



International Journal of Pharmacology

ISSN 1811-7775

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Efficacy of Plasma Transfusion in Acute Human Organophosphorus Poisoning: A Systematic Review and Meta-analysis

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Abstract: The present study is a meta-analysis of clinical studies evaluating the efficacy of Fresh Frozen Plasma (FFP) in the treatment of organophosphorus (OP) poisoning. PubMed, Scopus, Google Scholar and clinicaltrials.gov were searched for studies investigating the effects of FFP in the treatment of OP poisoning. Mortality, intermediate syndrome (IMS) and hospital stay duration were the key outcomes of interest. Data were searched in the time period of 1966 through April 2014. Three studies that met our inclusion criteria were included in the analysis. Pooling of data showed that the Relative Risk (RR) of mortality in OP poisoning for three included trials comparing FFP to placebo was 0.77 (95% CI = 0.28 to 2.07 (P = 0.6)). The summary of RR for IMS in 2 studies was 0.74 with 95% CI = 0.05 to 10.99 (P = 0.83). The summary of a standard effect for the hospital stay duration in OP poisoning for two trials comparing FFP with placebo was -0.37 with 95% CI = -4.68 to 3.94. According to these data, FFP effect on OP poisoning in mortality, hospital stay duration and IMS incidence was not significant.

Key words: Organophosphorus, fresh frozen plasma, poisoning, meta-analysis

INTRODUCTION

Organophosphorus (OP) poisoning is a major health problem, especially in the developing world because of wide availability as pesticides (Mostafalou and Abdollahi, 2013; Mostafalou *et al.*, 2013; Saadi and Abdollahi, 2012). These agents inhibit acetyl cholinesterase and lead to the accumulation of acetylcholine (ACh) at synapses. Acute cholinergic toxicity, intermediate syndrome (proximal and respiratory muscle weakness after resolution of the acute cholinergic toxicity) and neuropathy (usually in the second week) cause morbidity and mortality in patients.

There are several treatment modalities for OP treatment. Classically, atropine, benzodiazepines and oximes (e.g. pralidoxime) have been employed for treatment. In recent years, effectiveness of oximes has been questioned (Rahimi *et al.*, 2006; Eddleston *et al.*, 2009) and other newer treatment modalities (e.g. magnesium, bicarbonate, clonidine, charcoal lavage) had mixed results (Sivagnanam, 2002; Peter *et al.*, 2008; Buckley *et al.*, 2011). The search for more effective treatment has been going on.

Plasma is frozen within 8 h after phlebotomy in order to increase its substance longevity (Roback *et al.*, 2010). While this product; Fresh Frozen Plasma (FFP) has been used widely as a volume expander, coagulation factor replacement and warfarin toxicity reversal (Roback *et al.*, 2010), recently, it has attracted more attention as a bioscavenger. Theoretically, it “scavenges” toxins in OP poisoning and prevents their toxicity. In FFP transfusion or plasmapheresis, plasma cholinesterase (butyrylcholinesterase- BuChE) can bind to the OP, thereby protecting the more important AChE (Ashani, 2000).

In this systematic review, we have collected, meta-analyzed and criticized all the clinical trials which met meta-analysis inclusion criteria on plasma efficacy in OP intoxication.

MATERIALS AND METHODS

Data sources: PubMed, Scopus, Google Scholar and clinicaltrials.gov were searched for studies that investigated efficacy of plasma transfusion in treatment of

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OP intoxication. Data were collected from 1966 to April 2014. The search was conducted for the key words “plasma”, “FFP”, “organophosphorus” with truncation, “pesticide”, “poisoning”, “intoxication” and “trial”. Reference lists of the found articles were also reviewed for additional applicable studies. Studies comparing the plasma administration and placebo were taken into consideration. The outcomes of interest were mortality, intermediate syndrome (IMS) and hospital stay duration. Data were extracted in terms of patients’ characteristics, therapeutic regimens and outcomes.

Study selection: All studies investigated the effect of FFP on OP intoxication of humans were considered. The mortality was the key outcome of interest. Studies presented at the meetings that are retrievable by the internet were also considered.

