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Case Series

Effect of Therapeutic Plasma Exchange on Intermediate Syndrome by Organophosphate Poisoning

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INTRODUCTION

OP compounds are extensively employed in pesticides, farming, animal care, and pest control in residential environments. Because they prevent the enzyme acetylcholinesterase from functioning in erythrocyte membranes, skeletal muscle, and nerve tissue, these substances are poisonous and can produce a cholinergic crisis. These pesticides can enter the body through mucous membranes, the skin, conjunctiva, digestive, and respiratory systems. Accidental exposures, deliberate killings, and suicides are all possible causes of poisoning [1]. Three distinct clinical stages are observed in cases of OP poisoning:

1. Initial muscarinic symptoms of an acute cholinergic crisis.
2. Intermediate Syndrome
3. Delay neuropathy

Acute Cholinergic Crisis

The cholinergic crisis frequently presents with symptoms like nausea, vomiting, diarrhea, abdominal cramps, urine incontinence, miosis, salivation, lacrimation, bronchorrhea, bradycardia, hypotension, fasciculation, muscle paralysis, dizziness, confusion, seizures, coma, and respiratory failure. If life-threatening diseases, such as respiratory failure, are not treated quickly and effectively, death may result. Additionally known as Type I Paralysis.

Intermediate syndrome

This happens after the patient has recovered clinically from the acute cholinergic crisis. IMS was defined by weakness in the muscles of the proximal limbs, the neck flexors, the respiratory muscles, and the motor cranial nerves, and it was thought that this weakness was caused by muscle fiber necrosis after the acute cholinergic crisis. Additionally known as Type II Paralysis.

Delayed Neuropathy

OP-related delayed neurotoxic impact, also known as OP-induced delayed neurotoxicity (OPIDN), happens 2–3 weeks following acute exposure to specific organophosphate insecticides. Clinical signs of motor neuropathy include lower extremity numbness and weakness, followed by gradual ascending limb muscle weakening. Type III paralysis is another name for it [2].

TPE is used to replace some plasma proteins and coagulation factors and eliminate some plasma components such antibodies, immune complexes, and endogenous and exogenous toxins. For replacement during TPE, colloids, human albumin, and fresh frozen plasma are employed. During TPE, cholinesterase from plasma or serum may also be eliminated. TPE's significance in individuals who have OP poisoning is not well understood, nevertheless [3]. In our case series, we favored TPE therapy as a last resort for IMS patients who had undetected plasma PChE levels.

CASE 1

A 40-year male was admitted at midnight in local hospital with complaints of profuse diarrhea, vomiting, excessive sweating and cough with lots of secretion for 1 day; he was a known alcoholic, with history of accidental ingestion of pesticide (an OP). Where he had treated with Atropine 1mg, Ceftriaxone 1 gm and Diazepam, at the time of admission he was semiconscious, HR-78/min, BP-144/78, Temp-36.8, on auscultation there were bilateral crackles in lungs, heart sound was normal. As his diagnosis was chemical pneumonitis and was put on IV antibiotics, nebulization, mucolytics, IV fluids, antimotility drug (Loperamide), antispasmodic (cyclopam). After 2 hrs. Of admission, he developed respiratory distress with altered sensorium, so he was moved to high dependence unit (HDU). In HDU, he was drowsy, BP-108/64, HR-112/min, RR-36/min, SPo_2-82% on room air, chest was wet bilaterally. He was put on Nonrebreather oxygen mask (NRM) and atropine@ 100 micro drops/ min. His neurological status was improving and SPo_2 was 98%. He remained stable for next 6 days. On day 7th his atropine infusion was stopped, after few hours he became

