Effects of Standard Treatment Alone versus Standard Treatment Plus Plasmapheresis on the Levels of Serum Pseudocholinesterase and Erythrocyte Acetyl Cholinesterase in Critically Patients with Organophosphate Poisoning: Randomized Controlled, Open-Label, ClinicalTrial

Gulten Can Sezgin[1], Hilal Sipahioglu[2], Kursat Gundogan[2], Ramazan Coskun[2], Sahin Temel[2], Cevat Yazici[3], Okhan Akdur[4], Murat Sungur[2], Muhammet Guven[5]

[1] Erciyes University, Faculty of Medicine, Department of Internal Medicine, Division of Gastroenterology, Kayseri, Türkiye
[2] Erciyes University, Faculty of Medicine, Department of Internal Medicine, Division of Intensive Care, Kayseri, Türkiye
[3] Erciyes University, Faculty of Medicine, Department of Biochemistry, Kayseri, Türkiye
[4] Canakkale Onsekiz Mart University, Faculty of Medicine, Department of Emergency, Canakkale, Türkiye
[5] Lokman Hekim University, Faculty of Medicine, Department of Internal Medicine, Division of Intensive Care, Ankara, Türkiye

Adres for Correspodence: Lokman Hekim University, 06510, Cankaya, Ankara, Türkiye e-mail: muhammet.guven@lokmanhekim.edu.tr

Orcid ID: GCS: 0000-0001-5537-7882 KG: 0000-0002-8433-3480 ST: 0000-0002-2766-4312 OA: 0000-0003-3099-6876 MG: 0000-0001-9874-7185
HS: 0000-0002-7884-2094 RC: 0000-0002-5755-523X CY: 0000-0003-0625-9542 MS: 0000-0002-0011-3166

Cite As: Sezgin Can G, Sipahioglu H, Gundogan K, et al. Effects of standard treatment alone versus standard treatment plus plasmapheresis on the levels of serum pseudocholinesterase and erythrocyte acetyl cholinesterase in critically patients with organophosphate poisoning: Randomized controlled, open-label, clinical trial. Hitit Med J 2023;5(3): 209-215 https://doi.org/10.52827/hititmedj.1326182

Abstract

Objective: Organophosphates are the insecticides commonly used worldwide. Inadequate treatment for organophosphates poisoning increases morbidity, and mortality. Purpose of the work was to determine the effect of standard treatment alone versus standard treatment plus plasmapheresis on the levels of serum pseudo-cholinesterase, and erythrocyte acetyl cholinesterase in severe patients with organophosphates poisoning.

Material and Method: This research is a prospective study. Patients diagnosed with organophosphates poisoning were included in the work. The patients were divided into two groups as the intervention group, and the standard group. The intervention group, plasmapheresis was performed in addition to the standard treatment.

Results: The research was conducted with forty cases. (Intervention group n=21, standard group n=19). Serum pseudo-cholinesterase values were 482.5 u/L at baseline, 3723 u/L after plasmapheresis. Erythrocyte acetyl cholinesterase values were 1.91 u/mL on admission, 2.53 u/mL after plasmapheresis. Erythrocyte acetyl cholinesterase and serum pseudo-cholinesterase values were compared between the two groups daily from the admission of patients to intensive care units during the first 5 days, and on the last day in the intensive care units. There was no statistical difference between two groups ($p> 0.05$), except for the second day. It was observed that there was a statistically significant difference between the pseudo-cholinesterase values in the second day comparison of both groups ($p=0.028$).

Conclusion: In conclusion, plasmapheresis treatment may contribute positively to pseudo-cholinesterase level. This treatment may have provided additional time for the organophosphates to be eliminated from the body. Although acetyl cholinesterase reactivation is achieved with oxime treatment, the clinical effect of this treatment is not clear.

Keywords: Erythrocyte acetyl cholinesterase, Intensive care units, Organophosphate poisoning, Plasmapheresis, Pseudo-cholinesterase.

Özet

Amaç: Organofosfatlar dünya çapında yaygın olarak kullanılan insektisitlerdir. Organofosfat zehirlenmelerinde yetersiz tedavi morbidite ve mortaliteyi artırmaktadır. Çalışmanın amacı, organofosfat zehirlenmesi olan ciddi hastalarda serum psödo-kolinesteraz ve eritrosit asetil kolinesteraz düzeyleri üzerinde standart tedaviye karşı, standart tedavi artı plazmaferezin etkinliğini araştırmaktır.

Gereç ve Yöntem: Bu araştırma prospektif bir çalışmadır. Çalışmaya organofosfat zehirlenmesi tanısı alan hastalar dahil edildi. Hastalar müdahale grubu ve standart grup olarak iki gruba ayrıldı. Müdahale grubuna standart tedaviye ek olarak plazmaferez tedavisi uygulandı.

