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REVIEW ARTICLE

Effectiveness of Fresh Frozen Plasma in Management of Acute Organophosphate Intoxicated Patients: An Updated Systematic Review and Meta-Analysis

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Abstract

Background: Organophosphate (OP) poisoning is still a major health concern in both developed and developing countries. The standard treatment approaches of (OP) poisoning are not always available as well so they may show a limited success rate. Fresh frozen plasma (FFP) is one of Bio-scavengers that have been suggested as a useful therapy through elimination of free organophosphates. Therefore, this systematic review and meta-analysis was conducted to update the present evidence about the efficacy of FFP in management of acute OP-intoxicated patients.
Method: A computer literature search of PubMed and Scopus was conducted to identify the relevant randomized controlled trials (RCTs). In addition, a manual search of reference lists of the retrieved articles was conducted. Relevant outcomes were pooled as mean difference (MD) risk ratio (RR) by RevMan version 5.3 for Windows.
Results: Pooled data from 3 RCTs (169 patients) showed that adding FFP to conventional therapy to acutely OP intoxicated patients did not improve clinical outcomes regarding total atropine (MD = 35.05, 95% CI = [-41.14 to 111.24], P-value = 0.37) and pralidoxime dosages (MD = -0.41, 95% CI = [-2.34 to 1.51], P-value = 0.67), length of hospital stay (MD = -2.08, 95% CI = [-4.51 to 0.35], P-value = 0.09) and mortality (RR = 0.42, 95% CI = [0.14 to 1.27], P-value = 0.12).
Conclusion: Fresh frozen plasma did not provide any additional benefit in acutely-OP intoxicated patients compared to the conventional therapy. The limited number and sizes of the included trials are the most probable cause of such effects.

Keywords: Atropine; Fresh Frozen Plasma**;** Meta-analysis; Organophosphate; Pralidoxime

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INTRODUCTION

Organophosphates (OP) are greatly effective acetylcholinesterase (AChE) inhibitors widely used in agriculture as inexpensive, available pesticides(1). OP poisoning is still a major health concern in both developed and developing countries (2, 3).

Clinical manifestations of toxicity include early acute cholinergic crisis due to inhibition of AChE, intermediate syndrome (IMS) secondary to neuromuscular necrosis and lately organophosphate-induced delayed neuropathy (OPIDN) due to inhibition of neuropathy target esterase (NTE) (4).

The standard treatment approaches of OP poisoning comprise supportive critical care treatment with specific antidotal therapy as atropines and oximes (5). However, oximes are not always available as well so they may show a limited success rate. Their value in organophosphate poisoning is still a matter of debate in the medical community (6, 7). Furthermore, the absence of a standardized dose for both atropine and oximes is another difficulty during the clinical practice (8). Consequently, there seems to be critical need to find available, cheap and safe alternatives.

Previous studies have reported novel treatment modalities for management of OP toxicity. Fresh frozen plasma (FFP) is one of the bio-scavengers that has been suggested as a useful therapy through elimination of free OP (9). The effectiveness of plasma transfusion in severe malathion toxicity by reactivating the inhibited enzyme, its albumin content, and volume restoration were shown (10), while other studies proved the limited value of FFP in improving the outcomes in severely poisoned patients (5, 6).

Therefore, we conducted this systematic review and meta-analysis to update the present evidence about the efficacy of FFP in management of acute OP-intoxicated patients.

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METHODS

We followed the PRISMA statement guidelines during the preparation of this systematic review and meta-analysis.

Criteria for considering studies for this review

We used the following inclusion criteria:

(1) Study design: Randomized controlled trials comparing FFP with standard treatment (oximes, atropine).

(2) Intervention:

- FFP
- Dose: all available doses

(3) Comparator: standard (Std) treatment group

(4) Population: Acute OP intoxicated patients

(5) Outcome: At least one of the following outcomes (total atropine dose, total oximes dose, hospital stay length and death)

We excluded studies in the following conditions:

1- Studies on nerve gas rather than Ops.
2- Studies that used albumin in management.
3- Review articles.
4- Case reports.
5- Conference abstracts.
6- Studies unavailable in English language.

Literature search strategy

We searched medical electronic databases: PubMed and Scopus from inception till January 2017 using the following queries: ((organophosphate) OR organophosphorus) AND plasma.

Selection of studies

Two authors (Nafea. O and Saptan. F) applied the selection criteria. Eligibility screening was performed in two steps: the first step was to screen abstracts and in the second step, full-text articles of eligible abstracts were retrieved and screened in terms of eligibility for meta-analysis.