Two reviewers independently examined the title and abstract of each article to eliminate duplicates, reviews, case studies and studies without outcome of interest and studies in other languages. Disagreements were resolved by consensus.

Assessment of trial quality: The quality of studies was determined based on their description of randomization, blinding and dropouts (withdrawals) (Jadad, 1998) (Table 1) that is summarized as follows: (a) Whether randomized or not (Yes = 1 point, No = 0); (b) Whether randomization was described appropriately or not (Yes = 1 point, No = 0); (c) Double blind (Yes = 1 point, No = 0); (d) Was the double blinding described

appropriately (Yes = 1 point, No = 0); (e) Whether withdrawals and dropouts described or not (Yes = 1 point, No = 0). The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

Statistical analysis: Data from selected studies were extracted in the form of 2×2 tables by study characteristics. Included studies were weighted by effect size and pooled. Data were analyzed using Statsdirect software version 3.0.117. Relative Risk (RR) and 95% confidence intervals (95% CI) were calculated using Der Simonian-Laird (for random effects) method. Standardized effect size and 95% confidence intervals (95% CI) were calculated using Der Simonian-Laird (for random effects) methods. The Cochran Q test was used to test heterogeneity and $p < 0.05$ considered significant. In case of heterogeneity or few included studies, the random effects model was used.

RESULTS

We reviewed 4344 abstract and titles (Fig. 1), of which, 4331 were excluded on the basis of title and abstract irrelevancy or duplication. Therefore, 13 studies were scrutinized in full text, of which, 3 were considered eligible and met inclusion criteria for systematic review. Of excluded studies, seven were review article, one was case report, one was a comment and one was on IMS treatment. The quality of eligible clinical trial studies was assessed by Jadad score. Two studies received 2 and the

