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Role of N-Acetylcysteine in management of Rodenticide Poisoning: A Retrospective Analysis

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STUDY ON ROLE OF N- ACETYL CYSTEINE IN MANAGEMENT OF RODENTICIDE POISONING: A RETROSPECTIVE ANALYSIS

A Project Report submitted to

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MANIPAL COLLEGE OF PHARMACEUTICAL SCIENCES

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(A constituent unit of MAHE, Manipal)

CERTIFICATE

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I recommend this piece of work for acceptance for the partial fulfillment of the completion of the 5th year Pharm.D program of the Manipal Academy of Higher Education, Manipal for the Academic year 2017-2018.

Place: **Manipal**

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DECLARATION

We hereby declare that the project entitled **" Role of N-Acetylcysteine in management of Rodenticide Poisoning: A Retrospective Analysis"** was carried out under the guidance of **Dr. Girish Thunga**, M.Pharm, PhD, Assistant Professor, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal. The extent and source of information derived from the existing literature have been indicated throughout the project work at appropriate places. The work is original and has not been submitted in part or full for any diploma or degree purpose for this or any other university.

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Dedicated to

our

beloved

Family members.

ABSTRACT

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INTRODUCTION:

Rodenticide consumption is a very common form of poisoning, either accidental or intentional, and is mainly reported in the rural parts of India. Rodenticides generally comprise of Superwarfarins, Thallium, Barium Carbonate, Aluminium phosphide (AIP) and Zinc phosphide. They are quite inexpensive and highly toxic chemicals. Annually, around 50,000 cases are reported [1]. The agents present in rodenticides are hepatotoxic in nature and the outcome is often fatal. Therefore, it has always been a concern in major public health, especially in Asian countries. Absence of a definite antidote often results in high mortality rate among the patients. Recent studies suggest the positive role of N-Acetyl Cysteine (NAC) treatment in Rodenticide poisoning.

OBJECTIVES:

The present study was planned with the objective to understand the general treatment pattern and the effectiveness of N-Acetyl Cysteine in Rodenticide Poisoning.

METHODOLOGY:

A retrospective study was performed at Kasturba Hospital (a tertiary care hospital) on Rodenticide poisoning patients admitted during the period 2012- 2017. Details of patients including demographics, severity of poisoning, biochemical parameters, general treatment pattern, dose, duration and route of N-Acetyl Cysteine (NAC) treatment given along with the outcome were collected in the case report form. The results were analyzed using SPSS 20.0.

RESULTS:

A total of 229 patients were enrolled in the study with the mean age being 30.04 ± 15.67 years (Mean ± SD). There was no significant variation seen in gender-wise distribution among the study population. The mean hospitalization period was found to be 7.08 ± 5.48 days. Risk factors associated with mortality were analyzed. Yellow Phosphorus poisoning and Time lag greater than 24 hours from the ingestion of poison to the initiation of treatment were found to be significant among patients. Psychiatric illness was present in 17.7% of the patients which precipitates as a major risk factor for the Intentional Self Harm. Among general treatment approaches used for rodenticide poisonings, Activated Charcoal had significant effect on the outcome (94.8% versus 81.05%) with $p \leq 0.035$. There was no significant association of Gastric Lavage (89.7% versus 80.7%) and Vitamin K (80.91% versus 86.73%) with outcome. Outcome analysis with NAC showed that patients who received NAC had significant improvement [84.9 % (with NAC) versus 64.7 % (without NAC)] in survival with $p \leq 0.031$. The mean oral STAT dose and Maintenance dose was 7580.95 ± 2204.29 mg and 3694.53 ± 2322.58 mg respectively. The mean dose for 21- hour IV regimen of NAC given over 1 hour, 4 hours and 16 hours was found to be 7975.65 ± 2356.63 mg, 2913.79 ± 1580.85 mg and 5445.95 ± 1867.21 mg respectively.

CONCLUSION:

The study was conducted in a tertiary care hospital to understand the general treatment pattern and to evaluate its appropriateness.

Among all the Rodenticide Poisoning cases included in the study, majority were due to Intentional Self Harm. Yellow Phosphorus poisoning and Time lag greater than 24 hours from the ingestion of poison to the initiation of treatment are found to be significant Risk factors among patients. Presence of Psychiatric Illness can also contribute the suicidal tendencies. Treatment versus Outcome Analysis showed significance with NAC and Activated charcoal. However, recovery rate was found to be better with Gastric Lavage and administration of both Gastric lavage and Activated Charcoal. Outcome analysis with respect to IV NAC has shown recovery rate to be better in those patients who were treated with 21 hour regimen.

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LIST OF ABBREVIATIONS:

1. NAC → N- Acetyl Cysteine

2. FFP→ Fresh Frozen Plasma

3. BMI→ Body Mass Index

4. ATN→ Acute Tubular Necrosis

5. ALF→ Acute Liver Failure

6. NAI-ALF → Non-Acetaminophen Induced Acute Liver Failure

7. ALD→ Alcoholic Liver Disease

8. IV→ Intravenous

9. IM→ Intramuscular

10. S/C→ Subcutaneous

11. MODS→ Multiple Organ Dysfunction Syndrome

INTRODUCTION

INTRODUCTION

Rodenticides:

Rodenticides, colloquially **Rat Poison,** are non-specific pest control chemicals for the purpose of killing rodents. Acute poisoning may occur due to direct ingestion of these compounds or through inhalation of phosphine gas which is generated due to either moisture or by the action of dilute hydrochloric acid in the stomach and is highly toxic [2].