Data Extraction

Three authors (Ramadan. A, Ghanem. S, and Ahmed. M) extracted the data independently using an online data extraction form. The extracted data included the following:

1) Characters of study design
2) Characters of study population
3) Risk of bias domains
4) Study outcomes: total doses of atropine and pralidoxime administered, duration of hospitalization and mortality.

Data were exported from the online form into an MS Excel sheet, and other authors (Nafea. O OR Saptan. F) resolved the disagreements.

Assessment of bias risk in included studies

Two authors (Ahmed. M and Nafea. O) independently assessed the quality of each included study in strict accordance with the Cochrane handbook of systematic reviews of interventions 5.1.0 (updated March 2011). We used the quality assessment table provided in (part 2, Chapter 8.5) the same book.

Data Synthesis

Total doses of atropine and pralidoxime and duration of hospitalization were pooled as MD (mean difference). Mortality was pooled as risk ratio (RR) with a 95% CI in a meta-analysis model. We used RevMan version 5.3 for Windows to conduct the analysis.

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of the forest plots and measured by I-square and Chi-Square tests. In case of a significant heterogeneity (Chi-Square $P<0.1$), sensitivity analysis was performed to resolve heterogeneity. Sensitivity analysis was performed using leave-one-out method, i.e. removing one study each time and repeating the analysis to make sure that none of the included studies affected the results and to resolve any significant heterogeneity.

Publication bias

"We intended to assess publication bias using funnel plot techniques, Begg's rank test and Egger's regression test, as the appropriate known limitations of these methods given." (11)

RESULTS

1. Flow and characteristics of included studies

Our search retrieved 6,928 articles. Following the removal of duplicates and abstract screening, only 8 articles were eligible for full-text screening. Finally, 3 randomized

Table 1. Summary of the methods and results of included studies

Study	Country	Design	Intervention	Population	Results
Güven et al., (20)	Turkey	Partially randomized controlled trial	FFP (variable no. of units) *vs* std treatment	OP intoxication was diagnosed on the basis of history and BuChE levels	Elevated BuChE levels, prevent the development of IMS, increase the survival
Pazooki et al., (11)	Iran	Randomized controlled trial	FFP (4 units, at the onset of treatment) *vs* std treatment	OP intoxication was diagnosed clinically, laboratory (BuChE level) and by observation of the suspected poison	FFP showed no benefits on atropine and pralidoxime dose, hospitalization length and the survival
Dayananda et al., (14)	India	Randomized controlled trial	FFP(Daily reducing dose for 3 successive days) *vs* std treatment	Moderately to severely OP intoxicated patients. Diagnosis based on history, clinical presentation, BuChE level and and by observation of the suspected poison	Daily reducing dose of FFP therapy showed beneficial effect (elevated BuChE levels, reduced the total dose of atropine, reduced hospital stay, zero mortality)

Abbreviations; std, standard treatment, FFP-Fresh Frozen Plasma, OP-Organophosphate, BuChE -butyrylcholinesterase, IMS- Intermediate syndrome

controlled trials with 169 patients were eligible for the final analysis (Figure 1). In total, 80 and 89 patients were assigned to FFP group and to standard treatment group consecutively.

The summary of the included studies' main results are shown in Table 1. The baseline characteristics of their populations are shown in Table 2.