drowsy, developed lots of pulmonary secretion and shallow breathing arterial blood gas (ABG) revealed respiratory acidosis (PH7.21, $PaCO_2$ 86mmhg), he was intubated and put on MV support. He was still semiconscious and was following command on ventilator, chest was not clear, hemodynamics was unstable. On day 19th, he was referred to district hospital, U.P., India. At district hospital in emergency department, he was drowsy and having shallow breathing @5-6 bpm, SPO_2 92% on oxygen mask, ABG revealed respiratory acidosis (Ph 7.18, $PaCO_2$ 87.2 mmHg). Atropine infusion was restarted @ 60micro drops/min and shifted to medicine intensive care unit (MICU) department. It was noted that he had developed proximal muscles weakness in limbs and respiratory muscle weakness, developed quadriparesis, hence tracheostomy had done with MV support. His condition was continuously deteriorated hence, planned to performed TPE. At 20th day his 1st TPE cycle was successfully done without during and post procedural complications. After 24hrs. of 1stcycle he was magically responded and totally weaned of oxygen support with improved GCS 12. He had to allowed semisolid food by Ryles's tube and he was discharged at 22th day after full recovery.

CASE 2

An 18-year-old male was discovered sick at home, vomiting, sweating, groggy, and having trouble breathing. Rat poison (OP) that had been combined with rice unintentionally exposed him. He was brought by his attendants to the neighborhood community health center (CHC) with an RR of 30 breaths per minute, SPo2 of 100%, HR of 137 bpm, and bronchorrhea. He was also drowsy with pinpoint pupils. He received 100 micro drops of atropine intravenously (IV) every minute. He responded to atropine with tachycardia and a clearance of the secretions, but he maintained pinpoint pupils. He was intubated, moved to MV, and then transported to a district hospital in U.P., India with an atropine dose of 100 micro drops per minute since his oxygen saturation had dropped to 85%. He continued to perspire, had fine pupils, and experienced abrupt drops in heart rate (95 bpm) during the ride. On chest auscultation, there were bilateral crepitations; he sustained oxygen saturation levels of 98% throughout the transfer. Despite an ongoing atropine infusion, the patient had an oxygen saturation level of 62% at the district hospital emergency department, a heart rate of 97 beats per minute, a blood pressure of 153/70 mmHg, pinpoint pupils, and some oral secretions. ABG results revealed pH 6.7, $pCO_2$13.1 kPa, and pO_2 7.0 kPa. After manual ventilation using a self-inflating bag, his SPo2 increased to 100%. He continued receiving IV atropine at a rate of 40 micro drops per minute, along with 1.2 grams of IV ceftriaxone and 240 mg of acyclovir for the treatment of probable sepsis. Atropine was infused into him at a rate of 60 micro drops per minute as he was moved to the MICU area, where a tracheostomy was performed with MV support. On the fifth day, it was discovered that he had entirely lost his ability to move and was breathing only through gasps. He showed strong bilateral airway function, unwavering, light-unresponsive pupils, and no idiopathic movements. Atropine was infused into him at a rate of 100 micro drops per minute. His renal function was normal, and his ABG gradually improved, but initially, his coagulation parameters and liver enzymes were somewhat out of range. His situation was becoming worse all the time, therefore we decided to operate TPE right away. His GCS improved and was completely weaned off oxygen support after the first TPE cycle was completed safely and without any issues during or after the procedure. He was discharged after a full recovery and a GCS 12 on the second day of TPE.

CASE 3

A 38 yr. old female admitted in emergency department in district hospital, U.P., India. She ingested OP poison after domestic violence. She came to us with vomiting, sweating, breathing difficulty, semiconscious, poor GCS 8(E_3VTM_5). Her vitals were BP 140/70 mmHg, PR 92bpm, SpO_2 86%. She was shifted to MICU department, where she was intubated (Tracheostomy) shifted to MV support and starts atropine @100micro drops/ min. On examination, chest B/L clear, temperature 102.4^0F, pupil mild dilated sluggish reactive to light. After 4 days we noticed that she was not responded showed quadriparesis with B/L crepitation in chest wall. Now she was aspirated by ET (endotracheal) tube and starts ceftriaxone 1.2 gm and atropine dose @120micro drops/ min. Her condition become very poor with gradually decreased vitals. Hence, we decided to perform TPE therapy at 5th day. After 1st TPE cycle, her condition was slightly improved with improved GCS 10, but not significant improvement in her limbs. After 10th day her vitals became unstable, raised body temperature again 102^0F, on examination chest B/L not clear, she was suffering from VAP (ventilator associated pneumonia) hence, started meropenem 1gm IV TDS, Amikacin 750mg IV OD and atropine @100 micro drops/ min with MV support. After 15th day her condition was still same, she was on same treatment with atropine @40 micro drops/ min. At 20th day her condition was improved and she was shifted to nasal prone oxygen support from ventilator with GCS 12. At 25th day her atropine infusion was stopped and total weaned of oxygen support. She was shifted to semisolid food by Ryles's tube and her GCS was 14. At 30th day she was discharged after her full recovery with GCS 15.