Bulgular: Çalışmaya kırk hasta alınmıştır (müdahale grubu n:21, standart grup n:19). Başlangıçta serum psödo-kolinesteraz değerleri 482,5 u/L, plazmaferez sonrası 3723 u/L idi. Eritrosit asetil kolinesteraz değerleri başvuruda 1,91 u/mL, plazmaferez sonrası 2,53 u/mL idi. Eritrosit asetil kolinesteraz ve serum psödo-kolinesteraz değerleri hastaların yoğun bakıma kabulünden itibaren ilk 5 gün ve yoğun bakımdaki son gün değerleri iki grup arasında karşılaştırıldı. İki grup arasında 2. gün dışında istatistiksel fark yoktu ($p> 0,05$). Her iki grubun ikinci gün karşılaştırmasında psödo-kolinesteraz değerleri arasında istatistiksel olarak anlamlı fark olduğu görüldü ($p=0,028$).

Sonuç: Sonuç olarak, plazmaferez tedavisi psödo-kolinesteraz düzeyine olumlu katkı sağlayabilir. Bu tedavi organofosfatların vücuttan atılması için ek süre sağlamış olabilir. Asetil kolinesteraz reaktivasyonu oksim tedavisi ile sağlansa da bu tedavinin klinik etkisi net değildir.

Anahtar Sözcükler: Eritrosit asetil kolinesteraz, Organofosfat zehirlenmesi, Plazmaferez, Psödo-kolinesteraz, YBÜ.

Date of Submission: 14.07.2023
Date of Acceptance: 23.09.2023
Date of Publication: 10.10.2023

Orally presented the date and the place: 32nd Annual Congress, ESICM LIVES, 28 September – 2 October 2019, Berlin, Germany.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: A certificate was obtained from Erciyes University Faculty of Medicine Ethics Committee fort he study (Ethics Committee Decision no: 01/32).
Plagiarism Checks: Yes - iThenticate
Conflict of Interest: No conflict of interest has been declared by the authors.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: MG, GCS Design: MG, GCS Data Collection/Data Processing: RC, HS, CY, KG, ST Data Analysis: OA, KG, MG, GCS Article Preparation: GCS, HS, KG, ST, CY, OA, MS, MG
Informed Consent: Consent has been obtained personally for the conscious patients, and from their legal guardians for the unconscious patients.
Financial Disclosure: This study was supported by Erciyes University Scientific Research Committee (Project no: TT-07-27, Gulten Can Sezgin)

Introduction

Organophosphate (OP) compounds are among the most widely used insecticides around the world due to their low cost, and rapid effects (1, 2). These OP groups are also widely used in our country, and have an important place among the causes of poisoning (3, 4). When the causes of poisoning are examined, it is seen that they are caused by use in the field of agriculture, accidental exposure to the compounds, or suicide attempts (2, 4, 5). Delayed diagnosis, and inadequate treatment in patients with OP poisoning are factors that increase morbidity, and mortality (2, 6, 7). For this reason, early diagnosis, and appropriate treatment of OP poisoning is lifesaving. Patients diagnosed with OP poisoning should be followed up, and treated by multidisciplinary intensive care units (ICU), and their teams (3). New treatment modalities have recently been applied in addition to standard treatment in OP poisoning (8-11). Plasmapheresis is a therapeutic procedure used in many medical conditions that ensures the removal of plasma compounds such as antibodies, immunocomplexes, endogenous, and exogenous toxins from the body. In plasmapheresis, fresh frozen plasma (FFP), human albumin, and colloidal fluids may be used as replacement fluid. FFP is the most important source of pseudocholinesterase (PChE). In some previous studies, it has been determined that fresh frozen plasma has cholinesterase activity at adequate levels, and its use in patients with OP poisoning may reduce mortality, and morbidity, and it has been concluded that plasma cholinesterase functions as a reserve, and back-up for erythrocyte acetyl cholinesterase (AChE) (8, 11).

OP insecticides inhibit AChE, and cholinesterase enzymes, resulting in a clinical situation with overstimulation of cholinergic synapses. Today, in cases with OP poisoning, the serum PChE values are measured, and the diagnosis, and treatment management of the patients are performed (12). The serum cholinesterase enzyme can be highly variable due to hereditary deficiency. This situation reduces the diagnostic value of serum cholinesterase enzyme in OP poisoning cases. Some studies have shown that erythrocyte AChE activity serves as a key biomarker for synaptic AChE (13).

We hypothesize that if the patients with OP poisoning are subjected to standard treatment plus plasmapheresis with fresh frozen plasma, the PChE, and erythrocyte AChE levels return to normal in a shorter time. Rapid elevation of these enzymes may decrease morbidity, and mortality associated with OP poisoning.

Primary purpose of this study was to compare the levels of serum PChE, and erythrocyte AChE daily between the patients diagnosed with OP poisoning that are subjected to standard treatment plus a single plasmapheresis, and those subjected to standard treatment alone during the hospitalization in the ICU.

Secondary purpose was to compare clinical data, such as ventilator-associated pneumonia incidence, number of days on mechanical ventilation, and length of ICU stay between two groups above.

Material and Methods

Research design and setting

The work has been carried out prospectively in Medical ICU. A certificate was obtained from the Ethics Committee for the study (Ethics Committee Decision no: 01/32). Consent has been obtained personally for the conscious patients, and from their legal guardians for the unconscious patients.

