Acute Liver Failure Secondary to Yellow Phosphorus Rodenticide Poisoning: Outcomes at a Center With Dedicated Liver Intensive Care and Transplant Unit

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Background: **Accidental or suicidal poisoning with yellow phosphorus or metal phosphides (YPMP) such as aluminum (AlP) zinc phosphide (Zn_3P_2) commonly causes acute liver failure (ALF) and cardiotoxicity. These are used as household, agricultural, and industrial rodenticides and in production of ammunitions, firecrackers, and fertilizers. In absence of a clinically available laboratory test for diagnosis or toxin measurement or an antidote, managing their poisoning is challenging even at a tertiary-care center with a dedicated liver intensive care unit (LICU) and liver transplant facility.** ***Methods:*** **Patients with YPMP-related ALF were monitored using standardized clinical, hemodynamic, biochemical, metabolic, neurological, electrocardiography (ECG), and sequential organ failure assessment (SOFA) score and managed using uniform intensive care, treatment, and transplant protocols in LICU. Sociodemographic characteristics, clinical and biochemical parameters, and scores were summarized and compared between 3 groups i.e. spontaneous survivors, transplanted patients, and non-survivors. Predictors of spontaneous survival and the need for liver transplant are also evaluated.** ***Results:*** **Nineteen patients with YPMP-related ALF were about 32 years old (63.2% females) and presented to us at a median of 3 (0–10) days after poisoning. YPMP-related cardiotoxicity was rapidly progressive and fatal, whereas liver transplant was therapeutic for ALF. Spontaneous survivors had lower-dose ingestion (<17.5 g), absence of cardiotoxicity, < grade 3 hepatic encephalopathy (HE), lactate < 5.8, SOFA score < 14.5, and increase in SOFA score by < 5.5. Patients with renal failure need for continuous veno-venous hemodiafiltration (CVVHDF) and King College criteria positivity on account of prothrombin time and international normalized ratio (PT-INR) > 6.5 had higher mortality risk. Patients undergoing liver transplant and with spontaneous recovery required longer intensive care unit and hospital stay. At median follow-up of 3.4 (2.6–5.5) years, all spontaneous survivors and transplanted patients are well with normal liver function.** ***Conclusions:*** **Early transfer to a specialized center, preemptive close monitoring, and intensive care and organ support with ventilation, CVVHDF, plasmapheresis, and others may maximize their chances of spontaneous recovery, allowing accurate prognostication and a timely liver transplant. (J Clin Exp Hepatol 2021;11:424–434)**

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Abbreviations: ALF: acute liver failure; AKI: acute kidney injury; CVVHDF: Continuous veno-venous hemodiafiltration; DDLT: deceased-donor liver transplant; IEH: ingestion to encephalopathy interval; KCC: King College criteria; LDLT: living-donor liver transplant; MELD: model for end-stage liver disease; MOF: multi-organ Failure; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment; YPMP: yellow phosphorus or metal phosphides
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Yellow phosphorus and metal phosphides (YPMP) such as aluminum (AlP) and zinc phosphide (Zn_3P_2) are common (44–53%) causes of accidental or suicidal rodenticide poisoning.[1,2] They cause initial gastrointestinal (GI) symptoms, but progress to systemic multi-organ failure (MOF), most prominently cardiotoxicity and acute liver failure (ALF) which are often fatal.[3,4] This is a retrospective analysis of our outcomes in YPMP-related ALF using a standardized monitoring and management protocol in a dedicated liver intensive care unit (LICU) with appropriate use of continuous veno-venous hemodiafiltration (CVVHDF) for ammonia reduction,

plasmapheresis to control the systemic inflammatory response syndrome (SIRS), and liver transplant for non-recovering ALF.

PATIENTS AND METHODS

This is a retrospective analysis of a prospectively maintained database of all ALF patients admitted to the LICU at Global Hospital, Mumbai. The study population included patients with suicidal or accidental YPMP-related ALF admitted to our unit between January 2014 and December 2019. Patient demographic data, details of toxin ingestion, clinical presentation and in-hospital course, investigations, management details, and outcome were recorded. The study was approved by the institutional review board.

Our YPMP ALF LICU management protocol is detailed in Table 1. Briefly, patients were monitored for clinical, laboratory, and cardiac parameters. Those with grade ≥3 hepatic encephalopathy (HE) were electively mechanically ventilated. CVVHDF was instituted in patients with hyperammonemia, lactic acidosis, or renal dysfunction. Plasmapheresis was performed in all patients except those without any evidence of SIRS. All patients were evaluated and prepared for liver transplant, which was performed for deterioration despite appropriate organ support.