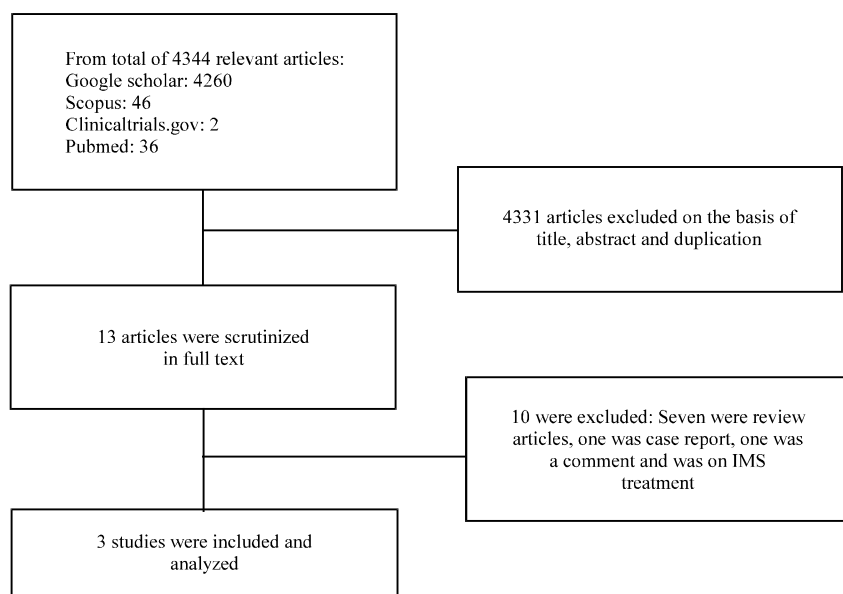


Fig. 1: Flow diagram for study selection

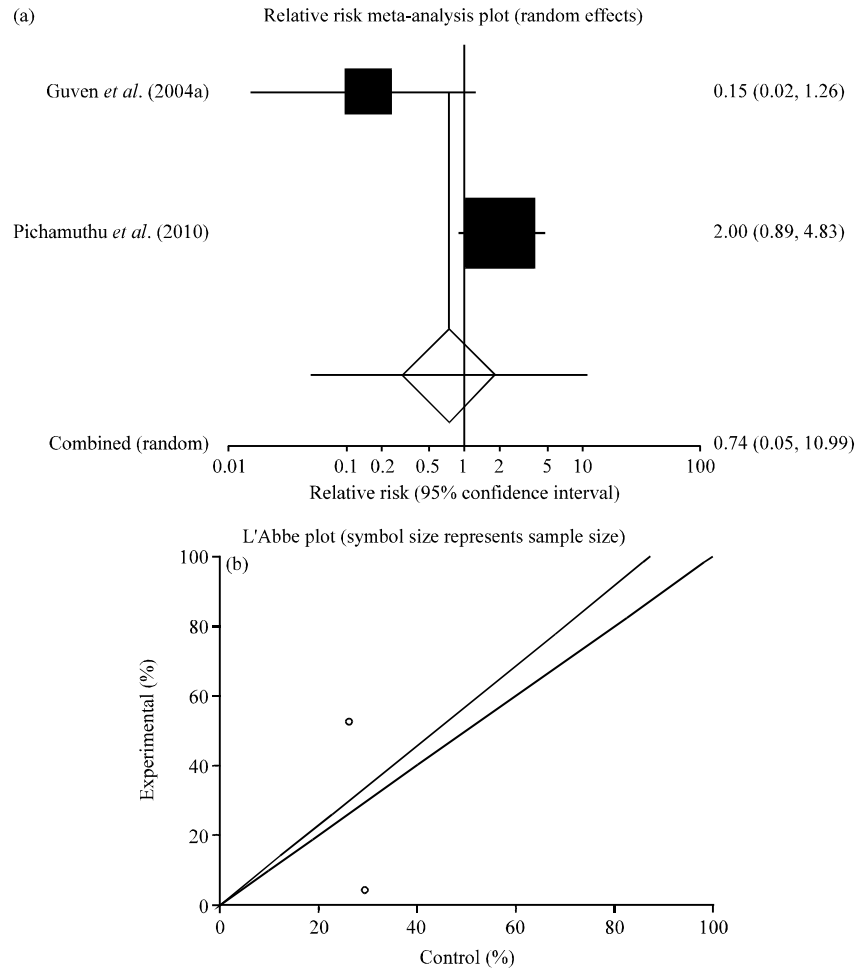


Fig. 2(a-b): (a) Individual and pooled relative risk and (b) Heterogeneity indicators for the outcome of "IMS" in the studies considering FFP comparing to placebo therapy in OP poisoning patients

Table 1: Jadad quality score of trial included in the meta-analysis

	Randomization	Blinding	Withdrawal described	Total
Guven <i>et al.</i> (2004a, b)	1	0	1	2
Pichamuthu <i>et al.</i> (2010)	2	0	1	3
Pazooki <i>et al.</i> (2011)	1	0	1	2

other one scored three (Table 1). The included trials covered 56 patients for FFP arm and 67 in the placebo arm. Exposure and outcome assessing methods and study type are shown in Table 2 and the results on outcomes have been provided in Table 3.

Effect of FFP in comparison to placebo therapy in IMS in OP poisoning patients: The summary for RR of IMS in OP poisoning patients for two included trials comparing FFP to Placebo (Guven *et al.*, 2004a; Pichamuthu *et al.*, 2010) was 0.74 with 95% CI = 0.05 to 10.99 (P = 0.83, Fig. 2a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P = 0.06, Fig. 2b) and

could be combined, but because of few included studies the random effects for individual and summary for RR was applied.

Effect of FFP in comparison to placebo therapy on mortality in OP poisoning patients: The summary for RR of mortality in OP poisoning patients for three included trials comparing FFP to Placebo (Pichamuthu *et al.*, 2010; Pazooki *et al.*, 2011) was 0.77 with 95% CI = 0.28 to 2.07 (P = 0.6, Fig. 3a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P = 0.9, Fig. 3b) and could be combined, but because of few included studies the random effects for individual and summary for RR was applied.

