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Role of N-Acetyl Cysteine in Rodenticide poisoning

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Abstract

Background: N-acetyl cysteine (NAC) has been shown to be effective in the treatment of non-acetaminophen-induced acute liver failure. NAC has anti-inflammatory, inotropic, and vasodilatory properties. It has also shown to improve microcirculation and oxygen delivery in cases of liver failure. Rodenticide poisoning affects many vital organs in the body including liver thereby causing acute liver failure with a high mortality rate. Our study aimed to examine the clinical parameters of rodenticide poisoning patients and compare the severity of liver failure and the outcome after NAC treatment.

Methods: From 2019 to 2021, a prospective study was conducted at Trichy SRM Hospital and Research Centre, Tamilnadu on patients who had a history of ingesting rat killer paste(RKP), a potent rodenticide. Patients who presented with RKP poisoning were administered NAC irrespective of the duration of poison intake, as an initial loading dose of 150 mg/kg infused in 200ml of 5% dextrose over 1 hour, followed by 50 mg/kg in 500ml of 5% dextrose over the next 4 hours, and then 100 mg/kg in 1000ml of 5% dextrose over the next 16 hours. The presence of liver injury or bleeding diathesis was assessed clinically and biochemically. Statistical analysis was done using chi-square test to compare the groups.

Results: Among the 57 patients who were treated with NAC, 16 expired and 41 recovered. Development of Jaundice($p=0.02$), hepatitis($p=0.028$) and hypotension had highly significant ($p < 0.01$) correlation with the delay in time of presentation to the ICU which marks the time of NAC administration. Mortality was observed in these set of patients who had increased serum transaminases, bilirubin and prolonged PT & aPTT.

Conclusion: In this study, patients who received NAC earlier had a higher percentage of complete recovery. Earlier administration use of NAC has prevented the emergence of negative outcomes.

Key words: Rodenticide poisoning, phosphorus-based compounds, Acute Liver Failure, N acetyl cysteine (NAC), rodenticide outcome

Introduction

India is an agrarian economy, with agricultural and allied sector activities employing approximately 54.6 percent of the total workforce (Census 2011). Various rodenticide formulations are easily accessible and available based on their needs. The term "rodenticides" refers to agents used to eliminate small rodents, which include a wide range of compounds that differ depending on geographical region as well as knowledge and availability of compounds in various populations. Common compounds include powerful anticoagulants and phosphorus-based compounds, as well as rarer compounds that cause hypercalcemia. The most common rodenticide in northern India is aluminium phosphide and yellow phosphorus in southern India [1].

Rodenticide poisoning is caused by 54.35% metal phosphide, 30.8% aluminium phosphide, 23.1% zinc phosphide, and 14.2% yellow phosphorus. Their toxicity manifests on various vital organs of the body, and mortality was significantly higher in these cases [2, 3, 4]. Many of them are hepatotoxic and can cause Acute Liver Failure (ALF) [5], and in the absence of a specific antidote, mortality is high when consumed [6]. N-acetyl cysteine (NAC) is used in the treatment of ALF caused by toxic doses of acetaminophen (paracetamol) [7]. It has been shown in various studies that NAC can also be used to treat non-Acetaminophen-induced ALF [8]. Because of its antioxidant property, ability to modify DNA, and multiple molecular mechanisms of action, it has a therapeutic effect in detoxification, reducing endothelial dysfunction, fibrosis, inflammation, and transplant prolongation.

This study aims to assess the effect of NAC on liver injury markers namely coagulation parameter, serum transaminases and serum bilirubin and to corelate the time interval from the consumption of rodenticide poisoning to the start of NAC with the outcome, either death or recovery.

Materials and Methods

An open label prospective interventional clinical trial was conducted at Department of Medicine, Trichy SRM Medical College Hospital and Research Center, Tamil Nadu between 2019 to 2021 after obtaining permission from the Institutional Ethics Committee for Human Research (CMCH&RC/IEC-22/11042017). Patients of both genders over the age of 12 years who have consumed rat killer paste(RKP), irrespective of the intention of ingestion were included in the study. Patients who consumed RKP in combination with other poisonous compounds (ex: Organo-Phosphorus compounds) and those with history of liver disease were excluded. Informed consent was obtained from the legally acceptable representatives (LAR) who are the patients relative who were present during their admission.

