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EARLY INITIATION OF THERAPEUTIC PLASMA EXCHANGE IN YELLOW PHOSPHORUS POISONING: A LIFE-SAVING STRATEGY – A CLINICAL CASE REPORT

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Abstract
Rodenticides containing yellow phosphorus (YP) are one of the most common poisonings, which has high mortality seen among the southern Indian population. It is a very potent toxin, which when consumed results in acute liver failure (ALF) followed by death. Presently there is no antidote available, and liver transplant is considered the only definitive treatment, while for liver transplantation, therapeutic plasma exchange (TPE) has been regarded as a bridge therapy. As per the TN-ISG (Tamil Nadu Chapter of the Indian Society of Gastroenterology Guidelines) for rodenticide poisoning, TPE is considered a non-transplant treatment option. A 28year old female case with a yellow phosphorus (YP) poisoning case has been presented here by us that was managed with early TPE. The patient responded well and was discharged after 8 days of hospitalization.

INTRODUCTION

Yellow phosphorus (YP) containing rodenticides is a frequent cause of poisoning, more commonly reported among rural communities, especially in the southern and western regions of the Indian subcontinent (1). Phosphorus exists in two main allotropes, mainly white and red phosphorus. White phosphorus more commonly known as YP is a highly toxic, non-metallic protoplasmic toxin, widely used in pesticides. Rodenticides usually contain 3% YP as an active component and are usually available in the form of paste, powder, and cake. Lethal dose is estimated to be 1 mg/kg of body weight (2). Rodenticides based on YP are relatively cheaper and easily available within India. It is highly toxic, with no available specific antidote, while poisoning can result from exposures from industrial accidents or accidental or deliberate intake. It quickly gets absorbed through the gastrointestinal tract while metabolized through liver. Once consumed, patient presents with three stages of the clinical course. The first stage is the initial 24 hours after the consumption, which usually presents with mild gastrointestinal symptoms, usually associated with nausea and vomiting. The second stage is from 24 hours up to 72 hours post consumption of the YP, where the patient is asymptomatic but lab parameters begin to get deranged. Lastly, in the third stage, after 72 hours of consumption of the YP, the patient develops derangement of liver functions, renal injury, and coagulopathy (3). During this stage, the patient will develop hepatocellular necrosis, followed by fulminant hepatic failure and death (4). Till now, the only known definitive curative treatment for YP poisoning-related liver failure is liver transplantation (3). Patients with rodenticide hepatotoxicity (RH) have a high mortality rate, mainly due to the lack of availability of urgent liver transplantation options (5). Hence, nontransplant options for the treatment of YP have to be evaluated and opted for for patient survival. TPE has been revealed to enhance the survival in YP poisoning cases, also TPE has gained attention as a potential treatment modality to mitigate YP toxicity, particularly in resource-limited settings where liver transplantation is not feasible. TPE involves the extracorporeal removal of macromolecules (toxins), replacement with FFPs (fresh frozen plasma) along with albumin (6). The TN-ISG has given guidelines on the management of RH, with the aim

of improving the survivability of the patients (5). Here we describe an instance of YP rodenticide poisoning that was successfully treated with rapid initiation of TPE therapy.

Case Presentation

Clinical Presentation

After deliberately consuming two full tubes of Ratol poison paste (3% yellow phosphorus) at her home in the evening, a 28year old woman without any comorbidities arrived at the emergency department. She had consumed a total of around 30 g of the poison. She arrived at our emergency room afebrile, with a heart rate of 80 beats per minute, a respiratory rate of 18 beats per minute, and a blood pressure of 110/70 mmHg.

INITIAL MANAGEMENT

The patient was initially given a stomach wash, normal saline, and vitamin K. Following admission, she underwent routine investigations and clinical evaluation. She was hemodynamically stable, and her initial blood reports of liver function tests (LFT), coagulation profile, blood glucose, and ABG (arterial blood gas analysis) had been within the normal range. The outcomes of other routine tests, that include an ECG (electrocardiogram), CXR (chest X-ray), echo, along with ultrasound (USG), were also normal.

