Case Report

DOI: 10.7860/JCDR/2024/65523.19445

Internal Medicine Section

Plasmapheresis as an Adjunctive Therapy for Yellow Phosphorus Poisoning: A Case Report

BRIAN WILLIAM DMELLO[1], ASHRAY VASANTHAPURAM[2], GIRISH NARAYAN[3], SHAKUNTALA MURTY[4], ANGELINE YVETTE MASCARENHAS[5]

ABSTRACT

Yellow Phosphorus (YP) poisoning is an infrequent, yet severe medical condition characterised by multi-systemic toxicity. The ingestion or inhalation of YP can lead to gastrointestinal irritation, hepatic injury, and Acute Liver Failure (ALF). Plasmapheresis, a therapeutic intervention involving the removal and replacement of plasma components, is a potential adjunctive treatment for YP poisoning. This case report aims to explore the mechanistic rationale, clinical efficacy, and safety considerations of plasmapheresis in the management of this toxicological emergency. Here, a 16-year-old female reported to the Emergency Department (ED), having consumed 1-2 g of Ratol poison at two different times of the day. She came to the hospital on day 4 post-consumption. On admission, the patient was jaundiced and Arterial Blood Gas (ABG) analysis was suggestive of respiratory alkalosis with hypokalemia. Treatment focused on fluid therapy, vitamin K therapy, and N-Acetyl Cysteine (NAC). She developed angioedema and urticaria with no airway compromise, in response to intravenous NAC. A diagnosis of acute liver injury secondary to YP poisoning was made. Close monitoring of liver function and coagulation parameters, and bleeding complications was done. Plasmapheresis was considered as NAC reinitiating was not feasible due to potential anaphylaxis. The patient responded well to the treatment and was discharged on day 7 of hospitalisation.

Keywords: Acute liver injury, N-acetyl cysteine, Ratol poison

CASE REPORT

A 16-year-old female presented to the Emergency Department (ED) after ingesting 1-2 g paste of undiluted Ratol poison (Zinc Phosphide containing 3% YP) twice within the same day (Total of 2-4g). She developed diffuse abdominal pain, profuse vomiting, and constipation on day 2. Her initial management at a local hospital involved conservative treatment with intravenous fluids, vitamin K, and N-Acetyl-Cysteine (NAC). Investigations revealed abnormal Liver Function Test (LFT) (transaminitis) and coagulation profile abnormalities on day 3. Due to deteriorating LFT and coagulation profile [Table/Fig-1], she was referred to the hospital (day four post-consumption). Upon admission, the patient was haemodynamically stable, febrile and jaundiced. Systemic Examination including Central Nervous System (CNS) examination was normal. Stat Blood glucose values were normal, Arterial Blood Gas (ABG) analysis was suggestive of respiratory alkalosis with hypokalemia [Table/Fig-2]. Other routine investigations like Electrocardiogram (ECG), Chest X-Ray (CXR), Screening ECHO and Ultrasonography (USG) of the abdomen were normal. Treatment continued along similar principles, focusing on fluid therapy, vitamin K, and NAC.

Additionally, prophylactic antibiotics and anti-encephalopathy measures (Syrup Lactulose TID and Tab Rifaximin BD) were initiated. However, she developed angioedema and urticaria (no airway compromise) in response to intravenous NAC, which resolved with hydrocortisone, pheniramine maleate and discontinuation of therapy. A diagnosis of acute liver injury secondary to Yellow Phosphorus (YP) poisoning and adverse drug reaction to NAC was made. Hospitalisation ensued to monitor anaphylaxis, closely assess liver function and coagulation parameters, prevent acute fulminant liver failure and manage bleeding complications. The patient's Model for End-Stage Liver Disease (MELD) score on the

