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Role of aggressive management on outcome in patients of acute aluminium phosphide poisoning

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Abstract

Aluminium phosphide poisoning is a common medical emergency in the Northern parts of India and South-East Asian nations. This poison is known to have high mortality ranging from 50% to 90% at various medical centres. In the absence of an antidote, an aggressive management is the need of the hour for reducing the mortality. A retrospective analysis of a set of variables was conducted on a group of 25 patients, followed by a prospective study of the same variables on a group of 25 consecutive patients who were enrolled into the study. Both the groups differed from each other principally in terms of management. The outcome of the management in both the groups were studied and analysed statistically. Factors strongly associated with mortality were consumption of fresh tablets, duration between consumption and treatment, low Glasgow coma scale (GCS), low mean arterial pressure (MAP) and metabolic acidosis. The group managed aggressively had lesser mortality rates than the group managed conservatively. Aggressive treatment benefitted even those individuals in whom prognostic variables were adverse. Aggressive management consisting of thorough gastric lavage, good fluid management, correction of metabolic acidosis, administration of magnesium sulphate, hydrocortisone and vitamin C has reduced the mortality rates in acute aluminium phosphide poisoning.

Keywords: Celphos- trade name of aluminium phosphide; Lactic acidosis; Bicarbonate therapy

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Introduction

Aluminium phosphide (Celphos) poisoning is a very common medical emergency, accounting for nearly 40% of all poisoning cases and also comprises ~40% of all fatalities happening due to poisoning in the South and South –East Asian nations.[1-6] The use of aluminium phosphide as a pesticide in granaries and its easy availability has been the reason for the common occurrence of this poisoning.

Immediately after opening of the celphos packets or tins, the tablet comes in contact with moisture, releases phosphine gas (PH3) and henceforth loses its toxicity slowly. A fresh tablet on ingestion mixes with the aqueous solutions in the stomach and immediately releases phosphine gas which is absorbed rapidly via lungs causing systemic poisoning.

The phosphine, that is absorbed, is known to inhibit key enzymes of cell respiration like cytochrome oxidase. *Chugh et al.* have shown that ingestion leads to high superoxide dismutase activity and low catalase levels that result in increased formation of free radicals and accelerated lipid peroxidation.[5] Lipid peroxidation in turn results in damage and disruption of ionic barrier, nucleic acid damage and cell death. It also interacts with the redox chain components leading to the impairment of electron transfer along the respiratory chain. Moreover, all these inhibitions were found to be "irreversible". As a result the cell suffers from hypoxia leading to irreversible

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cell injury, accumulation of lactic acid and eventually necrosis.[6-8]

The cardiac myocytes and capillary endothelial cells were found to be involved in the initial stages resulting in myocardial cell necrosis and endothelial dysfunction. Metabolic acidosis, secondary to lactic acid accumulation, predisposes the patient to potentially fatal ventricular arrhythmias, and can reduce cardiac contractility and the inotropic response to catecholamines, resulting in hypotension and congestive heart failure. This cardiovascular failure has been documented as the main cause of early mortality in this poisoning.[9] Understandably, any attempts in breaking the vicious cycle of metabolic acidosis and cardiovascular failure would reduce the mortality rates. A newly designed management protocol directed at combating metabolic acidosis with a target pH value of 7.25 has helped in reducing the mortality rates, as observed in our study. In this study we have also analysed the prognostic factors associated with mortality in two groups of patients, who differed from each other principally in terms of management.

Materials and Methodology

This study was conducted on the patients who were admitted in the emergency ward of the Department of Medicine, King George's Medical University, Lucknow, India, from January 2015 to August 2015. All those patients with history and clinical signs suggestive of celphos ingestion, such as garlic odour in breath, shock and metabolic acidosis were included in the study. Those with doubtful history, absence of clinical features of celphos poisoning and those with features of concomitant poisoning with any other agent were excluded from the study.

