Al Ameen J Med Sci 2019;12(3):160-165 ● US National Library of Medicine enlisted journal ● ISSN 0974-1143

ORIGINAL ARTICLE CODEN: AAJMBG

Evaluation of intravenous lipid emulsion as a novel therapeutic antidote in severe organophosphorous poisoning- A prospective randomized, comparative study

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Received: 09th April 2019; ***Accepted:*** 17th June 2019; ***Published:*** 01st July 2019

Abstract: *Background:* Organophosphorus compounds are usually esters, amides or thiol derivatives of phosphonic acid and form a large family (>50000 compounds). The principal use of these compounds are as pesticides in agriculture, mainly as insecticides. Some formulations are used in veterinary and human medicine, particularly as antiparasitics, against ticks, lice and fleas. The development and use of some of these compounds as very potent agents of chemical warfare (tabun, sarin) is of global significance. Many organophosphorus compounds are highly toxic to plants, animals and humans. *Methods:* A total of 100 adult otherwise healthy patients were included in the study. The patients were randomly recruited into the group I (atropine + PAM) and group II (atropine + intravenous lipid emulsion), each group comprising 50 patients. The randomization was done as per computer generated Random number tables and patients straightway allocated to either into group I (atropine + PAM) or group II (atropine+ intravenous lipid emulsion). Patients were assessed everyday for cholinergic signs, atropine requirements, muscle power and the level of consciousness by GCS. All the patients were monitored continuously with ECG, pulse oximetry, invasive BP monitoring, CXR as needed. *Results:* Duration of mechanical ventilation in group I (atropine + PAM) was 3.7200 ± 1.77327 days and in group II (atropine + intravenous lipid emulsion) was 2.6875±1.40146 days. Duration of mechanical ventilation in days was longer in patients receiving atropine and PAM than in those receiving atropine and intravenous lipid emulsion and the difference was found to be statistically significant (p value=0.002). In group I the mean duration of ICU stay was 5.8400±2.98541 days and in group II 4.8800±1.69802 days. Hence the difference in mean duration of ICU stay between two groups was statistically significant (p value =0.049). That is in group II (atropine + intravenous lipid emulsion) patients were discharged early than in group I (atropine + PAM). *Conclusion:* IV emulsion improves GCS, mean arterial pressure, thereby, decreases need for ventilation, duration of ventilation, ICU stay and overall mortality of organophosphorus patients. It is much more effective if used at the beginning of organophosphorus poisoning.

Keywords: Organophosphorus, Lipid Emulsion, Paraldoxime.

Introduction

Organophosphorus compounds are usually esters, amides or thiol derivatives of phosphonic acid and form a large family (>50000 compounds) of chemical agents with biological properties that have important, and sometimes unique, applications for the benefit of mankind. There is considerable structural diversity among the commonly used organophosphorus compounds. The principal use of these compounds are as pesticides in agriculture, mainly as insecticides. Some formulations are used in veterinary and human medicine, particularly as antiparasitics, against ticks, lice and fleas. The development and use of some of these compounds as very potent agents of chemical warfare (tabun, sarin) is of global significance [1].

Many organophosphorus compounds are highly toxic to plants, animals and humans. Organophosphate pesticides account for up to 3 million intoxication cases each year [2]. Organophosphorus pesticide self-poisoning is

a major clinical and public health problem across much of rural Asia [3-5]. Of the estimated 500,000 deaths self-harm in the region each year, about 60% are due to pesticide poisoning [6]. Deaths from unintentional organophosphorus poisoning are less common than those from intentional poisoning. Organophosphorus poisoning was described first in India by Vishwanathan et al in 1962 [7-8]. Kashmir is rich in agricultural heritage and the need of pesticides is quite high, so the organophosphorus compounds are readily available in almost all the houses especially in rural Kashmir [9].