Parameter	Day 1	Day 2		Day 3		Day 4		Day 5	Day 6	Day 7	Day 14	Day 28
Total bilirubin (mg/dL)	**2.01**	**3.32**	PLASMAPHERESIS	**4.07**	**4.11**			**4.48**		**3**	**1.21**	**1.08**
Direct bilirubin (mg/dL)	**1.29**	**1.91**		**2.42**	**2.9**			**3.29**		**1.9**	**0.64**	**0.53**
AST/SGOT (U/L)	**1213**	**1677**		**517**	**201**	**161**		**222**		**159**	**43**	23
ALT/SGPT (U/L)	**681**	**939**		**328**	**308**	**275**		**331**		**311**	**96**	27
ALP (U/L)	56	51		70				65		87	58	49
PT (seconds)	**57.2**	**80.7**		**21.3**	**26.7**	**22.4**		**15.2**	11.9	11.2	11.5	12.6
INR	**4.77**	**6.73**		**1.78**	**2.23**	**1.87**		**1.27**	0.99	0.93	0.96	1.05
APTT (seconds)	**45.3**	**45.9**		29.5	33.7	33.6		32.1				
Ammonia (mmol/L)	**87**			**82**				**45**				
Urea (mg/dL)	26.1	19		23.6				20.1				
Creatinine (mg/dL)	0.67	0.58		0.54				0.54				
Sodium (mEq/L)	**132**			**133**				**131**				
Potassium (mEq/L)	**3.4**			**3.4**		**2.7**	**3.4**	3.6				
Chloride (mEq/L)	103			103				104				

Magnesium (mg/dL)	2	2.1				1.6	1.6					
Calcium (mg/dL)	**7.7**	**7.8**		**7.1**		**6.5**	**7.7**					
Phosphorus (mg/dL)	**1.42**	2.62										
Haemoglobin (g/dL)	12.4			13.1				12				
Total count	4280			4690				6620				
Platelet count (Lakhs)	1.75			1.67				**1.47**				
Strip pregnancy	Negative											

[Table/Fig-1]: Summary of investigations (post-hospitalisation).
*Normal Plasma Ammonia Level: (11-35); AST/SGOT: Aspartate transaminase/Serum glutamic oxaloacetic transaminase; ALT/SGPT: Alanine transaminase/ Serum glutamic pyruvic transaminase; ALP: Alkaline phosphatase; PT: Prothrombin time; INR: International normalised ratio; APTT: Activated partial thromboplastin time

Parameter	Arrival/ED	Day 1	Day 2	Day 3	Day 4
pH	7.48	7.49	7.50	7.48	7.47
pCO_2	29.4	26.6	28.4	29.6	28.3
HCO_3	21.8	20.1	22	21.6	20.5
pO_2	96	95	104	93.3	90.4
Lactate	1.7	1.8	1.5	0.9	0.5
Base excess	-2.6	-2.8	0.2	-0.8	-1.8

[Table/Fig-2]: Blood gas analysis (Post-hospitalisation).

day of arrival was 29, which progressed to 33 on day 1. Deteriorating coagulation profile over subsequent days necessitated Fresh Frozen Plasma (FFP) transfusions (4 Units). Plasmapheresis was considered as NAC reinitiating was not feasible due to potential anaphylaxis. The procedure involved a Plasma Exchange (PLEX) volume of 2.6 L {2.4 L FFP + 0.2 L Normal Saline (NS)}, using 14 units of FFP with heparin and additional calcium supplementation after every 3-4 units of FFP. The patient tolerated the procedure well; her symptoms were managed conservatively, and subsequent measurements demonstrated gradual improvement in LFT and International Normalised Ratio (INR) over a week. The patient's condition improved, oral feeds were initiated on day 5, suitable consults were obtained, and she was discharged on day 7 of hospitalisation.

DISCUSSION

Yellow Phosphorus is a waxy, yellowish, crystalline solid with wide-ranging industrial applications, including the manufacturing of tracer bullets, incendiaries, semiconductor additives, fertiliser derivatives and fireworks (Asia and Latin America). It is commonly used as an insecticide and rodenticide and even finds application in homoeopathic medicine [1]. YP among adults is predominantly ingested with the intention of deliberate self-harm [2,3]. However, as rodenticide tubes (containing YP) resemble toothpaste, they may be accidentally ingested in the paediatric population.