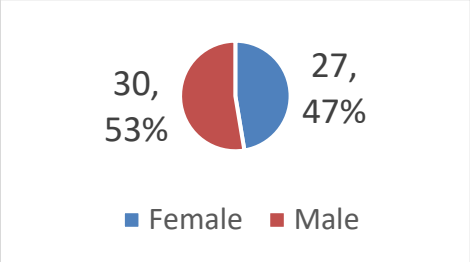
Patients were started on NAC Infusion with an initial loading dose of 150 mg/kg infused in 200 ml of 5% dextrose over 1 hour, followed by 50 mg/kg in 500 ml of 5% dextrose over the next 4 hours, and then 100 mg/kg in 1000 ml of 5 % dextrose over the next 16 hours. They were monitored for the presence or worsening of jaundice, abdominal pain, vomiting, bleeding tendencies, hepatitis, coagulopathy, hypotension both clinically and biochemically. The time interval between consuming rodenticide and beginning NAC infusion was recorded and correlated with the occurrence of complications and outcome.

Statistical Analysis

Descriptive Statistics such as frequency and percentage were used for categorical variables for expressing gender, clinical features and outcomes. Numerical variables such as age and durations are expressed in mean and standard deviation. Inferential statistics namely chi-square test was used for comparison of outcome with clinical features (Category vs Category). For comparison of duration between the consumption of the poison and administration of NAC with the outcome and clinical features, independent t-test was used.

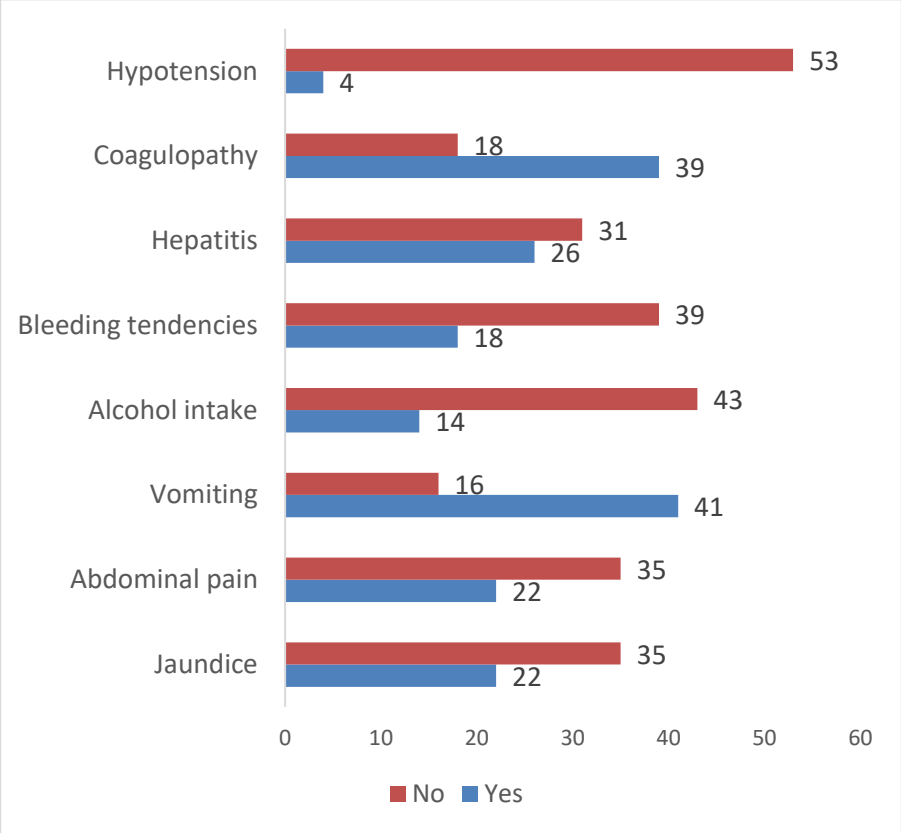
Results

The study was done in 57 subjects who consumed RKP poisoning. The average age of the patients was 27 years and ranged between 15 to 55 years. Gender distribution was balanced between the sexes with 27(47.4%) were being females and 30(52.6%) were males (Table/Fig 1).



