ROLE OF N – ACETYL CYSTINE IN OUTCOME OF PATIENTS WITH YELLOW PHOSPHORUS POISONING – AN OBSERVATIONAL STUDY

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ABSTRACT

Background & Aim: 3% Yellow phosphorus is a highly systemic toxin and lethal affecting hepatic and renal functions. The treatment options are very few and not standardized. Hence this study evaluates the available treatment options and its outcome.

Methods: This study is a prospective observational study conducted at Vinayaka Mission Hospital, Salem from 2010 to 2011. Victims presenting to Emergency Room [ER] with consumption of yellow phosphorus compound were included in this study. The details including personal details, history, laboratory investigations and treatment were individualized by the physicians. These were recorded meticulously on admission and daily basis, and patients were categorized based on the dose consumed and time duration in hours of consumption and whether patients received NAC. At the end of 72 hours, patients in each group were subcategorized based on the clinical and laboratory findings into mild, moderate or severe hepatic injury. With the acquired data, the results are analyzed to study the outcome.

Results: Among patients who consumed lethal dose of poison, presenting early and received NAC, 43% had moderate and 43% had severe hepatic injury. Among severe injury, 14% developed fulminant hepatic failure [FHF] and died. Among patients who consumed lethal dose, presenting early but not receiving NAC, 33.3% had moderate and 66.7% had severe hepatic injury. All severe cases in this group developed FHF with mortality of 100%. Patients presenting late after consumption of lethal dose, who receive did not NAC developed FHF with mortality of 100%. Patients consuming sub lethal dose had 100% survival without hepatic damage.

Conclusions: The use of NAC as an adjuvant in the management in yellow phosphorus poisoning improves survival when presented early to emergency room.

Keywords: Hepatic injury, N-Acetylcysteine, Ratol poisoning, Yellow phosphorus poisoning.

INTRODUCTION

Compounds of yellow phosphorus are commonly used as everyday rodenticides, fertilizers and in fire crackers. Therefore, the freely available forms of yellow phosphorus compounds are abused as substances of self harm [Suicidal and accidental]. The toxicity of the same is lethal and its morbidity and mortality is very high. A significant proportion of patients presenting with poisoning would have consumed yellow phosphorus compound. Yellow phosphorus [also referred to as white phosphorus], on the other hand, is a severe local and systemic toxin causing damage to gastrointestinal, hepatic, cardiovascular, and renal systems. It is commonly marketed as RATOL- as Rat Killer. The treatment details of this poisoning are not adequate in standard text books in emergency medicine and critical care Medicine. This toxicity is similar to paracetamol overdose. N-Acetylcysteine [NAC] which is used in paracetamol overdose as an adjunct therapy in yellow phosphorus poisoning has been quoted in some journals. Rodenticides are available as powders or pastes containing 2 to 5% of yellow phosphorus (1).

It emits smoke and has very strong garlic odor. It can get absorbed through skin, mucus membrane, respiratory and gastrointestinal epithelium. Intoxication occurs with suicidal or accidental ingestion. After absorption, it is