They have high human and avian toxicity and are responsible for high mortality [3] [4].

There are two types of rodenticides – Metal Phosphides and Superwarfarins.

Metal Phosphides which include **Zinc Phosphide (Yellow Phosphorus), Aluminium Phosphide** etc. emit phosphine gas which has a strong garlic odour. It can get absorbed through skin, mucous membrane, respiratory and gastrointestinal epithelium [5]. Due to presence of adequate water content and oxygen tension, phosphorus can remain stable in the gut for a longer period of time. Hence, they can cause cardiac, hepatic, renal and multi-organ failure. Other complications include hepatitis, respiratory alkalosis, disseminated intravascular coagulation, ATN, etc. which may be rare [2] [6] [7-13].

The inhalation of gas causes diarrhoea, cold, clammy sweats, pulmonary edema, tremors, convulsions, delirium and death from respiratory and cardiac arrest [6] [13] [14].

The Second generation anticoagulants (also referred to as "**superwarfarins**") which include **Bromodialone, Brodifacoum**, etc., are considered highly toxic. They effectively block the Vitamin K Epoxide Reductase, resulting in inability to produce essential blood clotting factors- mainly Prothrombin (Factor II), Factor VII, IX and X. Excessive blood loss and prolonged Prothrombin Time within 24-72 hours may be observed in patients after exposure [15].

There is no specific antidote for Rodenticide Poisoning. General treatment pattern includes decontamination, which can be done by gastric lavage within one hour of ingestion by an experienced professional only if the patient's airway is protected [16]. Activated Charcoal in the form of slurry is administered in the dose of 50-100 g in adults; 1 g/kg in infants; 25-50 g in children (1-12 years) [16] [17].

Recently, NAC is being used as an antidote in rodenticide poisoning, mainly metal phosphides. Taking into consideration the low side effect profile, wide availability, low cost and better survival, NAC should be considered for all rodenticide poisoning cases. It is given at the dose of 150mg/kg for one hour followed by 50 mg/kg over four hours, followed by 100mg/kg over 16 hours. Oral dose of NAC is 140 mg/kg, followed by 70 mg/kg, for a total of 17 doses, 4 hours apart within 6 hours of admission [18] [19].

Supportive therapy like oxygen, cardiac and respiratory stimulants are usually given. Hemodialysis can help to remove the free radicals, while Sodium Bicarbonate can correct the metabolic acidosis [20].

Intravenous Saline should be given along with supportive therapy [6] [21].

In case of severe bleeding, FFP or whole blood transfusion may be considered [22].

In Bromodialone poisoning, Vitamin K_1 (phytomenadione) is considered to be the antidote of choice. Its dose depends on the coagulation parameters such as Prothrombin Time [5].

Early referral to a tertiary-care hospital, continuous monitoring and supportive care is of primary importance for general management [23].

NEED FOR STUDY

NEED FOR STUDY

Rodenticides are chemical substances used for killing rodents in households and for crop protection. Their easy availability and low cost contributes to most accidental (especially children) or intentional consumption in humans. They are highly toxic agents and cause hepatotoxicity which can be very fatal [24]. Hence, they have a high rate of morbidity and mortality. Complications like multiple organ dysfunction, cardiac arrhythmia, hepatic encephalopathy, fulminant hepatic failure, pancreatitis, all of which caused by Rodenticide poisoning, ultimately leads to death. Also in patients with fulminant hepatic failure, there is 100% mortality [23-25].

Systematic literature reviews provide inadequate data and rationale for the efficient use of NAC in Rodenticide Poisoning. Healthcare researchers and policy makers need to integrate the existing information effectively into systematic reviews, for a generalized approach and specific treatment for Rodenticide poisoning.

Early referral to a tertiary-care hospital, continuous monitoring and supportive care is used for general management, however, the lack of specific antidotes and guidelines to treat such toxicities is a major challenge faced by the Health Care Providers [23].

Only a few studies have shown the effectiveness of NAC in rodenticide poisoning which is a commonly used antidote for acetaminophen poisonings. Additionally, it has anti-inflammatory, inotropic and vasodilatory effects [18].

The low cost and low adverse effect profile of NAC makes it suitable to be used for treating the ALF induced by rodenticides in humans [18] [39].

Hence, this study was performed to get a wider image, for the general treatment approach in Rodenticide poisoning as well as regarding the effectiveness of NAC, and also to contribute to the healthcare sector by providing efficient scientific data for the development of appropriate treatment guidelines for the same.

OBJECTIVES

OBJECTIVES

- To understand the general treatment pattern in Rodenticide Poisoning.
- To assess the effectiveness of N-Acetyl Cysteine in Rodenticide Poisoning.

METHODOLOGY

METHODOLOGY

Study Site: Kasturba Hospital, Manipal

Study Design: Retrospective Observational Study (2012-2017)

Study Period: Six Months

Ethical Clearance: Obtained from the Institutional Ethical Committee, Kasturba Hospital,

Manipal Academy of Higher Education, Manipal **[APPENDIX-1]**

Sample Size: 229 patients of Rodenticide Poisoning (2012-2017) were included in the study.

Study Criteria:

- **Inclusion Criteria-**

  Patients with definite diagnosed rodenticide poisoning, admitted in Emergency ward of Kasturba Hospital irrespective of age and sex.