Because the composition and strength of YPMP paste was not available retrospectively, the total amount of paste ingested was used for analysis. Any arrhythmias or cardiac dysfunction was labeled as cardiotoxicity. Bone marrow toxicity was defined as drop in all three cell lines i.e. hemoglobin <7 g/dL, white blood cells <4000/mm^3, and platelet count <50,000/mm^3. Hypoglycemia was defined as blood sugar on admission <70 mg/dL. Acute kidney injury (AKI) was defined per acute kidney injury criteria (AKIN).[7]

Data collection, groups, and analysis

Data were collected in a Microsoft Excel® file. The delta SOFA score were calculated as the difference between the peak and initial scores and used as measure of progression of systemic toxicity. Quantitative variables were summarized using mean, standard deviation, median, and range and compared using one-way ANOVA, Mann–Whitney U test, or Kruskal–Wallis test as appropriate. Variances were compared using *F*-test. Qualitative variables were summarized using frequency and percentages and compared using chi-square test. P value of 0.05 was considered significant. For quantitative variables with significant differences receiver operating characteristic curves were used to calculate area under the curve, optimum cut-offs, and their sensitivity and specificity. Multivariate regression analysis was done to identify risk factors for mortality. All statistical analyses were done using IBM SPSS 16®.

RESULTS

Of 199 ALF patients managed in our LICU between January 2014 and December 2019, 23 (11.6%) had YPMP-related ALF. Four patients were discharged or transferred to another hospital against medical advice without completion of adequate treatment; their outcomes were not available and were excluded from analysis. The study populations consisting of 19 patients were all transferred from other hospitals at a median of 3 (0–10) days after toxin ingestion. Patients were divided into three groups:

- **SS:** Spontaneous survivors with medical management
- **LT:** Liver transplant performed
- **NS:** Non-survivors despite medical management

Overall and group-wise results and differences between 3 groups have been outlined in Table 2 and discussed later. The overall mortality was 7 (36.8%).

Saraf *et al*. clubbed non-survivors and transplant patients as a single group (with an assumption that patients who underwent a transplant would not have survived without the transplant) and compared them against spontaneous survivors.[19] A result of our significant findings with the same assumption is presented in Table 3.

The mean age of patients was 32 years ±9.6, more commonly females (63.2%). More females survived spontaneously, and more men underwent a transplant, differences being similar across groups. Spontaneous survivors consumed significantly lesser YPMP than others, less than 17.5 g being favorable. No patients had history of pre-existing liver disease, consumption of other hepatotoxic drugs or food supplements at the same time.

Admission parameters

Admission and peak bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transpeptidase (GGTP), hypoglycemia, PT-INR (before plasmapheresis), creatinine, arterial ammonia and lactate (before CVVHDF), and lowest fibrinogen (before fresh frozen plasma [FFP] or cryoprecipitate transfusion) were similar across groups. Similarly, peak bilirubin, AST, ALT, alkaline phosphatase, GGTP, PT-INR, creatinine, and arterial ammonia were similar although spontaneous survivors had significantly lower peak lactate (<5.8 mg/dL) than others.

Cardiopulmonary toxicity

Four (21.1%) patients had cardiotoxicity, none among spontaneous survivors. Three (42.9%) non-survivors, one each had supraventricular tachycardia, ventricular tachycardia, and cardiomyopathy. Although they also had ALF, rapidly progressive cardiotoxicity caused mortality. One patient developed early myocardial suppression

Table 1 LICU Management Protocol for YPMP Toxicity.

- All YPMP ALF patients are monitored in the LICU for 3–5 days after ingestion and nursed in 30-degree head elevated position.
- Patients are assessed for clinical parameters especially for liver, cardiac, and neurotoxicity with hourly assessment for HE and pupillary reflexes and continuously monitored for vital parameters and electrocardiography (ECG).
- Gastric lavage is done without any additives for patients presenting within 24 h. A nasogastric tube is used for gastric decompression in patients with HE.
- Patients with HE > grade 3 are electively sedated and intubated. pCO_2 is maintained between 30 and 35 mm Hg.If raised intracranial pressure (ICP) is suspected, optic nerve diameter, reverse jugular oxygen saturation, transcranial Doppler or CT brain is done. Direct ICP monitoring may be done very selectively.Standard protocols for managing raised ICP are followed including mannitol, thiopentone and others.
- Fluid intake, output and balance are monitored hourly, serum electrolytes, acidosis, ammonia and lactate are monitored 2nd hourly using arterial blood gases (ABGs) and corrected appropriately. Serum sodium is maintained between 145 and 150 meq/dl.
- Blood glucose is monitored 6 hourly and corrected as required.
- Advanced hemodynamic monitoring using arterial and central venous lines and continuous pulse contour cardiac output (PiCCO) monitor to record cardiac output (CO), systemic vascular resistive index (SVRI), stoke volume variance (SVV), intrathoracic blood volume index (ITBVI) and inferior vena cava (IVC) assessment are done in patients with HE, SIRS, high lactate or acidosis and used to titrate fluids and ionotropes.
- Laboratory tests including complete blood counts, amylase, lipase, liver function tests (LFT), renal function tests, PT-INR are monitored twice a day until recovery.
- Chest X-ray, abdominal ultrasonography (USG) and 12-lead ECG and echocardiogram (ECHO) are done on admission. A cardiologist is consulted for suspected cardiotoxicity.
- Sequential organ failure assessment (SOFA) score is calculated on admission and daily.
- Awake patients are given high-carbohydrate, high-protein, low-fat or no-fat diet with supplementary intravenous dextrose and multi-vitamins. Patients with ≥ grade 2 HE or high dose inotropes are kept nil per orally (NPO).
- N-acetylcysteine (NAC) is given at 100 mg/kg IV over 24 h for 5 days.
- Prophylactic antimicrobials (ceftriaxone + sulbactam) and antifungals (fluconazole) are used in patients with HE, high lactate, or SIRS.
- Lactulose and rifaximin are given to patients with HE, not on CVVHDF.
- Patients with PT-INR > 2 are given vitamin K 10 mg IV for 3 days.
- Fresh frozen plasma (FFP), cryoprecipitate, tranexamic acid and platelet transfusions are used only for bleeding, guided by coagulation parameters (PT-INR, fibrinogen levels and platelet counts) and thromboelastography (TEG).
- CVVHDF is done for patients with renal failure related indications, severe lactic acidosis (despite adequate resuscitation) or as ammonia lowering therapy for two consecutive arterial ammonia values > 150 μmol/l or any single value > 200 μmol/l. Dialysate dose of 35 ml/kg/hr is used, although higher doses (60–100 ml/kg/hr) may be used for inadequate ammonia clearance.
- Three sessions of daily plasmapheresis are performed in all patients after admission except those without any evidence of SIRS. Replacement dose was calculated using the apheresis formula.
- Patients with suspected suicidal ingestion undergo psychiatry consultation before transplant when feasible but before discharge in all cases.
- Evaluation and preparation for liver transplantation is initiated on admission. All patients meeting King's College criteria (KCC) or national health services blood and transfusion services (NHSBT) ALF criteria (Kathy) are listed as 'super-urgent' with the Zonal Transplant Coordination Committee (ZTCC), Mumbai.[5,6] Living donor evaluation is done and approval from local or state authorization committee obtained. Transplant is performed only for patients with worsening despite medical therapy if no contraindications to transplant existed (irreversible neurological damage, systemic infection) and after recovery from bone marrow and cardiotoxicity.