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distributed to all tissues, particularly the liver, and the peak level is reached after 2 to 3 hours of toxic oral ingestion. Bile salts are important for absorption of phosphorus. Because of water content and low oxygen tension, phosphorus remains stable in gut for longer period (2). Yellow Phosphorus causes cardiac, hepatic, renal, and multi-organ failure. The patient with yellow phosphorus intoxication passes through three stages. The first stage occurs during the first 24 hours in which patient is either asymptomatic or has signs and symptoms of local gastrointestinal irritation. The second stage occurs between 24 to 72 hours after ingestion. It is an asymptomatic period. There may be mild elevation of liver enzymes and bilirubin in this stage. The third stage [advanced] occurs after 72 hours until the resolution of symptoms or death (1). Patients may present with acute hepatic failure, coagulopathy, and deranged liver function, as was witnessed in our patients. Some patients may develop acute tubular necrosis and present with acute renal failure (2). Central nervous system effects include changes in mental status like confusion, psychosis, hallucinations, and coma. Cardiac toxicity includes hypotension, tachycardia, arrhythmias and cardiogenic shock (3). There is no specific antidote for yellow phosphorus. Treatment is directed at removal of the poison and supportive therapy. Gastric lavage with tap water is recommended followed by activated charcoal with mineral oil. Careful monitoring of Serum electrolytes, hepatic function and coagulation profile and management of their failure is required. Liver transplantation has been done in suitable candidates for acute hepatic failure (4). The safest way to deal with such a lethal substance would be prevention. The indiscriminate use of yellow phosphorus in the manufacture of this paste should be eliminated. Since rodents are developing resistance to rodenticides containing warfarin, rat poisons containing yellow phosphorus are making a big come-back. The yellow phosphorus rodenticides pose special problems that the product directions suggest that the paste be applied to bread to enable ingestion by rodents, thus making it appealing to children as well (5). Emergency Physicians should therefore be aware of the toxicity and its management.

Therefore this study aims to understand the process of toxicity; it’s near lethal outcomes and the effect of interventions with N acetylcysteine in improving the overall mortality and morbidity of the victims.

**MATERIALS AND METHODS**

This is a prospective analytical study, done at Vinayaka Mission Kirupananda Variyar Medical College and hospital, Salem and was conducted from June 2010 to August 2011. All the patients Victims presenting to ER with alleged history of consumption of yellow phosphorus compound are identified and included in this study. Those who had mixed poisoning were excluded from our study. All the patients who are enrolled in the study were stabilized in the emergency room. Patients were initially managed with activated charcoal slurry with the dose of 1gm / kg followed by gastric Lavage and continued with multi-dose activated charcoal 0.5 gm /kg every 6th hour. The use of N-Acetylcystine (NAC) was individualized to the treating Physician’s decision. When used it was given as150mg /kg stat, 50mg/kg 4 – 6 hours, 100mg/kg – 16hours, 100mg / kg continued for next 24 hours as this poison is long acting. The dose of NAC used was similar to the dose of NAC used in paracetamol over dose

Patients were managed with IV fluids, oral activated charcoal and rectal charcoal 6th hourly for 48 hours and other standard supportive care including hepatoprotective drugs. Coagulation profile was checked every day and corrected accordingly. Any complication developed during the period of treatment was addressed accordingly till the patient got discharged from the hospital.

The following parameters like Age, Sex, amount ingested, duration on mechanical ventilation in days, duration of stay in hospital in days, duration of days taken for the coagulation profile to get altered, duration of days taken for the LFT derangement, Complications like Coagulopathy, Acute renal failure, cardiac arrhythmias, Fulminant hepatic failure were recorded. Outcome of patients with and without NAC and there mortality were recorded. With the acquired data, the results are analyzed and the outcome is studied.
All the patients were categorized based on the dose consumed into:

- Category I - Lethal dose (≥ 1mg/kg)
- Category II – Sub Lethal dose (≤ 1mg/kg)

Based on Time duration in hours from consumption to arrival to ER, they categorized into:

- Early Presentation - ≤ 24 hours
- Delayed Presentation - > 24 hours

Further based on the dose consumed and presentation, patients were divided into groups:

- Group A – Lethal dose with early presentation
- Group B – Lethal dose with late presentation
- Group C – Sub lethal dose with early presentation
- Group D – Sub lethal dose with late presentation

Further based on NAC use, these patients were divided into sub groups [FIGURE 1]:

- Group A1 – NAC given
- Group A2 – NAC not given
- Group B1 – NAC given
- Group B2 – NAC not given
- Group C1 – NAC given
- Group C2 – NAC not given
- Group D1 – NAC given
- Group D2 – NAC not given

The sub groups were assessed on the 4th day of consumption based on the clinical treatment and response and were categorized into:

- Mild – No clinical or biochemical evidence of hepatitis
- Moderate – Sub clinical hepatic injury
- Severe – Symptomatic hepatitis

The outcome was assessed in terms of severity of injury, morbidity and mortality.

