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Original Research Article

Predictable factors for intervention with heparin free plasmapheresis in impending liver cell failure due to consumption of phosphorus rodenticide

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ABSTRACT

Background: Yellow phosphorus containing rodenticide poisoning are common in Adult critical care. They cause coagulopathy and liver cell failure in humans. Till date, only liver transplants had been advocated as the final treatment of fulminant liver failure occurring as a complication of rodenticide poisoning. In this study, an innovative Treatment approach was given to liver cell failure cases who had consumed yellow phosphorus paste.
Methods: Retrospective analysis of case records of liver cell failure cases due to the consumption of phosphorus containing Rodenticide poisonings, were analysed for a period of 1 year from January 2018 to January 2019 in a public hospital. Medical case records were obtained from records department and Postmortem registers. Symptoms, signs, investigations, treatments, complications, and outcomes were tabulated.
Results: Total 11 cases were studied. 8 cases of liver cell failure and coagulopathy in whom therapeutic heparin free plasmapheresis was given, recovered completely from liver cell failure. A significant drop in Haemoglobin, platelet count, PT INR Ratio and rise in serum alkaline phosphatase, were the predictable factors used for the intervention of therapy with 5 cycles of heparin free plasmapheresis to eliminate toxic effects of phosphorus on liver cells and in the blood. A comparative analysis of untreated cases (n=3) vs treated with plasmapheresis (n=8), showed a significant statistical difference ($P < 0.005$) in outcomes with a degree of freedom=2.
Conclusions: Plasmapheresis can be a therapeutic treatment for liver cell failure caused due to the consumption of yellow phosphorus. Predictable factors for impending liver cell failure in whom plasmapheresis will be of benefit are dependent upon prothrombin time, INR ratio, Liver enzymes and time interval between consumption and onset of liver cell failure.

Keywords: Liver cell failure, Plasmapheresis, Rodenticide, Yellow phosphorus

INTRODUCTION

Rodenticides are commonly used suicidal poisons for suicidal purposes mainly by the young population. Warfarin, Coumarin, phosphorus, and Zinc phosphide have been used traditionally as rodenticides. Warfarin and coumarin derivatives cause bleeding disorders in humans while Zinc phosphide releases toxic phosgene gas inside the stomach and caused toxic effects. Phosphorus is abundantly present in the human body as phosphate and ionic intracellular form., However, the rodenticide phosphorus causes fulminant liver, renal cell failure and bleeding as a short-term complication and phossy jaw as a long-term complication in humans.

Unfortunately, it's easy availability and accessibility in household use, also has made it a cheap suicidal drug.[1] The lethal dose of oral phosphorus can be as minimal as 0.2 mg/kg. 18 cases of oral consumption of Phosphorus with suicidal intent were reported by Siddhartha et al.[4]

Sudden deaths have been reported if taken along with alcohol. 16 signs are seen in first 6-8 hours of consumption, if untreated, death occurs due to coagulopathy, internal bleeding and fulminant Liver cell failure in 24-72 hrs. 16 P-63-70.

Signs of yellow phosphorus paste consumption differ from acute toxicity due to exposure to elemental Yellow phosphorus and should not be confused with rodenticide phosphorus poisoning.[2] 27% Mortality has been reported in paste form consumption too making it a lethal systemic poison. Only liver cell failure causing rodenticide is considered in this study.

METHODS

The retrospective analysis of cases, who have consumed 3% yellow phosphorus or zinc phosphide rodenticide with suicidal intent, were selected for study over 1 year. (n=11) medical case records of symptoms, signs, treatments, complications, and outcomes were tabulated. Only registered cases with complete medical records of history and investigations cases who left against medical advice were not included. There were no Minors, children, pre-existing hepatic disorders or coagulation profile deranged patients. pregnant mothers were excluded. Findings were tabulated in percentage and observational forms. Table 1 and 2 Serial analysis of Prothrombin time, PT ratio and INR were tabulated for observations. Standard liver function tests coupled with criteria for liver cell failure and coagulopathy were recoded for diagnosing liver cell failure and coagulopathy.

