Effectiveness of Fresh Frozen Plasma as Supplementary Treatment in Organophosphate Poisoning

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SUMMARY
With the establishment of the inadequate efficiency of atropines and oximes in reducing morbidity and mortality of patients poisoned by organophosphates, more attention is given to using other methods such as Fresh Frozen Plasma (FFP) as a bioscavenger to mop up organophosphate toxins. This randomized clinical trial was conducted on 56 organophosphate poisoned patients who were randomly assigned to the FFP and control groups in order of admission. The routine treatment in both groups included atropine and, in moderate to severe cases of poisoning, pralidoxime. The FFP group received four packs of FFP as stat dose at the beginning of treatment. No significant difference was seen between the two groups on the atropine and pralidoxime dosage, hospitalization length and mortality. The present study showed that using four packs of FFP as stat dose at the onset of treatment had no significant effect on the clinical course of organophosphate poisoned patients.

KEY WORDS:
Organophosphate poisoning, FFP, Pralidoxime

INTRODUCTION
Organophosphate poisoning (OP) poses a serious health and clinical problem in the world in general and in the developing countries in particular. The gravity of the problem is so severe that more than 3 million OP's are reported annually with a mortality rate of more than 200 thousand deaths caused by intentional or accidental OP. The classic treatment for this poisoning includes supportive treatment, atropine and oximes (including pralidoxime). However, several studies show that atropines and oximes fail to prevent morbidity and mortality in these patients. Oximes have been widely studied and have shown protective effects under lab conditions against OP; hence coming to widespread use in treating OP in humans. However, the results of the studies on humans are not confirmatory and meta-analyses have yet to show their efficacy and it is only shown that oximes can be efficient in moderate to severe poisoning where the patient has immediately (within 6 hours of toxicity) been hospitalized for treatment. This, however, comprises a mere 15% of total OP cases. Other studies have shown that not only are oximes inefficient in treating OP but they may also pose certain harms, making their use in these patients cautionary. Therefore, other treatment methods for OP are warranted.

Today, various methods have been attempted for the treatment of OP, including magnesium, hemoperfusion and alkalinisation (on humans) and N-acetyl cysteine (NAC), diazepam, clonidine and adenosine receptor antagonists (on animals). Since neutralizing toxins has always been a treatment goal, today bioscavengers have taken center stage to mop up free organophosphates. Such treatments may include the use of enzymes such as cholinesterase to block organophosphate compounds before reaching the toxicity threshold. Therefore, in some human studies fresh frozen plasma (FFP) has been researched as a source for butyrylcholinesterase (BuChE) (pseudo- or nonspecific cholinesterase) as a treatment method for OP. Guven et al. were first to examine the effect of plasmapheresis using FFP on a patient poisoned by organophosphates and then in a partially randomized controlled study, they investigated the efficacy of FFP on 12 patients and compared the results with those of 21 patients receiving conventional treatment. However, another study in 2010 could not confirm the efficacy of FFP in OP patients. Since using FFP is a new treatment method revealing contradictory results in previous few studies, the present preliminary study attempts to examine the effect of four packs of FFP as stat dose for supplementary treatment in managing patients poisoned by OP.

MATERIALS AND METHODS
The present randomized clinical trial (RCT) study was performed on 56 OP patients referring to Vali-Asr Hospital (Arak, Iran) in 2006-2008. OP was confirmed using clinical signs and symptoms (sweating, bradycardia, miosis, diarrhea and wheeze) and through observation of poison and its properties and, if suspicious, by checking serum pseudocholinesterase level. For this purpose, after centrifuging 5cc of patient blood, the blood serum was separated and frozen at -20°C to check the cholinesterase level in the reference laboratory (Logman Hakim Medical Health Education Center, Tehran). In the lab, the serum was exposed to crystallized acetylthiocholine so that pseudocholinesterase enzyme would turn yellow and measured through gauging the wavelength of the color. Levels below 1800 IU were considered to be enzyme disorder. Study exclusion criteria included FFP contraindications such as simultaneous consumption of warfarin/ heparin, congestive heart failure (CHF), deep vein thrombosis (DVT), thromboemboli, valvular heart diseases and decreased consciousness level (GCS<4). Patients meeting the inclusion...
criteria were randomly assigned to FFP (conventional treatment plus FFP) and control (conventional treatment) groups in order of admission. The present study was conducted in compliance of the Declaration of Helsinki research ethics principles (1 and 2) and the ethical principles advised by Iranian Ministry of Health. Ethical approval was properly secured from the Arak University Ethical Committee and written informed consents were obtained from patients’ families.