CASE 4

This was the referred case from community health center to emergency department of district hospital, U.P., India. A 18 year old male came to us after 5 days treatment taken at CHC. He was on MV support, unconscious condition, GCS 2(E_1MTV_1) and vitals BP 160/90 mmHg, PR 90bpm, chest B/L clear, no history of fever, headache, pallor, icterus, and pedal edema. At 5days back he was admitted in CHC with chief complaints of sever vomiting, froth came out his nostrils and mouth, difficulty to breath, heavy sweating with poisoned by some substance. Immediately he was intubated and shifted to MV support and started treatment. But his condition was gradually deteriorated hence; he was referred to district hospital. At MICU he was intubated (Tracheostomy) with MV support and start atropine @100 micro drop/min, cefixime 2gm IV slow. At day 6th he became semiconscious, on examination we noticed that his neck was stiffed with unresponsive both upper and lower limbs suffering from quadriparesis. Hence, we decided to perform TPE immediately.

1st TPE cycle was performed successfully, without during and post procedural complications. After 1st TPE cycle, his condition was improved with some movement of upper limbs, GCS 10, and he was shifted to semisolid food via Ryle's tube. His atropine tapered @60 micro drops/min with tapered other antibiotics. After 10th day atropine @20 micro drops/ min, but his condition was remained same after 1st TPE cycle. Hence, we decided to performed 2nd TPE cycle next day. At 11th day, 2nd TPE cycle was performed, without during and post procedural complications. After 2nd TPE cycle at 14th day his, GCS 12 with improved body movements, became able to sit with support but not significant movement in his lower limbs. His treatment was remained same with atropine @20 micro drops/min. At day 16th totally weaned of oxygen support and stop atropine. He was able to sit yourself with full GCS 15 and he was discharged at day 18th.

CASE 5

A 50-year-old male came to emergency department of district hospital, U.P., India after suicidal attempted by pesticide (OP poison) with chief complaints of excessive sweating, vomiting, secretions came from nostrils and mouth, difficulty to breathing, pin point pupils, BP 190/100 mmHg, PR 120 bpm, unconscious, with very poor GCS. He was immediately intubated (Tracheostomy) with MV support and shifted to MICU. At MICU on examination his chest B/L not very clear, found some fine trimers, starts atropine @100 micro drops/ min with clobazam 10mg HS, nebulized with duolin and budcort 4hr and 6hr respectively, inj. ceftriaxone 1gm IV BD, his SpO_2 was not improved and he was still unconscious. After 2 days he became semiconscious, GCS 5 but on examination we noted that he became completely paralyzed. Hence, we decide to perform TPE immediately. At 3rd day TPE 1st cycle was done without during and post procedural complications. After 1st TPE cycle his condition was improved. After 7 days his atropine was shifted to @40 micro drops/ min and gradually tapered @ 20 micro drops /min at 10th day. At day 12th he became fully conscious with good GCS 11 without atropine. He was able to sit yourself with support and intake semisolid fluid by Ryle's tube. His trimmers were also gone with stable vitas. After 15th day of TPE cycle his GCS became 12 and shifted on spoon feeding and totally weaned of oxygen support with stop atropine. His condition was improved regularly. At 17th day he was discharged after full recovery.