Post stomach wash, the patient was given activated charcoal as initial management of poisoning consumption. The patient had complaints of nausea and vomiting, for which supportive medications were given. After ICU admission, patient had been started on NAC (N-acetyl cysteine) and was monitored closely. Throughout the first hour, NAC was infused at a rate of 150mg/kg in 250ml of 5% dextrose. For the next 4hs, she was to have 50mg/kg of NAC in 500ml of 5% dextrose, and for the last 16hs, she was to receive 100mg/kg in 1000ml of 5% dextrose. However, after initiation of NAC, patient developed anaphylaxis with severe respiratory distress, which required the patient to be intubated and given anaphylaxis medications like steroids, antihistamines, and adrenaline. Post intubation, the patient was started on inotropes.

In view of the amount of poison consumed by the patient, the patient was consulted with Gastromedicine and Gastrosurgery. The possibility of requirement for liver transplantation was informed to the patient bystanders. Since the initial blood reports had come within normal limits, rapid initiation of plasma exchange was planned for which the Transfusion medicine department was consulted. Central line insertion (dialysis catheter) was done via the right femoral vein for the TPE procedure.

The patient was planned for three consecutive procedures of TPE for 1 to 1.5 times of total plasma volume 24 hours apart, with a review planned on the fourth day. The patient underwent three procedures of TPE in total. For each procedure, the plasma volume to be exchanged was calculated, and the replacement FFPs were chosen accordingly.

The patient's second day Liver function tests and coagulation profile started worsening **(Table 1).** The patient underwent the first TPE while the patient was on mechanical ventilator and under inotrope support. By then, 15 hours has passed since consumption of the YP poison. The inotrope support was adjusted during the procedure such that patient's MAP (mean arterial pressure) had been maintained above 65mmHg throughout. Patient was weaned off ventilator support and inotropes and extubated by the third day. After extubation, the patient underwent a second TPE on 3rd day of admission. The coagulation profile had remained consistent with the values from the 2nd day of admission on the 4th day. Additionally, patient further received a third TPE. All three procedures were uneventful and were well tolerated by the patient.

Outcome

The patient underwent in total three TPE procedures, and the patient was observed for worsening of LFTs, coagulation profile, and overall condition after each. The patient had no worsening of her subsequent LFTs and coagulation profile. Her general condition had improved and she was discharged from the hospital by the eighth day of admission.

Throughout each procedure, the patient was supported with calcium gluconate infusion.

TPE Process

The TPE procedure was carried out using kit PL1 in the Com.Tec cell separator by Fresenius Kabi **(Figure 1).** Throughout the procedure, an anticoagulant called ACD (acid citrate dextrose) was employed.

The subsequent formula was utilized to determine each TPE's plasma volume:

Plasma volume (ml)=65*×(1-hematocrit)×body weight (kg)

[*Gilcher's rule of five for blood volume for women: 65ml/kg; weight of patient was 70kg

Each procedure of the TPE was done for 1.5 times calculated plasma volume.

Plasma volume exchanged and replacement fluid for each of the TPE are shown in **Table 2.** Group compatible plasma was used for the TPE.

Table 1: Clinical and biochemical results (* day of hospital stay)