Both the FFP and control groups underwent conventional procedures in poisoning cases, receiving atropine and, in cases of moderate to severe poisoning, pralidoxime. Atropine was administered at multiple steps: 1 mg as stat dose at the onset, 1 mg in 5 minutes, 2 mg within next 5 minutes, and followed by 4 mg within next 5 minutes until when the patient showed atropine poisoning symptoms (max. stat dose: 25 mg). Atropine poisoning symptoms include dry mouth, flushing, tachycardia, miosis, constipation and dry skin. Atropine administration is regulated on the basis of the emerged clinical symptoms. In moderate to severe poisoning, pralidoxime is administered by infusion at 3 mg/kg/hr until when poisoning symptoms emerge. The FFP group received 4 packs of FFP as stat dose at the onset of the treatment.

Recorded patient data included age, sex, baseline clinical signs and symptoms, atropine and pralidoxime dosage, hospitalization length and mortality. Qualitative variables were measured using frequency and percentage statistics and quantitative variables were measured using the mean (standard deviation, SD) and median (inter-quartile range, IQR) values. A chi-square test and Mann-Whitney U test were performed to compare the two groups. Significance level was set at P<0.05.

RESULTS
There were 28 (50%) male patients and the age range of 21 patients (38%) was 20-30. The groups were homogeneous in terms of sex and age group (P>0.05, Table I). The prevalence of baseline clinical signs and symptoms in all patients was as follows: sweating in 53 patients (95%), bradycardia in 48 patients (86%), miosis in 47 patients (84%), diarrhea in 34 patients (61%) and wheeze in 31 patients (55%). The two groups did not differ significantly on clinical signs and symptoms (P>0.05, Table I).

The mean (SD) and median (IQR) values for atropine consumption in all patients were 9.27±3.016 mg and 77 (26-241) mg, respectively. The mean (SD) and median (IQR) values for pralidoxime consumption in all patients were 709.3±753.9 mg and 4000 (2000-11500) mg, respectively. The two groups did not differ significantly on atropine or pralidoxime consumption dose (P>0.05, Table II).

DISCUSSION
The results of the present study on 56 patients showed that using four packs of FFP as stat dose at the onset of the treatment had no significant effects on the consumption doses of atropine and pralidoxime, hospitalization length and mortality rate of OP patients. Although no RCT study has yet been conducted on the efficacy of pure butyrylcholinesterase in treating OP patients (human studies), until the feasibility of stage III RCT studies on humans is made possible, FFP, which is rich in cholinesterase, has earned attention. Guven has reported on the efficacy of FFP in an OP case during plasmapheresis 18. In his another study on 33 OP patients, 21

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Table I: Demographic characteristics and clinical signs and symptoms at admission time

<table>
<thead>
<tr>
<th></th>
<th>FFP group (n=28)</th>
<th>Control group (n=28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (57%)</td>
<td>12 (43%)</td>
<td>0.285*</td>
</tr>
<tr>
<td>Female</td>
<td>12 (43%)</td>
<td>16 (57%)</td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 20</td>
<td>4 (14%)</td>
<td>5 (18%)</td>
<td>0.820*</td>
</tr>
<tr>
<td>20-30</td>
<td>10 (36%)</td>
<td>11 (40%)</td>
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</tr>
<tr>
<td>31-40</td>
<td>5 (18%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>4 (14%)</td>
<td>4 (14%)</td>
<td></td>
</tr>
<tr>
<td>More than 50</td>
<td>5 (18%)</td>
<td>6 (21%)</td>
<td></td>
</tr>
<tr>
<td>Clinical signs &amp; symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>27 (96%)</td>
<td>26 (93%)</td>
<td>1.000$</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>25 (89%)</td>
<td>23 (82%)</td>
<td>0.705$</td>
</tr>
<tr>
<td>Miosis</td>
<td>24 (86%)</td>
<td>23 (82%)</td>
<td>1.000$</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (64%)</td>
<td>16 (57%)</td>
<td>0.584*</td>
</tr>
<tr>
<td>Wheeze</td>
<td>16 (57%)</td>
<td>15 (54%)</td>
<td>0.788*</td>
</tr>
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* Fisher’s Exact test, $ Chi square test