- **Exclusion Criteria-**

  i. Patients having associated Acute/ Chronic kidney injury.
  ii. Patients on prolonged Acetaminophen therapy.
  iii. Patients belonging to pregnancy category.
  iv. Patients with mixed poisoning

Sources for Data Collection: Patient Case Records

Materials Used: Case Report Form (CRF) **[APPENDIX-2]**

Operational Modality:

Identification of Data-

Rodenticide Poisoning cases (ICD Coding – T.604X) were identified from the Medical Records Department of Kasturba Hospital.

Collection of Data-

The medical records of all Rodenticide poisoning cases were reviewed and the details of the patients were entered in the case report form. Demographical details such as age, economic status, BMI, and medical history were recorded. The type and quantity of the Rodenticide consumed, duration of hospitalization, time-lag between poison consumption and initiating NAC treatment, symptoms and complications of the patients during admission, laboratory parameters and if any pre-hospitalization treatment given to the patients were recorded. General treatment approaches and the route, dose, and duration of treatment provided with NAC, adverse effects of the treatment, any extracorporeal methods used, ventilation and survival outcomes in terms of the clinical status at the time of discharge were evaluated.

Interpretation of Data:

Statistical Analysis-

- Patient data including age, gender, type of poisoning, severity of poisoning, time-lag between poison consumption and initiating NAC treatment, previous hospitalization along with treatment and outcome were analyzed using SPSS 20.0. Categorical data was represented as frequency with percentage and was analyzed by Chi-square test. Continuous data was represented as mean ± SD.
- Treatment versus outcome with respect to N- Acetyl Cysteine and other treatment modalities was analyzed using Chi square test and outcome is represented in terms of percentage of survival or death. Outcome has been correlated with various factors such as age, gender, time lag using regression and the relative risk was calculated. A probability of $p \leq 0.05$ was considered statistically significant.

Outcome Analysis-

Outcome of therapy was evaluated by the analysis of *clinical improvement* or *clinical failure*.

- ***Clinical Improvement-*** Complete resolution of all signs and symptoms of poisoning, improvement of vital signs or deterioration of all abnormalities and abnormal biochemical values.
- ***Clinical Failure-*** The patients who died or got discharged against medical advice are said to have failed the therapy.

RESULTS

RESULTS

Basic Demographic characteristics of Rodenticide Poisoning patients:

During the 2012- 2017, a total of 250 patients were admitted in the Emergency Ward of Kasturba Hospital, Manipal with Rodenticide Poisoning. Among them 229 patients were enrolled for the study.

The demographical details of the rodenticide poisoning cases were given in the **table 1**. The mean age of the study population was found to be 30.04 ± 15.67 years. Gender distribution shows very slight variation between the male and female population in the study, with males being 50.2% and females 49.8%. Majority of the cases were found to be Suicidal (86.0%). The mean duration of Hospitalization was found to be 7.08 ± 5.48 days.

Among the study population, history of alcohol consumption was found in 23.5% (n = 47) patients, while 1.5% (n = 3) patients were reformed alcoholics. Psychiatric conditions were also found in 36 (17.7%) patients.

The most common clinical presentation in rodenticide poisoning includes vomiting 131 (57.2%), abdominal pain 82 (35.8%), nausea 59 (25.76%), jaundice 21 (9.17%), and hepatitis 52 (22.70%). Hypertension 16 (6.98%), and Diabetes 12 (5.24%), were the most common comorbidities.

Complications of Rodenticide Poisoning include Fulminant Hepatic failure 45 (19.65%), followed by Renal Failure 9 (3.93%) and MODS 5 (2.18%) as shown in **table 1**.

Table.1 Demographic Characteristics of Rodenticide Poisoning.

Total number of patients	N= 229
Patient's Demographic Characteristics	
Mean age ± SD	30.04 ± 15.67
Sex, n (%)	
● Male	115 (50.2%)
● Female	114 (49.8%)
Rodenticide Exposure	
Type of poisoning, n (%)	
● Suicidal	190 (86.0%)
● Accidental	29 (13.1%)
● Homicidal	2 (0.9%)
Duration of Hospitalization (mean days± SD)	7.08 ± 5.48
History of previous poisoning, n (%)	
● Yes	4 (1.7%)
● No	225 (98.3%)
Alcohol consumption, n (%)	
● Yes	47 (23.5%)
● No	150 (75%)
● Reformed	3 (1.5%)
Psychiatric illness, n (%)	
● Yes	36 (17.7%)
● No	167 (82.3%)
Clinical presentation, n (%)	
● Nausea	59 (25.76%)
● Abdominal Pain	82 (35.8%)
● Jaundice	21 (9.17%)
● Hepatitis	52 (22.70%)
● Vomiting	131 (57.2%)

Comorbid Conditions, n (%)	
● Diabetes	12 (5.24%)
● Hypertension	16 (6.98%)
● Tuberculosis	1 (0.43%)
● Hepatitis	3 (1.31%)
● ALD	1 (0.43%)
Complications of Poisoning, n (%)	
● Fulminant Hepatic failure	45 (19.65%)
● Renal Failure	9 (3.93%)
● Refractory Metabolic Acidosis	6 (2.62%)
● MODS	5 (2.18%)

List of different types of Rodenticides:

Among the different Rodenticide compounds consumed Yellow Phosphorus contributes 36 (15.6%) followed by Zinc Phosphide 22 (9.5%) and Superwarfarin 9 (3.9%).