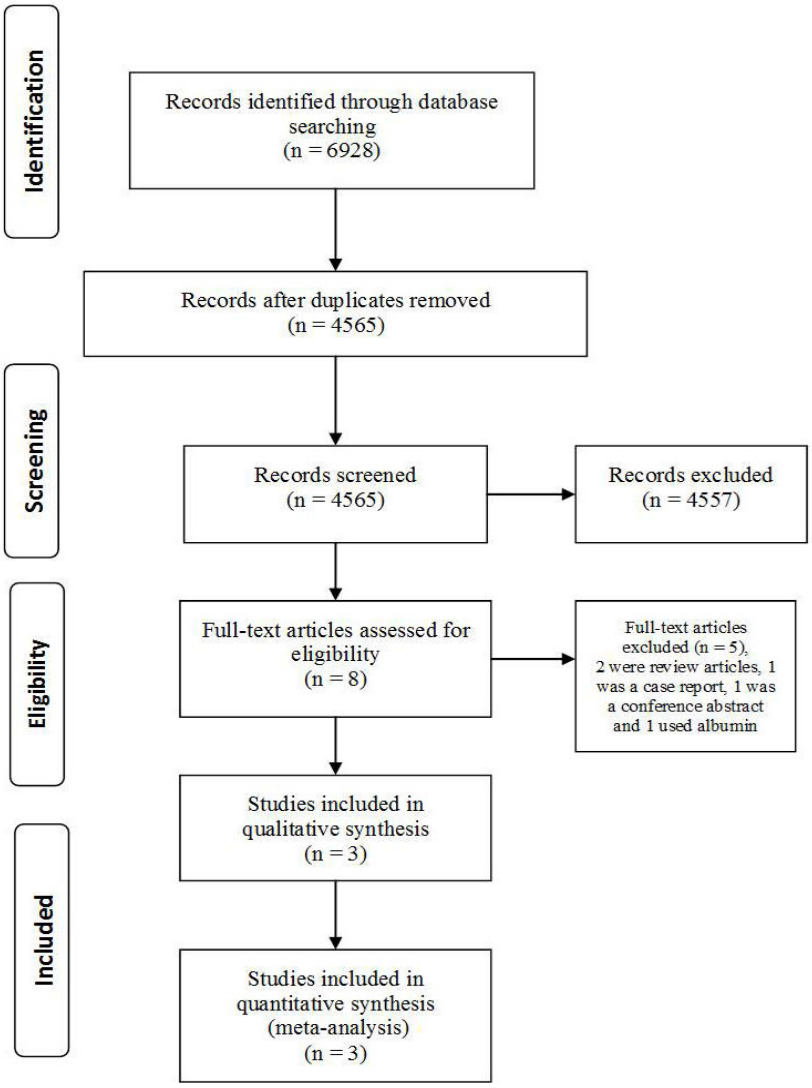

Figure 1. The PRISMA flow diagram of studies' screening and selection.

Table 2. Shows the baseline characteristics of enrolled patients in included studies.

Study	Group	Sex		Age N (%)					Total atropine (mg) Mean (SD)	Total pralidoxime (mg) Mean (SD)	Length of stay at ICU (days) Mean (SD)	Mortality N (%)
		M N (%)	F N (%)	< 20	20-30	31-40	41-50	>50				
Dayanada et al.,(14)	FFP	22(55)	18(45)	2(5)	18(45)	8(20)	10(25)	2(5)	-----	-----	8.35(4.3)	0(0.0)
	std	30(75)	10(25)	6(15)	12(30)	6(15)	10(25)	6(15)	-----	-----	12.45(4.13)	6(15)
Pazooki et al., (11)	FFP	16(57)	12(43)	4(14)	10(36)	5(18)	4(14)	5(28)	673(1590)	6700(8133)	3(3)*	1(3.6)
	std	12(43)	16(57)	5(18)	11(40)	2(7)	4(14)	6(21)	1180(3984)	7486(7022)	5(5)*	1(3.6)
Guven al., (20)	FFP	-----	-----	-----	-----	-----	-----	-----	175.8(110.7)	6100(3100)	9(3.22)	2(16.6)
	std	-----	-----	-----	-----	-----	-----	-----	139.5(101.8) (21)	6400(2800) (20)	8.71(4.53)	3(14.2)

* Indicates length of hospital stay.

2. Quality of included studies

According to "The Cochrane Collaboration risk of bias assessment tool", the quality of the included studies ranged from moderate to high. The summary of quality assessment domains of included studies is shown in Figure 2.

3. Assessment of the outcomes

3.1. Total Atropine dose

The mean difference of changes in the total atropine dose did not indicate the preference to add FFP to standard treatment (MD = 35.05, 95% CI = [-41.14 to 111.24], P-value = 0.37) (Figure 3A). All pooled studies were homogenous (P-value = 0.5, $I^2 = 0$ %).

3.2. Total Pralidoxime dose

The mean difference of change in total Pralidoxime dose did not show any significant effect for adding FFP to standard treatment (MD = -0.41, 95% CI = [-2.34 to 1.51], P-value = 0.67) (Figure 3B). Both pooled studies were homogenous (P=0.83, $I^2 = 0$%).

3.3. Length of hospitalization

The mean difference of change in length of hospitalization did not show a significant effect for adding FFP to standard treatment (MD = -2.08, 95% CI = [-4.51 to 0.35], P-value = 0.09) (Figure 3C). However, pooled studies were not homogenous (P-value = 0.03, I^2 = 73%). Heterogeneity was best resolved by excluding the study of Dayananda et al. (P-value = 0.19, $I^2 = 42$%).

3.4. Mortality

The pooled analyses of mortality show an insignificant need for adding FFP to standard treatment (RR = 0.42, 95% CI = [0.14 to 1.27], P-value = 0.12) (Figure 3D). Pooled studies were homogenous (P-value = 0.2, $I^2 = 39$%).

4 Publication Bias

Publication bias was not assessed as there were inadequate numbers of included trials to properly assess a funnel plot or more advanced regression-based assessments (12).