Retrospective analysis of 25 successive patients of suspected celphos poisoning, who were managed conservatively, was done with the help of the data obtained from the medical records of our Department, before December 2015. This set of 25 patients were named group 1. An 'aggressive' management was given in the 25 consecutive patients of suspected celphos poisoning, admitted into the department from January 2015 and labelled as group 2. Prospective study of various factors was done in this group of patients. At the end of the study, both the group of patients were compared on various variables including mortality rates.

The age, gender, type (exposed or fresh) and number of aluminium phosphide tablets consumed, the number of episodes of vomiting and time of consumption was noted. The pulse rate, blood pressure, respiratory rate and GCS of the patients were noted at the time of admission. Complete blood counts, random blood sugars, serum electrolytes, liver functions and renal functions were also studied in both the groups.

Conventional management (in group 1) included management of shock with I.V fluids (2-3 litres in the first 3 hours) and in the presence of refractory hypotension vasopressors were used (dopamine and/or noradrenaline starting at 10μg/kg/min and 0.3μg/kg/min respectively), along with continuos administration of fluids. Bicarbonate correction was given when arterial blood pH was below 7.1, based on the calculation of standardised base excess (as reported in the ABG analysis strip). Intravenous hydrocortisone 100 mg was administered every 8 hours. Magnesium sulphate was given at doses of 2 g I.V. stat followed by 1 g in infusion every 8 hours for 3 days.[10, 11]

Aggressive Management carried out in group 2, included management of shock (MAP ≤65mmHg) with normal saline (20 ml/kg/hr) and colloids (1 litre/hr) with simultaneous clinical monitoring of bilateral lung fields, central venous pressure and O2 saturation (SO2).The doses were titrated according to urine output (minimum of 0.5 ml/kg/hr was targeted). Steroid (Hydrocortisone) 100 mg stat followed by 100 mg every 8 hours was administered. Vasopressors (dopamine and when needed noradrenaline) were used according to MAP. Dobutamine was used to augment cardiac activity at doses of 5 μg/kg/hr when systolic blood pressure was above 90 mmHg.

ECGs and arterial blood gases were analysed every 8 hours. Bicarbonate correction was given when arterial blood pH was below 7.25, based on the calculation of base excess. The full amount of bicarbonate as revealed by the standardised base excess in the ABG analysis strip was administered in slow infusion over a period of 8 hours. This correction continued till the target was achieved and maintained over a period of at least 24 hours. Bicarbonate therapy was given under careful monitoring of the vitals, for the probable side effects like that of arrhythmias, hypokalemia and pulmonary edema.

Patients with paO2 less than 60 mmHg were administered oxygen. Those with GCS score ≤8 had to be given mechanical ventilator support. vitamin C was given in doses of 2 g IV stat followed by 2 g every 8 hours

by IV infusion. Magnesium sulphate was administered in doses of 2 g IV stat followed by 1 g in infusion every 8 hours, with monitoring of ECGs, urine output, knee jerk and respiratory rates. Serum magnesium levels were monitored. The dosages of steroids, vitamin C and magnesium sulphate were reduced and withdrawn once clinical stability (defined by adequate urine output of 0.5 ml/kg/hr and MAP > 65 mmHg for more than 24 hours) was achieved. The outcome of such an aggressive management was noted.

The quantitative variables were presented in terms of mean± standard deviation, and qualitative variables were presented in terms of total number and percentage. Statistical analysis was performed using software *Stata version 13 Texas, US*. Comparisons between group 1 and group 2 patients were made by Mann-Whitney U test/ two sample t-tests for quantitative data and Fisher Exact test for categorical data. *P* values of less than 0.05 were considered to indicate statistical significance. A multivariate logistic regression analysis was performed to identify factors independently associated with mortality.

Results and Discussion

Aggressive management differed from conventional management in terms of a better fluid management, early initiation of dopamine, correction of metabolic acidosis with a target pH of 7.25 and administration of vitamin C. In our study, all these ingredients of aggressive management collectively brought down the mortality rates from 88 % in group 1 to 24 % in group 2. Reported mortality in earlier studies ranged from 50% to 90%, which is comparable to our observations in group 1.[13] The mean age of presentation, was 28.3±8 years. Prevalence of celphos poisoning was more among males and in age group more than 20 years.