Selection of participants

Patients above 16 years old that were diagnosed with OP poisoning in emergency department, have PChE levels below normal value, and were indicated for hospitalization in the intensive care were enrolled in the study. The patient's relatives were requested to bring the causing OP compound from home, and OP compound was demonstrated to cause the poisoning. Among the patients visiting the emergency department with pre-diagnosis of OP poisoning, those with normal PChE level, without evidence of OP compound or rejecting to give consent have not been enrolled in the study. Standard treatment was applied to patients who applied to the emergency department with OP poisoning, plasmapheresis treatment was also recommended, and patients who accepted plasmapheresis treatment were included in the plasmapheresis intervention group. Although the cases included in the research were randomized, those who were in worse condition generally accepted the plasmapheresis procedure.

Randomization

-Patients admitted to the intensive care unit were then randomized. One session of plasmapheresis was performed to the patients in study group (intervention group) on the first day in addition to the standard treatment in the ICU for OP poisoning, and standard treatment alone was administered to the standard group (control group).

Outcome measures

Primary outcome was to compare serum PChE, and erythrocyte AChE levels of the patients in the intervention group, and the control group for the first 5 days from admission to the ICU, and on the discharge day in order to evaluate efficacy of plasmapheresis.

Secondary outcome was to compare clinical data, such as ventilator-associated pneumonia incidence rates, number of days on mechanical ventilation, number of days stayed in the intensive care unit, between the group treated with plasmapheresis, and the group administered standard treatment.

After admission of the patients to the ICU, demographic data, OP compound causing poisoning, way of poisoning, cause of poisoning were noted. Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Glasgow Coma Score (GCS) were calculated. Patients were also followed up daily for mechanical ventilation need, new infections, and rhythm disorders on electrocardiogram (ECG), and the findings were noted. Atropine and pralidoxime (PAM) usage durations, and amounts were noted. Intermediate syndrome (IMS) incidence, number of days on intensive care, and intensive care mortality were also noted. IMS occurs approximately 24-96 hours after toxicity. The clinical situation is after resolution of the acute cholinergic crisis, and before the onset of delayed neuropathy, some patients develop muscle paralysis (12,14).

Once the patients were diagnosed, standard treatment for OP poisoning was initiated. Standard treatment included administration of general care, and supportive therapy, providing respiratory support to the patient as well as administration of activated carbon, and gastric lavage in the conscious patients. The patients with respiratory failure were intubated and monitored on mechanical ventilation. Patients

whose breathing became shallow, who could not protect the airway due to excessive secretions or impaired consciousness, and whose GCS was <8 were intubated.

Atropine, and PAM treatment initiated in emergency department was continued in the ICU. Atropine was started in the diagnosed patients at the initial dose of 1-2 mg intravenously, and it was repeated every 5-10 minutes with dose adjustment based on their individual clinical status. Treatment was continued with infusion at 0.5-2 mg/hour based on the clinical status of the patient. Dose of atropine infusion was adjusted based on the cholinergic findings. It was administered until hypersecretion is controlled, and discontinued 24 hours after appearance of atropinization signs. In case of that the symptoms reoccurred atropine infusion was reinitiated. Intravenous bolus dose of PAM was 1000 mg. Thereafter, treatment was continued with infusion at 4 mg/kg/hour. PAM treatment was continued for 72 hours. Total doses of atropine, and PAM given to each patient were calculated.

Laboratory

In order to check PChE levels, 2 cc blood was taken into the biochemistry tubes with gel from intervention group patients before and after plasmapheresis, during the first 5 days in the ICU, and on the discharge day, and from control group patients during the first 5 days in the ICU and on the discharge day. Serum PChE levels were measured by OLYMPUS 2700 device using the original kit (reference range 3930-10800 u/L). PChE value of fresh frozen plasma used in plasmapheresis was 7069.81±305.18 u/L.

Similarly, blood was taken into CBC tube from the intervention group patients before and after plasmapheresis for erythrocyte cholinesterase testing. The blood samples were kept in the fridge at +4°C. Erythrocyte cholinesterase was measured by spectrophotometry kits. Erythrocyte cholinesterase was tested with Test-mate ChE Cholinesterase Test System Model 400 (EQM Research brand) device using AChE Erythrocyte Cholinesterase Assay Kit (Model 460) original kit. The procedure of this test uses the Elman method. Carboxylic acid, and thiocholine are formed upon hydrolysis of AchE, and Acetylcholine. Thiocholine Ellman reagent (DTNB, dithionitrobenzoic acid) reacts, the formed yellow color is measured with spectrophotometry at 450 nm wavelength.

Plasma corresponding to total plasma volume was used in one session of plasmapheresis. One session of plasmapheresis was performed on the first day. All side effects observed during the procedure were noted.

Statistical Analysis

SPSS 22.00 (Statistical Packages for Social Sciences; SPSS Inc. Chicago, Illinois, USA) and Sigma stat 3.5 133 programs were used for statistical analyses in the study. Qualitative variables were presented using percentages, and frequencies. Mean and standard deviation were used for normally distributed quantitative variables, median, and ranges were used for non-normally distributed quantitative variables. Normality of data was tested by 'Shapiro-Wilk' test. Comparisons between qualitative variables were done with using Chi-square test. Comparison of continuous variables was done with using Student's t test for normally distributed independent variables, and Mann Whitney U test for non-normally distributed independent variables. The statistical significance was set at $p<0.05$.