Effect of FFP in comparison to placebo therapy in hospital stay in OP poisoning patients: The summary for the standardized effect size of mean differences of hospital

Table 2: Characteristics of studies included in the meta-analysis

Study	Design	Intoxicated patients	Exposure assessing	Intervention	Outcomes assessing	Groups	
						FFP treated	FFP untreated
Guvan <i>et al.</i> (2004b)	Partially Randomized controlled trial	33	History and BuChE levels	FFP+/- (Atropine, Pralidoxime, Diazepam)	Plasma BuChE levels, intermediate syndrome, mortality, duration and doses of atropine and pralidoxime and length of stay at ICU	9	20
Pichamuthu <i>et al.</i> (2010)	Open-labelled Three-arm randomized trial	60	Clinical toxicidrome, compound ingestion identification, pseudochoolinesterase and organophosphate levels	FFP, albumin and saline	Incidence of IMS, need for mechanical ventilation, atropine requirement and mortality	19	Saline Albumin 20
Pazooki <i>et al.</i> (2011)	Randomized clinical trial	56 Male: 28 (50%)	Clinical signs and symptoms and serum pseudochoolinesterase level	Conventional treatment plus/without FFP	Atropine and pralidoxime dosage, hospital stay length and mortality	28	28

Table 3: Outcomes in included studies (Mean±SD)

Outcomes	BuChE levels in the plasma (IU/L)		IMS incidence after treatment		Hospital Stay (d)		Atropine dose (mg)		Pralidoxime dose (mg)		Mortality						
	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP							
Guvan <i>et al.</i> (2004b)	500.2±262.6	364.5±163.4	5/20 (25%)	0/9 (0%)	-	-	139.5±101.8	175.8±110.7	6400±2800	6100±3100	2/20 (10%)	0/9 (0%)					
Outcomes	BuChE levels in the plasma (IU L ⁻¹)		IMS incidence after treatment		Hospital Stay (d)		Atropine dose (mg)		Pralidoxime dose (mg)		Mortality						
	Without FFP	Saline	Albumin	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP					
Pichamuthu <i>et al.</i> (2010)	275 (SE: 90)	230 (SE: 68)	5/19 (26%)	5/20 (25%)	10/19 (53%)	14/19 (74%)	15/20 (75%)	15/20 (75%)	9.8 (SE:1.6)	9.8 (SE:1.4)	12.4 (SE:2.2)	789 (SE:334)	361 (SE:125)	536 (SE:132)	2/19 (11%)	5/20 (25%)	4/19 (21%)
Outcomes	BuChE levels in the plasma (IU/L)		IMS incidence after treatment		Hospital Stay (d)		Atropine dose (mg)		Pralidoxime dose (mg)		Mortality						
	Without FFP	Saline	Albumin	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP	FFP	Without FFP
Pazooki <i>et al.</i> (2011)	-	-	-	-	5±5	3±3	1180±3984	673±1590	7486±7022	6700±8133	1/28 (4%)	1/28 (4%)					