We compared the two treatment groups for any significant differences with respect to prognostic factors (Table 1) and found that, both the groups were similar in all the variables, except for consumption to treatment time (significantly shorter in group 2 patients), the number of patients presenting with consumption of fresh tablets, and the number of patients admitted with low GCS (significantly smaller in group 2). Favourable disposition of these three variables do potentially contribute for a higher survival in group 2 patients. However a stratified analysis (mentioned below) showed that aggressive management benefitted the patients in group 2, even in the presence of the above mentioned adverse factors. A post-hoc power analysis show that, for this effect size beta error is 0.002 (power 99.8%) and corresponding alpha error is 0.0139 with the sample size of 25 in each arm and two tailed rejection region.

Table 1. Comparison of variables between two Groups

Variables	Group 1 (n=25)		Group 2 (n=25)		P value[a]
	Mean ±SD	Median (Min, Max)	Mean±SD	Median (Min,Max)	
Age (yrs.)	29.64±9.1	25 (14,52)	26.96±6.5	25 (19,42)	0.296
Mean number of tablets	1.72±0.9	1.5(0.5,4)	1.62±1	1(0.5,5)	0.451
Consumption to treatment time (hrs.)	5.36±1.9	5(2,10)	4.28±1.8	4(2,8.5)	0.043
MAP(mmHg)	37.96±35.9	43(0,107)	55.72±31.2	63(0,97)	0.05
GCS	9.88±4.4	10(3,15)	13±3.3	15(3,15)	0.007
Fresh tablets	21		10		
Exposed tablets	4		15		
					0.003
Shock	19		17		0.753
GCS ≤ 8	10		4		0.113
Survivors	3		19		0.001
Non-survivors	22		6		

[a]Denotes P value on comparing Group 1 and Group 2,Group 1-Conventionally managed, Group 2-Aggressively managed, MAP-Mean arterial pressure, GCS-Glasgow Coma Scale

We studied 19 variables (age, sex, mean number of tablets consumed, consumption of fresh tablets, mean of consumption to treatment time, mean arterial pressure at the time of presentation, GCS score, mean hemoglobin, mean total leucocyte count, mean random blood sugar levels, mean sodium levels, mean potassium levels, mean serum bilirubin, mean alanine aminotransferase levels, mean serum creatinine levels, mean pH levels, mean serum bicarbonate levels, troponin T positivity and presence of ECG changes) for any significant association with mortality. Factors with strong association with mortality in descending order were consumption of fresh tablets, longer duration between consumption and treatment, low GCS, low MAP, metabolic acidosis (Table 2). Various studies have elicited the same variables (except consumption of fresh tablets) as significant prognostic indicators in celphos poisoning.[12]

Stratified analysis of survival among individuals exposed to consumption of fresh tablets, longer elapsed time ($\geq$ 5 hrs) between consumption of celphos and initiation of treatment and GCS score < 12 (an arbitrary cut off used to facilitate analysis as none survived at GCS < 8) showed that while none in group 1 survived, about a third to a half of such patients survived in group 2 (Table 3), clearly reflecting that the aggressive treatment benefitted even those individuals in whom prognostic variables were adverse.

The aforementioned variables, which were found to be

Table 2. Association of factors with mortality in both the groups

Variables	Survivors		Non survivors		P value [a]
	Group 1	Group 2	Group 1	Group 2	
	Mean ±sd (n=3)	Mean ±sd (n=19)	Mean ±sd (n=22)	Mean ±sd (n=6)	
Age (years)	26±5.3	27.37±6	30.14± 9.5	25.67±8.5	0.568
Mean no.of tablets	1.33±0.8	1.5±0.8	1.77±0.9	2±1.5	0.003
Consumption to treatment time (hours)	3±1	3.76±1.5	5.68±1.8	5.92±1.5	<0.001
Map (mmhg)	81.3±25	64.89±21.3	32.05± 33.3	26.67± 41.3	<0.001
GCS	15±0	14.42±1.1	9.18±4.2	8.5±4.1	<0.001
GCS≤8	0	0	10	4	<0.001
GCS<12*	0 (0.0%)	3 (37.5%)	17 (100.0%)	5 (62.5%)	0.024
pH	7.28±0.05	7.26±0.1	7.2±0.1	7.2±0.2	0.003
Consumption of fresh tablets	0 (0.0%)	6 (60.0%)	21 (100.0%)	4 (40.0%)	<0.001
Consumption to treatment time (>5hours*)	0 (0.0%)	6 (54.5%)	18 (100.0%)	5 (45.5%)	<0.001