Results

A total of 40 cases were included in this study. Twenty-one patients were assigned to the plasmapheresis group (intervention group), and 19 patients were assigned to the standard group (control group). Detailed demographic data, and clinical results of the patients are presented in Table I. OP poisoning was mostly caused by dichlorvos (20%), malathion (12.5%), and monocrotophos 12.5% (Table II).

Table I. Patient demographic and clinical characteristics

Variables	General (n=40)	Intervention group (n=21)	Control group (n=19)	*P value*
Age± SD, years	37±16	41 ± 16	33 ± 15	*0.114*
Gender, n (%)				
Male	24(60)	14(35)	10(25)	
Female	16(40)	7(17.5)	9(22.5)	*0.520*
APACHE II score, ± SD	9±5	11.38 ± 4.33	9 ± 3.85	*0.037*
Length of ICU stay (range), day	6 (3-26)	7 (5-26)	6 (3-10)	*0.153*
Duration of MV stay (range), day	4 (2-17)	5 (2-17)	4 (3-7)	*1.000*
Need for MV, n (%)	11 (%27)	7 (%33)	4 (%21)	*0.607*
VAP, n (%)	6 (15)	4 (60)	2 (40)	*0.550*

APACHE II: Acute Physiology, Age, Chronic Health Evaluation II, ICU: Intensive Care Unit, MV: Mechanical Ventilation, VAP: Ventilator Associated Pneumonia

Table II. OP compounds that cause of intoxication

OP compound	Number (%) (n = 40)
Dichlorvos	8 (20)
Monocrotophos	5 (12.5)
Malathion	5 (12.5)
Chlorpyrifos	4 (10)
Diazinon	4 (10)
Clofenvinfos	3 (7.5)
Methidathion	3 (7.5)
Coumaphos	2 (5)
Parathionmetil	2 (5)
Triklorfon	2 (5)
Azinphosmetil	1 (2.5)
Methamidophos	1 (2.5)

Based on the evaluation of the patients by the cause of poisoning, intervention group included 15 (71.4%) patients poisoned due to suicide attempt, and 6 (28.6%) patients accidentally poisoned. Control group included 14 (73.7%) patients poisoned due to suicide attempt, and 5 (26.3%) patients accidentally poisoned.

Based on the patient's history data, 20 (95.2%) patients were poisoned orally, and 1 (4.8%) patient was poisoned by respiratory route in the intervention group, while 19 (100%) patients were poisoned orally in the control group. Patients in both groups continued to live.

IMS occurred in 2 (9.5%) patients in the intervention group. IMS did not occur in control group. Morbidity was present 8 (38.1%) patients in the intervention group and 7 (36.8%) patients in the control group. Causes of morbidity are given in Table III. There was no significant difference between the two groups in terms of atropine administration time and atropine amount ($p = 0.454$, $p = 0.735$, respectively). Additionally, when both groups were compared, no statistically significant difference was observed in terms of PAM administration time and amount ($p=0.714$, $p=0.518$, respectively) (Table IV).

Table III. Causes of morbidity in patient with OP poisinin

Causes of morbidity	Intervention group (n)	Control group (n)	Total (n)
VAP	4	2	6
UTI	1	1	2
GIB	0	1	1
Aspiration pneumonia	1	2	3
Catheter infection	1	0	1
Thrombosis	1	0	1
Candida esophagitis	0	1	1
Total	8	7	15
p=0.550			

VAP:Ventilator associated pneumonia, UTI:Urinary tract infection, GIB:Gastrointestinal bleeding

Table IV. Comparison of atropine and PAM treatment, duration and dose amount between two groups

	Intervention group (n:21)	Control group (n:19)	*P value*
Atropin duration, SD (day)	4.31±2.11	3.84±1.76	*p=0.454*
Atropin total dose,SD (mg)	83.33 ±49.34	88.79±75.41	*p=0.735*
PAM duration, SD (day)	2.76±0.90	2.79±0.95	*p=0.714*
PAM total dose, SD (mg)	16641.14±5084.32	15497.68±5996.58	*p=0.518*

PAM: Pralidoxime

After admission to the ICU, serum PChE values of the patients of intervention group, and control group were compared daily during the first 5 days, and on last day of intensive care. There was no statistical difference between two groups, except for the 2nd day. It was observed that there was a statistically significant difference between the PChE values in the second day comparison of both groups (*p=0.028*). (Table V) (Figure I).

Figure I. Median serum PChE levels over time between intervention and control treatment groups