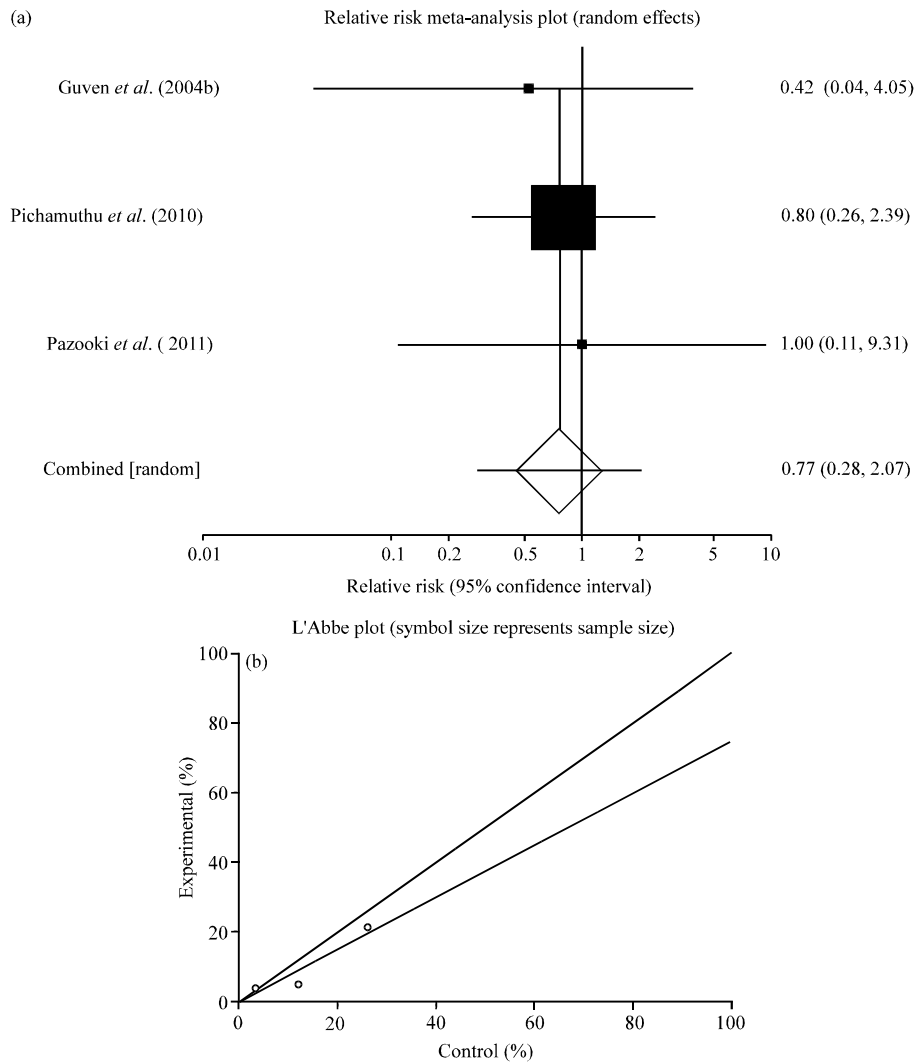


Fig. 3(a-b): (a) Individual and pooled relative risk and (b) Heterogeneity indicators for the outcome of “mortality” in studies considering FFP comparing to placebo therapy in OP poisoning patients

stay in OP poisoning patients “ΔHS” for FFP therapy for two included trials compared to placebo (Pichamuthu *et al.*, 2010; Pazooki *et al.*, 2011) was -0.37 with 95% CI = -4.68 to 3.94 (P = 0.87, Fig. 4). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P = 0.12) and could be combined, but because of few included studies the random effects for individual and summary of effect size for standardized mean was applied.

DISCUSSION

The result of this meta-analysis indicates that the FFP effect on the mortality, IMS and hospital stay duration was insignificant. This must be interpreted in regard to the paucity of literature.

Recently, on the physiologic basis, a treatment strategy was developed; free OP in plasma can be scavenged by butyrylcholinesterase (BuChE) in the FFP (Doctor and Saxena, 2005). Although this enzyme has different durability in stored FFP (Ashani, 2000; Zhong *et al.*, 2000), it reduces available OP. As the result, AChE in tissues such as the nervous system is spared from this toxin (Blain, 2011). After some case reports, this theory was put into the action in a trial by Guven *et al.* (2004b). It yielded non-significant reductions in mortality and IMS. This finding was attributed to the long lag time between intoxication and FFP administration among patients in the study which results in inability to scavenge the OP at the neuronal level, the cause for the neuromuscular manifestations. Later on, this lag time was lowered by Pichamuthu *et al.* (2010). They found that OPs

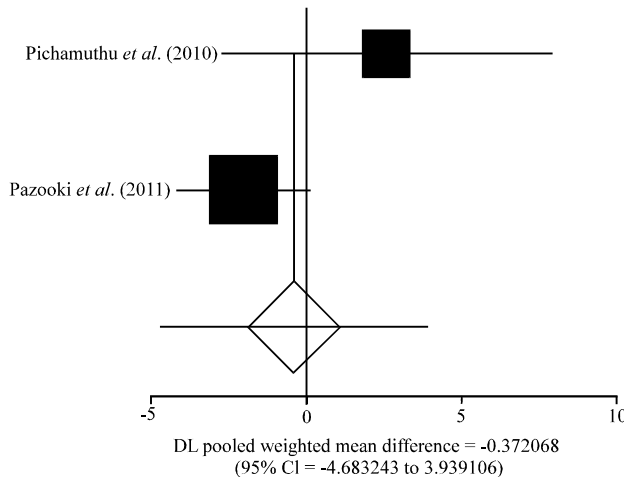


Fig. 4: Individual and pooled effect size for standardized mean for the outcome of “ΔHS” in the studies considering FFP comparing to placebo therapy in OP poisoning patients