ALF, acute liver failure; CVVHDF, continuous veno-venous hemodiafiltration; ECG, electrocardiography; HE, hepatic encephalopathy; YPMP, yellow phosphorus or metal phosphides.

(ejection fraction decreased from 60% to 30%) and cardiogenic shock that improved with resuscitation and levosimendan. She then underwent a successful deceased-donor liver transplant (DDLT). Another transplant patient had severe pulmonary hypertension with right heart dysfunction and preserved left ventricular contractility, requiring inhaled nitric oxide and milrinone perioperatively, which was tapered off postoperatively (this case was not included as cardiotoxicity).

AKI and CVVHDF

Ten (52.6%) patients developed AKI which was significantly higher in non-survivors than in spontaneous survivors, but not different from transplant patients. Fifteen patients (78.9%) needed CVVHDF, including all transplant patients and non-survivors, which was significantly higher than spontaneous survivors. The indication for CVVHDF was renal in three (20%), hyperammonemia alone in three (20%), severe lactic acidosis in two (13.3%), renal with hyperammonemia in two (13.3%), renal with lactic acidosis in three (20%), and all these three indications in two (13.3%) patients.

MOF, SOFA score, and plasmapheresis

Six (31.6%) patients developed bone marrow suppression, similar across groups that recovered spontaneously. One patient required filgrastim before transplant. One spontaneous survivor and two non-survivors required platelet transfusions based on thromboelastography (TEG) for bleeding, whereas four patients required platelets during transplant. No patients had GI toxicity or pancreatitis. The admission SOFA score was similar between groups, but peak (<14.5) and delta (<5.5) SOFA scores were lower in spontaneous survivors than those in others, probably indicating slower progression to MOF. Fifteen (78.9%) patients underwent median of 3 (1–4) cycles of

Table 2 Overall Results and Comparison Between Three Groups.