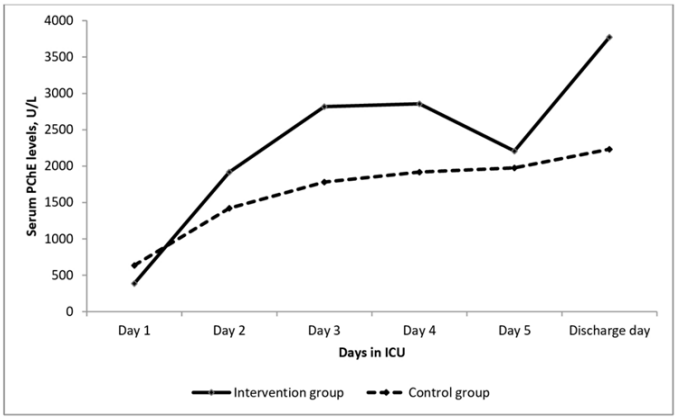

Figure 1 legend: On day 1, serum PChE level of the patients was 388 (218- 2092) u/L in plasmapheresis group, and 637 (177-3883) u/L in control group (*p=0.155*). On day 2, serum PChE level of the patients was 4112 (174-7078) u/L in plasmapheresis group, and 1423 (194-4800) u/L in control group (p=0.028). On day 3, serum PChE level of the patients was 2819 (181-1918) u/L in plasmapheresis group, and 1781 (231-4764) u/L in control group (*p=0.250*). On day 4, serum PChE level of the patients was 2857 (161-9993) u/L in plasmapheresis group, and 1920 (263-4029) u/L in control group (p=0.323). On day 5, serum PChE level of the patients was 1175 (178- 8464) u/L in plasmapheresis group, and 1477 (181-3439) u/L in control group (*p=0.514*). Serum PChE level of the patients was 3773 (121-10597) u/L in plasmapheresis group, and 2233 (239-4454) u/L in control group (*p=0.261*) on the discharge day.

Table V. Serum PChE levels over time between intervention and control treatment groups

PChE level	Intervention, u/L	Control, u/L	*P-value*
Day 1	388 (251.50-643.75)*	637 (351.50-1966.25)	*0.155*
Day 2	4112 (174-7078)	1423 (194-4800)	*0.028*
Day 3	2819 (181-1918)*	1781 (231-4764)	*0.250*
Day 4	2857 (161-9993)	1920 (263-4029)	*0.323*
Day 5	1175 (178-8464)*	1477 (181-3439)	*0.514*
Discharge day	3773 (121-10597)*	2233 (239-4454)	*0.261*

PChE: Pseudo-cholinesterase , *P*=<0.001*

The mean PChE value of the intervention group at the first admission to the hospital was found to be 388 (range: 218-2092) u/L, but after plasmapheresis treatment, mean PChE value was found to be 3723 (range:541.50-5422.25) u/L. There was a significant difference when PChE hospitalization value, and post-plasmapheresis value were compared (*p<0.050*). There was also a significant difference, when PChE admission value was compared with the 3rd day, 5th day, and discharge value (*p <0.001*) (Table V).

Intervention group AChE values were compared between days, there was no significant difference (*p>0.05*). After admission to the ICU, erythrocyte AChE values of the patients of intervention group, and control group were compared daily during the first 5 days, and on last day of intensive care. There was no statistically significant difference between two groups (Table IV) (Figure II).

Complication occurred in 5 patients (23.8%) during plasmapheresis procedures. The most frequent complication was hypocalcaemia (3 patients, 14.2%). Urticaria was observed in 2 patients (9.5%). No patient died due to the complications of plasmapheresis.

Figure II. Median plasma erythrocyte AChE levels over time between intervention and control treatment groups

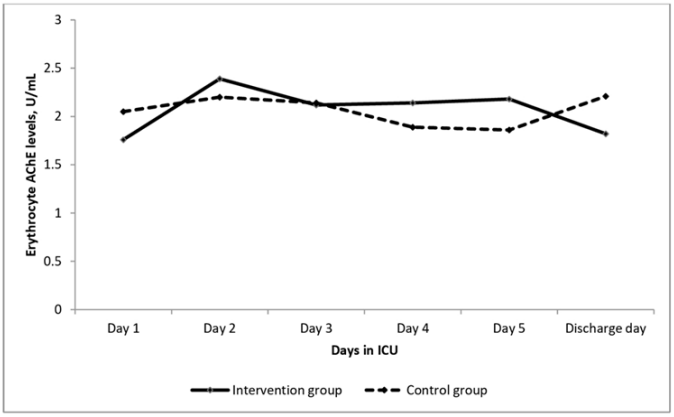

Figure 2 legend: On day 1, plasma erythrocyte AChE level of the patients was 1.76 (0.12- 4.85) um/L in plasmapheresis group, and 2.05 (0.19-4.84) u/mL in control group (*p=0.871*). On day 2, plasma erythrocyte AChE level of the patients was 2.39 (0.01-3.90) u/mL in plasmapheresis group, and 2.20 (0.19-4.27) u/mL in control group (p=0.914). On day 3, plasma erythrocyte AChE level of the patients was 2.12(0.07-4.30) u/mL in plasmapheresis group, and 2.14 (0.27-4.20) u/mL in control group (*p=0.705*). On day 4, plasma erythrocyte AChE level of the patients was 2.14(0.07-3.58) u/mL in plasmapheresis group, and 1.89 (0.27-4.24) u/mL in control group (*p=0.645*). On day 5, plasma erythrocyte AChE level of the patients was 2.27 (0.12-4.19) u/mL in plasmapheresis group, and 1.45 (0.19-4.01) u/mL in control group (*p=0.581*). Plasma erythrocyte AChE level of the patients was 1.81 (0.09-3.92) u/mL in plasmapheresis group, and 2.21 (0.41-4.37) u/mL in control group (*p=0.250*) on the discharge day

Table VI. Erythrocyte AChE levels over time between intervention and control treatment groups