Absorption of YP occurs predominantly through the gastrointestinal (GI) tract but can also happen via the respiratory tract, skin, and mucous membranes, following which it is evenly incorporated into various tissues. The liver is the primary site of distribution due to its first-pass metabolism [4].

YP acts as a fat-soluble protoplasmic poison and a potent hepatotoxin, leading to severe tissue hypoxia by generating phosphine gas that inhibits cytochrome C oxidase and oxidative metabolism [5]. The exact mechanism of toxicity remains largely unknown; however, it is believed to alter ribosomal function, protein synthesis [6], blood glucose regulation, glycogen deposits [7], lipoprotein and triglyceride synthesis. Consequently, intracellular accumulation and fatty degeneration of organs such as the liver, kidney, heart, and brain can also occur [8,9]. The central nervous, cardiovascular, haematological, renal, and hepatobiliary systems are particularly susceptible to hypoxic injury, with progression to shock and cardiovascular collapse. Even small amounts of YP can cause profound multiorgan dysfunction and death, although the usual fatal dose is 60 mg (1 mg/kg body weight).

The progression of YP poisoning has been categorised into three distinct clinical stages [10]. Stage 1- <24 hours of ingestion, symptoms reflective of GI irritation occur due to the development of phosphine gas upon contact between phosphorus and hydrochloric acid in the stomach.

Stage 2 (1-3 days), patients may remain asymptomatic, but liver enzyme and bilirubin levels deteriorate due to toxic hepatitis.

Stage 3 (>72 hours) Acute Liver Failure (ALF) can manifest, accompanied by coagulopathy, encephalopathy, arrhythmias, Acute Renal Failure/Acute Kidney Injury (ARF/AKI), and haemodynamic instability. Recovery or death can occur at this stage. The symptoms manifested by the patient in the present case report were consistent with the known pharmacological effects of YP.

This patient also exhibited lower total counts (bone marrow toxicity) and hypocalcaemia consistent with YP poisoning due to the preferential binding of calcium by phosphorus in serum [11]. YP causes necrobiosis of the liver [12], manifesting as ALF with deranged LFTs and coagulopathy as the most common presentation [13], clinically ranging from mild transaminitis to fulminant liver failure.

NAC, conventionally used for paracetamol poisoning due to its antioxidant and hepatoprotective properties, has been studied in cases of ALF [14,15]. Its effectiveness in rodenticide-induced ALF is still under investigation, showing promising results in some and questionable benefit in others [16]. A recent study conducted in the Indian sub-population suggest that NAC may be beneficial if initiated early in YP intoxication, with delays in initiation linked to higher mortality [17]. One possible mechanism is NAC's role in lowering von Willebrand Factor (vWF) levels in the blood, which is elevated in YP poisoning. Anaphylactoid reactions to intravenous NAC have been extensively documented [18,19], which are rarely fatal but generally non-life threatening and easily treatable. A similar anaphylactoid reaction was observed in the present patient and was amenable to conventional treatment [20,21]. Other treatment modalities include corticosteroids have been used and found to be ineffective and potentially harmful in YP poisoning, and the combination of corticosteroids and exchange transfusion did not prevent coma progression or reduce mortality rates [22].

Poisoning with YP presents a significant challenge in terms of effective treatment options. Recent Liver Transplant Society of India (LTSI) guidelines focus on urgent liver transplantation to treat rodenticide hepatotoxicity [23]. While a liver transplant remains the definitive therapy in YP poisoning and has been implemented in select cases of ALF [24], including in an Indian setting, high cost and limited availability render it inaccessible to many patients [25]. Moreover, the scarcity of liver donors exacerbates this issue. Hence, developing countries focus on maximising patient survival with nontransplant treatments. Alternatively, Continuous Renal Replacement Therapy (CRRT) and Therapeutic Plasma Exchange (TPE) have demonstrated some promise in paediatric YP poisoning cases [26], but their affordability remains a barrier to widespread implementation. TPE is the removal of a patient's plasma and replacement of it with plasma from a donor along with a colloid using an extracorporeal device.