Variables	Overall (n = 19)	SS (n = 7)	LT (n = 5)	NS (n = 7)	Significance
Demographics					
Age	32.0 ± 9.6	33.4 ± 9.6	31.2 ± 13.7	31.1 ± 7.3	0.896
Sex (M:F)	7 (36.8%):12 (63.2%)	1 (14.3%):6 (85.7%)	3 (60%):2 (40%)	3 (42.9%):4 (57.1%)	0.248
Toxicity details					
Dose ingested (grams)	21.3 ± 11.2	11.4 ± 6.9	24.0 ± 6.5	29.3 ± 10.2	0.003
Ingestion to presentation to our unit	3(0–10)	3(2–10)	5 (3–5)	2.5 (0–10)	0.728
Clinical details					
Comorbidities	Hypertension (1)	Hypertension (1)	0	0	
Jaundice to encephalopathy (JEI) (days)	4.1 ± 2.3	5.1 ± 2.5	4.2 ± 0.8	2.9 ± 2.4	0.178
Ingestion to HE (IHEI) (days)	4.9 ± 2.5	6.2 ± 2.2	5.2 ± 1.1	3.7 ± 3.2	0.247
HE on admission	12 (63.2%)	4 (57.1%)	5 (100.0%)	3 (42.9%)	0.119
Peak HE grade > 3	12 (63.2%)	2 (28.6%)	3 (60%)	7 (100%)	0.021
Cardiotoxicity	4 (21.1%)	0 (0%)	1 (20%)	3 (42.9%)	0.144
Acute kidney injury (AKI)	10 (52.6%)	1 (14.3%)	3 (60%)	6 (85.7%)	0.026
Bone marrow suppression	6 (31.6%)	2 (28.6%)	2 (40%)	2 (28.6%)	0.895
Investigations					
Admission hypoglycemia	4 (21.1%)	2 (28.6%)	2 (40%)	0 (0%)	0.203
Peak bilirubin (mg/dL)	9.7 ± 6.3	11.1 ± 6.2	11.0 ± 7.8	7.4 ± 5.3	0.487
Peak AST (U/L)	897(28–6291)	725(28–2378)	3378(187–6291)	1258(97–4229)	0.109
Peak ALT (U/L)	786.8 ± 538.4	655.0 ± 417.1	1088.0 ± 691.3	703.4 ± 522.5	0.361
Peak alkaline phosphatase (U/L)	153.5 ± 71.6	161.1 ± 78.8	203.0 ± 56.1	110.4 ± 52.9	0.074
Peak GGTP (U/L)	110(13–1081)	110(15–1081)	288(142–518)	34(13–118)	0.156
Lowest Fibrinogen (mg/dl)	146.9 ± 91.4	185.6 ± 104.1	88.6 ± 39.0	149.9 ± 92.8	0.198
Pre-plasmapheresis peak PT-INR	7.8 (1.2–30.1)	3.4 (1.2–30.1)	7.9 (5.6–22.2)	10.1 (7.2–20.7)	0.733
Pre-CVVHDF peak lactate (mmol/L)	11.9 ± 9.2	3.8 ± 2	15.0 ± 7.2	17.7 ± 9.7	0.005
Pre-CVVHDF peak Ammonia (μ/dl)	144(67–997)	137.5(67–178)	145(106–208)	150(98–997)	0.414
Pre-CVVHDF peak creatinine (mg/dl)	1.1 (0.6–5.8)	0.8 (0.6–5.8)	1.7 (0.7–5.7)	1.3 (0.8–5.1)	0.753
Prognostic scores					
Patients meeting KCC	15 (78.9%)	4 (57.1%)	5 (100%)	7 (100%)	0.047
Admission MELD score	29.9 ± 12.6	29.9 ± 12.6	36.4 ± 8.0	25.3 ± 12.7	0.293
Peak MELD score	35.2 ± 8.0	30.7 ± 11.8	36.2 ± 3.5	38.9 ± 2.3	0.156
Admission SOFA score	9.3 ± 3.9	9.1 ± 4.0	8.6 ± 3.6	9.9 ± 4.5	0.867
Peak SOFA score	15.0 ± 4.0	11.4 ± 3.7	15.6 ± 2.1	18.1 ± 2.4	0.002
Delta SOFA score	5.7 ± 4.2	2.3 ± 2.4	7.0 ± 2.5	8.3 ± 4.5	0.012
Management					
Need for ventilator	13 (68.4%)	3 (42.9%)	3 (60%)	7 (100%)	0.063
Need for CVVHDF	15 (78.9%)	3 (42.9%)	5 (100%)	7 (100%)	0.013
Need for plasmapheresis	15 (78.9%)	4 (57.1%)	5 (100%)	6 (85.7%)	0.171
No of plasmapheresis sessions required	3 (1–4)	3(2–4)	2 (1–3)	2.5 (1–3)	0.34
Outcomes					
Hospital admission (days)	11.1 ± 7.9	12.3 ± 9.2	21 ± 2	6.1 ± 3.5	0.0002
ICU stay (days)	9.2 ± 5.4	8.3 ± 4.9	14.8 ± 4.4	6.1 ± 3.5	0.01

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVVHDF, continuous veno-venous hemodiafiltration; GGTP, gamma-glutamyl transpeptidase; HE, hepatic encephalopathy; KCC, King College criteria; MELD, model for end-stage liver disease; SOFA, sequential organ failure assessment

Table 3 Comparison Between Two Groups (Spontaneous Survivors V Others).

	SS (n = 7)	Others (n = 12)	*P* value	AUROC	Cut-off	Sensitivity	Specificity
Amount of toxin ingested (grams)	11.4 ± 6.9	27.1 ± 8.9	0.0009	0.932	17.5	91%	83%
Grade 3 HE	2 (28.6%)	10 (83.3%)	0.017				
AKI	1 (14.3%)	9 (75%)	0.011				
Peak lactate	3.8 ± 2	16.6 ± 8.5	0.001	0.864	5.8	82%	83%
Peak SOFA	11.4 ± 3.7	17.1 ± 2.5	0.0009	0.894	14.5	73%	83%
Delta SOFA	2.3 ± 2.4	7.8 ± 3.7	0.003	0.947	5.5	82%	83%
Peak PT-INR	8.9 ± 10.5	11.8 ± 5.7	0.442				
Meeting KCC	4 (57.1%)	12 (100%)	0.013				
Need for CVVDHF	3 (42.9%)	12 (100%)	0.003				

AKI, acute kidney injury; CVVHDF, continuous veno-venous hemodiafiltration; HE, hepatic encephalopathy; KCC, King College criteria; SOFA, sequential organ failure assessment.

plasmapheresis, which was similar between groups. Three of four patients who did not undergo plasmapheresis did not have any evidence of SIRS, and one patient was too unstable for it. None of the patients had any morbidity related to plasmapheresis.