Table 1: Serial demographic factors, liver function tests, PT & INR ratio, serum Alkaline phosphatase on day 1 and 5, Serum ammonia levels.

Gender	Age	Time interval	Bili D/I	SGOT	SGPT	PT/C	PT/INR	NH^{3+}	$ALKPO_4$	HB/	Platelets $x10^9$
M	25	6	1.6/0.7	33	28	38/14	2.71	72	44/56	11.3	149
M	36	8	2.6/1.0	113	78	15/13.5	1.11	54	32/54	9.8	172
M	32	12	1.8/0.5	45	52	24/14	1.83	99	67/78	16.1	160
F	30	30	7.16/2.43	381	376	23/14	2.93	398	46/123	12.1	99
F	23	2	1.0/0.5	35	28	14/14	1.1	89	103/111	13.3	173
M	25	8	2.0/0.8	46	68	18/13.5	1.33	56	111/126	10.1	145
M	30	3	3.1/1.8	23	34	23/14	1.64	44	33/60	17	223
M	25	12	2.0/0.8	112	96	56/14	4.29	276	65/84	16	190
F	19	36	1.6/0.9	114	34.4	39/14	2.93	138	63/68	12	226
F	19	8	2/0.7	17.6	10	19/14	1.36	60	109/145	10.3	138
F	23	48	1.6/0.5	51	32	18/13.5	1.33	98	29/56	12.3	60
	25.18	12.3 hrs		81.45	88.23	26.09	1.24	128.6			

Table 2: Enumerating factors for patents in whom plasmapheresis showed successful outcomes.

Predictable factors for better outcomes of plasmapheresis
Plasmapheresis when best given when Prothrombin Time was between 17-24 seconds with control of Standard 14. INR between 1.24-2.93, had successful outcomes and no relapse or complications within 3 months of follow up.
Liver cellular enzymes in the range of 23-381 units SGPT and SGOT 10-376, responded best to plasmapheresis.
Advanced age beyond 60 years was associated with complications.
The liver function tests restored to normal within 7-21 days after therapy with plasmapheresis.
Plasmapheresis given for Only the cases in whom phosphorus-containing rodenticide was confirmed on history and blood investigations showed deranged PT, INR and liver cell dysfunction was evident. Not as a blanket therapy for general rodenticide poisoning.

Arterial blood gasses, CBC, Platelets X-ray chests, pre- and post-plasmapheresis. blood grouping and cross matching, prothrombin time with control, INR ratios, serum electrolytes, serum phosphorus levels, arterial blood gases, serum creatinine, BUN, urine routine, stool for occult blood, ecg, coombs tests. Ultrasonography findings were not included for analysis. Interesting photographs kept as departmental records showing serial

changes in plasma colour after filtration, recorded (Figure 1, 2 and 3).

Figure 1: Haemolytic plasma in phosphorus consumption.

Figure 2: Liver cell failure plasmas high coloured.

Figure 3: Post plasmapheresis colour of plasma.

Standard Protocol for plasmapheresis given with informed consent by experts for 2 hours. Certified and checked 4-6 packs of fresh frozen Human Plasma at room temperature, Albumin 20%, Calcium gluconate 10ML, Potassium chloride 40 Meq. Serial clearance of plasma seen. Day 1=Haemolysed plasma, day 2 clearing from icteric to straw coloured plasma. 1-1.5 lit plasma replaced. Filter used was standard plasmapheresis Flux filter for all 5 cycles. Filtrate plasma was discarded and replaced with fresh plasma. Post-procedure patient was monitored for all possible complications. The decision to evaluate for 5 cycles was considered with the biophysical capacity of plasma filters used which needed to be changed after 5 cycles. All patients responded in 5 cycles. Each cycle was planned daily. A comparative analysis of untreated cases (n=3) vs treated with plasmapheresis (n=7), showed a significant statistical difference in outcomes, IV vitamin k (Phytomenedion), 10 gm/day L-Ornithine-L aspartate (LOLA) and 5 cycles of plasmapheresis were given as treatment. with a degree of freedom=2. Postmortem gross reports and histopathological reports were studied in deaths that occurred in the untreated group (n=3).