Table.2 Type of Rodenticide consumed

Total number of patients	**N= 229**
Type of Rodenticide consumed, n (%)	
● Yellow Phosphorus	36 (15.6%)
● Zinc Phosphide	22 (9.5%)
● Superwarfarin	9 (3.9%)
● Unspecified	162 (70.1%)

Overall Treatment and Outcome Analysis of Rodenticide Poisoning:

As the initial treatment, Gastric lavage in 45 (52.3%) patients and Activated charcoal in 17 (19.8%) patients was used. Among the different treatment approaches, majority of the patients, 212 (94.2%) were treated with NAC. Vitamin K was administered in 131 (57.2%) patients. Atropine and Furosemide were used in only 1(1.2%) patient. Extracorporeal methods were used in 2 (1.7%) patients. A total of 27 (20.8%) patients received ventilation.

The outcome analysis of Rodenticide poisoning cases admitted during the study period showed 191 patients (83.4%) survived while 38 patients (16.6%) died.

Table.3 Overall Treatment and Outcome Analysis

Total number of patents	**N= 229**
Type of Treatment, n (%)	
• NAC	212 (94.2%)
• Vitamin K_1	131 (57.2%)
• Gastric Lavage	45 (52.3%)
• Activated Charcoal	17 (19.8%)
• Atropine	1 (1.2%)
• Furosemide	1 (1.2%)
• Extracorporeal methods	2 (1.7%)
• Ventilation	27 (20.8%)
Outcome Analysis, n (%)	
• Survived	191 (83.4%)
• Dead	38 (16.6%)

Treatment with Vitamin K:

As shown in **table 4,** Vitamin K_1 was administered to 131 patients who were enrolled in the study. Total of 80 (61.06%) patients among them were administered Vitamin K_1 through the IV, while 45(34.35%) patients received Vitamin K_1 subcutaneously. Only 1(0.76%) patient was given Vitamin K_1 orally and 2(1.52%) patients received IM doses of Vitamin K_1. In 3(2.29%) of the patients, route of administration of Vitamin K_1 was not specified.

Table.4 Route of Vitamin K1 treatment given

No of patients treated with Vitamin K_1	**N=131**
Vitamin K_1 Route ● IV ● Oral ● IM ● S/C ● Not specified	 80 (61.06%) 1(0.76%) 2 (1.52%) 45 (34.35%) 3 (2.29%)

Other Treatment Approaches:

Of all the other treatments that were done for the patients who were admitted for rodenticide poisoning, Gastric Lavage was done in 45 (52.3%) patients, which was the most common. Activated Charcoal was given for 17(19.8%) patients. Atropine and Furosemide were given only for 1 patient each (1.2% each) while 22 (25.6%) patients received a combination of Gastric Lavage and Activated Charcoal. Among the 229 patients who were included in the study, only 2(1.7%) patients underwent extracorporeal methods of treatment which was probably done for the Acute Renal Failure which occurred as a complication to the poisoning.

Table.5 Other treatments given during the Hospital stay

Total number of patients	**N= 229**
Other treatments given, n (%)	
• Gastric Lavage	45 (52.3%)
• Activated Charcoal	17 (19.8%)
• Atropine	1 (1.2%)
• Furosemide	1 (1.2%)
• Both Gastric Lavage & Activated Charcoal	22 (25.6%)
• Extracorporeal methods	2 (1.7%)

Vitamin K and outcome Analysis:

Among the patients enrolled in the study, 131 patients were administered Vitamin K_1 through various routes, and 98 patients did not receive Vitamin K_1. Outcome analysis has not shown any statistically significant effect of Vitamin K_1 administration in rodenticide poisoning cases.

Table. 6 Vitamin K_1 and outcome Analysis

Vitamin K_1 given	Outcome		Total
	Dead	Survived	
No	13 (13.26%)	85 (86.73%)	98 (100.0%)
Yes	25 (19.08%)	106 (80.91%)	131 (100.0%)

Values are in frequency and percentage, data was analyzed by Chi Square for Pearson and $p \leq 0.242$

Gastric Lavage and Outcome Analysis:

Among the patients enrolled in the study, 68 patients were given Gastric Lavage, while 161 patients did not receive Gastric Lavage. Outcome analysis has not shown any statistically significant effect of Gastric Lavage in rodenticide poisoning cases. However, the recovery rate was found to be better among patients in whom Gastric Lavage was performed as compared to the other group.

Table. 7 Gastric Lavage and Outcome Analysis

Gastric Lavage	Outcome		Total
	Dead	Survived	
No	31 (19.2%)	130 (80.7%)	161 (100.0%)
Yes	7 (10.2%)	61 (89.7%)	68 (100.0%)

Values are in frequency and percentage, data was analyzed by Chi Square for Pearson and $p \leq 0.096$

Activated Charcoal and Outcome Analysis:

In our study population, 39 patients were given Activated Charcoal, while 190 patients did not receive Activated Charcoal. Outcome analysis has shown statistically significant effect of Activated Charcoal in rodenticide poisoning cases. The recovery rate was found to be better in the group of patients in whom Activated Charcoal was given as compared to the other group.

Table. 8 Activated Charcoal and Outcome Analysis

Activated Charcoal given	Outcome		Total
	Dead	Survived	
No	36 (18.9%)	154 (81.05%)	190 (100.0%)
Yes	2 (5.1%)	37 (94.8%)	39 (100.0%)

Values are in frequency and percentage, data was analyzed by Chi Square for Pearson and $p \leq 0.035$

Both Gastric lavage and Activated charcoal and Outcome Analysis:

Among the patients enrolled in the study, 22 patients were given both Gastric lavage and Activated Charcoal, while 207 patients did not receive these treatments. Outcome analysis has not shown statistically significant effect of both Gastric lavage and Activated Charcoal in rodenticide poisoning cases but the recovery rate was found to be better in the group of patients in whom both Gastric lavage and Activated Charcoal were given when compared to the group in which it is not done.

