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An Updated Meta-Analysis on the Efficacy of Oximes in Acute Human Organophosphorus Poisoning

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Abstract: The present study is a meta-analysis on clinical trials evaluating the efficacy of oximes on organophosphorus (OP) intoxication treatment. PubMed, Scopus, Google Scholar and clinicaltrials.gov were searched for studies investigating the effects of oximes in the treatment of OP poisoning. Mortality, intermediate syndrome, Intensive Care Unit (ICU) admission rate, hospital stay duration and intubation rate were the key outcomes of interest. Data were searched in the time period of 1966 through April 2014. Thirteen studies (eleven clinical trials and two historical cohorts) that met our criteria were included in the analysis. Pooling of data showed that Relative Risk (RR) of need for intubation in OP poisoning for ten included trials comparing oximes with placebo was 1.18 with 95% CI = 0.76 to 1.84 (p = 0.27). RR of the single observational study was 1.57 (95% CI = 0.79 to 3.2, p>0.05). The summary of RR for mortality rate in 11 studies was 1.4 (95% CI = 0.77 to 2.54, p = 0.41) and for two observational studies was 1.19 (95% CI = 0.5 to 2.85, p>0.05). The RR for ICU admission rate in OP poisoning for three trials comparing oximes to placebo was 2.12 with 95% CI = 0.89 to 5.03 (p = 0.09). For the single observational study, RR was 0.81 (95% CI = 0.49 to 1.25, p>0.05). For intermediate syndrome while the RR of only trial comparing oximes with placebo was 1.89 (95% CI = 1.27 to 2.91, p<0.05), for the single observational study, it was 1.43 (95% CI = 0.7 to 2.96, p>0.05). For hospital stay duration (difference), the RR of four studies was 0.75 with 95% CI = -0.51 to 1.99. According to these data, oximes beneficence in OP poisoning is unclear and there is a potential increase in the incidence of intermediate syndrome.

Key words: Organophosphorus, oxime, poisoning, meta-analysis

INTRODUCTION

Accidental or intentional pesticide intoxication is a major health problem in many rural areas especially those with farming activities. World Health Organization (WHO) reported that pesticide ingestion is the most predominant method of suicides worldwide (Bertolote *et al*., 2006). Among them, organophosphorus (OP) pesticides are responsible for most of the fatalities, particularly among the new age group (Eddleston *et al*., 2002; Gunnell *et al*., 2007; Mostafalou and Abdollahi, 2013).

More than 100 OP pesticides are used worldwide. They are liquid at room temperature and can produce a vapor which is capable of penetrating through skin, respiratory system and cornea (Rahimi *et al*., 2006). They cause overactivity in the cholinergic system through covalent inhibition of neural acetylcholinesterase (AChE) (Johnson *et al*., 2000). As the result, the patients experience muscarinic, nicotinic and central nervous system stimulations. In addition to these acute effects, intermediate syndrome (IMS) and delayed neuropathy might happen afterward (Shivakumar *et al*., 2006; Eddleston *et al*., 2009).

Treatment consists of decontamination, intensive supportive care and antidotal therapy (atropine as an antimuscarinic agent and axioms as the reactivators if administered before aging of the AChE (Abdollahi *et al*., 1995). While atropine has been well accepted for this purpose, the role of oxime has been always questioned in the recent years. To update the previous meta-analyses of the efficacy of oximes in OP poisoning (Eddleston *et al*., 2002; Rahimi *et al*., 2006; Buckley *et al*., 2011), the recent clinical trials which met inclusion criteria were collected, meta-analyzed and criticized.

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MATERIALS AND METHODS

Data sources: PubMed, Scopus, Google Scholar and clinicaltrials.gov were searched for studies that investigated efficacy of different oxides in the treatment of OP intoxication. Data were collected from 1966 to April 2014. The search was conducted for the key words "Oxime", "Pralidoxime", "Obidoxime", "organophosphorus" (with truncation), "pesticide", "poisoning" and "intoxication". Reference lists of the found articles were also reviewed for additional applicable studies. Studies comparing the oxime therapy and placebo were taken into consideration. The outcomes of interest were "mortality", "intubation rate", "hospital stay duration" and "ICU admission". Data were extracted in terms of patients' characteristics, therapeutic regimens, study type and outcomes.

Study selection: All studies investigated the effect of oximes on OP intoxication on human were considered. The mortality rate 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 according to Jadad based on their description of randomization, blinding and dropouts (withdrawals) (Jadad, 1998) (Table 1) that is summarized as follows: (a) Whether the study was randomized or not (Yes = 1 point, No = 0); (b) Whether randomization was described were 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) and (e) Whether withdrawals and dropouts described or not (Yes = 1 point, No = 0). The quality scale ranges from 0-5 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 and pooled. Data were analyzed using StatsDirect 3.0.107. Relative Risk (RR) and 95% confidence intervals (95% CI) were calculated using Mantel-Haenszel, Rothman-Boice (for fixed effects) or 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. Funnel plot was used as publication bias indicator.