RESULTS

All patients commonly presented with vomiting, generalized abdominal pain and constipation. Icterus developed after an average 2.6 days after admission. Mental irritation was found in 9.9%. 55% were adult males and 45% females. The mean age of the patients was 25.1 years. The average stay in patients given plasmapheresis was 7 days without complications. INR was the guide to predict the initiation of therapy. Mean Serum Bilirubin levels of 2.22 mg/dl were found. Indirect more than direct in 27.27%. Icterus presents 2.6 days after admission. The rise in bilirubin was observed after an average of 2.6 days after admission, Direct bilirubin was higher in 80%. SGOT was observed higher than SGPT in and Alkaline phosphatase was normal in 100% cases on day 1. Ammonia was observed to be in the range of 44-398 mg/dl. All patients had been subjected for psychiatric counselling and reasons for suicidal tendencies were tabulated. Alcoholism, poverty and domestic verbal violence with loved ones, were some reasons cited. Table 2 shows details of investigations, PT INR ratios, HB and Platelet counts Bilirubin levels with direct/indirect levels. SGOT and SGPT levels. Hepatitis, leptospirosis, existing liver disease was ruled out as a differential diagnosis. Reasons for suicidal consumptions were noted. Time intervals between consumption and onset of toxicity. Alkaline phosphatase was recorded on the day showed a rise in levels on day 4. Recordings were done on excel sheets. Since the sample size was small, the 95% confidence interval was applied to the data.

Difference between icteric plasma pre-and post-plasmapheresis was clearly visible. Clinical signs of icterus were not evident in-spite of plasma being so high coloured indicating the clinical signs in hepatic failure

appear much later after the failure has set in. Other Causes of bright pink plasma-like Carbon monoxide poisoning, Haemolysis, Cyanide poisoning, were also ruled out after seeing the colour of plasma filtrate. Since patients responded well in first five days to plasmapheresis, an autoimmune response after consumption of Zinc phosphide or Phosphorus could be responsible for triggering the cellular damage, rather than the toxic effects of phosphorus or phosphine gas.

In this study, all patients had given a history of ingestion but the physician must be aware about patients presenting with similar presentation to ask a history of accidental consumption regularly. The postmortem reports show acute fatty change and tubular necrosis in kidney and liver tissue with no detection in chemical analysis on viscera. This kind of cellular changes with acute lymphocytic infiltrates can be seen in radioactive substance/radiation injury post-cancer therapy. Since the patients had consumed 3% P containing paste, the rest 97% containing contents must be made mandatory to understand what exactly has led to the rise in a fatality and quick absorption of paste to cause deaths. No rebound platelet or haemoglobin disturbances were found after completion of plasmapheresis. Plasmapheresis worked only with INR rations between 1.17-2.93 above which deaths were shown even with plasmapheresis. Advanced age was associated with the complication of altered mental status post plasmapheresis. Once complications of coagulopathy had set in, the terminal events were mainly cardiac or acute renal failure.

Correlating with postmortem findings, the possibility of capillary petechial bleeding in pericardium and endocardium. The liver and kidneys were the main target organs affected as shown on the histopathology of postmortem tissues of deceased patients. Postmortems of deceased patients showed acute but diffused fatty changes in liver cells and early necrosis and inflammation in renal tubules on histopathology (Figure 4 and 5).

Gross viscera could not detect yellow Phosphorus or zinc phosphide on chemical analysis. Hence only primary gastric lavage sampling during lavage obtained remains a reliable source for chemical analysis of rodenticide and should be preserved well till the discharge of the patient. Post-mortem of 3 patients in whom plasmapheresis could not be given due to late arrival, showed similar changes on histopathology.