Table. 9 Both Gastric Lavage and Activated Charcoal and Outcome Analysis

Both Gastric lavage and activated charcoal	Outcome		Total
	Dead	Survived	
No	37 (17.8%)	170 (82.1%)	207 (100.0%)
Yes	1 (4.5%)	21 (95.4%)	22 (100.0%)

Values are in frequency and percentage, data was analyzed by Chi Square for Pearson and $p \leq 0.110$

Treatment with NAC:

Among the patients who got admitted, NAC was administered to 212 (94.2%) patients. Total of 28(12.2%) patients enrolled in the study received both oral and IV. The route of administration was mainly IV for 102 (44.5%) patients and oral for 82 (35.8%) patients. The mean duration of treatment with NAC through oral route was found to be 4.24± 4.30 days (mean ± SD), whereas, through IV it was 2.55 ± 2.00 days. Patients who were treated with both oral and IV NAC was treated for an average of 3.96 ± 4.16 days.

In patients who were treated with NAC orally, the mean STAT dose that was given initially was found to be 7580.95 ± 2204.29 mg. The oral maintenance dose averaged out to be 3694.53 ± 2322.58 mg.

In patients treated with IV NAC, 21- hour Regimen was found to be the most common. The mean dose given over 1 hour, 4 hours and 16 hours was found to be 7975.65 ± 2356.63 mg, 2913.79 ± 1580.85 mg and 5445.95± 1867.21 mg respectively.

Table.10 Treatment with NAC

Total number of Patients	**N = 229**
NAC given, n (%)	212 (94.2%)
Route of Administration, n (%)	
● Oral	82 (35.8%)
● IV	102 (44.5%)
● Both oral and IV	28 (12.2%)
● None	17 (7.4%)
Duration of Treatment with NAC, (mean days ± SD)	
● Oral	4.24 ± 4.30
● IV	2.55 ± 2.00
● Both Oral and IV NAC given to patients	3.96 ± 4.16

Oral NAC Dose, (mean dose ± SD) ● STAT Dose ● Maintenance Dose IV NAC Dose- 21 hour Regimen, (mean dose ± SD) ● Dose given over 1 hour ● Dose given over 4 hours ● Dose given over 16 hours	 7580.95 ± 2204.29 mg 3694.53 ± 2322.58 mg 7975.65 ± 2356.63 mg 2913.79 ± 1580.85 mg 5445.95 ± 1867.21 mg

NAC Treatment and Outcome Analysis:

Among the study population, 212 patients received NAC, whereas 17 did not receive NAC. Survival rate was found to be higher in patients who received NAC (84.9%) compared to those who did not (64.7%).

Table.11 NAC Treatment and Outcome Analysis

NAC given	survival outcome of treatment		Total
	Dead	Survived	
No	6 (35.3%)	11 (64.7%)	17 (100.0%)
Yes	32 (15.1%)	180 (84.9%)	212 (100.0%)

Values are in frequency and percentage, data was analyzed by Chi Square for Pearson and $p \leq 0.031$

IV NAC Regimen and Outcome Analysis:

Among the study population, 131 patients were administered IV NAC, of which 28 patients were given infusion (irregular regimen) and 21 hour regimen was followed in 103 patients. Outcome analysis of these groups has not shown any statistical significant of IV NAC in treating rodenticide poisoning, although recovery rate was found to be better in patients who were treated with 21 hour regimen when compared to the other group.

Table.12 IV NAC Regimen and Outcome Analysis

IV NAC Regimen	Outcome of treatment		Total
	dead	survived	
Infusion	4 (21.4%)	24 (85.71%)	28 (100.0%)
21 hour regimen	19 (18.4%)	84 (81.6%)	103 (100.0%)

Values are in frequency and percentage, data was analyzed by Chi Square for Pearson and $p \leq 0.864$

NAC given and Outcome Analysis with respect to Child Pugh Score:

Outcome was assessed based on the Child Pugh Score for effectiveness of NAC in Rodenticide Poisoning. The entire study population was categorized as least severe, moderately severe and most severe based on the Child Pugh Score. Within the least severe category, survival rate was higher among patients treated with NAC (89.9%) as compared to the group in which NAC was not administered. In moderately severe patients, a higher survival rate was observed in patients who were given NAC as compared to the group without NAC (73.3% versus 33.3%). In the most severe category, the efficacy of NAC was inconclusive since there was no significant difference observed, which could be due to the presence of other risk factors or insufficient sample size. However, the study showed 55.6% survival rate among these patients who were treated with NAC.

Table.13 NAC given and Outcome Analysis with respect to Child Pugh Score

Child Pugh Score	NAC given	Treatment outcome		Total
		Dead	Survived	
Least severe	Yes	17(10.1%)	151(89.9%)	168 (100%)
	No	1(11.1%)	8(88.9%)	9(100%)
	Total	18(10.2%)	159(89.8%)	177(100%)
Moderately severe	Yes	8(26.7%)	22(73.3%)	30 (100%)
	No	2(66.7%)	1(33.3%)	3 (100%)
	Total	10(30.3%)	23(69.7%)	33 (100%)
Most severe	Yes	4(44.4%)	5(55.6%)	9 (100%)
	No	1(100%)	0 (0.0%)	1 (100%)
	Total	5(50.0%)	5(50.0%)	10 (100%)
Total	Yes	29(14.0%)	178 (86.0%)	207 (100%)
	No	4(30.8%)	9 (69.2%)	13 (100%)
	Total	33 (15.0%)	187 (85.0%)	220 (100%)

Adverse effects of NAC:

Of all the patients that were included in the study, 8(3.5%) of them developed vomiting associated with NAC administration, while 5 (2.2%) patients had diarrhoea. Severe cough was seen in 2(0.9%) patients in whom NAC was given, while majority 214 (93.4%) did not develop any adverse reactions to NAC treatment.