RESULTS

We reviewed 9140 abstract and titles (Fig. 1), of which, 9119 were excluded on the basis of title and abstract irrelevancy or duplication. Therefore, 21 studies were scrutinized in full text, of which, 13 (De Silva *et al*., 1992; Abdollahi *et al*., 1995; Cherian *et al*., 1997; Balali-Mood and Shariat, 1998; Afzali, 2002; Cherian *et al*., 2005; Chugh *et al*., 2005; Eddleston *et al*., 2009; Baloch *et al*., 2011; Banerjee *et al*., 2011; Chaudhary *et al*., 2013; Raja *et al*., 2013; Banerjee *et al*., 2014) were considered eligible and met inclusion criteria for systematic review. Of them, 11 (Abdollahi *et al*., 1995; Cherian *et al*., 1997; Balali-Mood and Shariat, 1998; Afzali, 2002; Cherian *et al*., 2005; Chugh *et al*., 2005; Eddleston *et al*., 2009; Baloch *et al*., 2011; Banerjee *et al*.,

Table 1: Quality assessment of included trials

Study	Randomization	Blinding	Dropouts	Total
Abdollahi *et al.* (1995)	1	0	1	2
Cherian *et al.* (1997)	2	2	1	5
Balali-Mood and Shariat (1998)	0	0	1	1
Afzali (2002)	2	2	1	5
Chugh *et al.* (2005)	0	0	1	1
Cherian *et al.* (2005)	1	2	1	4
Eddleston *et al.* (2002)	2	2	1	5
Banerjee *et al.* (2011)	2	0	1	3
Baloch *et al.* (2011)	0	0	1	1
Chaudhary *et al.* (2013)	0	0	1	1
Banerjee *et al.* (2014)	2	0	1	3

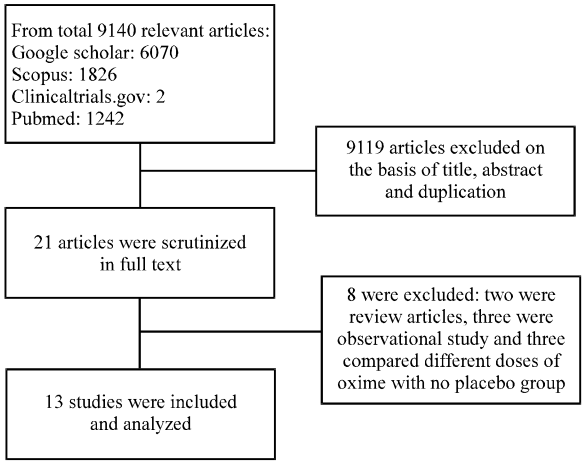

Fig. 1: Flow diagram of the study selection process

2011; Chaudhary *et al*., 2013; Banerjee *et al*., 2014) were clinical trial and two (De Silva *et al*., 1992; Raja *et al*., 2013) was historical cohort and included in the meta-analysis. The studies were conducted in Iran, India, Pakistan and Serilanka. Of excluded studies, two were review article, three were observational study and three compared different doses of oxime with no control group. The quality of eligible clinical trials was assessed by Jadad score. Four (Balali-Mood and Shariat, 1998; Chugh *et al*., 2005; Baloch *et al*., 2011; Chaudhary *et al*., 2013) out of 11 studies received a Jadad score 1. Abdollahi *et al*. (1995) received 2. Two studies (Banerjee *et al*., 2011; Banerjee *et al*., 2014) received a Jadad score of 3, one study (Cherian *et al*., 2005) scored four and three studies (Cherian *et al*., 1997; Afzali, 2002; Eddleston *et al*., 2009) received 5 (Table 1). The included trials covered 582 patients for oxime arm and 518 for the placebo arm. Oxime type and dose, patients' gender and age and study country are shown in Table 2 and the results on outcomes have been provided in Table 3.