Hepatotoxicity and liver transplantation

At presentation, all patients had transaminitis and coagulopathy, 16 (84.2%) had jaundice and 12 (63.2%) had HE. All patients developed HE at some point; all non-survivors progressed to develop ≥ grade 3 HE, which was significantly higher than that in others. Seventeen (89.5%) patients had hyperacute presentation with jaundice to encephalopathy interval 4.1 ± 2.3 days, which was similar across groups. Ingestion to encephalopathy interval was shortest in non-survivors and longest in spontaneous survivors, although not significantly different. There was no mortality because of raised intracranial pressure (ICP) or its complications. The MELD score on admission (29.9 ± 12.6), and peak (35.2 ± 8) were similar across groups. All non-survivors and transplant patients met King College criteria (KCC) compared with only four (57.1%) spontaneous survivors (P = 0.013). Most 14 (73.7%) patients met KCC on account of PT-INR > 6.5.

All patients with encephalopathy meeting KCC were considered for transplant. All patients in LT and NS groups met KCC and were offer a transplant. In the NS group, one patient rapidly deteriorated after admission and expired, two patients developed cardiac side effects and deteriorated of which one had a prospective living related donor under evaluation and one was waiting for a deceased-donor organ; two other patients developed progressive MOF and expired, and two patients did not undergo transplant because of financial constraints. In the SS group, four (57.1%) patients fulfilling KCC were offered a transplant although they improved with medical management. Five patients underwent liver transplants, two living-donor liver transplant (LDLT), and three DDLT at 6.2 ± 5.1 days from admission. In patients undergoing transplant, CVVHDF was continued during the transplant. Intraoperatively hepatomegaly with soft consistency and pale color was observed. Histopathology of explanted livers showed mild to severe balloon degeneration and bridging necrosis and minimal to marked portal infiltration in all patients, diffuse micro- and macro-steatosis in three patients, and none in two patients.

Post-transplant course

There was no mortality after undergoing a liver transplant in our series. Three patients had postoperative ventilator–associated gram-negative pneumonia, and one had and intra-abdominal infection collection, all of whom responded to antibiotics. Two patients had vocal cord palsy that recovered with speech therapy. One patient each had an early bile leak and stricture, both responding well to endoscopic biliary stenting. Three patients had non-compliance–related acute cellular rejection (ACR): one of them had cholestatic steroid–resistant ACR that responded to thymoglobulin, also required endoscopic biliary stenting for a late stricture and is currently hospitalized and recovering from a COVID-19 infection. The other two responded to steroid boluses: one of them also had late hepatic artery thrombosis with spontaneous collateralization. Two patients had CMV infection on follow-up that were treated successfully.

The ICU and hospital stay were significantly longer for transplant patients, because of initial trial of supportive management and slower recovery after transplant, whereas it was shortest for non-survivors, probably because of rapidly progressive systemic toxicity and fatal outcome.

Three (60%) patients needed a median of 1 (0–2) unit of packed red blood cells, and one patient needed 3 units of random donor platelets after transplant. None of the

patients needed FFP or cryoprecipitate. INR normalized at 15.6 ± 6.9 days after ingestion and a median 5 (1–20) days after transplant. Renal failure recovered at 13.3 ± 9.3 days after ingestion and a median 2 (2–16) days after transplant. Bone marrow suppression reversed 14 days after ingestion and 9 days after transplant in the only patient. At median follow-up of 3.4 (2.6–5.5) years, all spontaneous survivors and transplanted patients are well with normal liver function.

DISCUSSION

YPMP are highly soluble in lipids and bile and get rapidly absorbed through the skin, mucosal, respiratory, and GI linings. On exposure to environment or contact with gastric acid, they release phosphene (PH_3) gas which is highly corrosive.[8] They are rapidly distributed systemically in 2–3 h, predominantly in the liver (69–73%), heart (12%), kidneys (4%), and smaller quantities (<1%) in the pancreas, spleen, brain and other organs causing their toxicity, which could explain their predilection for hepatotoxicity and cardiotoxicity.[9] YPMP are cheaply, widely, and freely available over the counter as household and agricultural rodenticides in the Indian subcontinent and as components of firecrackers in other countries with varied composition and strength (Figure 1, Table 4).[10,11]

In our series, suicidal ingestion of raw Zn_3P_2 rodenticide paste caused toxicity, consistent with reports from South India and different from North India where AlP toxicity is most common, which may be due to referral bias.[15] Impulsive suicidal consumption with alcohol or water (as death is believed to be painless) and accidental consumption by children (as directions for use include applying the paste on bread) and by adults (mistaken for toothpaste) have been reported.[16] Lethal dose of 13.42 ± 7.069 g of household rodenticide has been reported, similar to spontaneous survival with dose <17.5 g in our series.[17]