DISCUSSION

The present meta-analysis of data from 3 randomized controlled trials (RCTs) showed that adding FFP to conventional therapy of acute-OP intoxication patients did not improve clinical outcomes as it did not influence the total atropine and pralidoxime doses, length of hospital stay and/or mortality.

Dayananda et al. (13) showed that FFP improves the patients' outcome. They explained their results by the ability of FFP to neutralize organophosphate toxins as a source of BuChE.

However, other studies showed that the use of four packs of FFP as a start dose had no significant effect on the clinical outcome of organophosphate poisoned patients. The administration of FFP did not improve the response to the traditional clinical course of acute organophosphate poisoning (14, 15). Nonetheless, the ability of FFP to scavenge organophosphorus by increasing BuChE levels is still controversial (15-17). Meanwhile, there was a minimum evidence of consistent benefit from using FFP infusion either as a prophylactic or therapeutic setting (18).

FFP shows a limited efficacy in the following situation; (i) intake of massive amounts of OP pesticides in case of a suicidal poisoning that overwhelms the detoxifying capacity of transfused FFP and/or (ii) late use of FFP may allow complete absorption of pesticides and distribution through systemic circulation into the target tissues (18).

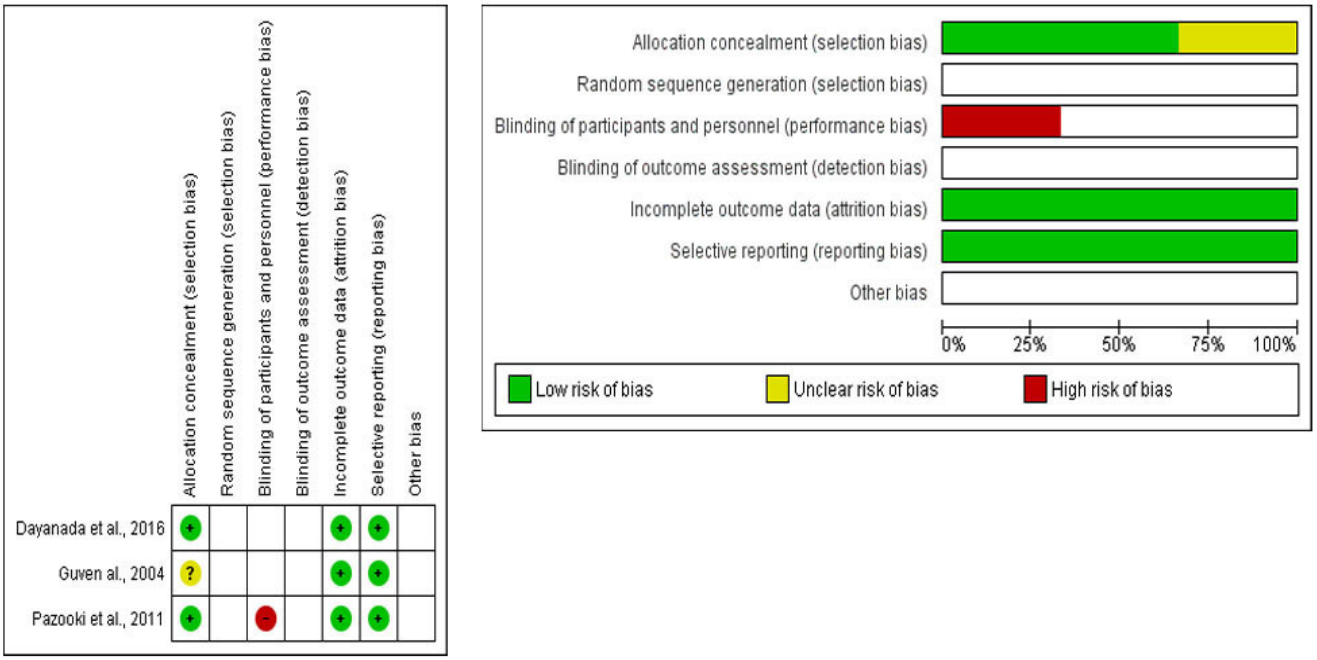

Figure 2. Summary of risk bias according to Cochrane Risk of Bias assessment tool.