Need for intubation due to oximes therapy in comparison to placebo in organophosphoruses poisoning: The summary of Relative Risk (RR) of the need for intubation in organophosphoruses poisoning for ten included trials comparing oximes to placebo (Abdollahi *et al*., 1995; Cherian *et al*., 1997; Balali-Mood and Shariat, 1998; Cherian *et al*., 2005; Chugh *et al*., 2005; Eddleston *et al*., 2009; Baloch *et al*., 2011; Banerjee *et al*., 2011; Chaudhary *et al*., 2013; Banerjee *et al*., 2014) was 1.18 with 95% CI = 0.76 to 1.84 (p = 0.46, Fig. 2a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p<0.0001, Fig. 2b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for need for intubation in organophosphoruses poisoning among oximes vs. placebo therapy was 1.27 (95% CI = -2.31 to 4.85, p = 0.44) and Kendall's tau = 0.11, p = 0.73 (Fig. 2c). Relative Risk (RR) of the single observational study (De Silva *et al*., 1992) is 1.57 (95% CI = 0.79 to 3.2, p>0.05) for need for intubation in oximes therapy in organophosphoruses poisoning in comparison to placebo.

All-cause mortality due to oximes therapy in comparison to placebo in organophosphoruses poisoning: The summary of Relative Risk (RR) of all-cause mortality in organophosphoruses poisoning for eleven included trials comparing oximes to placebo (Abdollahi *et al*., 1995; Cherian *et al*., 1997; Balali-Mood and Shariat, 1998; Afzali, 2002; Cherian *et al*., 2005; Chugh *et al*., 2005; Eddleston *et al*., 2009; Baloch *et al*., 2011; Banerjee *et al*., 2011; Chaudhary *et al*., 2013; Banerjee *et al*., 2014) was 1.4 with 95% CI = 0.77 to 2.54 (p = 0.27, Fig. 3a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p = 0.0022, Fig. 3b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for all-cause mortality in organophosphoruses poisoning among oximes vs. placebo therapy was 0.72 (95% CI = -1.45 to 2.89, p = 0.47) and Kendall's tau = -0.16, p = 0.45 (Fig. 3c).

Relative Risk (RR) of two observational study (De Silva *et al*., 1992; Raja *et al*., 2013) is 1.19 (95% CI = 0.5 to 2.84, P = 0.7) for all-cause mortality in oximes therapy in organophosphoruses poisoning in comparison to placebo.

ICU admission rate due to oximes therapy in comparison to placebo in organophosphoruses poisoning: The summary of Relative Risk (RR) of ICU admission rate mortality in organophosphoruses poisoning for three included trials comparing oximes to placebo (Abdollahi *et al*., 1995; Balali-Mood and Shariat, 1998; Cherian *et al*., 2005) was 2.12 with 95% CI = 0.89 to 5.03 (p = 0.09, Fig. 4a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.45, Fig. 4b) and could be combined, but because of few included trials the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for ICU admission rate in organophosphoruses poisoning among oximes vs. placebo therapy could not be calculated because of too few strata.

Relative Risk (RR) of the single observational study (De Silva *et al*., 1992) is 0.81 (95% CI = 0.49 to 1.25, p>0.05) for ICU admission rate in oximes therapy in organophosphoruses poisoning in comparison to placebo.

Intermediate syndrome due to oximes therapy in comparison to placebo in organophosphoruses poisoning: Relative Risk (RR) of the single RCT (Cherian *et al*., 1997) is 1.89 (95% CI = 1.27 to 2.91, p<0.05) for intermediate syndrome in oximes therapy in organophosphoruses poisoning in comparison to placebo.

RR of the single observational study (De Silva *et al*., 1992) is 1.43 (95% CI = 0.7 to 2.96, p>0.05) for intermediate syndrome in oximes therapy in organophosphoruses poisoning in comparison to placebo.