Table.14 Adverse Drug Reactions associated with NAC

Total number of Patients	**N= 229**
ADRs associated with NAC, n (%) ● Vomiting ● Diarrhoea ● Severe Cough ● None	 8 (3.5%) 5 (2.2%) 2 (0.9%) 214 (93.4%)

Analysis of Risk Factors with Outcome:

Various risk factors such as Gender, Type of Rodenticide, Time Lag, Child- Pugh score and Age have been compared with the outcome by using Cox Regression and Relative Risk was calculated.
Among the different risk factors, Yellow Phosphorus and Time Lag greater than 24 hours were found to be statistically significant with respect to the outcome.
Yellow Phosphorus poisoning is relatively 2.89 times at a higher risk for mortality and Time lag greater than 24 hours has 3.48 times higher risk of mortality.

Table.15 Analysis of Risk Factors with Outcome

Factors		P value	RR
Gender	Male Female	0.251	0.598
Type of Rodenticide	Yellow Phosphorus Zinc Phosphide Unspecified	0.020 0.304	2.888 1.993
Time Lag	<12 hours 12 - 24 hours > 24 hours	 0.523 0.029	 1.501 3.479
Child Pugh Score	Least Severe Moderately Severe Most Severe	0.564 0.620 0.285	 1.318 2.237
Age	Below 20 years 20 – 44 years 45-60 years	0.807 0.913 0.401	0.875 1.076 1.875

Relative Risk was analyzed using Cox Regression.

DISCUSSION

RODENTICIDE POISONING:

The present study was conducted by collecting data from the Medical Records Department of Kasturba Hospital, Manipal. This retrospective study was carried out on 229 Rodenticide poisoning cases, to evaluate the efficacy of NAC and the general treatment pattern for the same.

In our study, the mean age of our study population was found to be 30.04 ± 15.67 years. Gender wise distribution did not show any significant difference in Male to Female ratio (1.01:1). In a study conducted by Chug et al 1991, the mean age was found to be 26.5 years and the gender ratio was 2:1 [26]. Another study by Acharya R et al incidence of rodenticide poisoning was slightly more in Males than females [27].

In our study, we observed that the type of rodenticide consumed in majority of patients was Yellow Phosphorus (15.6%) followed by Zinc Phosphide (9.5%) and Superwarfarin (3.9%) which was also observed in the study by Acharya R et al [27].

In the present study, majority of the rodenticide poisonings were due to Intentional Self-harm (86.0%), followed by Accidental poisoning (13.1%). In an uncontrolled retrospective study carried out by Lohani SP et al on 178 Zinc Phosphide poisoning cases in Nepal for a five year period from July 1997 - June 2002 showed that 79% cases were intentional poisoning [28]. In another study by Monigari N, Acharya R et al, majority of patients were suicidal 92(94.8) and only 5 (5.2%) patients presented with accidental ingestion [27].

Among the 229 patients in our study population, 36(17.7%) patients had psychiatric illness which is probably one of the major risk factors for Intentional Self Harm. According to a study by Eddleston & Phillips (2004), psychiatric illness is one of the major risk factors for Self-poisoning and prophylactic medical management of psychiatric conditions can possibly reduce the incidences of self-harm [29].

The mortality rate among patients in our study was 16.6% which is comparatively lesser than in the studies conducted by Singh et al, 1991, where mortalities ranged from 40-77% [30]. This is probably due to the effective treatment regimen followed to manage the critical cases in our study.

In our study, we analyzed various risk factors contributing for the mortality in rodenticide poisoning. We observed Yellow Phosphorus (RR- 2.89) and Time lag greater than 24 hours (RR- 3.48) to be associated with a higher mortality rate. In a study conducted by Acharya et al, mortality rate was found to increase with the increase in time lag [27]. Similarly, comparison of different types of rodenticides with respect to mortality showed 10- 50% mortality rate with Yellow Phosphorus [31].

The most common clinical presentation in rodenticide poisoning includes vomiting 131 (57.2%), abdominal pain 82 (35.8%), nausea 59 (25.76%), jaundice 21 (9.17%), and hepatitis 52 (22.70%). Hypertension 16 (6.98%), and Diabetes 12 (5.24%), were the most common comorbidities. These clinical features are observed in Zinc Phosphide poisoning and are similar to those of Aluminium Phosphide but slower in onset [32] [33] [34]. In case of Yellow Phosphorus poisoning, the initial symptoms include vomiting, burning sensation in the throat, chest, and abdomen [35] and in some cases CNS signs such as lethargy, restlessness and irritability are seen [36]. In case of Superwarfarin poisoning, evidence of excessive blood loss may be observed and the Prothrombin Time will be prolonged within 24 hours and a maximum of 37-72 hours will be attained after exposure [27] [37].