Parameter	Day 1* (Admission)	Day 2	TPE 1	Day 3 7 am	Day 3 8 pm	TPE 2	Day 4	TPE 3	Day 5	Day 6	Day 7	Day 8 (Discharge)	Day 17 (Follow up)
Haemoglobin	13.8	14.0		13.5	-		13.6		13.8	11.6	12.0	13.1	11.4
PCV	42.6	42.0		40.5	-		41.0		41.9	35	36.9	40.0	35.5
Platelet	2.25	2.15		1.60	-		1.24		1.14	1.07	1.41	2.10	3.89
Total bilirubin (mg/dL)	0.62	0.79		0.81	-		1.03		0.88	0.54	0.39	0.57	0.5
Direct bilirubin (mg/dL)	0.13	0.29		0.12	-		0.17		0.19	0.22	0.13	0.22	0.3
SGOT (U/L)	44	37		25	-		34		26	22	27	24	44
SGPT (U/L)	27	23		21	-		22		17	15	17	18	42
PT (seconds)	11.8	13.3		15.6	19.9		19.8		15.0	12.9	-	10.1	10.0
INR	0.98	1.11		1.29	1.64		1.63		1.24	1.13	-	0.84	0.84
APTT (seconds)	28.1	29.2		31.2	29.4		31.5		27.8	25.5	-	29.1	29.5
Magnesium (mg/dl)	2.0	1.6		-	-		-		-	-	1.7	-	-
Calcium (mg/dl)	9.5	8.6		7.0	-		7.8		7.6	-	8.0	-	-
pH	-	7.40		7.42	-		7.41		7.40	7.41	-	-	-
pCO^2	-	44		31.7	-		38		41	40	-	-	-
HCO^3	-	24		20.1	-		23		24	24	-	-	-
pO^2	-	140		128	-		102		98	99	-	-	-
Lactate	-	1.2		0.9	-		0.8		0.9	0.9	-	-	-

Table 2: TPE Replacement fluids

Procedure	Total Blood Volume =Body weight x 65ml/kg	Hematocrit HCT (%)	Plasma Volume = TBV(1-HCT)	Plasma Exchanged 1.5 times PV	Replacement Fluid NS: Normal Saline FFP: Fresh Frozen plasma	
TPE 1	4,550 ml	42.0	2,639 ml	3,958.5 ml	1,900ml NS	12 units FFPs
TPE 2	4,550 ml	40.5	2,707 ml	4,060.5 ml	2030 ml NS	13 units FFPs
TPE 3	4,550 ml	41.0	2,684.5 ml	3,753.75 ml	1850 ml NS	12 units FFPs