Table/Fig 1: Gender distribution

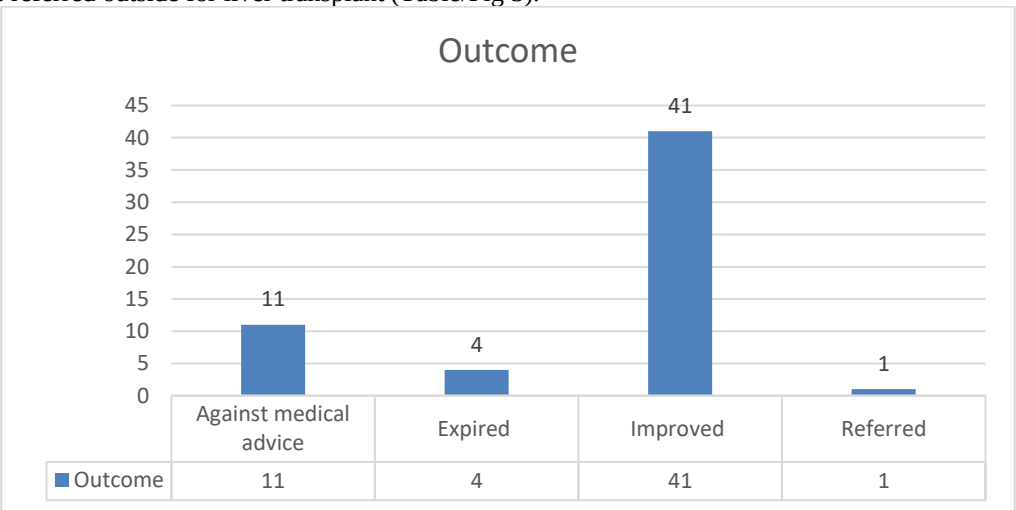
The mean duration of onset of clinical features was 49.88 hours with a median of 33 hours. Majority of the study population, had vomiting followed coagulopathy, hepatitis and abdominal pain (Fig/Table 2).



Table/Fig 2: Clinical features

Outcome status of the patients

Among the treated patients, recovery was observed in 41(71.9%) patients, 4(7%) patients expired in spite of NAC administration and 11(19.3%) patients left the hospital against medical advice, after getting recovered. One patient was referred outside for liver transplant (Table/Fig 3).



Table/Fig 3: Outcome status of the patients

Association between the outcome and the clinical features

The outcomes of the cases who proceeded against medical advice, died and referred to other hospitals were clubbed as not discharged alive and healthy. The proportion of the cases who were not discharged alive and healthy were 16 (28.1%) and that of the case who were discharged alive and healthy were 41 (71.9%). Recovery of the

patients, that is being discharged alive and healthy, had a significant negative association with the presence of Jaundice (p=0.021), hepatitis (p=0.028) and hypotension (p=0.03) and not associated with rest of the clinical parameters like vomiting, bleeding tendency, coagulopathy, abdominal pain and gender difference (Table/Fig 4).