Table II: Treatment characteristics

<table>
<thead>
<tr>
<th></th>
<th>FFP group (n=28)</th>
<th>Control group (n=28)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine dose (mg)</td>
<td>673 ± 1590</td>
<td>63 (28-241)</td>
<td>0.935</td>
</tr>
<tr>
<td>Pralidoxime dose (mg)</td>
<td>6700 ± 8133</td>
<td>3100 (600-10000)</td>
<td></td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>3 ± 3</td>
<td>2 (1-4)</td>
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* Mann-Whitney U test
patients received atropine and pralidoxime and 10 patients received two packs of FFP on a daily basis from the second day of treatment up to the time when they needed atropine. In addition, two patients received FFP after developing intermediate syndrome. Although intermediate syndrome happened in 28.8% of the patients in the routine treatment group, it was not seen in any of the patients in the FFP group. Mortality was 18.2% in the routine treatment group, but was absent in the FFP group except for those two patients who received FFP after developing intermediate syndrome. In Guven’s study, although atropine and pralidoxime dosages were not different in the two groups, the final conclusion was that FFP could prevent intermediate syndrome and mortality thereof and was recommended for treatment of OP patients especially when pralidoxime was not used. In spite of this recommendation, the quality of Guven’s study was reported as low in a review article about alternative therapies in OP patients done by Peter et al. (16). In addition, Pichamuthu et al. reported that although FFP could increase butyrylcholinesterase, it failed to benefit the clinical treatment course of poisoning; moreover, more intermediate syndrome cases were observed in the FFP group compared with the control and albumin groups. Furthermore, the atropine consumed dose, hospitalization length, the need to mechanical ventilation and mortality were not significantly different either between the groups. The results of our study is much in line with those of the aforesaid studies as it shows no significant difference in the two groups in atropine and pralidoxime consumption dose, hospitalization length and mortality. Therefore, one may conclude that use of FFP, either in stat dose (as in our study) or in a constant dose (as in Guven’s and Pichamuthu’s), results in no significant effect on the treatment and consequences of OP.

Although it is generally claimed that butyrylcholinesterase remains active in plasma up to seven days and some studies have shown that butyrylcholinesterase may lead to the sequestration of organophosphates in the blood circulation before inhibiting the acetylcholinesterase in target areas, other reasons could account for the inefficacy of FFP in the treatment of OP patients. On the one hand, the length of preservation and the manner of freezing the plasma may affect acetylcholinesterase activity and reduce cholinesterase activity by 30%. On the other hand, organophosphate toxins enjoy a high half-life due to accumulation in fatty tissues and consequently their gradual release. In addition, in the studies conducted so far (including ours) the required FFP dosage was not set according to the level of butyrylcholinesterase enzyme level in the patient in order to make a clearer evaluation of the role of FFP in the treatment of OP patients.

Although the present study is one of the few that examined the effect of FFP on OP patients, we did not measure the patients’ butyrylcholinesterase enzyme level since we had only used static dosage of FFP. Since conventional treatment of OP using atropine and pralidoxime had no significant effect on the mortality of patients, the authors intend to expand on this preliminary study by maintaining the butyrylcholinesterase level at a given value through FFP and then examine the efficacy of FFP on these patients.

CONCLUSION

The present study showed that using four packs of FFP as stat dose at the onset of treatment had no significant effect on atropine and pralidoxime dosage, hospitalization length and the mortality of organophosphate poisoned patients. Since the effect of butyrylcholinesterase as prophylaxis for prevention of OP is mentioned earlier, further studies are highly recommended to use a larger sample size and different dosages of FFP commensurate with the butyrylcholinesterase level of patients in order to demonstrate the efficacy of FFP in OP patients.

REFERENCES