Table 2: Characteristics of included studies

Study	Study type	Oxime type and dose	No. of patients in oxime group	No. of patients in control group	Age		Male/female		Comment
					Oxime	Non-oxime	Oxime	Non- oxime	
De Silva *et al.* (1992) (Srilanka)	Historical cohort	P 4 g first 24 h, then 1 g day^{-1} upto 5 day	24	21	25[a]	26.5[a]	12/9*	15/9*	
Abdollahi *et al.* (1995) (Iran)	RCT	P 600–800 mg every 4-8 h based on patient's condition	17	17	30[a]	29.5[a]	14/8*	7/5*	It has published dose and days of atropine need
Cherian *et al.* (1997) (India)	RCT	P 12 g over 3 day	55	55	28[b]	26.5[b]	41/14	34/21	All the patients in ICU
Balali-Mood and Shariat (1998) (Iran)	Clinical trial	O 8 mg kg^{-1} loading, then 2 mg kg^{-1} h g^{-1} P 30 mg kg^{-1} loading, then 2 mg kg^{-1} h^{-1}	20	43	25[b]	25[b]	9/11	24/19	It has published respiratory arrest rate, convulsion rate and atropine and oxime doses
Afzali (2002) (Iran)	RCT	P NA	66	74	NA	NA	NA	NA	It has published complications and treatment duration. Full text in Persian
Chugh *et al.* (2005) (India)	Clinical trial	P 1g every 6 h, then maintained continuously till clear clinical improvement occurred or serum AchE level returned to normal or up to a maximum of 5 days	15	15	NA	NA	NA	NA	Moderate to severe intoxicated patients. ICU admission and stay, days on a ventilator and atropine total dose were provided
Cherian *et al.* (2005) (India)	RCT	P 12 or 36 g	10	11	NA	NA	NA	NA	Moderate to severe intoxicated patients. It has published ICU stay days, complication rate and total dose and days of atropine need
Eddleston *et al.* (2009) (Srilanka)	RCT	P 2 g loading dose followed by an infusion of 0.5 g h^{-1} for up to 7 day	121	114	31[a]	29.5[a]	96/25	92/22	It has been published time to intubation, time ventilated, and time to death
Banerjee *et al.* (2011) (India)	RCT	P 0.5-1 g every 6 h based on patient's condition	30	30	34.6[b]	34.3[b]	14/16	11/19	
Baloch *et al.* (2011) (Pakistan)	Clinical trial	P 1 g then repeated until fasciculation disappear	100	30	NA	NA	NA	NA	All the patients in ICU. It has published full recovery duration
Chaudhary *et al.* (2013) (India)	Clinical trial	P 30 mg kg^{-1} over 30 min followed by 2 mg at 6 h interval for 72 h	35	35	25.17[b]	24.8[b]	24/11	25/10	It has published the total atropine dose and supplementary oxygen requirement
Raja *et al.* (2013) (India)	Historical cohort	NA	29	13	34.8[b]	33.3[b]	23/6	8/5	It has published ICU stay days
Banerjee *et al.* (2014) (India)	RCT	P 1 g every 6 h for a period of 5 days	60	60	34.63[b]	34.3[b]	23/37	26/34	It has published OP type

RCT: Randomized controlled clinical trial, ChE: Cholinesterase,g:gram, ICU: Intensive care unit, NA: Not available, O: Obidoxime, P: Pralidoxime, RCT: Randomized controlled trial, [a]Median, [b]Mean, *: Patients in intention to treat

Table 3: Treatment outcomes in oximes and placebo groups

	Need for intubation		Intermediate syndrome		All-cause mortality		ICU admission rate		Hospital stays duration (days)	
Study	Oxime	Non-oxime	Oxime	Non-oxime	Oxime	Non-oxime	Oxime	Non-oxime	Oxime	Non-oxime
De Silva *et al.* (1992)	11/21	8/24	10/21	8/24	7/21	6/24	12/21	17/24	7(1-14)[a]	7(1-16)[a]
Abdollahi *et al.* (1995)	7/17	8/17	-	-	3/17	3/17	9//17	8/17	4(2-5)[a]	4(2-6)[a]
Cherian *et al.* (1997)	37/55	22/55	36/55	19/55	16/55	3/55	-	-	-	-
Balali-Mood and Shariat (1998)	O: 4/12 P: 5/8	2/43	-	-	O: 6/12 P: 0/8	4/43	O: 4/12 P: 5/8	7/43	O: 7.5±4.3[b] P: 14±10[b]	6.1± 3.7[b]
Afzali (2002)	-	-	-	-	0/74	3/66	-	-	-	-
Chugh *et al.* (2005)	7/15	6/15	-	-	1/15	0/15	7/15	6/15	-	-
Cherian *et al.* (2005)	7/10	4/11	-	-	1/10	1/11	-	-	-	-
Eddleston *et al.* (2009)	26/121	24/114	-	-	30/121	18/114	-	-	-	-
Banerjee *et al.* (2011)	6/30	2/30	-	-	2/30	1/30	-	-	5.4± 1.499[b]	5.77±1.596[b]
Baloch *et al.* (2011)	25/100	20/30	-	-	20/100	14/30	-	-	-	-
Chaudhary *et al.* (2013)	21/35	17/35	-	-	5/35	3/35	-	-	7.65±2.4[b]	7.05±2.3[b]
Raja *et al.* (2013)	-	-	-	-	1/29	1/13	-	-	7.4±4.1[b]	5.7±2.3[b]
Banerjee *et al.* (2014)	3/60	5/60	-	-	11/60	8/60	-	-	7.02±1.12[b]	5.68±1.87[b]

