropine and pralidoxime has shown to be less effective,
Continuous search for new modalities has been attempted [19]. Fresh frozen plasma (FFP) that is rich in butyrylcholinesterase (BuChE; plasma or pseudocholinesterase) has been used to neutralize free toxin [12]. BuChE could be sufficient for sequestration of OPs in the circulation before they inhibit AChE at target sites [20]. One molecule of BuChE is required to neutralize one molecule of OP; hence, a large quantity of BuChE may be needed for neutralization and inactivation of less potent OP insecticides [3]. BuChE serves as a backup to AChE in supporting and regulating cholinergic transmission [21]. Administration of plasma dilutes patient’s plasma volumes; these may also provide a beneficial effect in clearance of OPs [22-23]. BuChE activity is maintained in banked blood up to 7 days in FFP [24] and its half-life in healthy subjects given 460 ml of plasma was found to be ten days [25].

Guven et al., [2] in their partially randomized controlled prospective study has two groups [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) (proximal muscle paralysis including muscles that innervated by motor cranial nerves, neck muscles, and respiratory muscle [2]). 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. They concluded that FFP is effective for preventing mortality and improving the outcome from OP toxicity however it is not effective in the neuromuscular system. Their results agree with other studies that concluded that administration of plasma cholinesterase by plasmapheresis was shown to be beneficial for patients with acute OP toxicity [26,27].

The results of the present study agreed with those of the previously mentioned studies. The present study revealed that FFP significantly increased Pseudo-Cholinesterase level from 2.48 ± 0.7 U/ml at admission time to 10.36 ± 1.9 U/ml (p < 0.0001). An improvement in the clinical outcome was also observed in the form of decreased duration of hospital stay (2.43 ± 0.5 days in FFP group vs. 3.06 ± 1.4 days in control group; p<0.01). Table 6, 18 patients were released from emergency room after observation in FFP group vs. 6 patients in the control group (p<0.005), ICU admission in the FFP group was 4 vs. 12 patients in the control group (p<0.04). In the present study three patients died in the control group while no mortality was recorded in FFP group.

On the other hand, Pazooki et al., [28] conducted a randomized clinical trial on 56 patients; where 28 of them received four packs of FFP as stat dose at the onset of the treatment + atropine + pralidoxime administered in moderate and severe cases only. No significant effects on the consumption doses of atropine and pralidoxime, hospitalization length and mortality rate of OP patients was detected. The results of this study are in line with those of Pichamuthu et al., [6] in their pilot open label, three-arm, randomized controlled study. They concluded that, although FFP increased pseudocholinesterase levels significantly in FFP group (as detected in the present study), more cases of the intermediate syndrome were observed in FFP group compared to albumin and saline groups. Furthermore, the mortality rates, atropine requirements, duration of hospital stay were similar in the three groups. Additionally, two patients developed adverse effects with FFP. The authors of this study questioned their results due to the small sample size and inability to blind the study which might lead to bias in the outcome measures [6].

It was recorded that large amounts of BuChE are required to neutralize OP and should be administered early before AChE inhibition. Pichamuthu et al., [6] related the lack of response to FFP to the possibility that low quantities of free OP were in the circulation by the time therapy was administered (cases

### Table 1 Socio-demographic characteristics of the participants in both groups.

|                      | FFP group (n=35) | Control group (n=35) | P value |
|----------------------|------------------|----------------------|---------|
| **Age**<sup>b</sup> |                  |                      |         |
| Range                | 16 – 60          | 18 – 60              | t = 0.11 |
|                      | P = 0.91         |                      |         |
| **Gender**<sup>a</sup> |                  |                      |         |
| Male                 | 15 42.9%         | 19 54.3%             | P = 0.34 |
| Female               | 20 57.1%         | 16 45.7%             |         |
| **Residence**<sup>a</sup> |                |                      |         |
| Rural                | 21 60 %         | 23 65.7%             | P = 0.8 |
| Urban                | 14 40 %         | 12 34.3%             |         |
| **Marital status**<sup>a</sup> |               |                      |         |
| Single               | 20 57.1%        | 18 51.4%         | P=0.81  |
| Married              | 15 42.9%        | 17 48.6%             |         |
| **Occupation**<sup>a</sup> |                |                      |         |
| Student              | 19 54.3%       | 20 57.1%            | P=0.97  |
| Farmer               | 13 37.1%        | 12 34.3%             |         |
| Housewife            | 3 8.6%          | 3 8.6%               |         |