MATERIAL AND METHODOLOGY

One common TPE method (totally automatic COM. TEC, Fresenius Kabi, Germany) involved 1.5 plasma volume exchanges with FFP as a replacement fluid. Before every procedure, the patient's consent was sought in full. Under strict aseptic conditions, operations were performed on the double lumen femoral dialysis catheter. One ampoule of calcium gluconate, diluted in 100 ml of 0.9% normal saline, was administered prophylactically for every 1000 ml of plasma extracted in the event that complications arose during the process. We performed all the procedure @ 25-30 ml/minute blood flow and ACD (acetate, citrate, dextrose) as anticoagulant at 1:10 ratio. All cycles of TPE were successfully done without during and post procedural complications. Due to some financial issues, we had not done serum PChE level in all the patients.

RESULTS

In all cases we noticed that after each TPE cycle patient's condition was improved with improved GCS. In each TPE we always considered patient's hematological and renal profile before and after the procedure. (Table 1)

In all the cases, in each TPE cycle patients responded, depends on how much plasma volume exchanged at total duration. (Table 2)

In some cases, we investigated plasma ChE level after the TPE procedure. (Table 3)

DISCUSSION

IMS's mechanism is unclear. It can be caused by the nicotinic symptoms of AChE inhibition. After absorption, the OP poison is stored in adipose tissue and acts on nicotinic receptors. These individuals experience a quick regeneration of the AChE enzyme, which leads to a recovery from neuromuscular blockade. Later, the paralysis is caused by the release of a previously inactivated ChE inhibitor. The symptoms and neurophysiological results of IMS may be explained by Ach receptor downregulation. These receptors have a half-life of 10 days before becoming inactive within the muscle fibers. Even though ACh receptors have a half-life of 10 days, IMS may manifest 24 to 96 hours after poison administration because the highly activated receptors become desensitised, making them easier to endocytose. Events that occur after acute OP poisoning create an environment that is

Table 1: Patients hematological and renal profile pre and post-TPE procedure.

	Case-1		Case-2		Case-3		Case-4 1st cycle		Case-4 2nd cycle		Case-5	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Hb gm/dL	11.9	12	14	12.9	8.086	8	14	13.7	13.7	8.5	12	11.6
Hct%	35.6	34	36	36	27.92	21.1	36.9	36.4	36.4	21.8	32.5	32.5
Plt Lac cells/ mm^3	3.2	3.2	1	1.9	5.2	1.22	4.22	4.22	4.22	0.95	2.91	2.91
S.Cr mg/dL	1.09	1.98	1.15	1.1	0.71	1.78	0.77	0.77	0.77	0.6	0.74	0.74
Na mmol/l	133.3	--	143	--	143.8	--	138.6	--	138.6		139.4	--
Ca mg/dL	4.32	6.98	6.78	5.87	5.2	4.6	5.12	5.12	5.12	5	4.28	4.28