O: Obidoxime, P: Pralidoxime, [a]Median (range), [b]Mean±SD

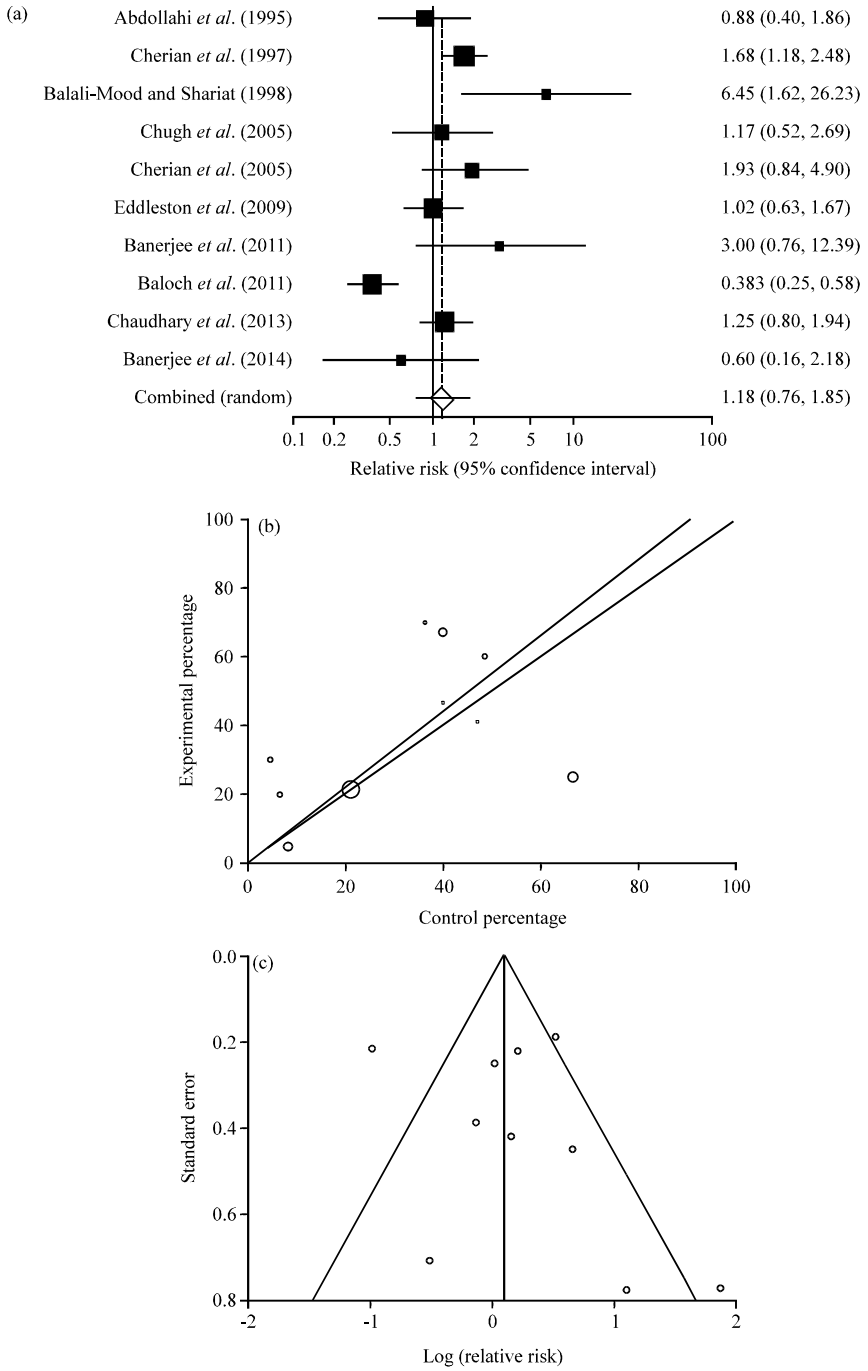

Fig. 2(a-c): (a) Individual and pooled relative risk, (b) Heterogeneity indicators and (c) Publication bias indicators for the outcome of "need for intubation" in the studies considering oximes comparing to placebo therapy in organophosphoruses poisoning

Hospital stay duration (days) due to oximes therapy in comparison to placebo in organophosphoruses poisoning: The summary for the standardized effect size of mean differences of hospital stay in organophosphorus poisoning patients "ΔHS" for oximes therapy in organophosphoruses poisoning for four included trials compared to placebo (Balali-Mood and Shariat, 1998; Banerjee *et al*., 2011; Chaudhary *et al*., 2013;