<sup>b</sup>: student t test; <sup>a</sup>: chi square test; FFP: fresh frozen plasma.
Table 2  Circumstances of intoxication among the participants in both groups:

|                        | FFP group (n=35) | Control group (n=35) | P value |
|------------------------|------------------|----------------------|---------|
| **Route of intoxication** |                  |                      |         |
| Oral                   | 9 (25.7%)        | 8 (22.9%)            |         |
| Inhalation             | 21 (60.0%)       | 19 (54.2%)           | P= 0.65 |
| Dermal                 | 5 (14.3%)        | 8 (22.9%)            |         |
| **Mode of intoxication** |                  |                      |         |
| Homicidal              | 4 (11.5%)        | 3 (8.6%)             | P= 0.91 |
| Suicidal               | 11 (31.4%)       | 12 (34.3%)           |         |
| Accidental             | 11 (57.1%)       | 20 (57.1%)           |         |
| **Time interval between exposure and hospital arrival (hours)** | 2.54 ± 0.8 | 2.51± 0.7 | t = 0.167 |
| Mean ± SD              | 1 - 4            | 2 – 4                | P= 0.87 |
| Range                  |                  |                      |         |

*b* ±: student t test; *a*: $X^2$ = chi square test; FFP: fresh frozen plasma

presented up to 12 hours after exposure were included and they did not mention when FFP administration correctly started; referred to in day 1, not the exact timing), while in the present study the lag of time was shorter in FFP group (FFP administered 30 minutes after hospitalization) which means that more free OP compounds might have been circulating leading to more efficient results in the present study. Pichamuthu et al., [6] also postulated that FFP could bind the OP compound without detoxifying it then releasing it over time.

Other factors might be responsible for the difference in results among various studies as it was noticed that Pazooki et al., [28] administered FFP as four packs as stat dose (they did not mention the time lag between exposure and hospitalization), however, they did not detect positive clinical outcome in their study. On the hand, although Guven et al. [2] administered FFP starting from the 2nd day, they recognized positive clinical outcome, which might be due to the administration of repeated doses for several days until reaching BuChE $\geq$ 2100 UI/L.

In Pichamuthu et al., [6] study; oximes were not administered to the patients, while in the present study and Guven et al. [2], oximes were used in moderate to severe cases. This might have promoted favorable outcome in those studies. Oximes have shown protective effects against OP. Hence they are widely used in treating OP in humans. They can be efficient in moderate to severe poisoning where the patient has immediately been hospitalized for treatment (within 6 hours) [29]. A significant improvement in OP/ enzyme stoichiometry may be achieved by combining enzyme pretreatment with oxime reactivation [30-31-32].

Eddleston et al., [33] reported that chemical structure of the OP compound might determine its toxicity and its clearance from plasma, so each OP is considered as an individual poison. Furthermore, different OP compounds appear to bind to BuChE with different affinities. It was found that dimethoate had a lesser BuChE inhibition despite the median concentration being much higher than that of chlorpyrifos or fenthion. Therefore, a raised BuChE activity may be more useful for organophosphate compounds such as chlorpyrifos that are highly bound to the enzyme, compared with dimethoate that is a poor inhibitor of BuChE. This might explain why different OP compounds respond differently to FFP which might account for the difference in results between various studies.

The length of preservation and the manner of freezing of the FFP might also be responsible for the differences in the results among various studies as they were recorded to reduce cholinesterase activity by 30% [34].

The study concluded that early management with a large dose of fresh frozen plasma (FFP) might be an effective method that can be used in the treatment of OP toxicity. BuChE in FFP was able to improve the clinical outcome through decreasing mortality, duration of hospital stay and reducing the need for ICU admission.

**LIMITATIONS OF THE STUDY**

Although we used a larger sample size than that used in Pichamuthu et al., [6] the sample size was still small and the study could not be blinded which might have introduced some bias into the results. Additionally, the type of the organophosphorus compound could not be precisely detected from history and diagnosis was based on clinical toxidrome of cholinergic and nicotinic manifestations. It is worth to mention that the particular type of OP was not determined in the present study. This might be responsible for the differences in the results of various studies, as different OP might respond differently to FFP therapy. As in all previously mentioned studies the dose of FFP
Table 3 Clinical signs and symptoms of the participants in both groups at admission time.