The demographic profile of our patients is consistent with other studies.[18]Clinical manifestations of YPMP poisoning may be divided into three phases (Table 5), which are consistent with our series, except a very low rate of GI toxicity in our patients, probably due to late presentation beyond the first two phases (at about 3 days).[19]

In our series, all patients had ALF with HE; none had cholestatic presentation. Other causes of ALF such as viral hepatitis, autoimmune, drug-induced liver injury, and others should be ruled out if the history of poisoning is unavailable or unclear. Ultrasonography showed hepatomegaly with the fatty liver in all cases, consistent with the literature, although not specific for YPMP.[22,23] A high index of suspicion should be kept, and specific history of

Figure 1 Commonly available YPMP rodenticide preparations in India.

Table 4 Chemical and Toxicity Characteristics of Elemental YPMP.[12–14]

Phosphorus compound lethal dose	Chemical characteristics	Clinical toxicity	Common preparations, uses
Red phosphorus	• Amorphous, non-volatile, insoluble, non-absorbable	Non-toxic	
White/yellow phosphorus Toxic dose: < 1 mg/kg Lethal dose: > 1 mg/kg	• Luminous, shiny, waxy, translucent • On exposure oxidizes and turns yellow on surface to produce dense smoky phosphoric and phosphorus acid fumes with very strong garlicky odor	Highly toxic	• Household rodenticides
Aluminum phosphide (AlP) lethal dose: 20 mg/kg	• Unstable, rapidly releases phosphene gas on exposure or contact with gastric acid	• GI irritation, nausea, severe vomiting due to corrosive action of phosphene • Hypotensive shock and metabolic acidosis (in a few hours) • Early hepatotoxicity and mortality	• Agricultural and industrial rodenticides (fumigant, powder, tablet, or pellet) • Production of ammunitions, fire-crackers, and fertilizers
Zinc Phosphide (Zn_3P_2) Lethal dose: 1–5 g	• Stable, releases phosphene gas slowly on contact with gastric acid	• Minor early symptoms/local toxicity • Delayed (in 3–5 days) severe hepato-toxicity	• Household rodenticide (2–7% paste in 15 gm and 35 gm tubes, granules) • Agricultural rodenticide (powder, tablet) (32–80%)

GI, gastrointestinal; YPMP, yellow phosphorus or metal phosphides.

YPMP ingestion elicited in all poisoning cases with GI symptoms, cardiotoxicity, or hepatotoxicity as details by the patient or their families may be often incomplete or inaccurate.[24] They should be requested to bring the empty/remaining tube or its picture.

The severity of toxicity, clinical presentation and course, treatment plan, and mortality risk prognostication depends on the composition, strength and amount of toxin ingested, severity of vomiting in the 1st phase (leading to expulsion of part of the toxin), feasibility of very early gastric lavage (within a few hours of ingestion), the interval between ingestion and institution of treatment (to enable organ protective measures before widespread absorption, distribution and systemic toxicity), monitoring and treatment facilities available, and management protocols followed.[25] Patients with warfarin-based (super-warfarins) rodenticide toxicity present with coagulopathy without HE, and correction of coagulopathy is adequate to prevent bleeding, complications, and mortality.

Management

Stable or asymptomatic patients should be monitored for 3–5 days and those with a high dose of ingestion, hemodynamic instability, clinical, biochemical, or ECG abnormalities should be managed in a LICU with liver transplant facility.[26–28] Patients with ≥ grade 2 HE should be electively mechanically ventilated for transfer, airway protection, and to prevent rise in ICP.[23]

Milk or fatty foods may promote phosphorus absorption; therefore a high-carbohydrate, high-protein, low-fat, or no-fat diet with supplementary intravenous glucose and vitamins is preferred, except in patients on high-dose inotropes where oral feeds are avoided or in HE where nasogastric feeding is preferred.[29] Proton pump inhibitors or H2 receptor antagonists inhibit PH_3 release by reducing gastric acid secretion and for ulcer prophylaxis.

Patients presenting within few hours of ingestion may benefit from cautious gastric decontamination.[30] In our series, only one patient was admitted within 24 h of ingestion where normal saline gastric lavage was done. Additives such as potassium permanganate, charcoal, activated charcoal, and copper sulfate may further hasten disintegration and increase toxicity and therefore not advised.[31,32]

Metabolic acidosis is corrected using sodium bicarbonate infusion.[33] Lactulose is used to reduce ammonia load in patients with ALF with constipation.[34] Cholestyramine, ursodeoxycholic acid (UDCA), and sertraline may be used for cholestatic presentation.[35] Rifaximin, s-adenosyl methionine, L-ornithine L-aspartate, steroids, and exchange transfusion have not shown benefit.[36]

Inconsistent benefit of N-acetylcysteine (NAC) has been reported in ALF, especially with early (within 6 h) use, although it may be confounded by the benefit of early gastric lavage.[37] NAC being a safe and low-cost drug is a part of our protocol.[38] Preemptive vitamin K (phytomenadione) (10–30 mg × 5 days) or FFP has been recommended to reduce bleeding risk or platelets transfusion for thrombocytopenia (bone marrow toxicity).[39] We used vitamin K 10 mg for 3 days and in patients with PT-INR > 2. Coagulopathy was corrected for nasal bleeding in one patient, guided by coagulation parameters and TEG.