The cerebellum showed congestion. Liver showed acute fatty changes with portal triaditis. Lungs showed septal congestion with infiltration of macrophages in interstitial. The focal fatty change was also seen in the Lungs. The Heart showed interstitial congestion. Kidney showed peritubular and periglomerular inflammation, interstitial congestion and cloudy changes. Predominant lymphocytic infiltration was seen in the stomach mucosa, again indicating a T cell-mediated and immune response mechanism.

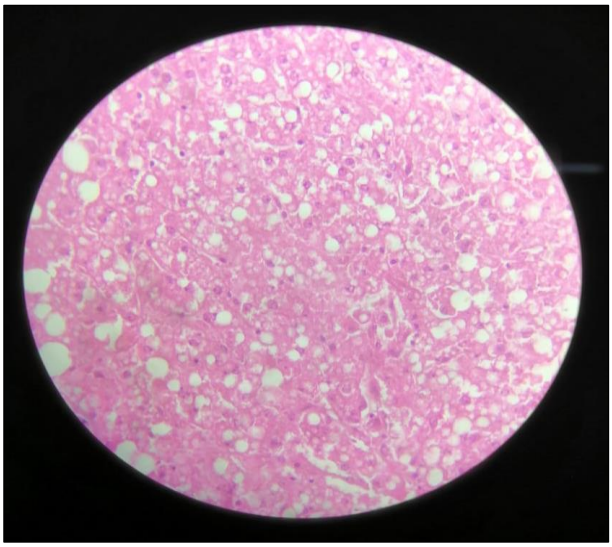

Figure 4: Liver cells in rodenticide toxicity diffuse fatty changes and lymphocyte infiltration around portal triad.

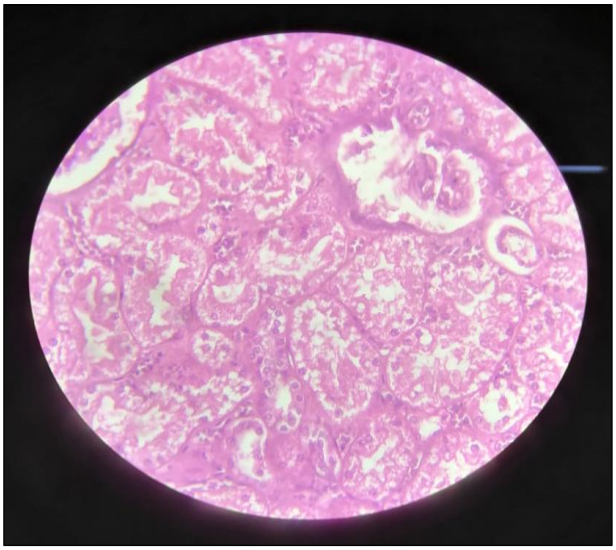

Figure 5: Renal Peri tubular lymphocyte infiltration H and E stain.

DISCUSSION

Rodenticides are toxic to human systems. The class 2 rodenticides containing yellow phosphorus paste and zinc phosphide form phosphoric acid and phosgene gas respectively in humans. This causes RBC membrane damage and hepatocellular Damage in rodents as well as humans. We propose plasmapheresis as a life-saving therapeutic treatment for liver cell failure and coagulopathy caused due to complications of rodenticide poisoning. The predictable factors for successful outcomes based on our study were as mentioned in Table 2. Early initiation of plasmapheresis based on investigations done on day 0, 3, 5, 7 and 14 after confirmation of consumption of only yellow phosphorus-