| Signs and symptoms of toxicity | FFP group (n=35) | Control group (n=35) |
|--------------------------------|------------------|----------------------|
| Eye                            |                  |                      |
| Miosis                         | 31               | 35                   |
| Hyper lacrimation              | 19               | 20                   |
| Conjunctival congestion        | 14               | 8                    |
| Skin                           |                  |                      |
| Normal                         | 4                | 2                    |
| Dry                            | 18               | 20                   |
| Moist                          | 11               | 11                   |
| Cyanosis                       | 2                | 0                    |
| Pallor                         | 5                | 2                    |
| Jaundice                       | 2                | 0                    |
| Temperature                    |                  |                      |
| Normal                         | 28               | 29                   |
| Hypothermic                    | 7                | 6                    |
| Gastrointestinal system        |                  |                      |
| Nausea/vomiting                | 8                | 4                    |
| Abdominal colic                | 4                | 3                    |
| Diarrhea                       | 4                | 3                    |
| Hypersalivation                | 33               | 32                   |
| Respiratory system             |                  |                      |
| Rate (cycle/min) $^a$          | 17.9 ± 0.66      | 18.06 ± 0.54         |
| Wheezes                        | 9 25.7           | 11 31.4              |
| Crackles                       | 22 62.89         | 21 60                |
| Oxygen saturation $^a$         | 94.97 ± 2.4      | 95.1 ± 2.13          |
| Cardiovascular system          |                  |                      |
| Pulse (beat/min) $^a$          | 81.4 ± 7.03      | 80.57 ± 6.7          |
| SBP (mmHg)$^a$                 | 129.4 ± 18.14    | 130.3 ± 19.47        |
| DBP (mmHg)$^a$                 | 74.8 ± 9.8       | 75.7 ± 11.45         |
| Central nervous System         |                  |                      |
| Confusion                      | 17               | 19                   |
| Agitation                      | 16               | 16                   |
| Convulsion                     | 2                | 0                    |
| Musculoskeletal system         |                  |                      |
| Weakness                       | 25               | 22                   |
| Fasciculation                  | 10               | 13                   |
| Urinary system                 |                  |                      |
| Urinary incontinence           | 21               | 22                   |

$^a$ mean± SD; FFP: fresh frozen plasma

SBP: systolic blood pressure; DBP: diastolic blood pressure
Table 4  Laboratory and radiological findings in all participants at time of admission:

|                      | FFP group (n=35) | Control group (n=35) | p-value |
|----------------------|------------------|----------------------|---------|
| CBC                  |                  |                      |         |
| Normal               | 35 100%          | 35 100%              |         |
| Abnormal             | 0 0%             | 0 0%                 |         |
| PT(sec) \(^2\) \(^b\) | 13.11± 0.32      | 13.14 ± 0.36         | 0.714   |
| RBS \(^b\)          | 131.3± 90.6      | 114.23 ± 85.4        | 0.420   |
| Serum Na \(^b\)     | 135.23± 1.46     | 135.22 ± 1.47        | 0.977   |
| Serum K \(^b\)      | 3.97± 0.36       | 4.01 ± 0.37          | 0.648   |
| BUN \(^b\)          | 25.49± 7.61      | 26.54 ± 8.77         | 0.594   |
| Serum creatinine \(^b\) | 0.78± 0.15     | 0.74 ± 0.16          | 0.284   |
| CK MB \(^b\)        | 24.8± 11.65      | 24.9 ± 11.62         | 0.971   |
| Chest X-ray \(^d\)  |                  |                      |         |
| Normal               | 17 48.6%         | 18 51.4%             | 0.811   |
| Pulmonary edema      | 18 51.4%         | 17 48.6%             |         |
| ECG \(^a\)          |                  |                      |         |
| Normal               | 33 94.3%         | 34 97.4%             | 0.555   |
| ST elevation         | 2.5 %            | 1.3 %                |         |
| ABG finding \(^a\)  |                  |                      |         |
| Compensated metabolic acidosis | 27 77.1% | 25 71.4% | 0.35 |
| Uncompensated metabolic acidosis | 8 22.9% | 8 22.9% |         |
| Respiratory acidosis | 0 0%             | 2.5 %                |         |
| Cholinesterase levels at admission time | 2.48 ± 0.7 | 2.24± 0.5 | 1.34 |
| Cholinesterase levels 1 hour after treatment | 10.36 ± 1.9 | 3.1 ± 0.9 | .0001* |

\(^a\): Chi square test; \(^b\): Student t test;  
\(^*\) statistically significant (p-value <0.05; FFP: fresh frozen plasma)
Table 5 Outcome of the participants in both groups:

| Outcome                                      | FFP group (n=35) | Control group (n=35) | (Fisher’s exact test ) p-value |
|----------------------------------------------|------------------|----------------------|--------------------------------|
| Discharged after observation in,ER.          | 18 (51.5%)       | 6 (17.1%)            | 0.005**                        |
| Inpatient admission.                        | 13 (37.1%)       | 14 (40%)             | 1.0                            |
| ICU admission.                               | 4 (11.4%)        | 12 (34.3%)           | 0.04*                          |
| Death                                        | 0 (0%)           | 3 (8.6%)             | 0.24                           |
| Duration of Hospital stay (days) b           | 2.43±0.5         | 3.06±1.4             | t = 2.51, P=0.01*               |

* Statistically significant (p-value <0.05); ICU: intensive care unit; * * highly statistically significant; FFP: fresh frozen plasma;

b: Student t-test

was not determined according to the activity of AChE enzymes and severity of toxicity.

Conclusion

Early management with FFP may be an effective method for the management of acute OP, as it can improve the clinical outcome through decreasing mortality, duration of hospital stay and the need for ICU admission.

Competing Interests

Written informed consent obtained from the patient for publication of this case report and any accompanying images.

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