Consensus for CVVHDF use in ALF is evolving.[40] Five cycles of plasmapheresis have been suggested to modulate immune response, although we use 3

Table 5 Clinical Presentation of YPMP Poisoning.[20,21]

Phase 1 (GI stage)
• Starting within minutes to hours (5.7 ± 6.3 h) of ingestion
• Lasts for about 24 h
• Nausea, vomiting, diarrhea, burning sensation and pain in mouth, throat, retrosternal area and epigastrium due to local irritation
• Rarely present with hematemesis, duodenal perforation, smoky or luminescent breath, vomitus or stools with garlic odor, which may even cause spontaneous combustion or explosion (of phosphene gas)
• May present with profound fluid loss and dehydration leading to refractory hypotension, shock, metabolic acidosis, and electrolyte imbalance.
• Hyperchloremic hypocalcemia causing tetany, hypokalemia, hyperkalemia, hyperphosphatemia, or hypophosphatemia
• Severe cardiotoxicity may manifest with T-wave changes, corrected QT interval prolongation, ST depression, low voltage ECG, tachycardia, dysrhythmias including atrial fibrillation, ventricular arrythmia, ventricular tachycardia or ventricular fibrillation causing sudden death due to hypocalcemia coupled with hyperphosphatemia (causing reversed calcium–phosphorus ratio).
Phase 2 (quiescent/asymptomatic stage)
• 24–72 h duration
• Patients experience significant improvement in symptoms or become asymptomatic
• False sense of security
• Often discharged from the hospital
Phase 3 (systemic toxicity)
• Starts after 72 h
• Gastrointestinal toxicity (100%): nausea, protracted vomiting, diarrhea, and hematemesis may recur
• Pancreatitis
• Hepatotoxicity (50–87%)
o Jaundice, firm tender hepatomegaly, rapidly rising transaminitis, PT-INR, ammonia, lactic acidosis, reduced urea, fibrinogen, hypoglycemia or ALF (in about 30–35% cases).
o May rarely present with cholestatic pattern with deep icterus, severe and sleep-disturbing pruritus, raised bilirubin and alkaline phosphatase.
• Metabolic acidosis is most commonly due to hepatotoxicity, although it could be hypovolemic
• Cardio-respiratory toxicity (25%)
o May be similar to that described in phase I
o May present with ischemic heart disease or simulate acute myocardial infarction leading to reduced contractility and cardiogenic shock due to direct toxicity on myocardium or conduction fibers.
o Acute pulmonary edema has also been reported.
• Renal toxicity (25%): uremia, oliguria, albuminuria, hematuria and rarely phosphorescent urine, may be due to hypovolemic shock or direct toxicity.
• Bone marrow toxicity: neutropenia is common, although any cell lines could be affected.
• Central nervous system (CNS) toxicity: headache, restlessness, irritability, tinnitus, confusion, deafness, impaired vision, convulsions, psychosis, hallucinations, delirium, drowsiness, lethargy or coma.Some of these may be due to hepatic encephalopathy or direct CNS toxicity.
• Multi-organ failure (MOF) (25% patients)
• Extensive hemolysis and/or rhabdomyolysis have been associated with poor prognosis.

ALF, acute liver failure; GI, gastrointestinal; YPMP, yellow phosphorus or metal phosphides.

cycles.[39]Psychological evaluation, counseling, and support by trained personnel should be offered to patients with suicidal poisoning and their families during all phases of treatment, and the treating team should adhere to local medicolegal norms.[27]

Outcome, risk factors, and indication for transplant

Most series report 23–73% mortality depending on risk factors such as age, hemodynamic instability at presentation, early central nervous system compared with GI symptoms, INR ≥6, elevations in transaminases (ALT > 10x), alkaline phosphatase, metabolic acidosis, hypoglycemia, bilirubin, urea, creatinine, hypernatremia, hyperkalemia, arterial ammonia, MELD score (36 or 40 cut-off), renal dysfunction, need for mechanical ventilation or inotropes.[41] Spontaneous survival 3 days after ingestion and minimal elevation of LFT predict good prognosis.[42]

Most patients with mortality had high dose of ingestion and MOF in our series, with no losses after liver transplant. Early HE has been reported to have poorer outcomes; although IHE was shortest in non-survivors, it was not significant from other groups in our series.[43]Spontaneous survivors had lower dose ingestion (<17.5 g), absence of cardiotoxicity, <grade 3 HE, lactate < 5.8, SOFA score < 14.5, and increase in SOFA score by < 5.5. Patients with AKI need for CVVHDF, and KCC positivity on account of PT-INR > 6.5 had higher mortality risk.