[a] Denotes P value on comparing non-survivors and survivors.
*Arbitrary cut-off used to facilitate comparison
Group 1-conventionally managed, Group 2-Aggressively managed, MAP-Mean Arterial Pressure, GCS-Glasgow Coma Scale

Table 3. Comparison of adverse factors between the 2 groups

Adverse Factor	Conservative Treatment (Group 1)		Aggressive Treatment (Group 2)		Fisher's Exact Probability
	Total	Survived	Total	Survived	
Consumed Fresh Tablets	21	0	10	6	<0.0003
Treatment started 5 hrs. after consumption of Tablets	18	0	11	6	<0.001
GCS Score < 12*	17	0	8	3	=0.024

*Arbitrary cut off used to facilitate comparison

significantly associated with mortality, were considered for logistic regression to adjust for confounders (Table 4). All patients with low GCS (≤8) expired and hence were not included in the logistic regression analysis. However, the effect of aggressive management was adjusted with the number of fresh tablets consumed and mean of consumption to treatment time (on a continuous scale). We observed that aggressive management (odds ratio of 0.03, p=0.001) had a significant role in reducing the mortality. This further substantiates our earlier observation about the beneficial role of aggressive management in reducing mortality even in the presence of adverse prognostic factors.

Table 4. Logistic regression analysis

Variables	Odds ratio (95% C.I)	P Value
Aggressive management	0.03(0.003, 0.21)	0.001
Fresh tablets	1.18 (0.48, 2.89)	0.725
Consumption to treatment time	2.58 (1.30, 5.12)	0.007

Log likelihood = -15.962557, Pseudo R^2=0.5346, CI=confidence interval

The whole concept of aggressive management centres on the "effective" correction of metabolic acidosis along with good fluid management. Numerous studies in the past have found metabolic acidosis as the main culprit behind the cardiovascular instability and early mortality in aluminium phosphide poisoning

A normally functioning liver is essential for the body to regenerate bicarbonate from lactate (Cori's cycle). At the least, the cause for lactic acidosis has to be reversible (as in diabetic ketoacidosis), so that we could delay the administration of bicarbonate therapy. Keeping in mind the probable blunted response of the liver and the irreversible cause of lactic acidosis and its detrimental effects on the cardiovascular system in aluminium phosphide poisoning, it is prudent to initialise and maintain bicarbonate therapy with a target pH of 7.25. A few studies conducted in the past have also confirmed the importance of full correction of metabolic acidosis in this poisoning.[13]

Consumption of fresh tablets leading to high mortality is a significant and a unique finding in our study. This lays importance on interrogating the patient or their bystanders on the exposure of the Celphos tablets consumed. This finding is explainable as the older tablets may have a lesser potency than the fresh ones, due to release of phosphine gas from the tablets with time. The median lethal dose of celphos tablets irrespective of exposure was 1.5 tablets (4.5g).

Conclusion

This study stresses the collective effect of thorough gastric lavage, good fluid management, prompt and full correction of metabolic acidosis with a target pH of 7.25 in reducing the mortality rates. A meta analysis of similar studies on bicarbonate therapy in metabolic acidosis can help in advocating the need for a lower threshold for intiation of bicarbonate therapy in aluminium phosphide poisoning.

Aluminium phosphide poisoning has claimed many lives in the northern parts of India and so in many developing countries due to widespread use and easy accessibility. An aggressive management, as adopted in our study, may be helpful in combating this lethal poison.

Conflict of Interest

None Declared

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