AChE level	Intervention, u/mL	Control, u/mL	*P-value*
Day 1	1.76 (0.12-4.85)	2.05 (0.19-4.84)	*0.871*
Day 2	2.39(0.01-3.90)	2.20 (0.19-4.27)	*0.914*
Day 3	2.12(0.07-4.30)	2.14 (0.27-4.20)	*0.705*
Day 4	2.14(0.07-3.58)	1.89 (0.27-4.24)	*0.645*
Day 5	2.27 (0.12-4.19)	1.45 (0.19-4.01)	*0.581*
Discharge day	1.81 (0.09-3.92)	2.21 (0.41-4.37)	*0.250*

AChE: Acetyl cholinesterase

Discussion

In this study, serum PChE and erythrocyte AChE levels of the patients hospitalized due to OP poisoning that were subjected to standard treatment, and standard treatment plus plasmapheresis were compared daily during their treatment in the ICU. The main treatment for OP poisoning is administration of atropine, and PAM (15). Atropine is a muscarinic antagonist (16,17). The oximes provide reactivation of the AChE by removing the phosphoryl group attached to the active site of AChE as a result of OP toxicity in its region (18). Oximes are supportive agents in treatment, and some studies have shown that they may have some adverse effects (19). PAM increases AChE reactivation, however, does not lead to improved survival, or decreased intubation need (20). In a study, duration and amount of atropine administration were not associated with prognosis (21). In our study, there was no significant difference between the two groups in terms of the duration, and amount of both drugs.

Plasmapheresis is not a new treatment method for toxic conditions and has been clearly shown to play an effective role in many conditions (22). Under such difficult circumstances, it may elevate cholinesterase levels and may be an effective alternative (23). Guven et al. reported that plasmapheresis was successfully used in the sepsis associated with organophosphate poisoning. It was shown that the patient who developed sepsis with OP intoxication, after performing plasmapheresis with FFP for sepsis treatment, the PChE level increased to normal levels, plasmapheresis increased the PChE level, and contributed to the recovery of the patient (8).

Qiu et al. published a meta-analysis on 433 severe, and acute OP poisoning cases. 211 patients were administered standard treatment plus plasmapheresis, while 222 patients were administered standard treatment alone. Meta-analysis showed that mortality was lower in the plasmapheresis group (24). In addition, in the case report presented in the literature, it was shown that an effective treatment was performed with plasmapheresis in a patient diagnosed with Guillain-Barre Syndrome due to OP poisoning (25).

Measuring both plasma cholinesterase, and erythrocyte cholinesterase levels are methods used to diagnose. The results of these are important in terms of evaluating the treatment (26, 27). In the study carried out by Liu et al., PChE level elevated to 3823 IU/l from 200 IU/l within 21 days (28). In our study, PChE level was 344 u/L during the first five visit and on the discharge day. When the two groups were compared in each other, there was no difference, except for the second day. It was observed that there was a significant difference between the second day values of the two groups (p=0.028). AChE levels were not different between control, and intervention groups. When the enzyme values of the patients after plasmapheresis were compared with their admission values, there was a significant increase in PChE value. The positive effects of plasmapheresis may be in the form of AChE increase, and / or PChE loading its role in the absence of AChE. Possible mechanisms for AChE increase; the affinity of PChE to OP may be greater than AChE. In this way, AChE may be leaving the OP, and increasing in level, or the PChE may act as a reserve for AchE, and be transforming. The exact function of the PChE enzyme measured in OP toxicity is unknown. AChE levels may be more important. It is generally accepted that PChE normally has no physiological function in the body. Before the physiologically important AChE enzyme is inhibited by OP compounds in the target areas, it is thought that replacement of PChE to the patient may be a useful therapy by binding the circulating OP. PChE has natural physiological functions in certain regions, and functions by accompanying AChE in the regulation, and support of cholinergic transmission (29). This supportive role seems to become important, when AChE activity for some reason is reduced, or lost (9). PChE in plasma binds to OP, and inactivates them, thus protecting AChE. One PChE enzyme can inactivate one OP compound (30). Brahmi et al. showed that the decrease in erythrocyte AChE activity is a very important prognostic factor in patients with OP poisoning. Levels below 23.5 mmol/mL is associated hypoxemia, hypotension, and bradycardia (13).

Ashani et al. claimed that early administration of PChE with good timing could prevent the crises that develop with OP poisoning, the development of IMS, and the delayed toxic effects of OP (30). FFP can be an important source of PChE. Guven et al. showed that because FFP is an important source of cholinesterase, it has sufficient enzyme activity, and may play an important role in increasing the low PChE level seen in OP poisoning (8). Increased PChE levels were seen to be effective in preventing the development of IMS, and associated mortality. In this study, it is thought that the early application of FFP together with the initial antidote treatment is more beneficial especially in the development of IMS and the prevention of mortality (9). Yilmaz et al. applied plasmapheresis treatment to 17 patients who developed IMS as a result of OP poisoning, and a significant decrease in plasma OP level, and a very significant increase in PChE enzyme level in the early period were observed in patients due to this treatment (31).