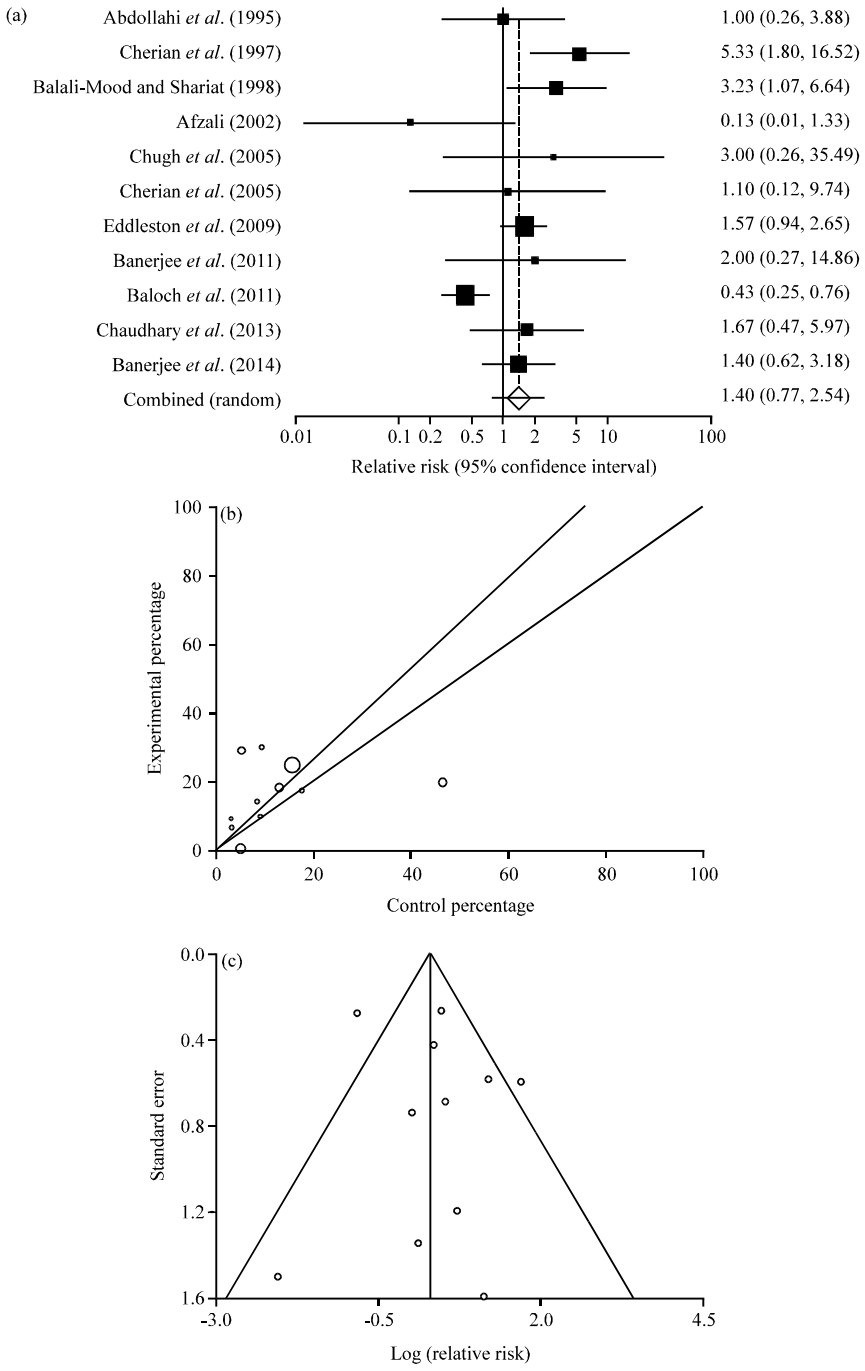

Fig. 3(a-c): (a) Individual and pooled relative risk, (b) Heterogeneity indicators and (c) Publication bias indicators for the outcome of "all-cause mortality" in the studies considering oximes comparing to placebo therapy in organophosphoruses poisoning

Banerjee *et al.*, 2014) was 0.75 with 95% CI = -0.51 to 1.99 (p = 0.24, Fig. 5a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p = 0.0008) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean was applied. Regression of normalized effect vs. precision for all included studies for hospital stay duration in organophosphorus poisoning among oximes vs. placebo therapy was 2.25 (95% CI = -12.76 to 17.25, p = 0.59) and Kendall's tau = 0.33, p = 0.75 (Fig. 5b).