Although PLEX transfusions in acute YP intoxication were described as early as 1971, the landmark study by Larsen FS et al., introduced the first open randomised controlled trial of PLEX for ALF, leading to the incorporation of plasmapheresis into the therapeutic options for ALF [27]. Before this publication, existing studies on PLEX in liver failure primarily consisted of retrospective case series or cohort studies, exhibiting considerable variability in the protocols employed. The 2019 guidelines from the American Society for Apheresis (ASFA) establish High-Volume Plasma Exchange (HV-PLEX) as the preferred first-line treatment for ALF, either as a standalone therapy or in combination with other modalities (category 1 indication) [28]. HV-PLEX has received Level I, Grade 1 recommendation in the European guidelines as well as in Asia-Pacific guidelines [29] for ALF management, attributed to its proposed mechanism of removing plasma cytokines and drivers of the systemic inflammatory cascade and an added advantage of providing deficient clotting factors and albumin. Emerging evidence also suggests the efficacy of standard-volume PLEX (SV-PLEX) [30] and low-volume PLEX (LV-PLEX) in ALF management [31].

Plasmapheresis thus emerges as a potential therapeutic modality, serving either as a standalone treatment or as a bridge to liver transplantation in YP poisoning, thereby enhancing survival rates. Early elevations in transaminase and ALP, a >10-fold increase in ALT, severe PT derangement, metabolic acidosis, and hypoglycaemia predict poor prognosis. At the same time, the latter two are significantly associated with mortality. Several studies attest to PLEX showing therapeutic benefits in YP poisoning in improving transplant-free survival, [32] reducing total bilirubin, SGOT, INR, Total Leucocyte Count (TLC) ammonia, Sequential Organ Failure Assessment (SOFA) and MELD Na score [33,34] albeit with some caveats like the amount consumed and time to initiation from consumption [35]. The discrepancy also exists with regard to protocol deployed, the number of sessions required [36], and the type of PLEX therapy to be used- with all, LV-PLEX, SV-PLEX and high volume PLEX (HV-PLEX) showing considerable success in YP poisoning. The authors deployed SV-PLEX for the patient with considerable success.

CONCLUSION(S)

Previously, the management of YP poisoning had remained mainly supportive, with the accepted definitive management being liver transplantation among those who developed ALF. Emerging evidence suggests that plasmapheresis is beneficial when initiated early and prevents the necessity for a liver transplant in ALF.