IMS may develop because of insufficient administration of oximes used in medical therapy, and/or paralysis of neuromuscular transmission because of long-term nicotinic receptor stimulation. The administration of PChE, which is not dependent on OP, with plasmapheresis can play an important role in these cases. PChE administered to the patient may also prevent the long-term adverse effects seen because of AChE inactivation by the OP. In the presented study, IMS developed in 2 patients in the plasmapheresis group, but the patients continued to live. Plasmapheresis may have contributed positively to the recovery of these patients.

The incidence of complications during plasmapheresis varies from 4.6% to 36%. The most frequent complications are chills, rigors, urticaria, and paresthesia and muscle cramps

associated with hypocalcaemia caused by citrate (32-34). In our study, mild hypocalcaemia symptoms in 3 patients, and urticaria in 2 patients were observed. No severe complication occurred. In the light of these data, when we evaluate the plasmapheresis procedure in terms of risk, and incidence of complications, it can be concluded that it is a safe method.

Studies have shown that APACHE II values have high prognostic importance in OP poisoning (35, 36). In our study, absence of mortality in the patients group treated with plasmapheresis with high APACHE II values indicates that plasmapheresis treatment is an important treatment method in OP poisoning. Acute respiratory distress syndrome (ARDS) has been reported after OP poisoning. It is not clear whether ARDS in people with OP poisoning occurs after aspiration or due to the direct effect of OP. Perhaps the cause of post-aspiration deaths is related to ARDS. Differential diagnosis of aspiration pneumonia and ARDS is very important for effective treatment in these patients (37). In our study, aspiration pneumonia was observed in a total of 3 patients in both groups (intervention group: 1 patient, control group: 2 patients). There were no patients diagnosed with ARDS in both groups.

Studies show that PChE has natural physiological functions, accompanies AChE in regulating, and supporting cholinergic transmission, and this back-up role becomes more important, when AChE is suppressed, or absent. Although AChE enzyme values did not differ between groups in our study, the increase in AChE values after the procedure in the patient group who underwent plasmapheresis supports that PChE has a reserve, or back-up role for AChE. The idea that the PChE enzyme given externally plays the role of this enzyme in OP poisoning, in which AChE is inhibited, prevents mortality, and morbidity that may develop, strengthened with this study. PChE enzyme administered by plasmapheresis binds to OP by competing with endogenous AChE, thus it is thought to prevent, or reduce the toxic effect of OP.

The limitations of the study were that we did not perform a power analysis according to the number of patients, single session plasmapheresis, and open-label design. Another limitation of our study was that it consisted of patients poisoned by different physical characteristics OP that may affect the benefit of plasmapheresis.

Conclusion

As a result, plasmapheresis treatment increases PChE levels. Even if the APACHE II score is high, individual death may be prevented with PChE administered externally to the patient. However, the effectiveness of these records is not yet clear. This is a broad research area and new research needs to be done.

References

1.Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet (London, England). 2008; 371(9612): 597-607.

2.Sungur M, Guven M. Intensive care management of organophosphate insecticide poisoning. Critical care (London, England) 2001; 5(4): 211-215.

3.Coskun R, Gundogan K, Sezgin GC, et al. A retrospective review of intensive care management of organophosphate insecticide poisoning: Single center experience. Nigerian journal of clinical practice 2015; 18(5): 644-650.

4.Ozturk MA, Kelestimur F, Kurtoglu S, Guven K, Arslan D. Anticholinesterase poisoning in Turkey--clinical, laboratory and radiologic evaluation of 269 cases. Human & experimental toxicology 1990; 9(5): 273-279.

5.Guven M, Unluhizarci K, Goktas Z, Kurtoglu S. Intravenous organophosphate injection: an unusual way of intoxication. Human & experimental toxicology 1997; 16(5): 279-280.

6.Simsek ZO, Simsek Y, Sungur M, Gundogan K, Guven M. Effects of Organophosphate Poisoning on Endocrine System in Long-Term: A Pilot Study. Erciyes Med J 2019.

7.Selim K. Acute and Long-term Effects of Organophosphate Poisoning. Erciyes Medical Journal 2019; 41(1): 3-4.

8.Guven M, Sungur M, Eser B. The effect of plasmapheresis on plasma cholinesterase levels in a patient with organophosphate poisoning. Human & experimental toxicology 2004; 23(7): 365-368.

9.Guven M, Sungur M, Eser B, Sari I, Altuntas F. The effects of fresh frozen plasma on cholinesterase levels and outcomes in patients with organophosphate poisoning. Journal of toxicology Clinical toxicology. 2004; 42(5): 617-23.

10.Disel NR, Acikalin A, Kekec Z, Sebe A. Utilization of plasmapheresis for organophosphate intoxication: A case report. Turkish journal of emergency medicine 2016; 16(2): 69-71.

11.Yukselmis U, Ozcetin M, Cag Y, Yildizdas D, Yilmaz HL. The role of plasmapheresis in organophosphate poisoning: Case reports of three pediatric patients. The Turkish journal of pediatrics 2017; 59(4): 491-496.

12.Dayananda VP, Bhaskara B, Pateel GN. A study of effectiveness of fresh frozen plasma in organophosphorous compound poisoning in reducing length of Intensive Care Unit stay and in reducing need for tracheostomy. Anesthesia, essays and researches 2016; 10(2): 268-272.