The incidence of organophosphorus poisoning in our country is varied. P.G Kamath reported 34% incidence of organophosphorus poisoning among poisoning [10]. Recent data from National Crime Bureau of India shows suicide by consumption of pesticides account for 19.4% and 19.7% of all the cases of suicidal poisoning in the year 2006 and 2007 respectively [11]. According to, SKIMS Medical Statistical Bulletian, total number of organophosphorus patients admitted in this Institution from 2012 to 2014 were 215 (60 in 2012, 75 in 2013 and 80 in 2014), Out of which 112 patients were admitted in Anaesthesiology and Critical Care Medicine.

The toxic mechanism of Organophosphorus (OP) compounds is based on the irreversible inhibition of acetyl cholinesterase (AChE) due to phosphorylation of the active site of the enzyme. This leads to accumulation of acetylcholine and subsequent over-activation of cholinergic receptors at the neuromuscular junctions and in the autonomic and central nervous systems. The rate and degree of AChE inhibition differs according to the structure of the Organophosphorus compounds and the nature of their metabolite.

In general, pure thion compounds are not significant inhibitors in their original form and need metabolic activation (oxidation) in vivo to oxon form. For example, parathion has to be metabolized to paraxon in the body so as to actively inhibit AChE [12-13]. The toxic mechanism of Organophosphorus pesticides differs from that of carbamates which inhibit the same enzyme reversibly and are sometimes useful as medicines (neostigmine, pyridostigmine) as well as insecticides (carbaryl) [14].

Material and Methods

This prospective randomized, comparative study, "Evaluation of intravenous lipid emulsion as a novel therapeutic antidote in severe organophosphorous poisoning" was conducted in the department of Anesthesiology and Critical Care, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir from November 2012 - October 2014.

The investigation protocol was approved by the institutional review board. Patients included in the trial had clinical evidence of Organophosphorus poisoning (i.e., bronchorrhoea, increased salivation, miosis or fasciculations) or report by relatives of Organophosphorus poisoning. After obtaining the informed consent from eligible (History of alleged organophosphorus intake, age of more than 14 years, clinical signs and symptoms of organophosphorus poisoning) patients or legally authorized representatives, the details of history and clinical examination were recorded. A total of 100 adult otherwise healthy patients were included in the study.

The patients were randomly recruited into the group I (atropine + PAM) and group II (atropine + intravenous lipid emulsion), each group comprising 50 patients. The randomization was done as per computer generated Random number tables and patients straightway allocated to either into group I (atropine + PAM) or group II (atropine+ intravenous lipid emulsion).

Exclusion Criteria

- Patients with age< 14 years or > 60 years.
- Known pregnancy.
- Patients with coagulation disorders, hyper lipidemia, anaemia, severe liver damage.
- Allergy to egg or soyabean.
- Any other Chronic medical or Surgical Illness.
- Interval from time of Poisoning to initiation of treatment of ≥12 hours.
- Prehospital cardiac or respiratory arrest.

Identity of the organophosphorus pesticide ingested was ascertained on the basis of observation of attendants, evidence from

empty bottles of pesticides. All eligible patients were assessed as per severity scoring scale (Bardin grade). Management of all the patients was uniform on presentation to hospital. All the patients were decontaminated (stomach-wash, body wash, removal of contaminated clothes). All the patients were resuscitated for airway, breathing and circulation. Baseline characteristics of two groups i.e. number of patients, age, Cholinestrase levels; severity of poisoning, type of compound ingested was analyzed and balanced.

Following parameters were recorded after admission:

- GCS
- Heart rate
- Mean arterial pressure
- Blood sample for cholinesterase levels were collected during following periods.
  - At the time of admission
  - On day 1.
  - On day 3.
  - On day 5.
  - On the day of discharge/death.
- In addition following investigations were sent.
  - ABG, Na, K, KFT, LFT, Blood sugar ECG and CXR.
- Serum triglycerides

All the patients received atropine 2-3 mg I/V stat and then dose was doubled every 5 minutes till atropinisation and once target end points for atropine therapy (Heart rate >100bpm, dry mouth, clear lungs on auscultation, normal bowel sounds, mid dilated pupils) were achieved, atropine was given as a continuous infusion at the rate of 20-80 mcg/min titrated to achieve set end points. Pralidoxime was given to group I (atropine + PAM) as per WHO recommendations i.e. 30 mg/kg loading dose over 30 minutes followed by 8mg/kg/hr continuous infusion for a maximum of 5 days or until clinical improvement i.e. resolution of muscle fasciculations and weakness, or until atropine was no longer required indicating the presence of sufficient cholinesterase levels at the synapses.