Preparation for an emergency orthotopic DDLT or LDLT (not auxiliary transplant) should be initiated early although optimal criteria and timing for transplant are not well known.[44] Development of HE has been suggested as an indication for transplant.[19,27] In our series all spontaneous survivors also had HE, and only ≥ grade 3 HE was associated with poor outcomes. We suggest offering transplant to patients with ≥ grade 3 HE. KCC and national health services blood and transfusion services ALF criteria have also been used to offer transplant, although they have not been validated for YPMP poisoning. In our series, 43% patients survived spontaneously despite meeting KCC. In absence of HE, markers of severe acute liver injury such as PT-INR > 6.0, MELD score > 37, persistently elevated serum lactate despite resuscitation and with plasmapheresis PT-INR > 2.5; at least 12 h after second cycle have been proposed for transplantation.[27] In absence of ≥ grade 3 HE, we believe progression of systemic toxicity evidenced by progressive increase in SOFA score or lack of response to treatment such as persistently high ammonia or lactate despite CVVHDF or persistently elevated PT-INR, despite plasmapheresis should be indications for transplant.[45] Toxin-mediated graft injury in the early post-transplant period may present as early allograft dysfunction for which a biopsy and plasmapheresis may be considered.[27]

Post-mortem liver explants were yellow and extremely firm on gross pathological examination. Microscopic findings of ballooning degeneration, bridging necrosis, portal infiltration, and diffuse micro- and macro-steatosis in our cases are consistent with other reports. The preserved lobular pattern, reticulin framework collapse, hepatocyte vacuolization, and centrilobular intracellular and intracanalicular cholestasis have also been reported.[46]

In absence of a clinically available laboratory test for diagnosis or toxin measurement or an antidote, early transfer to a specialized center, preemptive close monitoring, intensive care and organ support with ventilation, CVVHDF, plasmapheresis, and others may maximize their chances of spontaneous recovery and allow accurate prognostication and a timely liver transplant. Prevention of toxicity by restricting access to this toxin to public and by banning its sale, storage, or promotion of alternative safer rodenticides has been suggested. Safer packaging which is difficult to open for kids and prominent labeling of toxicity may be useful.[47] Awareness of its severe toxicity and high lethality in very small quantities among public, people handling the toxin, and clinicians could be helpful too. We acknowledge the inherent biases in this retrospective case series and inability to draw conclusions about causation or treatment efficacy. Because the toxicity is more common in the Indian subcontinent, a multicenter study from this region would be able to better define optimal management including the role of plasmapheresis and develop criteria for liver transplant for YPMP toxicity.

YPMP are common household rodenticides in Indian subcontinent that cause GI, cardiac, and liver toxicity leading to acute liver failure and multi-organ failure which are often fatal. Patients with low dose of ingestion (<17.5 g), absence of cardiotoxicity, HE < grade 3, low lactate (<5.8) and PT-INR levels, low (<14.5) or non-progressive SOFA score may have higher chances of spontaneous survival. High dose ingestion, grade 3 or higher HE, progressive systemic toxicity, or lack of response to treatment such as CVVHDF and plasmapheresis in patients should be indications for transplant. Legislation restricting availability, labeling, packing, and storage of these rodenticides may help reduce poisoning.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Ravi Mohanka: study concept and design, analysis and interpretation of data, writing the manuscript, critical revision of the manuscript, final approval. **Prashantha Rao:** conception and design of the study, analysis and interpretation of data, critical revision of the manuscript, final approval. **Mithul Shah:** acquisition of data, drafting the article, critical revision, final approval. **Amit Gupte:** analysis and interpretation of data, final approval. **Vinayak Nikam:** acquisition of data, critical revision, final editing and formatting, final approval. **Mihir Vohra:** acquisition of data, critical revision, final approval. **Ruhi Kohli:** conception and design of the study, acquisition of data, critical revision, final approval. **Anurag Shrimal:** interpretation of data, critical revision, final approval. **Ankush Golhar:** acquisition of data, critical revision, final approval. **Ameya Panchwagh:** acquisition of data, critical revision, final approval. **Saurabh Kamath:** acquisition of data, critical revision, final approval. **Akash Shukla:** acquisition of data, critical revision, final approval. **Priyesh Patel:** acquisition of data, critical revision, final approval. **Somnath Chattopadhyay:** study concept and design, writing the manuscript, critical revision of the manuscript, final approval. **Gaurav Chaubal:** acquisition of data, critical revision, final approval. **Yasmin Shaikh:** acquisition of data, critical revision, final approval. **Vidhi Dedhia:** acquisition of data, critical revision, final approval. **Shivali Sarmalkar:** acquisition of data, critical revision, final approval. **Ravikiran Maghade:** acquisition of data, critical revision, final approval. **Kavita Shinde:** acquisition of data, critical revision, final approval. **Priyanka Bhilare:** acquisition of data, critical revision, final approval. **Rohini Nalawade:** acquisition of data, critical revision, final approval. **Jacob AS:** acquisition of data, critical revision, final approval. **Samir Shah:** study concept and design, analysis and interpretation of data, writing the manuscript, critical revision of the manuscript, final approval.

CONFLICTS OF INTEREST

The authors have none to declare

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SUPPLEMENTARY DATA

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