containing rodenticide since plasmapheresis does not have a role in other toxic rodenticides containing coumarin or warfarin which are also colloquially called rat poisons. The successful innovative treatment of 5 cycles of Plasmapheresis, IV 3 gmsL Ornithine-Aspartate/day x 5 days and IM Vitamin K X 5 days given monitoring the INR ratio, was shown of benefit in this study (P=0.0173, P<0.05). Null hypothesis of all cases being well without Plasmapheresis was rejected. plasmapheresis benefitted the survival of 6 patients who were given plasmapheresis. Liver toxicity developed after 3rd of hospitalization but coagulopathy developed in 6-24 hrs after consumption. In this study, the coagulation profile was seen affected much earlier than in liver cell failure with different aetiology. The contents did not contain class 1 group of anticoagulants to cause direct prolonged prothrombin time. A possibility of a source of the phosphorus compound being radioactive, could not be ruled out. Since radioactive phosphorus has been used in the treatment of polycythaemia and thrombasthenia. The rapid decline in HB and platelets could not be explained only by liver cell failure without significant enzyme affection or bilirubin rise. Hence physicians must capriciously suspect rodenticide consumption or accidental exposure when patients present with rapidly progressing fulminant hepatic failure with early coagulopathy and no apparent cause is found. Innovative Treatments for rodenticide poisonings have been advocated in the form of IV N-acetylcysteine, Vitamin K, fresh frozen plasma, L ornithine-L-aspartate, Exchange transfusions, and liver transplants. In this study, the authors have presented observations of clinical signs, symptoms, investigations, management and predictable factors for interventional plasmapheresis in the management of rodenticide poisoning. The drug rationale of using Vitamin K (Phytomenadione), LOLA- L ornithine-L aspartate and plasmapheresis has been discussed further. Vitamin K is a pro-coagulant administered in coagulopathy occurring due to class 1 rodenticides, namely Warfarin and Coumarin. In YP containing compounds, the role of vitamin K comes when liver failure starts and coagulopathy occurs due to depletion of Vit K and its dependent clotting factors-Prothrombin. Administration of prophylactic Vitamin K only in the Phytomenedione form is helpful in coagulopathy. Synthetic analogues of menadione are not advocated. IM vitamin K is given as IV forms can have severe anaphylaxis reactions. The Authors hence find the use of Vitamin K justified given in the dose of 10-30 mg IM daily till PT/INR normalized. since all contents of the compound were not documented. Warfarin use has been traditionally used as a rodenticide. 2) l-ornithine-l Aspartate being stable salts of 2 amino acids, their role as ammonia lowering agents has been advocated in Cochrane trials as supplementary hepatoprotective amino acids.[14] In the study, only one case showed a rise in serum ammonia so the administration of a standard dose of LOLA in lower doses could be of hepatoprotective significance in the prevention of CNS reactions occurring due to increased serum ammonia. A meta-analysis indicated an association between LOLA therapy and improvement of grade I or II overt hepatic encephalopathies showed Lactulose and LOLA to be same ineffectiveness to control levels of ammonia. In cases of YP oral consumption since patients were kept nil by mouth for 24 hours, IV LOLA would be a justified substitute for Lactulose given orally. 15 None of the patients showed CNS manifestations even when the serum ammonia was raised in 2 cases significantly. Case 4,8,9. NH_3 was significantly in deceased patients than expected in liver cell failure. Effective therapy with LOLA in liver cell failure has shown no significant advantage over lactulose 15 but when the patients are kept nil by mouth or in poisoning cases with involvement of liver where water or drugs are not advocated per orally, LOLA becomes an effective drug to be used to lower levels of serum ammonia to avoid subacute hepatic encephalopathy. The rationale of plasmapheresis in rodenticide poisoning. Exchange transfusions have been tried in 13 cases of Ratol or yellow phosphorus poisoning successfully.[16] sanchan et al, None of the patients' required ventilators, liver transplants, prolonged hospital stays for recovery. A ban the paste form has been recommended by S khaja et all. In our study, patients who were given 5 cycles of plasmapheresis along with routine supportive treatment, showed dramatic recovery to Normal state without liver cell failure or respiratory failure seen in both YP Paste and zinc phosphide poisoning cases.

Limitations of study the small sample size for quantitative data but effective for qualitative data and factorial analysis. Required experts and technological support for treatments. Expensive therapy. Availability of plasma, platelets, albumin, and blood is the precondition to therapy.

Life-saving measures in poisonings. The critical predictable levels for impending coagulopathy and liver cell failure may be further evaluated for all liver cell failures awaiting transplants. The study proposes the possibility of an immune response, making it open for molecular and enzyme related research.

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