are absorbed and bound to the BuChE and replenish bounded plasma cholinesterase. But again the results were not changed.

Theoretically, large quantity of BuChE may be required for neutralization and inactivation of moderate to severe OP poisoning in the right time (Eddleston *et al.*, 2008). But as the last study revealed, there was an increase in the pseudocholinesterase level. This is lead to some other proposals for FFP mode of action in order to explain these findings; BuChE might adsorb the OP without actual detoxification and this could lead to slow release of the toxin over time. In addition, some other effects of FFP contents might also play a role. This last theory can be answered by a purified BChE administration, which is under development for human study.

In addition, although all the OPs have a similar mechanism of action, they have different classes according to fatality and the difference in the binding affinity of OPs to the BuChE which is merit mention in order to help explain the findings. FFP might work more effectively if small amounts of highly toxic OP such as WHO Class IA OPs (e.g. phorate) was present rather than less toxic ones like WHO Class II OPs such as dimethoate which require large doses of OP to be fatal (and therefore vast quantities of BuChE to have any effect) (WHO, 2010). Of secondary important, a study has found that chlorpyrifos or fenthion inhibit BuChE more than dimethoate (Eddleston *et al.*, 2005). In this regard, adding BuChE (by FFP transfusion) in the former substances might have better outcomes and needs to be studied more specifically.

FFP has been also studied in IMS as one of the serious complication of the OP intoxication (Eyer, 1995). In this syndrome the patient may experience respiratory complication after a period of improvement. The FFP treatment had conflicting results in IMS treatment and prevention. Guven *et al.* (2004a) reported results on FFP treatment starting after IMS incidence. It showed a mortality of 1 in 5 (20%) among the control group and 2 of 2 (100%) patients in FFP group. In aspect, Guven *et al.* (2004b) and Pichamuthu *et al.* (2010) have studied the IMS incidence after FFP treatment. In the first study, it was 0/9 (0%) in FFP treated group and 5/20 (25%) in control patients. Unlike Guven *et al.* (2004a) the incidence in the second study was 10/19 (53%) and 5/19 (26%) respectively (Table 3). The analysis of the pooled data showed no significant increase in the incidence.

There are some case reports of successful implantation of plasmapheresis on OP poisoned patients (Guyen *et al.*, 2004a; Ahila Ayyavoo *et al.*, 2011). In addition to adding BuChE, this technique may also have a role in removing some OP pesticides with small volume of distribution (Blain, 2011). There is only a cohort study of patients with IMS (Yilmaz *et al.*, 2013). This study indicated a significant decrease in the level of plasma OP and a significant increase in the level of BuChE was achieved. The authors concluded that this modality can be considered as one of the effective treatment options for IMS.

FFP transfusion carries risk of adverse effects, including infectious (e.g. hepatitis and HIV) and non-infectious complications. In the included studies, Pichamuthu *et al.* (2010) reported two cases of FFP

transfusion complication. One patient developed urticaria and another one lung injury (a well-known adverse of FFP transfusion (Murad *et al.*, 2010). In that study, FFP transfusion was discontinued and both patients were discharged with no complication.

CONCLUSION

According to the result of this meta-analysis, since there are only a few studies, solid recommendation cannot be made against FFP as a part of OP poisoning treatment. In this regard, in addition to larger size studies, future studies should be conducted with different dosing in different subgroups of the patients (e.g. with different OP type or different exposure-treatment lag) and plasmapheresis.

ACKNOWLEDGMENT

This invited paper is the outcome of an in-house financially non-supported study. Authors have no conflict of interest.

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