**DATA ANALYSIS**

All data were compiled into Microsoft Excel 2007 spreadsheet and statistical analysis was accomplished using statistical method for calculations provided within “Statistical package for social science” software [version 11.5]. Analysis of variants was performed and classifications of observed and predicted values of LFT and coagulation profile of the study and control group were identified. Descriptive analysis was carried out to compare the predictive outcome on the 4th day of consumption of the poison.

**RESULTS**

The study sample analyzed consisted of 21 cases, of which 62% were male and 38% were female. Of 21 patients in the study, 33.3% consumed sub lethal amount and 66.7% consumed lethal amount of yellow phosphorous compound. The mean time duration in hours from consumption to arrival to ER was 17.9 hours.

Patients divided into groups based on the dose consumed and presentation included 10 patients in Group A, 4 in Group B, 4 in Group C and 3 patients in Group D [Figure 2]. Further based on NAC use, these patients divided into sub groups included 7 patients in Group A1, 3 in Group A2, 2 in Group B1, 2 in Group B2, 2 in Group C1, 2 in Group C2, 1 in Group D1 and 2 patients in Group D2 [Figure 3]. Mean of SGOT among sub groups included 92 IU in Group A1, 414 IU in Group A2, 444 in Group B1, 676 IU in Group B2, 24 IU in Group C1, 42 IU in Group C2, 34 IU in Group D1 and 40 IU patients in Group D2. Mean of SGPT among sub groups included 78.43 IU in Group A1, 200.67 IU in Group A2, 476 IU in Group B1, 345.5 IU in Group B2, 29.5 IU in Group C1, 52.5 IU in Group C2, 36 IU in Group D1 and 39 IU patients in Group D2. Mean of PT among sub groups included 22.41 seconds in Group A1, 37.4 seconds in Group A2, 56.35 seconds in Group B1, 49.17 seconds in Group B2, 14.95 seconds in Group C1, 15.6 seconds in Group C2, 15.3 seconds in Group D1 and 14.75 seconds patients in Group D2. Mean of INR among sub groups included 1.41 in Group A1, 1.81 in Group A2, 1.92 in Group B1, 2.49 in Group B2, 1.16 in Group C1, 1.16 in Group C2, 1.18 in Group D1 and 1.17 patients in Group D2. Mean of aPTT among sub groups included 30.9 seconds in Group A1, 46.3 seconds in Group A2, 56.3 seconds in Group B1, 49.2 seconds in Group B2, 24.7 seconds in Group C1, 25.35 seconds in Group C2, 25.3 seconds in Group D1 and 25 seconds in Group D2. Out of 20 patients, 10 had severe injury, 4 had moderate and 7 had mild injury [Figure 4]. Among 7 patients who were intubated and ventilated, 1 patient was ventilated for 1 day, 3 patients for 2 days and 3 patients for 3 days [Figure 5].
Among Patients who consumed lethal dose of yellow phosphorus presenting early and received NAC, 43% had moderate and 43% had severe hepatic injury. Among severe injury, 14% developed fulminant hepatic failure [FHF] and died. Among patients who consumed lethal dose presenting early but not receiving NAC, 33.3% had moderate and 66.7% had severe hepatic injury. All severe cases in this group developed FHF with mortality of 100%. Patients presenting late after consumption of lethal dose, who receive did not NAC had 100 % severe injury and all developed FHF with mortality of 100%. Patients consuming sub lethal dose had 100% survival without hepatic damage. Standard Deviation of Liver Function Tests and severity among sub groups are given in TABLE 1 and 2.
## TABLE 1: STANDARD DEVIATION OF LIVER FUNCTION TESTS AMONG SUB GROUPS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A1</th>
<th>A2</th>
<th>B1</th>
<th>B2</th>
<th>C1</th>
<th>C2</th>
<th>D1</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT (IU)</td>
<td>29.88</td>
<td>515.33</td>
<td>16.97</td>
<td>82.02</td>
<td>1.41</td>
<td>4.95</td>
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<tr>
<td>SGPT (IU)</td>
<td>23.00</td>
<td>166.69</td>
<td>63.64</td>
<td>293.45</td>
<td>2.12</td>
<td>10.61</td>
<td>1.41</td>
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<tr>
<td>PT (Sec)</td>
<td>3.68</td>
<td>8.40</td>
<td>1.41</td>
<td>23.33</td>
<td>0.35</td>
<td>0.00</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>0.14</td>
<td>0.69</td>
<td>0.16</td>
<td>0.95</td>
<td>0.03</td>
<td>0.00</td>
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</tr>
<tr>
<td>aPTT (Sec)</td>
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<td>12.50</td>
<td>5.59</td>
<td>9.69</td>
<td>0.00</td>
<td>0.07</td>
<td>0.28</td>
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</table>

