Effect of N-Acetylcysteine Therapy on Mortality Rate in Patients of Acute Aluminium Phosphide Poisoning

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Abstract

Objective: To determine the effect of N-acetylcysteine therapy on mortality rate in patients of acute aluminium phosphide poisoning.

Method: This Randomized Controlled Trial was conducted in the Department of Medicine, , King Edward Medical University/ Mayo Hospital, Lahore from January 2018 to March 2019. Ninety-six patients with acute aluminium phosphide poisoning were selected via simple random sampling technique. The patients were divided into two groups, group A received supportive management and group B received N-acetylcysteine therapy along with supportive care. The patients were followed up to the primary end points of the study i.e. either discharge from hospital after recovery or death. Relevant information was recorded on a pre-designed proforma. Data analysis was done using SPSS Version 23.0.

Results: Out of a total of 96 patients, 50(52.1 %) were males and 46(47.9 %) were females. Mean age of the patients was 27.5± 9.8 years. In Group A (supportive therapy), 29(60.4%) patients died while 19(39.6%) were discharged after recovery. In Group B (N-acetylcysteine + supportive therapy), 17(35.4%) patients died while 31(64.6%) were discharged after recovery. N-acetylcysteine therapy significantly reduced mortality in patients with acute aluminium phosphide poisoning (p=0.024)

Conclusion: N-acetylcysteine in combination with supportive therapy significantly reduced mortality rate in patients with acute aluminum phosphide poisoning compared to supportive therapy alone.

Keywords: Aluminum Phosphide, N-acetylcysteine, Supportive Therapy.

How to cite: *Ashraf S, Nazar T, Aziz B, Farooq H, Nazar N. Effect of N-acetylcysteine Therapy on Mortality Rate in Patients of Acute Aluminium Phosphide Poisoning. Esculapio - JSIMS 2022;18(03):324-328*

DOI: https://doi.org/10.51273/esc22.2518317

Introduction

Aluminum phosphide(AlP) tablets, commonly referred to as Wheat Pills are used as fumigant, rodenticide and pesticide in closed grain storages in rural areas.[1] Because it is inexpensive and readily available, it is commonly used for suicide especially by people of third world countries leading to hundreds and thousands of deaths yearly.[2] India reported its first cases of AlP poisoning in 1980s. Ever since, innumerable cases of AlP poisoning have been reported in Pakistan, India, Iran, Sri Lanka, Morocco and other developing countries. Effectees are mainly inhabitants of rural areas and mostly young males and females.[3]

AlP exerts its toxicity through phosphine gas which is released when its tablet reacts with atmospheric moisture. The powder residue left after phosphine gas is released consists of aluminium hydroxide which has a low potential for causing toxicity.

The proposed mechanisms of phosphine toxicity include overactive acetylcholine signaling, reduction of cellular metabolism and increased production of free radicals.[4]

Once ingested, AlP reacts with water and acid in stomach,

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Submission Date: 18/06/2022
1st Revision Date: 03-07-2022
Acceptance Date: 31-08-2022

producing phosphine gas which causes local and systemic toxicity.[5] Local effects are mainly corrosive including gastric irritation, epigastric pain, nausea, vomiting, diarrhea and later on dysphagia and esophageal strictures.[6] Findings on upper gastrointestinal endoscopy include gastric and duodenal erosions and hyperemia of gastric mucosa. Cases of upper gastrointestinal bleed and acute liver failure have also been reported. [7]

Systemically, it increases oxidative stress that triggers apoptosis and eventually cell necrosis.

Cardiac manifestations result from toxicity of cardiac myocytes leading to atrial and ventricular dilatation resulting in reduced left ventricular ejection fraction.[8] This toxic myocarditis causes hypotension which is refractory to inotropic support. Persistent cardiogenic shock leads to acute kidney injury and further worsens metabolic acidosis. Cardiac myocyte dysfunction can also lead to cardiac dysrhythmias. Restlessness, anxiety, seizures, coma, hypo or hyperglycemia, electrolyte imbalance, aspiration pneumonitis, acute respiratory distress syndrome also occur.[5,9] Cases of methemoglobinemia and intravascular hemolysis secondary to AlP have also been reported in literature.[10]