REFERENCES

[1] Bellavite P, Conforti A, Pontarollo F, Ortolani R. Immunology and homeopathy. 2. Cells of the immune system and inflammation. Evid Based Complement Alternat Med. 2006;3(1):13-24.
[2] Nalabothu M, Monigari N, Acharya R. Clinical profile and outcomes of rodenticide poisoning in tertiary care hospital. Int J Sci Res Publ. 2015;5(8):01-02.
[3] Chikkaveeraiah SK, Marijayanth M, Reddy PK, Kaluvakuri S. Clinical profile and outcome of rodenticide poisoning in patients admitted to a tertiary care teaching hospital in Mysore, Karnataka. India. Int J Res Med Sci. 2016;4(11):5023-27.
[4] Cameron JM, Patrick RS. Acute phosphorus poisoning-The distribution of toxic doses of yellow phosphorus in the tissues of experimental animals. Med Sci Law. 1966;6(4):209-14.
[5] Brent J, Wallace KL, Burkhart KK, Phillips SD, Donovan JW. Phosphorus In: Critical Care Toxicology-Diagnosis and Management of the Critically Poisoned Patient. Philadelphia, PA: Elsevier Mosby, USA; 2005.
[6] Chretien TE. Acute phosphorus poisoning: Report of a case with recovery. N Engl J Med. 1945;232(9):247-49.
[7] Talley RC, Linhart JW, Trevino AJ, Moore L, Beller BM. Acute elemental phosphorus poisoning in man: Cardiovascular toxicity. Am Heart J. 1972;84(1):139-40.
[8] Seakins A, Robinson DS. Changes associated with the production of fatty livers by white phosphorus and by ethanol in the rat. Biochem J. 1964;92(2):308.
[9] Ghoshal AK, Porta EA, Hartroft WS. The role of lipoperoxidation in the pathogenesis of fatty livers induced by phosphorus poisoning in rats. Am J Pathol. 1969;54(2):275.
[10] Rubitsky HJ, Myerson RM. Acute phosphorus poisoning. Arch Int Med. 1949;83(2):164-78.
[11] Thomas L, Chandran J, Goel A, Jacob E, Chacko B, Subramani K, et al. Improving transplant-free survival with low-volume plasma exchange to treat children with rodenticide induced hepatotoxicity. J Clin Exp Hepatol. 2023;13(2):252-58.
[12] Krishna V. Textbook of Forensic Medicine and Toxicology: Principles and Practice, 3rd Edn, Elsevier: A division of Reed Elsevier India Pvt Ltd, New Delhi; 2005. ISBN: 81-8147-568-2.
[13] Diaz-Rivera RS, Collazo PJ, Pons ER, Torregosa MV. Acute phosphorus poisoning in man: A study of 56 cases. Medicine. 1950;29:269-98.
[14] Nabi T, Nabi S, Rafiq N, Shah A. Role of N-acetylcysteine treatment in non-acetaminophen-induced acute liver failure: A prospective study. Saudi J Gastroenterol. 2017;23(3):169.
[15] Squires RH, Dhawan A, Alonso E, Narkewicz MR, Shneider BL, Rodriguez-Baez N, et al. Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: A placebo-controlled clinical trial. Hepatology. 2013;57(4):1542-49.
[16] Bhat S, Kenchetty KP. N-acetyl cysteine in the management of rodenticide consumption-life saving? J Clin Diagn Res. 2015;9(1):OC10-OC13.
[17] Patil S, Khatri M, Avhad A, Jaju G. Study of clinical profile and outcome of Ratol poisoning in tertiary care hospital. Med Pulse Int J Med. 2019;9:200-04.
[18] Mark K, Hyder S, Rashid M, Chandran VP, Seshadri S, Seshadri S, et al.. Survival benefits of N-acetylcysteine in rodenticide poisoning: Retrospective evidence from an Indian tertiary care setting. Curr Rev Clin Exp Pharmacol. 2021;16(2):201-08.
[19] Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. Clin Toxicol. 2009;47(2):81-88.
[20] Appelboam AV, Dargan PI, Knighton J. Fatal anaphylactoid reaction to N-acetylcysteine: Caution in patients with asthma. Emerg Med J. 2002;19(6):594-95.
[21] Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. Ann Emerg Med. 1998;31(6):710-15.
[22] Marin GA, Montoya CA, Sierra JL, Senior JR. Evaluation of corticosteroid and exchange-transfusion treatment of acute yellow-phosphorus intoxication. N Engl J Med. 1971;284(3):125-28.
[23] Reddy MS, Rajakumar A, Mathew JS, Venkatakrishnan L, Jothimani D, Sudhindran S, et al. Liver transplantation society of India guidelines for the management of acute liver injury secondary to yellow phosphorus-containing rodenticide poisoning using the modified delphi technique of consensus development. J Clin Exp Hepatol. 2021;11(4):475-83.