Table/Fig 4: Association between the outcome and the clinical features

		Discharged alive and Healthy			Chi-Square test used
		No	Yes	Total	P-value
Gender	Female	9 (33.3%)	18 (66.7%)	27 (100.0%)	0.402 (Not significant)
	Male	7 (23.3%)	23 (76.7%)	30 (100.0%)	
Jaundice	Yes	10 (45.5%)	12 (54.5%)	22 (100.0%)	**0.021 (significant)**
	No	6 (17.1%)	29 (82.9%)	35 (100.0%)	
Abdominal Pain	Yes	5 (22.7%)	17 (77.3%)	22 (100.0%)	0.477 (Not significant)
	No	11 (31.4%)	24 (68.6%)	35 (100.0%)	
Vomiting	Yes	12 (29.3%)	29 (70.7%)	41 (100.0%)	0.747 (Not significant)
	No	4 (25.0%)	12 (75.0%)	16 (100.0%)	
Bleeding tendency	Yes	4 (22.2%)	14 (77.8%)	18 (100.0%)	0.504 (Not significant)
	No	12 (30.8%)	27 (69.2%)	39 (100.0%)	
Hepatitis	Yes	11 (42.3%)	15 (57.7%)	26 (100.0%)	**0.028 (significant)**
	No	5 (16.1%)	26 (83.9%)	31 (100.0%)	
Coagulopathy	Yes	11 (28.2%)	28 (71.8%)	39 (100.0%)	0.973 (Not significant)
	No	5 (27.8%)	13 (72.2%)	18 (100.0%)	
Hypotension	Yes	3 (75%)	1 (25%)	4 (100.0%)	**0.03 (significant)**
	No	13 (24.5%)	40 (75.5%)	53 (100.0%)	
Total		16 (28.1%)	41 (71.9%)	57 (100.0%)	

Association between the clinical features and duration (between poison consumption and NAC administration) in hours

Clinical features such as jaundice, abdominal pain, vomiting, bleeding tendencies, hepatitis, coagulopathy and hypotension were associated with time duration between the consumption of the poison and administration of NAC (independent t test was used). In the study population, among the patients who received the NAC earlier, there

was a higher proportion of them, getting discharged alive and healthy. But this difference was not statistically significant. The mean duration between the consumption of the poison and administration of NAC was significantly higher among the study population presented with jaundice, hepatitis and coagulopathy. And these factors were also significantly associated with the adverse outcomes (Table/Fig 5).

Table/Fig 5: Association between clinical features and duration (between poison consumption and NAC administration) in hours

	Duration in hours	N	Mean	Std. Deviation	Std. Error Mean	p-value (t-test used)
Jaundice	Yes	22	80.0000	45.92229	9.79067	**0.001 (significant)**
	No	35	30.9429	31.83592	5.38125	
Abdominal Pain	Yes	22	52.7273	42.20154	8.99740	0.706 (Not significant)
	No	35	48.0857	46.51525	7.86251	
Vomiting	Yes	41	50.7561	45.11141	7.04522	0.814 (Not significant)
	No	16	47.6250	44.52846	11.13211	
Bleeding Tendencies	Yes	18	59.3333	37.82156	8.91463	0.280 (Not significant)
	No	39	45.5128	47.17988	7.55483	
Hepatitis	Yes	26	72.6154	48.63092	9.53731	**0.001 (significant)**
	No	31	30.8065	30.22959	5.42939	
Coagulopathy	Yes	39	66.6154	43.37208	6.94509	**0.001 (significant)**
	No	18	13.6111	17.44281	4.11131	
Hypotension	Yes	4	36.2500	33.72808	16.86404	0.531 (Not significant)
	No	53	50.9057	45.37123	6.23222	

Association between outcome and duration (between poison consumption and NAC administration) in hours
The final recovery outcome, getting discharged alive and healthy doesn't have any significance association with the duration of the NAC administration (Table/Fig 6).

Table/Fig 6: Association between outcome and duration (between poison consumption and NAC administration) in hours

	Duration in hours	N	Mean	Std. Deviation	Std. Error Mean	p-value (t-test used)
Recovered (Discharged Alive and Healthy)	Yes	41	44.4146	38.43955	6.00325	0.140 (Not significant)
	No	16	63.8750	56.44688	14.11172	