Diagnosis of AlP poisoning is based on history, presence of the material ingested and silver nitrate test.[11] Management of AlP poisoning is mainly supportive.[5,12] On presentation, firstly gastric lavage with edible oil, diluted potassium permanganate (1:10000) or sodium bicarbonate is done.[13] Specific treatment includes magnesium sulphate that reduces frequency of cardiac dysrhythmias and reduction in overall mortality, from no reduction to significant reduction in mortality rates.[14] In a study by Goharbari MH et al, liothyronine 50µg when administered through nasogastric tube, improved arterial blood pressure, pH and lipid peroxidation.[15]

Another study conducted by Halvaei Z et al showed improved systolic blood pressure, oxidative stress and mortality rate with antioxidant vitamin E therapy.[16] Mohan B et al showed significantly reduced mortality rate in patients who received extracorporeal membrane oxygenation therapy along with supportive therapy as compared to the patients who received only supportive treatment.[17] On the basis of its important role in mitochondrial electron transport chain, coenzyme Q10 therapy has been proposed by Marashi SM et al for management of acute AlP poisoning.[18] Numerous studies have shown the beneficial effect of N-acetylcysteine (NAC) mainly attributable to its antioxidant effect. Results have also shown comparatively reduced rates of mortality in patient groups treated with oral or intravenous NAC but reduction was not shown to be statistically significant. One study by Bhalla A et al showed no mortality benefit of intravenous NAC therapy.[19]

Material and Methods

This Randomized Controlled Trial was conducted in the Department of Medicine, King Edward Medical University/ Mayo Hospital, Lahore from January 2018 to March 2019. A sample size of 96 patients (48 patients in each group) was taken using 90% power of test, 5% level of significance and by taking expected percentage of mortality with supportive therapy and supportive therapy + NAC therapy as 81.8% and 54.2% respectively.[20] Simple random sampling technique was applied in selecting the patients. Patients of either sex between the age of 14-60 years with history of AlP (wheat pill) ingestion, confirmed with silver nitrate test or material documentation and presenting within 24 hours of ingestion were included in the study. History of ingestion of multiple poisons, known hypersensitivity to NAC and cardiopulmonary resuscitation on presentation resulted in exclusion from the study. After getting approval from the Board of Studies (BOS) and Institutional Review Board (IRB) of King Edward Medical University, 96 patients conforming to the inclusion criteria were enrolled in the trial. Informed written and verbal consent was taken from the patients or their first degree relatives. Patients' demographic data was obtained. At the time of presentation to medical emergency, initial resuscitative measures including stomach wash was done. The patients were then divided into two groups A and B by computer generated method. Patients in group 'A' received supportive care, that included intensive monitoring, adequate hydration, MgSO4 2g I/V 4-6 hourly, inotropic support (dopamine, dobutamine, norepinephrine) and ventilatory support as required. While the patients in group 'B' received N-acetylcysteine therapy (140mg/kg PO loading dose followed by 70mg/kg PO, 4 hourly for 72 hours) in addition to supportive care. Laboratory investigations like complete blood count (CBC), Liver function tests(LFTs) including serum ALT, AST, alkaline phosphatase and bilirubin levels, Renal profile including serum creatinine, blood urea nitrogen, cardiac biomarkers like serum LDH, serum CK-MB, arterial blood gas analysis, urine complete and electrocardiography were carried out at the time of presentation. The patients were followed up to the primary end points of the study i.e. either discharge from hospital after recovery or death. The study variables

included age, gender, outcome (death or discharge after recovery), number of ingested tablets, time after ingestion till presentation to emergency room and blood pressure at presentation. All this information was recorded on a predesigned proforma. Data was analyzed using Statistical Package for Social Science (SPSS) Version 23.0. Quantitative variables like age, number of tablets ingested, time after ingestion till presentation to hospital, systolic and diastolic blood pressure at presentation were presented as mean±SD. Qualitative data like gender and primary outcome were presented as frequency tables, percentages and appropriate charts. Chi-square test was used to compare mortality between the two groups. P value<0.05 was considered significant.