[24] Santos O, Restrepo JC, Velásquez L, Castaño J, Correa G, Sepúlveda E, et al. Acute liver failure due to white phosphorus ingestion. Ann Hepatol. 2009;8(2):162-65.
[25] Ravikanti K, Yadav K, Rangappa P, Jacob I, Rao K, Lochan R. Liver transplantation for fulminant hepatic failure in yellow phosphorus poisoning. Indian J Case Rep. 2022;8(8):243-45.
[26] Trepatchayakorn S, Chaijitraruch N, Chongsrisawat V, Chanakul A, Kongkiattikul L, Samransamruajkit R. Therapeutic plasma exchange with continuous renal replacement therapy for pediatric acute liver failure: A case series from Thailand. Indian J Crit Care Med. 2021;25(7):812.
[27] Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. J Hepatol. 2016;64(1):69-78.
[28] Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, 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 eighth special issue. J Clin Apher. 2019;34(3):171-354.
[29] Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL): An update. Hepatol Int. 2019;13:353-90.
[30] Maiwall R, Bajpai M, Singh A, Agarwal T, Kumar G, Bharadwaj A, et al. Standard-volume plasma exchange improves outcomes in patients with acute liver failure: A randomized controlled trial. Clin Gastroenterol Hepatol. 2022;20(4):e831-54.
[31] Zachariah U, Kumar SE, Alexander V, Patel L, Goel A, Eapen CE. Low-volume plasma exchange and low-dose steroid to treat severe liver injury. Gastroenterol Hepatol Endosc Pract. 2021;1(2):47.
[32] Varghese J, Joshi V, Bollipalli MK, Malleeswaran S, Patcha R, Nair H, et al. Role of therapeutic plasma exchange in acute liver failure due to yellow phosphorus poisoning. Indian J Gastroenterol. 2020;39:544-49.
[33] Mohanka R, Rao P, Shah M, Gupte A, Nikam V, Vohra M, et al. Acute liver failure secondary to yellow phosphorus rodenticide poisoning: Outcomes at a center with dedicated liver intensive care and transplant unit. J Clin Exp Hepatol. 2021;11(4):424-34.
[34] Janardhanan S. Role of Therapeutic Plasmapheresis (PLEX) in acute liver failure due to rodenticide Yellow Phosphorous (YP) paste poisoning: A single tertiary centre experience. J Clin Exp Hepatol. 2022;12:S21.
[35] Angraje S, Sekar M, Mishra B, Matcha J. Outcome of plasma exchange in acute liver failure due to yellow phosphorus poisoning: A single-center experience. Indian J Crit Care Med. 2021;25(9):1020.
[36] Mathew J, Gnanaraj J, Basavarajegowda A, Venkateswaran R. Plasmapheresis in lethal yellow phosphorus poisoning: A scope for recovery. BMJ Case Rep. 2021;14(4):e239676.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Emergency Medicine, St. John's Medical College Hospital, Sarjapur Road, Koramangala, Bengaluru, Karnataka, India.
2. Assistant Professor, Department of Emergency Medicine, St. John's Medical College Hospital, Sarjapur Road, Koramangala, Bengaluru, Karnataka, India.
3. Professor, Department of Emergency Medicine, St. John's Medical College Hospital, Sarjapur Road, Koramangala, Bengaluru, Karnataka, India.
4. Professor and Head, Department of Emergency Medicine, St. John's Medical College Hospital, Sarjapur Road, Koramangala, Bengaluru, Karnataka, India.
5. Junior Resident, Department of Emergency Medicine, St. John's Medical College Hospital, Sarjapur Road, Koramangala, Bengaluru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Brian William Dmello,
Junior Resident, Department of Emergency Medicine, St. John's Medical College Hospital, Sarjapur Road, Koramangala, Bengaluru-560034, Karnataka, India.
E-mail: brian03011992@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 20, 2023
- Manual Googling: Nov 27, 2023
- iThenticate Software: Nov 30, 2023 (7%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 19, 2023**
Date of Peer Review: **Jun 17, 2023**
Date of Acceptance: **Dec 02, 2023**
Date of Publishing: **May 01, 2024**