Discussion

Rodenticides are hepatotoxic and cardiotoxic, causing acute fulminant hepatic failure (ALF) and supraventricular, ventricular, and cardiomyopathy. Aluminum or zinc phosphide poisoning frequently results in hepatic necrosis, renal failure, metabolic acidosis, and refractory hypotension [9,10]. Patients admitted to our study with rodenticide poisoning developed jaundice, abdominal pain, vomiting, a tendency to bleed, hepatitis, coagulopathy, and hypotension. Many cases (68.4% (39) had coagulopathy, 45.6% (26) had hepatitis, and only three (75%) had hypotension. With jaundice, hepatitis, and hypotension, the relationship between outcome and clinical features was statistically significant. During the study period, the overall mortality rate of patients admitted with rodenticide consumption in our centre was 7%. Out of these 41 (71.9%), 41 (71.9%) recovered, 4 (7% died), 11 (19.3%) were discharged against medical advice, and 1 (1.8%) was referred to a higher level of care. The most common symptoms of rodenticide poisoning were abdominal pain (52.53%), jaundice (22.21%), bleeding manifestations (15.15%), encephalopathy (10.10%), shock (10.10%), AKI (7.08%), and multi-organ dysfunction (17.17%) [11]. In another study, 87% of patients had some form of hepatic dysfunction, and 27% died from fulminant hepatic failure [12]. All patients had transaminitis and coagulopathy at the time of presentation, 16 (84.2%) had jaundice, and 12 (63.2%) had HE. [10]. Acute liver failure caused by rodenticide poisoning is frequently fatal, with mortality rates ranging from 40 to 80% [11]. The mortality rate from zinc phosphide varies between 37% and 100%[13]. The mortality rate was 9.1% (n = 9), with fulminant hepatic failure accounting for 77.78% (n = 7). The average time to death after exposure was 4.22 days (range 2-8 days) [14].

A recent study in South India found that yellow phosphorus was the most commonly used rodenticide in suicide attempts in the region, with a 30% mortality rate despite maximal supportive therapy.[4] Yellow phosphorus toxicity is caused by the production of phosphoric acid, which causes an exothermic reaction and direct tissue damage due to the production of free radicals. NAC, a hepatoprotectant and antioxidant, acts as a glutathione precursor by donating sulfhydryl groups [11]. It also helps with mitochondrial energy metabolism [12]. It functions as an oxygen free radical scavenger and replenishes glutathione stores. When administered early, it has been found to have a good prognosis in patients with yellow phosphorus poisoning [13,14]. The patient's liver enzymes were extremely elevated.

There are no guidelines for the use of NAC in the treatment of non-acetaminophen-induced organ damage/injury caused by rodenticide consumption. A placebo-controlled trial of NAC in patients with non-acetaminophen-induced ALF found a significant survival benefit in patients treated with NAC, particularly those in the early stages of encephalopathy. However, studies in children with ALF treated with NAC have yielded mixed results, with some studies demonstrating a clear benefit. However, in other studies, NAC treatment had no therapeutic benefit

In our study population, patients who had previously received NAC had a higher proportion of being discharged alive and healthy. This difference, however, was not statistically significant. The mean time between RKP consumption and NAC administration was significantly longer in the study population with Jaundice, Hepatitis, and Coagulopathy. These factors were also significantly related to the negative outcomes. As a result, administering the NAC early will prevent the emergence of these negative outcomes.

The proportion of cases that were not discharged alive and healthy was 16 (28.1%), while the proportion of cases that were discharged alive and well was 41 (71.9%). Gender and the presence of clinical features such as abdominal pain, vomiting, alcohol consumption, bleeding tendency, and coagulopathy had no effect on outcome. With a p-value of 0.05, the proportion of patients not being discharged alive and healthy outcomes was significantly higher in the presence of clinical features such as jaundice, hepatitis, and hypotension.

Conclusion

In this study, patients who received NAC had a higher proportion of being discharged alive and healthy. Among the various outcome predictors, presence of jaundice, hepatitis & hypotension were significantly associated with the mortality. Also, the presence of jaundice, hepatitis and coagulopathy signifies delayed presentation. From this we conclude that delayed administration of NAC beyond 30 hours of consuming rat killer paste when presented with jaundice and hepatitis signifies poor prognosis. Also, the presentation of coagulopathy increases beyond 13 hours of ingestion of rodenticide and is also associated with poor prognosis The NAC's administration has prevented the emergence of negative outcomes but time association of NAC administration with the overall outcome doesn't show significant association. The use of NAC for the treatment of rodenticide poisoning has proven to be effective in saving patients' lives.

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