In group II (atropine + intravenous lipid emulsion) intravenous lipid emulsion (20%) was given as per Association of Anesthesiologists of Great Britain and Ireland recommendations that is 1.5 ml/kg bolus followed by1.5 ml/kg/hr infusion for 5 hours and then 0.25 ml/kg/hr upto a maximum of 1500ml in 24 hours. Patients were assessed everyday for cholinergic signs, atropine requirements, muscle power and the level of consciousness by GCS. All the patients were monitored continuously with ECG, pulse oximetry, invasive BP monitoring, CXR as needed. Atropine was slowly withdrawn slowly over a period of 3-5 days. Outcome parameters analyzed were:

- Primary i.e. mortality.
- Secondary i.e. need for intubation, need for ventilation and duration of ventilation, duration of stay in ICU, incidence of Intermediate Syndrome,, total dose of Atropine , ILE and PAM.

Statistical analysis: Fisher's exact test, Chi square test and independent sample test were done to compare the efficacy parameters between the two groups. Interval data was expressed as Mean± SD (standard deviation) and categorical data in terms of frequency and percentages. A p-value<0.05 was considered as statistically significant. Statistical software used was Statistical Package for Social Sciences (SPSS) version 20.

Results

The two groups were comparable with respect to age. The mean age of patients in the Group I (atropine + pralidoxime) was 27.90±10.25 years, whereas in group II (atropine + intralipid) is 26.58±6.887 years (table1).

Table-1: Comparison of Mean Age in years between two groups

Group	Number	Age(yrs) Mean±SD	P Value
Group I	50	27.90±10.025	0.445
Group II	50	26.58±6.887	

The difference was statistically insignificant (p=0.445). In Group I (atropine + PAM) 36% patients were males and 64% were females, whereas in group II (atropine + intravenouslpid emulsion) there were 32% male patients and 68% female patients (table2).

Table-2: Sex distribution between two groups			
Group	Sex		P value
	Male	Female	
Group I	18	32	0.673
%age	36.0%	64.0%	
Group II	16	34	
%age	32.0%	68.0%	

Therefore, two groups were homogenous with respect to sex distribution. (p value > 0.05). A total of 92 out of 100 patients were put on ventilator during treatment. In group I (atropine + PAM) all the patients, 50 out of 50 patients (100%) required ventilatory support, while 42 out of 50 patients were put on ventilator in group II (atropine + intravenous lipid emulsion). The difference was found to be statistically significant (P value =0.006) (table3).

Table-3: Comparison of need for mechanical ventilation between two groups			
	Ventilated		P value
Group	No	Yes	
I	0	50	0.006
%	0.0%	100%	
II	8	42	
%	16%	84%	

Duration of mechanical ventilation in group I (atropine + PAM) was 3.7200±1.77327 days and in group II (atropine + intravenous lipid emulsion) was 2.6875±1.40146 days. Duration of mechanical ventilation in days was longer in patients receiving atropine and PAM than in those receiving atropine and intravenous lipid emulsion and the difference was found to be statistically significant (p value =0.002) (table-4).

Table-4: Comparison of mean duration of ventilation (in days) between two groups		
Group	Duration of mechanical ventilation (days) Mean ±SD	P value
I	3.7200±1.77327	0.002
II	2.6875±1.40146	

Discussion

Organophosporus pesticide self poisoning is a major clinical problem in rural Asia and it results in the death of 200000 people every year. The high mortality rate depends on the amount of toxic absorption. The management of acute organophosphate poisoning depends very much on its severity. In mild cases, removing the patient from the area of exposure and low dose of Atropine may suffice. However, in severe cases, resuscitation, artificial ventilation and high doses of antidotes becomes necessary. Intravenous lipid emulsion can be used as an antidote in fat soluble drug poisoning.