### DISCUSSION

Yellow phosphorus, a compound used as rodenticides in India, is a highly systemic toxin when consumed in lethal doses. In our study, the male: female ratio for suicidal or accidental consumption of yellow phosphorus poison was 1.6:1. It was quoted in the journal of forensic medicine, a study conducted in southern India that male were predominantly affected by poisoning with male female ratio of 2.8:1 (6).

The lethal dose for consuming yellow phosphorus was more than 1mg /kg and 62% of patients of this study had consumed lethal dose. The mortality rate of the patient who received NAC was significantly low as 14.3% where as in those who did not receive was 66.7%. This is probably attributed to the anti Oxidant property and hepatoprotective nature of NAC.

NAC role in yellow phosphorus has been quoted in some journals and text as mentioned below in having a role in the management of yellow phosphorus poisoning and here it may be recommended that we may use NAC as an adjuvant therapy in hospital based yellow phosphorus poisoning management protocol.

Flanagan RJ et al, Poisons Unit, Guy’s Hospital, London mentions the use of N-acetylcysteine in clinical toxicology and states that NAC may have a role in yellow phosphorus poisoning (7).

Baumgardner JN, Shankar K et al, Departments of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, USA studied the role of NAC in a rat model of nonalcoholic steatohepatitis and demonstrated that NAC prevents many aspects of NASH progression by decreasing development of oxidative stress and subsequent increases in TNF alpha but does not block development of steatosis (8).

Goldfrank’s toxicology emergencies by Lewis R Goldfrank and Medical toxicology by Richard C Dart quotes that as NAC is a benign therapy, it is recommended that it may be used in treatment of yellow phosphorus poisoning (9).


This study noted that patient’s presenting within 24 hours of consumption of this poison had significantly higher survival chances and this may be attributed to significant toxin removal by effective gastric lavage, use of activated multi dose charcoal decontamination and use of NAC. 66.6% of these patients had also received NAC during their management.

Patients who consumed sub lethal dose [33.33%] had showed no significant hepatic injury whether presented...
early or late and who received or did not receive NAC. Hence quantification of poison consumption may help physicians to predict the severity scoring.

Survival may be improved in patients developing clinical hepatic injury transforming to fulminant hepatic failure with early liver transplantation.

CONCLUSION
The use of NAC as an adjuvant in the management in yellow phosphorus poisoning improves survival when presented early to emergency room.

REFERENCES
7. Flanagan RJ et al, Poisons Unit,Guy’s Hospital, London mentions the use of N-acetylcysteine in clinical toxicology and states that NAC may have a role in yellowphosphorus poisoning.
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9. Goldfrank's toxicologic emergencies by Lewis R Goldfrank quotes that as NAC is a benign therapy, it is recommended that it may be used in treatment of yellow phosphorus poisoning.
11. Emel Ahishali et al, Dr. Lütfi Kirdar Kardal Education and Training Hospital, Istanbul published a case report of severe acute hepatitis due to oral intake of yellow phosphorus and used NAC in the management of this case.
12. Michael Christian, MD et al published case reports of phosphorus poisoning and quoted that NAC ,can be administered if evidence of phosphorous-induced hepatotoxicity.