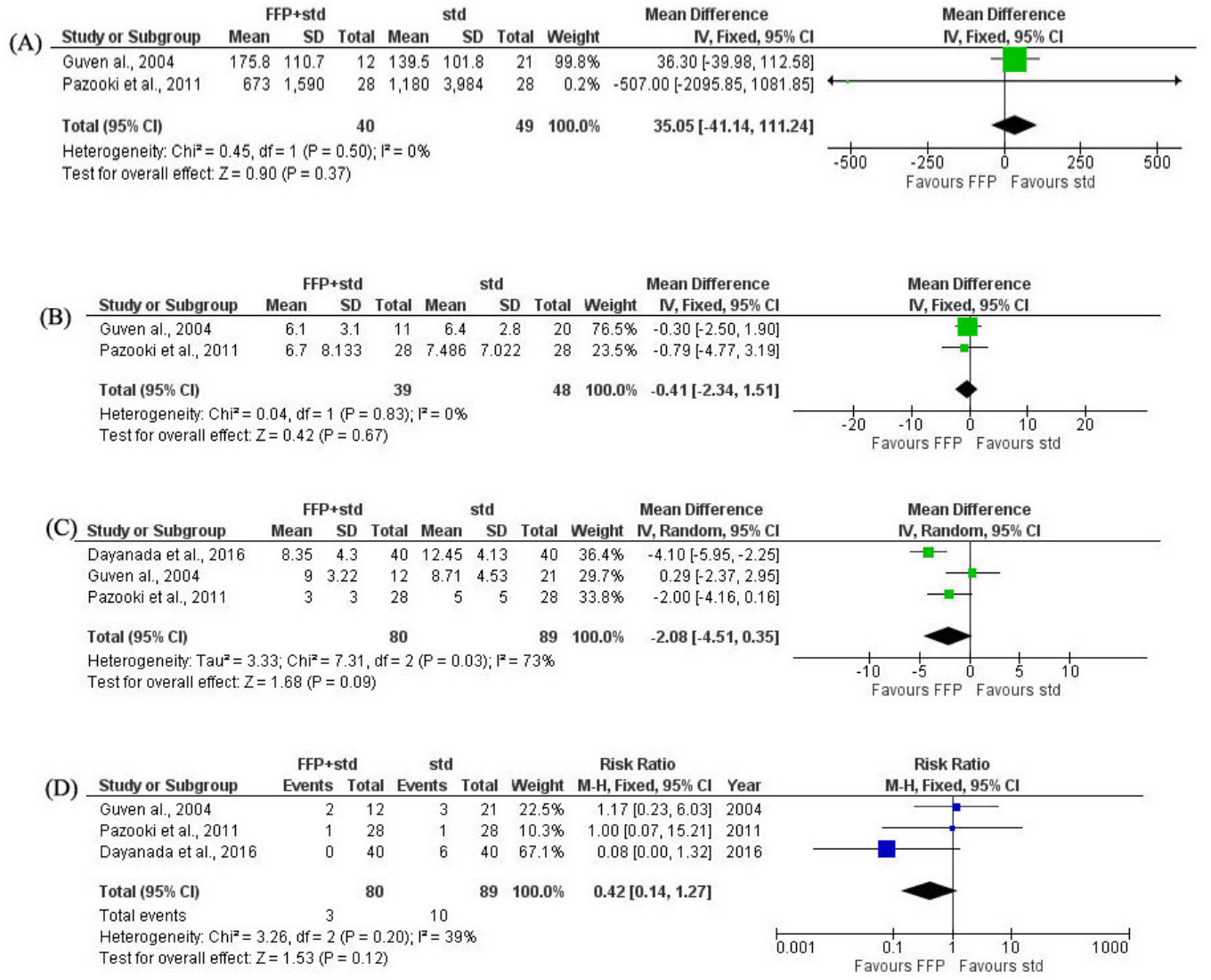

Figure 3. Forest plot displaying the results of the meta-analysis of effectiveness of FFP in management of acute organophosphate intoxicated patients vs standard treatment (std). (A) Total atropine dose (mg) presented as mean difference between the two groups with 95% confidence interval; (B) Total pralidoxime dose (g) presented as mean difference between the two groups with 95% confidence interval; (C) The length of hospitalization presented as mean difference between the two groups with 95% confidence interval; (D) Mortality presented Risk Ratio between the two groups with 95% confidence interval. IV = inverse variance; M–H = Mantel–Haenszel; CI = Confidence Interval.

LIMITATIONS

The limitation of the study involves variability of FFP administrated doses in the collected studies. We also could not calculate the total dose of atropine in the study of Dayananda et al., (13) as they compared the number of the days rather than the number of patients. Other limitations were that the included studies did not provide the serial measurement of BuChE levels except the study of Dayananda et al., (13) and the limited number and sample sizes of the included trials.

CONCLUSION

Fresh frozen plasma did not provide any additional benefit in acutely-OP intoxicated patients compared to the conventional therapy. However, the limited number and sample sizes of the included trials may be the limiting factor.

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