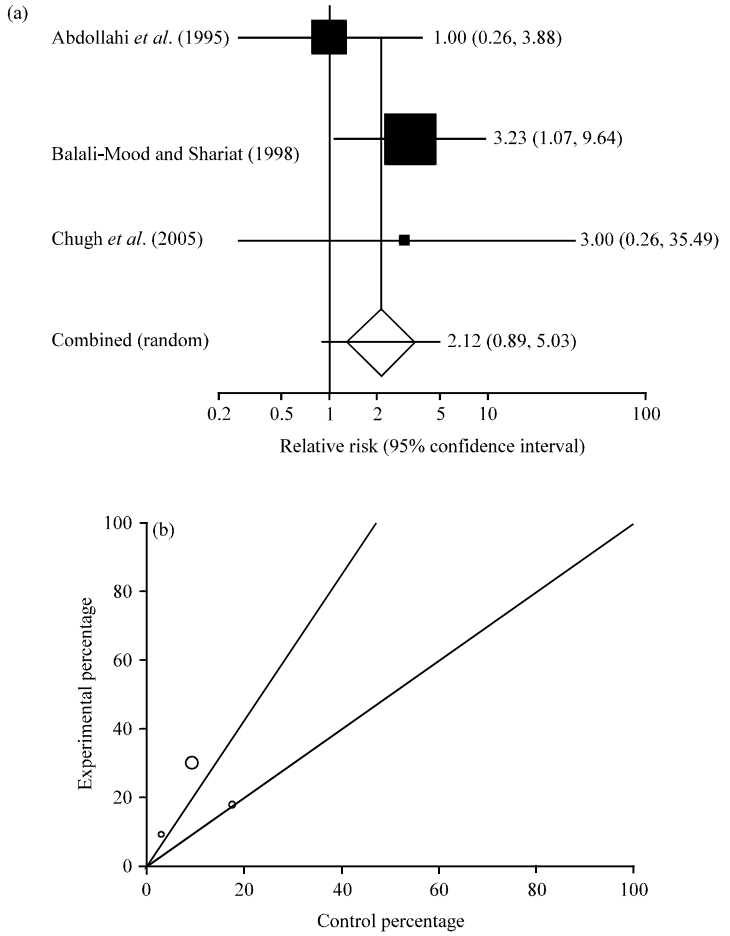

Fig. 4(a-b): (a) Individual and the pooled relative risk and (b) Heterogeneity indicators for the outcome of "ICU admission rate" in the studies considering oximes comparing to placebo therapy in organophosphoruses poisoning

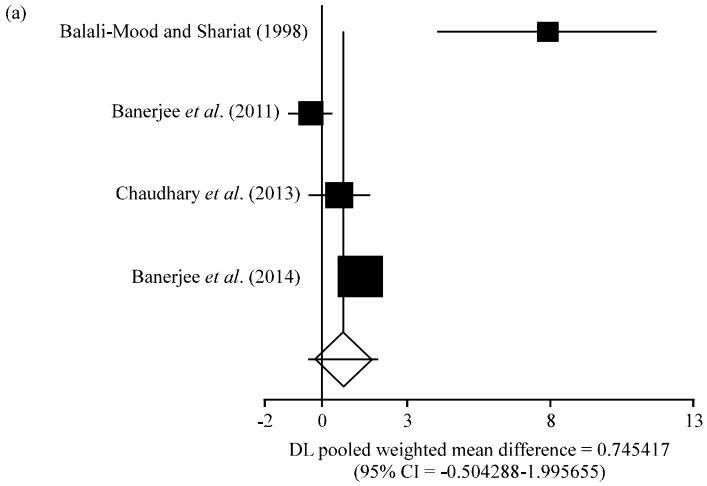

Fig. 5(a-b): Continue

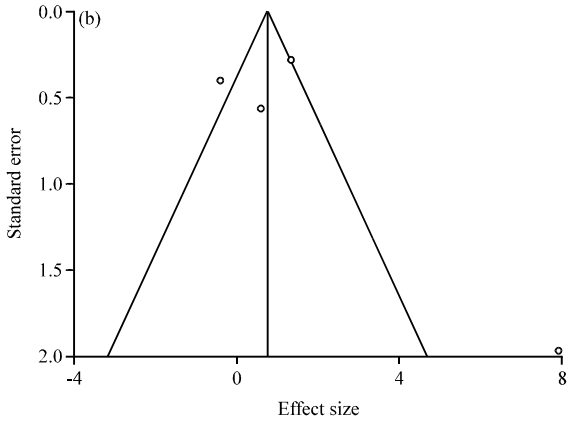

Fig. 5(a-b): (a) Individual and pooled effect size for standardized mean and (b) Publication bias indicators for the outcome of "ΔHS" in the studies considering oximes comparing to placebo therapy in organophosphoruses poisoning

DISCUSSION

The result of this meta-analysis indicates that oximes efficacy in need for intubation, mortality, hospital stay duration and ICU admission was insignificant. The IMS was significantly higher in patients who were treated with oximes in clinical trials.

After the discovery in 1955 (Wilson and Ginsburg, 1955), the oximes became popular as an antidote and were even proposed as an atropine sparing agent according to animal and human studies (Namba *et al*., 1971; Farrar *et al*., 1990). According to studies reactivation can be achieved after oximes administration even after several hours (Sungur and Güven, 2001). This is attributed to different conditions, most importantly AChE aging phenomenon (Buckley *et al*., 2011). In early 1990s, when pralidoxime supplies broke down in the Sri Lanka, De Silva *et al*. (1992) took the opportunity to run a historical cohort (De Silva *et al*., 1992). The result of their study and another retrospective study (Duval *et al*., 1990) cast a doubt on oxime effectiveness and paved the way for clinical trials. While there are several oximes used with different potencies (Worek *et al*., 1997, 1998, 1999), these trials were mainly on pralidoxime.