Figure 1: Com.Tec cell separator by Fresenius Kabi

Figure 2: Collected Patient Plasma

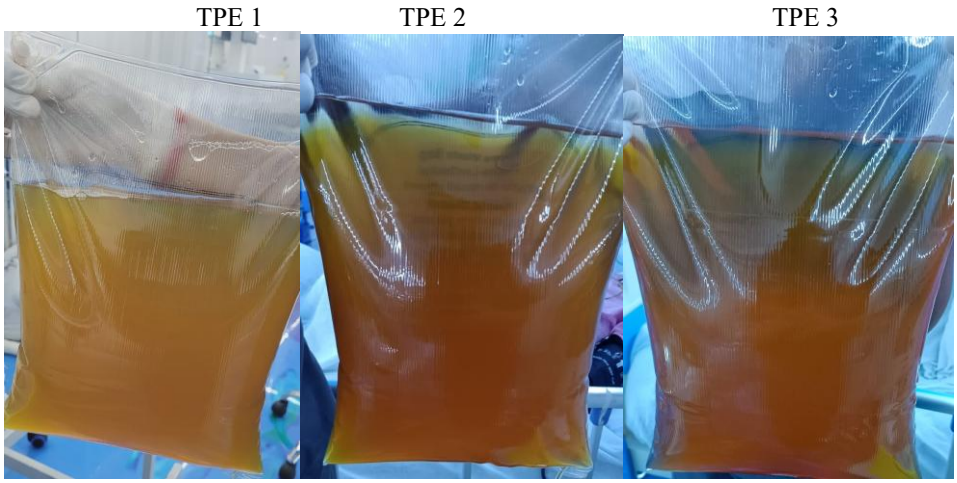


Figure 3: SGOT/SGPT parameters trend during hospital stay

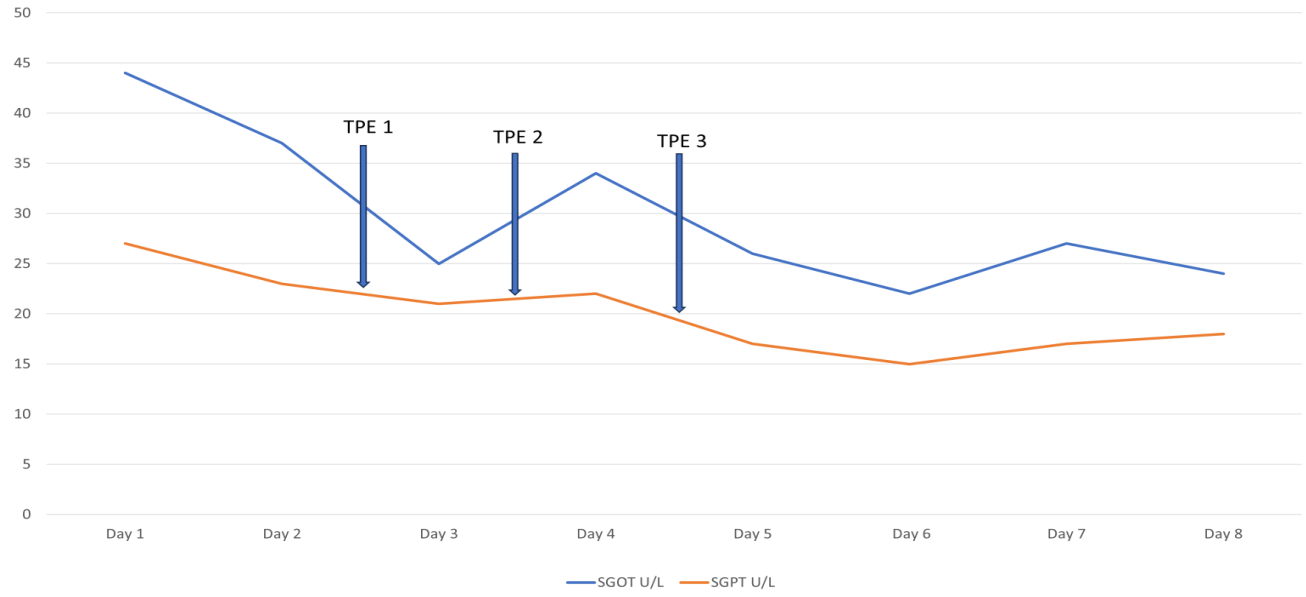
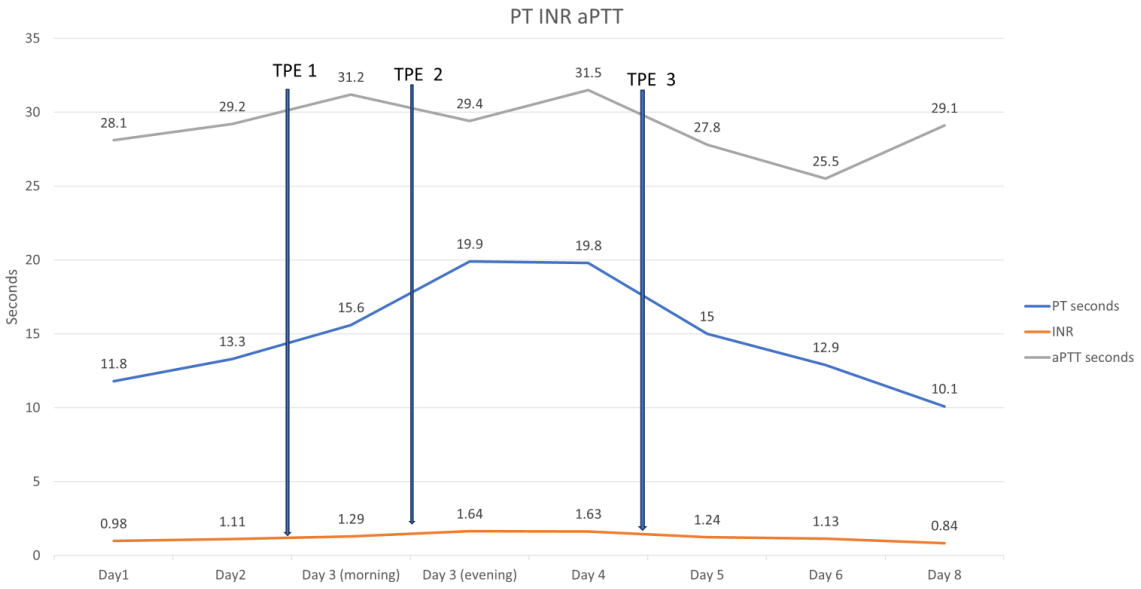