Complications of Rodenticide Poisoning include Fulminant Hepatic failure 45 (19.65%), followed by Renal Failure 9 (3.93%) and MODS 5(2.18%) as observed in our study. According to a study conducted by Mohideen S, Kumar K, in some cases the patient may not have any symptoms initially and may directly show complications like MODS, Cardiac Arrhythmia, Hepatic Encephalopathy, Fulminant Hepatic Failure, Pancreatitis, all of which ultimately lead to death [25].

The treatment analysis pattern of our study showed that 45 (52.3%) patients were treated with Gastric Lavage and 17 (19.8%) patients with Activated Charcoal at the initial stage of therapy. Outcome analysis showed that there was no statistical significance in treatment with Gastric Lavage and the clinical outcome, however, Activated Charcoal was found to be clinically significant. Gastric Lavage as well as Activated Charcoal was found to be beneficial as the recovery rate was high in patients who received these treatments. According to a study by Hsin-Ying Yu et al, there is no specific antidote for rodenticide poisoning and management is mainly supportive and symptomatic which includes gastric lavage, followed by infusion of active charcoal, vitamin K1 therapy, and FFP transfusion in the case of bleeding [17] [21]. The treatment depends upon the route of exposure. If the route of exposure is by oral ingestion, then administration of slurry of Activated Charcoal is preferred in the dose of 50 - 100 g in adults, 1 g/kg in infants, and 25 - 50 g in children (1 - 12 years) [16] [17].

Among the patients enrolled in the study, 131 patients were administered Vitamin K_1 through various routes, and 98 patients did not receive Vitamin K_1. Outcome analysis has not shown any statistical significance of effect of Vitamin K administration in rodenticide poisoning cases but recovery rate was found to be better in patients with Vitamin K administration when compared with the other group. Among the 131 patients, 8 were admitted with consumption of Superwarfarin and all of them recovered after administration of Vitamin K_1. In Superwarfarin poisoning, Vitamin K_1 (phytomenadione) is considered to be the antidote of choice. Its dose depends on the coagulation parameters such as Prothrombin Time [5] [27].

In our study, 212 (94.2%) patients were treated with NAC. Clinical significance was observed between NAC treatment and clinical outcome and the recovery rate was found to be higher in patients who received NAC. It has been found that blood concentration of glutathione were reduced in patients in Phosphide poisoning, hence, NAC therapy should be considered [38]. An observational study conducted by Syed Idris Kafeel et al showed that the use of NAC as adjuvant therapy in Yellow Phosphorus poisoning improved survival rate in patients [39]. In another study by Mumtaz K et al, the use of NAC has shown reduction in NAI-ALF mortality [40]. A study conducted at Vinayaka Mission Hospital, Salem from 2010 to 2011, concluded the use of NAC as an adjuvant in the management in Yellow Phosphorus poisoning [18].

Among the patients who got admitted, NAC was administered to majority of the patients i.e., 212 (94.2%). The route of administration was mainly IV for 102 (44.5%) patients and oral for 82 (35.8%) patients. Among the patients enrolled in the study 28(12.2%) received both oral and IV NAC.

The mean duration of treatment with NAC through oral route was found to be 4.24± 4.302 days (mean ± SD), whereas, through IV was 2.55 ± 2 days. Patients who were treated with both oral and IV NAC was treated for an average of 3.96 ± 4.16 days. According to a study conducted by Kortsalioudaki C. et al on the safety and efficacy of N-acetylcysteine in children with NAI-ALF, the mean duration of treatment was found to be 5 days [41].

In patients who were treated with NAC orally, the mean STAT dose that was given initially was found to be 7580.95 ± 2204.29 mg. The oral maintenance dose averaged out to be 3694.53 ± 2322.58 mg. Oral dose of NAC is 140 mg/kg, followed by 70 mg/kg, for a total of 17 doses, 4 hours apart within 6 hours of admission [40].

In patients treated with IV NAC, 21- hour Regimen was found to be the most common. The mean dose given over 1 hour, 4 hours and 16 hours was found to be 7975.65 ± 2356.63 mg, 2913.79 ± 1580.85 mg and 5445.95 ± 1867.21 mg respectively. NAC is given at the dose of 150 mg/kg over one hour in 200 mL of 5% Dextrose followed by 50 mg/kg in 500 mL of 5% Dextrose over four hours, followed by 100 mg/kg in 500 mL 5% Dextrose over 16 hours [18] [19].

Among the study population, 131 patients were administered IV NAC, of which 28 patients were given infusion (irregular regimen) and in 103 patients the 21 hour regimen was followed. Outcome analysis of these groups has shown recovery rate was found to be better in patients who were treated with 21 hour regimen.

Of all the patients that were included in the study, 8 (3.5%) of them developed vomiting associated with NAC administration, while 5 (2.2%) experienced diarrhoea, severe cough was seen in 2(0.9%) patients, while majority 214 (93.4%) did not develop any adverse reactions to NAC treatment. Common side effects of NAC treatment is vomiting, diarrhoea, bronchospasm and maculopapular rash, all of which can be observed within 4 hours of administration [40].

KEY FINDINGS

KEY FINDINGS OF THE STUDY

- Majority poisoning cases were due to Intentional Self Harm.
- Yellow Phosphorus poisoning has a higher relative risk associated with mortality than the other classes of rodenticides.
- Time lag greater than 24 hours is also a risk factor associated with a higher mortality rate.
- Initial treatment with Activated charcoal has shown clinically significant benefit with the outcome.
- Treatment with Gastric Lavage was also found to be beneficial at the initial stages
- Vitamin K_1 should be used in all Superwarfarin poisoning cases as an antidote.
- NAC treatment was found to be clinically significant with the Outcome.
- Among the different dosage regimens of NAC, 21 hour IV regimen showed better recovery rate in moderate and severe poisoning cases.