Results

Out of a total of 96 patients, 48 (50%) in each group, 50(52.1 %) were males and 46(47.9 %) were females with a mean age of 27.5± 9.8 years. Mean time taken from ingestion to presentation to Mayo Hospital was 4.94± 4.11 hours. Mean systolic and diastolic blood pressure at presentation was 88.75± 40.73 mmHg and 55.31± 29.62 mmHg respectively. Out of 96 patients, 46(47.9 %) died in hospital while 50(52.1 %) were discharged after recovery. In group A, 29(60.4%) patients died while 19(39.6%) were discharged after recovery while in group B, 17(35.4%) patients died while 31 (64.6%) were discharged after recovery. Means of variables along with their standard deviation is depicted in Table 1 and comparison of means between the two groups analyzed with Independent Sample t-test is shown in Table 2. Table 3 shows therapy outcome.

Table 1: *Means of Variables*

	Age (years)	No. of Tablets Ingested	Time from ingestion to presentation (hours)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Mean	27.5	1.37	4.94	88.75	55.31
Std. Deviation	9.8	0.83	4.11	40.73	29.62

Table 2: *Comparison of Means in Therapy Groups*

Variable	Mean in supportive therapy group	Mean in NAC + Supportive therapy group	Sig. (2 tailed)
Age	27.13± 10.21	27.83± 9.42	0.73
Tabs ingested	1.44 ± 0.94	1.3 ± 0.7	0.41
Time to presentation(hours)	4.61 ± 3.12	5.26 ± 4.92	0.44
Systolic BP	83.74 ± 45.5	93.33 ± 34.89	0.25
Diastolic BP	52.92 ± 30.73	57.29 ± 28.41	0.47

Table 2: *Comparison of Means in Therapy Groups*

		Outcome		Total
		death	recovery	
Therapy NAC+ supportive	Count	17	31	48
	% within Therapy	35.4%	64.6%	100.0%
supportive	Count	29	19	48
	% within Therapy	60.4%	39.6%	100.0%
Total	Count	46	50	96
	% within Therapy	47.9%	52.1%	100.0%