Figure 4: PT INR and aPTT trend during hospital stay



DISCUSSION

Availability of rodenticides containing yellow phosphorus has been legally restricted in Tamil Nadu, a southern state of India, as a preventive step, yet there still exist incidences of YP poisoning (1,7). These rodenticides are relatively easily available and highly effective. General public awareness programs have been conducted to prevent further rodenticide poisoning cases within the state of Tamil Nadu. Most of the cases of YP poisoning have the intention of deliberate self-harm, while some cases have been accidental, especially among children (8). It is used in match industries and fireworks industries also, where cases of accidental exposure have been observed. YP rodenticide mostly exists as paste formulations and is considered a highly lethal rodenticide. It is a fat-soluble protoplasmic poison that causes tissue hypoxia, especially affecting the CNS (central nervous system), hematological, renal, along with hepatobiliary systems, which can progress to shock and cardiovascular collapse. The YP, on contact with the gastric contents (hydrochloric acid and water), releases phosphine gas (9). The resulting phosphorus gas suppresses oxidative metabolism as well as cytochrome C oxidase. It is also thought to affect ribosomal functions, glycogen deposition, lipoprotein, blood glucose regulation, synthesis of protein, along with synthesis of triglyceride. The toxic effect leads to diminished ATP (adenosine triphosphate) production, suppression of fatty acid oxidation, as well as diminished production of the lipoprotein component of very low-density lipoproteins (10). This consequently results in fat deposition and cellular damage to the kidney, brain, liver, heart (8). Binding of calcium with the blood's excess phosphorous can also result in hypocalcemia (9). Usual consequences of YP poisoning are acute liver failure (ALF), acute tubular necrosis, cardiac arrhythmias, neurological symptoms and circulatory shock. Early derangements in transaminases and ALP, or a ten-fold enhancement in SGOT, severe prolonged PT (and INR), metabolic acidosis along with hypoglycemia indicate poor prognosis. 1mg/kg body weight (7) is the lethal dose (LD50) of the YP or it is around 60mg, though even lower doses have been known to cause multiorgan dysfunction and even death.

Although YP can enter through the skin, respiratory system, mucous membranes, it is primarily absorbed via the gastrointestinal tract. Once ingested, the clinical phases of the progression of the poisoning can be divided into three main stages. Stage 1 (within 24 hours of poisoning): patients usually present with gastrointestinal irritation, mainly due to the generation of phosphine gas. Symptoms of severe gastroenteritis like abdominal pain, nausea, and vomiting can be presented. Breath, vomitus and diarrhea with characteristic garlic odors are pathognomonic of YP poisoning. Another peculiar finding may be luminescent vomitus and feces(11).

Stage 2 (1 to 3 days of poisoning): patients at this stage remain asymptomatic with derangement of the LFTs and coagulation profile, indicating toxic hepatitis.

Stage 3 (less than 72 hours of poisoning): patients present with ALF, which is associated with coagulopathy, cardiac arrhythmias, encephalopathy and renal failure. Usually, by this stage, the patient will develop acute kidney failure and hemodynamical instability. By this stage, the patient can worsen, resulting in death (11).
Most of the phosphine generated within the body (from YP) is excreted through the respiratory tract unchanged, while some will get converted to phosphite and hypophosphite ions, which are excreted through the renal route (9).