The unfavorable results on the first trials were questioned by some of their inadequate dosing. Many pros of oxime efficacy (including WHO) proposed that in contrast to low dose accidental OP exposure in developed countries which can be treated by low dose oximes, higher oxime doses were recommended in mega dose self-poisoning in developing countries to have a complete reactivation of AChE (Johnson *et al*., 1992; Eddleston *et al*., 2009). In this regard, Johnson *et al*. (1996) compared two different doses (12 g infusion with 2 g bolus) (Johnson *et al*., 1996). They found that higher doses exerted negative results. This study was followed in 2009 by Eddleston *et al*. (2009) who conducted a larger study on WHO-recommended doses (at least 30 mg kg^{-1} pralidoxime salt loading dose followed by 8 mg kg^{-1} h^{-1} infusion) (Johnson *et al*., 2000; Eyer, 2003). Eddleston *et al*. (2009), although did not finish the predetermined sample size, reported negative results on efficacy of the oximes with higher dose. Although not supported by studies, some others proposed that the oximes might have some unknown biological effects in addition to its innate reactivator properties.

While delayed polyneuropathy is a well-known OP poisoning complication, IMS is of more importance because of its life threatening nature. As first described in 1978, it usually occurs 24 to 96 h after resolution of a severe cholinergic crisis. It is a neuromuscular junction disorder and can be recorded by electrophysiological studies upon the onset of respiratory failure (Karami-Mohajeri *et al*., 2014). The initial presentation includes proximal limb weakness, neck flexion weakness and decrease in reflexes that result in respiratory failure, long ICU stay and mortality (Kwong, 2002). Of course, the present meta-analysis does not support a favorable effect of oximes on IMS prevention.

Several adverse effects have been attributed to oximes. According to the previous reports, pralidoxime can cause cardiac dysrhythmias or respiratory arrest (Cherian *et al*., 1997; Peter *et al*., 2006) and laryngospasm and muscle rigidity in the case of rapid infusion (Rahimi *et al*., 2006). Of the studies included in the present meta-analysis, Eddleston *et al*. (2009) and Banerjee *et al*. (2014) did not encounter significant side effects in their patients (Eddleston *et al*., 2009; Banerjee *et al*., 2014). But in another study, Balali-Mood and Shariat (1998) have reported hepatotoxicity in the obidoxime group, but no

adverse effect on the pralidoxime group. In their study, three patients developed hepatitis of which two patients died with liver failure (Balali-Mood and Shariat, 1998).

Results of laboratory AChE activity assay (mostly by Ellman calorimetric method (Ellman *et al*., 1961) in relation with oxime therapy are conflicting. While some studies showed statistically insignificant recovery in an oxime group in comparison to the control group (Balali-Mood and Shariat, 1998; Cherian *et al*., 2005; Chugh *et al*., 2005), Balali-Mood and Shariat (1998) found the difference only in the reactivation rate (Balali-Mood and Shariat, 1998). Abdollahi *et al*. (1995) also showed that pralidoxime would effectively reactivate inhibited AChE. Eddleston *et al*. (2009) found significantly higher AChE levelin survivors in comparison to non-survivors in both placebo and oxime arms. They also showed that patients who did not receive oxime and survived had lower AChE in comparison with patients who died after that treatment.

The meta-analysis of previous studies showed a harmful effect on mortality, IMS and the ventilator need (Peter *et al*., 2006; Rahimi *et al*., 2006). The review and analysis results of the RCTs in Cochrane database by Buckley *et al*. (2011) are also lead to conclude that current evidence is not sufficient to indicate whether oximes are harmful or beneficial in the management of acute OP poisoning (Buckley *et al*., 2011). The present meta-analysis consists of several new studies and added a new efficacy parameter for oximes effectiveness (i.e., Hospital stay duration).

CONCLUSION

We conclude that with known differences in the methods, patients, treatment lag, the different nature of Ops and with some other limitations, the oximes efficacy is not clear at the present and with greater cost there is a possible increase in the incidence of IMS. Since other treatment modalities have been also studied such as magnesium, alkalization, fresh frozen plasma and hemoperfusion reporting controversial results (Peter *et al*., 2008; Mirfazaelian *et al*., 2014), future studies are still needed to be carried out on oximes to find whether different dosing in different subgroups (e.g., with different OP type or different exposure-treatment lag) of the patients is useful or not.

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