LIMITATIONS

LIMITATIONS

- As this is a Retrospective study, information on GCS, BMI, pre-hospitalization period, type and amount of poison consumed was not available in all patient case records.
- Sample size in the present study may not be sufficient to analyze all treatment modalities.
- Lack of follow up of discharged patients led to unavailability of proper information on the long-term complications in those patients.
- Lack of proper monitoring of laboratory parameters in some patients.

CONCLUSION

CONCLUSION

This study was conducted in a tertiary care hospital to understand the effectiveness of NAC in Rodenticide Poisoning.

A total of 229 patients were enrolled in the study in which majority cases were of Intentional Self Harm belonging to the reproductive age group.

The mortality rate in our study was significantly low as compared to the studies reported in the literature, probably due to the effective treatment approach in the emergency settings.

Yellow Phosphorus poisoning and Time Lag greater than 24 hours were found to be the major risk factors associated with a higher mortality rate.

Fulminant Hepatic Failure was found to be the most common complication in Rodenticide Poisoning.

Administration of Activated Charcoal in the initial stage showed better recovery rate in patients.

NAC showed clinically significant outcomes as an adjuvant therapy in Rodenticide Poisoning. Outcome analysis showed better results in patients who were administered with NAC compared to the patients where NAC was not given.

The 21 hour IV NAC regimen was found to be effective and associated with mild tolerable side effects such as nausea, vomiting and rashes.

This study provides a significant clinical scenario with respect to the effective use of NAC in the management of Rodenticide Poisoning. Results from this study strongly support the efficacy of NAC in Rodenticide Poisoning.

FUTURE DIRECTIONS

FUTURE DIRECTIONS

- A Prospective Study on weight based dosing regimen of NAC for treatment of Rodenticide Poisoning.
- Studies to develop standard treatment guidelines for Rodenticide Poisoning.
- Checking serum poison levels in patients at the time of admission can help to determine the severity of the case and to choose the treatment.
- Conducting studies to understand specific treatment approaches by selecting a specific rodenticide such as Yellow Phosphorus or Superwarfarins, etc.

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APPENDICES

APPENDIX 1: IEC Approval Certificate

KASTURBA HOSPITAL
MANIPAL
An associate Hospital of Manipal University

Institutional Ethics Committee

(Registration No. ECR/146/Inst/KA/2013/RR-16)

Communication of the decision of the Institutional Ethics Committee

Wednesday 13th September 2017 **IEC : 559/2017**

Project title	:	Role of N Acetyl-cysteine in management of rodenticide poisoning: A retrospective analysis.
Principal Investigator	:	Shabnam Hyder
Guide/ Co Guide/ Co Investigators	:	Dr. Girish Thunga, Karen Mark, Dr. Shubha Seshadri, Dr. Sneha S
Name & Address of Institution	:	Dept. of Pharmacy Practice, MCOPS, Dept. of Medicine, KMC, Manipal.
Status of review	:	New
Date of review	:	12.09.2017
Decision of the IEC	:	Approved for the study period from 12.09.2017 to 31.03.2018 as mentioned in protocol.

- The PI and all members of the project shall ensure compliance to current regulatory provisions (as per Schedule Y of Drugs and Cosmetics Act and ICH-GCP), Ethical Guidelines for Biomedical Research on Human Participants by ICMR, and the SOP of IEC including timely submission of Interim Annual Report and Final Closure Report
- Participant Information Sheet and a copy of signed Informed Consent shall be given to every research participant
- Inform IEC in case of any proposed amendments (change in protocol / procedure, site / Investigator etc)
- Inform IEC immediately in case of any Adverse Events and Serious Adverse Events.
- Members of IEC have the right to monitor any project with prior intimation.

Dr. Stanley Mathew
MEMBER SECRETARY - IEC

ETHICS COMMITTEE KASTURBA HOSPITAL, MANIPAL APPROVED

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(Yoga and Ayurveda services are excluded from the scope of NABH accreditation)

MR-798

APPENDIX II: Case Report Form

Age : Sex : Weight/Height: BMi :	Date of admission : Date of discharge :
Type of Rodenticide consumed :	Quantity :
Type of poisoning : Suicidal	Accidental Homicidal
Socioeconomic status : Low	Moderate High
Occupation :	
Time lag between consumption and initiation of NAC :	
Signs and Symptoms of toxicity :	
Medical / Medication History : Alcoholic : Y or N Psychiatric diseases : Y or N	
BIOCHEMICAL VALUES	

T. Bilirubin													
D. Bilirubin													
AST													
ALT													
ALP													
Albumin:													
Globulin													
Total Protein													
PT													
INR													
APTT													

ABG:													
pH													
pO_2													
pCO_2													
HCO^3													
O_2 Saturation													
BP													
PR													
RR													
Others :													

Days / IV NAC	1	2	3	4	5	6	7	8	9	10
Dose										
Duration										
Oral NAC										

Other Management:

TREATMENT	DOSE	DURATION
Gastric Lavage		
Activated Charcoal		
Steroids		
Furosemide		

Vitamin K1		
Haemodialysis/Haemoperfusion		

Survival Outcomes	ADR associated with N-Acetyl Cysteine
Recovered : Dead : DAMA :	

Duration of Hospitalization	
Duration of ventilation	
Duration of intubation	

SCORING TOOLS :

APACHE	
GCS	