The definitive treatment for rodenticide poisoning resulting in liver failure is early liver transplantation. However, this is not accessible to a large portion of the cases, mostly due to financial constraints. Thus the new focus of treatment is to ensure maximum patient survival by nontransplant mode of treatments. In January 2022, the TN-ISG published the recommendations for managing rodenticide poisoning. The guidelines are aimed at improving the survival of patients without urgent liver transplantation. As per the guidelines, the patient is managed under three main sections. The first section involves day 1 of the management, which includes gastric lavage, oral activated charcoal, N-acetyl cysteine, and other supportive measures. The second section of the guidelines involves the management of hepatotoxicity due to the rodenticide, which mainly involves liver transplantation and TPE. TPE can be performed either as an independent treatment or as a bridge to liver transplantation. The final section involves the discharge criteria for the patient (5).
As per the ASFA (American Society for Apheresis), the high-volume plasma exchange is considered Category 1 (with Grade 1A) to treat ALF, usually as a bridge for liver transplantation. TPE is categorized as low volume (LV-TPE), standard volume (SV-TPE) and high volume (HV-TPE). In LV-TPE, 50percent of the plasma volume will be eliminated in every procedure, with replacement by an equal volume of FFPs (12). In SV-TPE, the target plasma exchange volume will be 1.5-2 times the plasma volume of the patient per procedure, with replacement by FFPs (up to 90%) with remainder saline (13). HV-TPE involves the replacement of 8 to 12 liters of plasma, which is around 15percent of the ideal body weight, and replacement with FFPs in equivalent volume (14). TPE acts by removing toxins and DAMPs (damage-associated molecular patterns), which are accountable for the toxic effects of rodenticide poisoning. Removal of the inflammatory mediators, replacement of plasma factors, and immune modulation also play a therapeutic role in the management (15). TPE is also considered to improve the patients by attenuating the innate immune activation, which would result in multiorgan failure. It is supposed that TPE results in a lowering of VWF, which may have a therapeutic effect in rodenticide poisoning cases (16–18).
In this case, the patient had consumed around 30 grams of the rodenticide and was brought to the hospital the same day. There was no history of vomiting following the consumption of the poison. Following consumption of the rodenticide, the patient had complaints of nausea and vomiting. On arrival at our hospital, she was given gastric lavage and other supportive medications like anti-emetics, proton pump inhibitors and IV fluids. She was hemodynamically stable during admission time. She was shifted to ICU, where she was started on NAC infusion. After NAC infusion initiation, the patient developed anaphylaxis with respiratory compromise. She was intubated and supported with inotropes and anaphylaxis medications like antihistamines, steroids and adrenaline. The patient was started on standard volume TPE within 18 hours of the consumption of the YP poisoning as advised by the gastro medicine and gastrosurgery consultants. The patient's blood investigations initially were within normal limits. TPE was done as per calculations and has been tabled in Table 2. After the first plex, the patient was extubated and underwent two more TPE procedures. Each TPE procedure was done around 24 hours apart and with continuous calcium gluconate infusion to prevent hypocalcemia caused by ACD used during the apheresis. Post the third TPE, the patient was regularly monitored for any signs of ALF. She had no worsening of the LFTS and coagulation profile subsequently Table 1. She was shifted to the ward and was given psychiatric consultations. The patient was discharged after 8days. After 10days of discharge, the patient was followed up, and her LFTs and coagulation profile were within the normal ranges.
In this case, the patient had been managed with early standard volume TPE with regular monitoring of the LFTs and coagulation profile. NAC was attempted but discontinued as the patient developed severe anaphylaxis. The patient had the advantage of getting a plasma exchange procedure done within 15 hours of consuming the rodenticide. The patient was regularly monitored for any signs of liver failure. During and after the three TPE procedures, the LFTs and coagulation profile had deranged initially but eventually returned to normal limits (Figure 3 and Figure 4).
As per the TN-ISG guidelines for rodenticide poisoning management, TPE can be a stand-alone treatment that has improved survival rates among patients or as a bridge therapy for liver transplantation. Currently, no guidelines specify the timing of TPE initiation, the type of TPE to be used (low volume, standard volume, or high volume), and the number of sessions required (5). There is also no data available on the lethal dose beyond which TPE may not be effective.

CONCLUSION

ALF caused by YP containing rodenticides can be effectively managed with TPE. This case highlights the potential of TPE as an effective and life-saving intervention in managing YP poisoning. Early initiation of TPE may improve outcomes and serve as an effective nontransplant therapeutic option, particularly in settings with limited access to liver transplantation. Future studies are needed to establish standardized protocols for TPE, including initiation criteria, dosing regimens, and long-term outcomes.

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