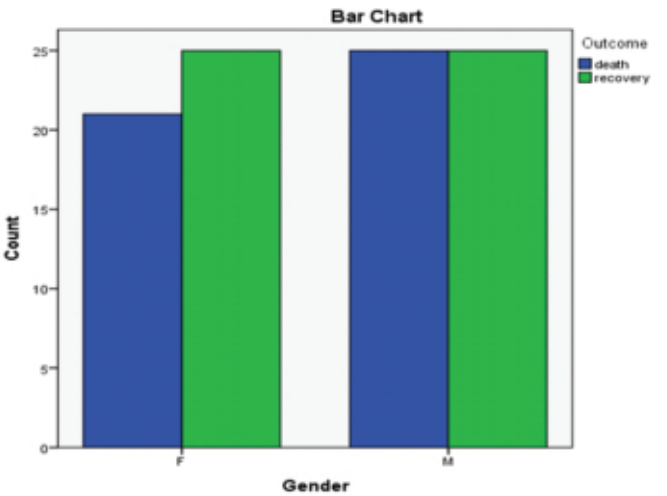

Fig-1: *Gender and outcome distribution*

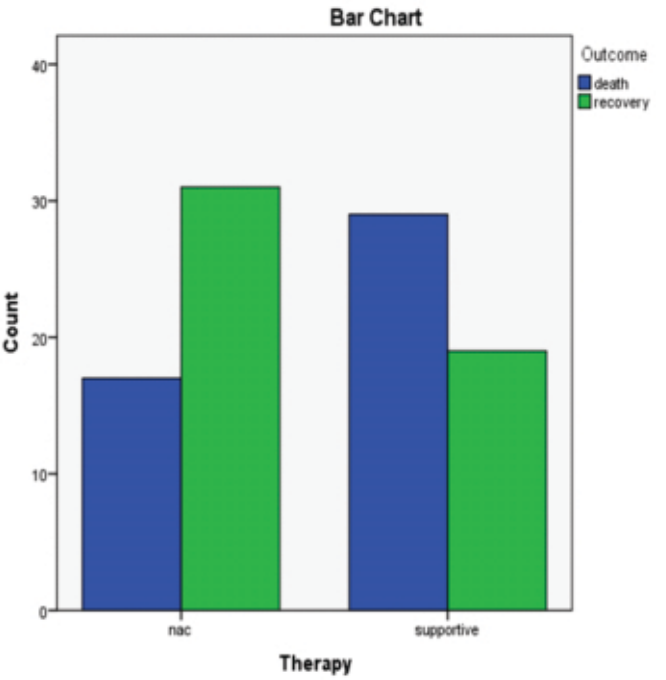

Fig-2: *Therapy and Outcome Distribution*

Discussion

This study was conducted to determine the effect of N-acetylcysteine (NAC) therapy on mortality rate in patients of acute aluminium phosphide poisoning and a significant improvement in primary outcome (mortality rate) was observed. Mortality rate was 60.4 % in supportive therapy group and 35.4 % in patient group treated with NAC along with supportive therapy, with p value of 0.024, hence showing statistically significant reduction of 25% in mortality rate. The results were comparable to the previous studies conducted by Tehrani H et al and Agarwal A et al, who observed 24% and 27% reduction in mortality rates, respectively, with NAC therapy.[21,22] However the results differed greatly to the study by Taghaddosinejad F et al who did not observe any statistically significant reduction in mortality rate with NAC therapy.[19] Overall mortality rate was 47.9%, in line with the range of 33% to 87% reported in literature.[8,9]

Most of the patients in this study were young and there was no gender predominance. This was opposed to the observation in the study by Agarwal A et al that predominantly involved male patients.[22] No significant gender bias was noted in relation to outcome (mortality rate). Mean values of age, number of tablets ingested, time taken from intake to presentation, systolic and diastolic blood pressure at presentation were comparable in both groups leading to reduction in bias. Aluminum phosphide poisoning has very high mortality rates ranging from 33% to 87% according to different studies.[8,9] Intake of more than one tablets, hypotension, cardiac dysrhythmia, metabolic acidosis, development of acute kidney injury, high Sequential Organ Failure Assessment (SOFA) score, high Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score and need for mechanical ventilation have been shown to be important predictors of mortality.[8] The patients that survive the acute episode make good recovery without any major long term organ dysfunction. Some survivors may develop gastrointestinal symptoms due to local damage caused by phosphine gas. Cases of esophageal stricture and tracheo-esophageal fistula formation after Aluminium phosphide poisoning have been reported.[6] Survivors also need psychosocial counselling to avoid further incidence of self-harm.

Aluminium phosphide tablets are increasingly being used as poison for self-harm in rural areas of Pakistan. Given its high rates of mortality, it is important to strive for finding further modalities of treatment in order to minimize mortality from aluminium phosphide poisoning. No specific antidote has been described to date. Melatonin has shown promising results in animal studies. In a study by Halvaei Z et al, vitamin E therapy significantly improved antioxidant capacity and survival.[16] A case report by Oghabian Z et al described successful treatment of a case of aluminum phosphide poisoning with combination of NAC and vitamin C.[23]

Although the interventions described above show protective effects to various degrees, the mortality rates are still very high even with the use of these therapies. Even in this study, although mortality rate was reduced with NAC therapy but it was still too high at 35%. Better interventions are needed to reduce mortality rates further with a goal to bring survival rates to near 100%. Reduction of oxidative stress is an important target for further research. While the search for better interventions is ongoing, NAC has shown promising results in current scenario. Protective role of NAC needs to be studied further. Double blind randomized controlled studies and meta-analysis of currently available data is needed to produce better quality evidence in favor of routine use of NAC therapy in patients of acute AlP poisoning. Synergistic effect of NAC therapy in combination with other interventions like vitamin E, vitamin C, Melatonin, early CRRT and IOBP, also needs to be further explored. And finally, the supply side dynamics need to be improved. Easy availability of AlP tablets needs to be checked. Use of alternative, less toxic fumigants needs to be encouraged.

Conclusion

Aluminum phosphide (wheat pill) is a lethal toxin with high in-hospital mortality rate. Currently, supportive therapy is the mainstay of management in such patients. In this study, statistically significant reduction in mortality rate was observed with oral N-acetylcysteine therapy. Beneficial effect of NAC therapy alone and in combination with other emerging interventions needs to be further explored.

Conflicts of interest *None*

Funding Source *None*

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Authors Contribution

SA: Conceptualization of Project
BA: Data Collection
BA: Literature Search
BA: Statistical Analysis
HF, NN: Drafting, Revision
HF, NN: Writing of Manuscript