13.Brahmi N, Mokline A, Kouraichi N, et al. Prognostic value of human erythrocyte acetyl cholinesterase in acute organophosphate poisoning. The American journal of emergency medicine 2006; 24(7): 822-827.

14.Senanayake N KL. Neurotoxic effects of organophosphorus insecticides: An intermediate syndrome. N Engl J Med 1987; 316: 761–763.

15.Choi P T-L, Quınonez LG, Cook DJ. Acute Organophosphate insecticide poisoning. Clinical Intensive Care 1995; 6:5.

16. Johnson MK, Jacobsen D, Meredith TJ. Evaluation of antidotes for poisoning by organophosphorus pesticides. Emerg Med 2000; 12:22–37.

17. Connors NJ, Harnett ZH, Hoffman RS. Comparison of current recommended regimens of atropinization in organophosphate poisoning. J Med Toxicol 2014; 10: 143–147.

18. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. Toxicol Rev. 2003; 22:165–190.

19. Samuel J, Thomas K, Jeyaseelan L, Peter JV, Cherian AM. Incidence of intermediate syndrome in organophosphorous poisoning. The Journal of the Association of Physicians of India 1995; 43(5): 321-323.

20. Eddleston M, Eyer P, Worek F, et al. Pralidoxime in acute organophosphorus insecticide poisoning a randomised controlled trial. PLoS medicine 2009; 6(6): e1000104.

21.Lin TJ, Jiang DD, Chan HM, Hung DZ, Li HP. Prognostic factors of organophosphate poisoning between the death and survival groups. The Kaohsiung journal of medical sciences 2007; 23(4): 176-182.

22. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue J Clin Apher 2016; 31:149-162.

23. Zhong P, Wang Q, Sheng H. Alteration of banked blood cholinesterase level and its significance in emergency treatment of acute organophosphorus pesticide poisoning. Zhonghua Nei Ke Za Zhi 2000; 39(10):658-659.

24. Qiu HM, Zheng SC, Wan WG, Zou HJ. Meta-analysis of the effectiveness of plasma exchange in treatment of severe and acute organophosphate poisoning. Zhonghua lao dong wei sheng zhi ye bing za zhi = Zhonghua laodong weisheng zhiyebing zazhi = Chinese journal of industrial hygiene and occupational diseases 2011; 29(10): 779-781.

25. Bibi S, Kauser S, Ahsan I. Guillain-Barre Syndrome: A Rare Complication of Organophosphate Poisoning. J Coll Physicians Surg Pak 2022; 32(4): 52-54.

26. Lotti M. Clinical toxicology of anticholinesterase agents in humans. In: Krieger R, editor. Handbook of pesticide toxicology. Volume 2. Agents. 2 edn. Academic Press; San Diego: 2001.p.1043–1085.

27. Li B, Sedlacek M, Manoharan I. Butyrylcholinesterase, paraoxonase, and albumin esterase, but not carboxylesterase, are present in human plasma. Biochem Pharmacol 2005;70:1673–1684.

28. Liu H, Kan B, Jian X, Zhang W, Zhou Q, Wang J. Parasuicidal poisoning by intramuscular injection of insecticide: A case report. Experimental and therapeutic medicine 2013; 6(3): 696-698.

29. Li B, Stribley JA, Ticu A, et al. Abundant tissue butyrylcholinesterase and its possible function in the acetylcholinesterase knockout mouse. J Neurochem. 2000; 75:1320-1331.

30. Ashani Y. Prospective of human butyrilcholinesterase as a detoxifying antidote and potential regulator of controlled-release drugs. Drug Dev Res 2000; 50:298-308.

31. Yilmaz M, Sebe A, Ay MO, et al. Effectiveness of therapeutic plasma exchange in patients with intermediate syndrome due to organophosphate intoxication. The American journal of emergency medicine 2013; 31(6): 953-957.

32. Korach JM, Guillevin L, Petitpas D, Berger P, Chillet P. Apheresis registry in France: indications, techniques, and complications. French Registry Study Group. Therapeutic apheresis: official journal of the International Society for Apheresis and the Japanese Society for Apheresis 2000; 4(3): 207-210.

33. Ring A, Sieber WA, Studt JD, et al. Indications and Outcomes of Patients Receiving Therapeutic Plasma Exchange under Critical Care Conditions: A Retrospective Eleven-Year Single-Center Study at a Tertiary Care Center. J Clin Med 2023; 12(8): 2876.

34. Norda R, Stegmayr BG. Therapeutic apheresis in Sweden: update of epidemiology and adverse events. Transfusion and apheresis science: official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis 2003; 29(2): 159-66.

35. Lee P, Tai DY. Clinical features of patients with acute organophosphate poisoning requiring intensive care. Intensive Care Med 2001; 27: 694-699.

36. Tsai JR, Sheu CC, Cheng MH, et al. Organophosphate poisoning: 10 years of experience in southern Taiwan. Kaohsiung J Med Sci 2007; 23:112-119.

37. Eddleston M. The pathophysiology of organophosphorus pesticide self-poisoning is. Fundam Appl Toxicol.1991;17:177-185. Neth J Med 2008; 66:146-148.