favourable for the production of free radicals [2]. In S.Vucinic, M. Zlatkovic, B. Antonijevic et al. study [4], Malathion severely poisoned the patient, producing strong muscarinic and nicotinic effects as well as a notable suppression of AChE and BuChE. FFP was provided over the course of two days along with atropine, oximes, and supportive measures. An immediate rise in BuChE activity. This was attributed to the positive benefits of FFP therapy. According to A. Acikalin, N. Disel, S. Matyar et al. [5], TPE results in an increase in plasma ChE levels and an improvement in respiratory functioning. The findings of their study show that TPE is helpful in patients receiving prolonged MV support; 7 out of 10 patients who had TPE had healthy discharges. According to Umakant M, [6] In the TPE procedure, freshly frozen crystalloids and albumin are substituted for extracted plasma. Not simply the elimination of OP, but also the replacement of cholinesterase with fresh frozen plasma through clinical improvement in OP-damaged patients. According to M. Yilmaz, A. Sebe, M. Ay et al. [7]. They discovered that the body excretes some organic phosphate compounds together with waste plasma. The TPE treatment performed in the early stages of the IMS results in a significantly lower amount of blood plasma OP and a significantly higher level of PChE. This study suggests that TPE might play a small part in the treatment of IMS brought on by OP drugs. According to M. Guven, M. Sungur, B. Eser [3] Following TPE, ChE levels increased and subsequently fell within normal ranges, and the patient's clinical state also improved, leading to the eventual weaning of mechanical breathing. According to N. Disel, A. Acikalin, Z. Kekec et al [1]. Clinical improvement was made after a single TPE procedure on our patient. To handle unusual and serious cases of OP poisoning, we recommend the widespread use and accessibility of TPE in toxicology clinics. According to U. Yukselmis, M. Ozcetin, Y. Cag et al [8]. They demonstrate in their case studies that TPE might be an option for OP poisoning if medical treatment is ineffective. After atropine and oximes-based medical treatment failed to work for the three young patients exposed to OP, they all fully recovered with TPE application. According to S. Saad, M. Ismail, R. Hashish et al [9]. For the treatment of OP toxicity, the early management with a high dose of FFP may be an efficient strategy. By lowering mortality, length of hospital stays, and the necessity for ICU admission, FFP was able to enhance clinical outcomes. According to Y. C. -C., D. J. F., [10] by restoring plasma AChE, repeated doses of TPE treatment may stop the onset of IMS and the associated mortality.

In our case series, we had managed all the cases by TPE which was suffering from IMS due to OP Poison. Our all the cases came to us too late like after 7 days to 20 days gap after OP poisoning. At the time of admission, they had already treated by atropine with other supportive treatment, which was unable to improved patient's condition hence, we immediately planed TPE as an emergency treatment of choice for all the cases. After TPE all the patients' conditions was magically improved and they were gain their full GCS with weaned of oxygen support and discharged after full recovery.

CONCLUSION

The most well-known pesticide harm in underdeveloped countries is OP poisoning. It has a significant mortality rate, which is typically indicated by a postponement in diagnosis

Table 2: Plasma Treatment and Techniques.

	Case-1	Case-2	Case-3	Case-4	Case-5
Weight(kg)	70	50	60	70	70
Hematocrit(%)	35.6	36	27.92	36.9	32.5
No of FFP Units used	18	20	22	20	22
Total blood volume (TBV) in 1st cycle ml	3456	3765	3624	4598	4650
TBV in 2nd cycle	--	--	--	4860	--
Technique of the TPE	COM.Tec; Fresenius cabi Germany	COM.Tec; Fresenius cabi Germany	COM.Tec; Fresenius cabi Germany	COM.Tec; Fresenius cabi Germany	COM.Tec; Fresenius cabi Germany
Total plasma volume (TPV) in 1st cycle ml	2333	2306	2645	3021	3019
Total plasma volume in 2nd cycle ml	--	--	--	3546	--
Venous accesses	Central line	Central line	Femoral line	Femoral line	Femoral line
Plasma volume exchange	1.3	1	1.3	1.3	1.5
TPE duration(min) in 1st cycle	176	89	80	169	170
TPE duration in 2nd cycle				176	

Table 3: Plasma ChE level after TPE.

	Case-1	Case-2	Case-3	Case-4	Case-5
TPE cycle	Serum ChE level post procedure	Serum ChE level post procedure	Serum ChE level post procedure	Serum ChE level post procedure	Serum ChE level post procedure
1st cycle	-	3429.00 U/L	253.60 U/L	3729.36 U/L	4285.30 U/L

or an ineffective course of treatment. Even though the clinical course of OP poisonings can be very severe, prompt diagnosis and appropriate treatment can save lives. Mortality is observed to be caused by difficulties encountered during MV support in OP poisoning patients as well as any concomitant comorbidity. Inability to manage respiratory depression despite receiving effective antidote medications, low GCS scores, prolonged MV support and hospitalization, high creatinine, and low initial PCh are signs of a bad prognosis. Acute and chronic OP poisoning can be effectively managed early with TPE and supportive care, which can enhance the clinical result by reducing mortality, length of hospital stays, and the requirement for ICU hospitalization.

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