The detoxification mechanism of intravenous lipid emulsion is ("lipid sink") by which lipid emulsion can dissolve the fat soluble drugs and separate poison away from the sites of toxicity. Most of Organophosphorus pesticides are highly fat soluble. So Intravenous lipid emulsion has the potential clinical application in the treatment of Organophosphorus poisoning [15].

Both the groups were homogenous with reference to age, sex and ingestion to treatment interval. Total number of organophosphorus poisoning patients admitted in the Sheri Kashmir Medical Institute were 215 during our study period (2012-2014), Out of them 112 patients were admitted to Intensive and Critical Care Medicine (ICCU). Total number of overall poisoning including other poisons, 135 patients were admitted in (ICCU) during our study period, out of which 112 were of organophosphorus poisoning constituting 82.96% of total poisoning admissions.

Our observation is in semblance with that of Jokanovic M who also reported organophosphorus poisoning as the commonest form of poisoning in their centre with an incidence of 89.75% [16]. In Group I (atropine + PAM) all patients, 50 out of 50 patients (100%) required ventilatory support, while 42 out of 50 patients (84%) required mechanical ventilation in Group II (atropine +intravenous lipid emulsion). The difference was statistically significant (p value 0.006). Our results are in agreement with those of

Johnson S et al [17] and Cherin MA et al [18] who reported increased incidence of ventilator requirement in patients treated with PAM.

Mean duration of days of ventilation in days in group I (atropine +PAM) were 3.7200 ± 1.77327 and in group II (atropine +intravenous lipid emulsion) were 2.6875 ± 1.40146, and the difference was statistically significant (p value 0.02). The most important reason for less duration of ventilation in group II was rapid improvement in GCS and hemodynamic stability. Mean duration of ICU stay in group I (atropine + PAM) were 5.84±2.99 days and 4.88±1.69 days in group II (atropine + intravenous lipid emulsion).

The difference was statistically significant (p value=0.049). Cause for less duration of ICU stay in group II was early improvement in GCS, hemodynamic stability, less complications than in group I. Overall mortality in our study was 29 out of 100 patients (29%). Case fatality was higher (20/50:40%) in patients of group I (atropine + PAM) compared to those in II group who received atropine and intravenous lipid emulsion (9/50; 18%). The difference was statistically significant (p value<0.05) (table5).

Table-5: Comparison of outcome between two groups

Group	Outcome		P value
	Died	Survived	
I	20	30	<0.05
%age	40%	60%	
II	9	41	
%ages	18%	82%	

This study points to the fact that original research regarding organophosphorus poisoning has been published in last 2 decades and we expect in the next decade evidence from continuing research across the world especially Asia will provide clear guidance to treat organophosphorus poisoning and will include this novel antidote to reduce morbidity and mortality.

One of the important limitation of our study was that we used the intravenous lipid emulsion in the dose range recommended by Association of Aneathesioligists of Great Britian and Ireland (AAGBI) for local anesthetic toxicity, and did not try other (less or more) doses in this separate class of poisoning. Second limitation of our study is that we did not study the effect of intravenous lipid emusion infusion in patients less than 14 years of age. Therefore, we recommend further studies in this area to determine the optimum dose and may probably decrease the cost of treatment in the patients which remains an important concern in our population.

Conclusion

This randomized clinical trial, "Effectiveness of Intravenous Lipid Emulsion as a novel therapeutic antidote in severe Organophosphorus poisoning" suggests that Intravenous lipid emulsion is highly safe effective therapy in severe organophosphorus poisoning. It improves GCS, mean arterial pressure, thereby, decreases need for ventilation, duration of ventilation, ICU stay and overall mortality of organophosphorus patients. It is much more effective if used at the beginning of organophosphorus poisoning. We recommend further research before ILE therapy should be considered as antidote for clinical use after organophosphorus poisoning.

Financial Support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

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Cite this article as: Majeed S, Malik AH and DAR BA. Evaluation of intravenous lipid emulsion as a novel therapeutic antidote in severe organophosphorous poisoning - A prospective randomized, comparative study. *Al Ameen J Med Sci* 2019; 12(3):160-165.

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