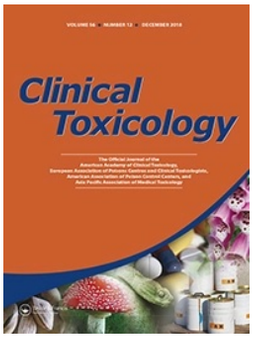

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CLINICAL RESEARCH

Glucose-insulin-potassium infusion for the treatment of acute aluminum phosphide poisoning: an open-label pilot study

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ABSTRACT

Introduction: Acute aluminum phosphide poisoning is common in low- and middle-income countries, and is associated with very high case fatality. The addition of glucose-insulin-potassium (GIK) infusion to the standard supportive care has been proposed to improve outcomes. We aimed to assess the effectiveness of GIK infusion in acute aluminum phosphide toxicity.

Methods: We performed a prospective open-label pilot study in a tertiary care hospital in north India in patients over 13 years of age with acute aluminum phosphide poisoning, to determine whether the treatment with GIK infusion improved outcomes. The primary outcome was in-hospital case fatality, and the secondary outcomes were the duration of hospital stay, the requirement of mechanical ventilation, and the change in hemodynamic and metabolic parameters.

Results: A total of 60 patients were randomly assigned to groups that received either GIK infusion with supportive care or supportive care alone. Baseline parameters in both groups were comparable. Treatment with GIK infusion was associated with significantly lower in-hospital case fatality compared with supportive care alone (46.7% versus 73.3%; *p*-value 0.03). It was associated with a longer duration of hospital stay (*p*-value < 0.01) and reduced requirement of mechanical ventilation (*p*-value < 0.01). The treatment improved blood pressure (systolic, diastolic, and mean arterial pressure) and Glasgow coma scale score at various time intervals; however, pulse rate and metabolic acidosis (blood pH and bicarbonate levels) remained comparable in both the groups. Hyperglycemia was significantly higher in the GIK group but was easily managed.

Conclusion: Treatment with GIK infusion may improve survival and hemodynamics in patients with acute aluminum phosphide poisoning.

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Aluminum phosphide; pesticide; poisoning; glucose-insulin-potassium; hyperinsulinemia-euglycemia treatment

Introduction

Agriculture is a major source of income for large scale Asian population, and the pesticides are readily available in rural areas, which make them the most frequent cause of poisoning after intentional ingestion [1–3]. Aluminum phosphide is a highly effective fumigant against insects and rodents in the preservation of stored grain [4,5]. It accounts for a large number of poisoning cases in India, mainly in the northern states [1,6,7]. The common mode of exposure is intentional ingestion. Aluminum phosphide poisoning is associated with a very high case fatality rate (CFR) ranging from 30–80%, mostly within 24–48 h [8–11].

Aluminum phosphide releases phosphine gas after exposure to the moisture, and this reaction is enhanced by acidity (hydrochloric acid) of the stomach [12]. Phosphine is then rapidly absorbed through the gastrointestinal or respiratory tracts, and it causes toxicity principally through the inhibition of cytochrome C oxidase, a key enzyme of cellular respiration and the production of oxidative free radicles [12–18]. The severe toxidrome of aluminum phosphide poisoning mainly results from the cellular hypoxia and include gastrointestinal upset, circulatory shock, dysrhythmias, and respiratory failure. The garlic smell of the breath is characteristic [15,19–26]. As no antidote is available, the treatment remains supportive, including vasopressors and mechanical ventilation. The poisoning has a high CFR despite high-quality intensive care. Many therapeutic options have been tried, targeting to remove phosgene from gastrointestinal tract or circulation and scavenging free radicals, which include intravenous magnesium sulfate, gastrointestinal decontamination with potassium permanganate, sodium bicarbonate or coconut oil, gastric ventilation, N-acetyl cysteine, intravenous lipid emulsion, whole blood exchange transfusion, and extracorporeal membrane oxygenation [9,12–14,27–37]. However, these treatments either remain controversial or require further studies to confirm their usefulness.

The use of hyperinsulinemia-euglycemia treatment or infusion of GIK in aluminum phosphide poisoning was suggested after its beneficial positive inotropic effect in improving myocardial contractility in patients with severe calcium channel blockers and beta-blockers poisoning [38–50]. Calcium channel blockers overdose often results in metabolic abnormalities resembling diabetic ketoacidosis, i.e. metabolic acidosis, hyperglycemia, and insulin deficiency [50]. Acute aluminum

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phosphide toxicity also has similar metabolic derangements. Phosphine induced production of free radicals and oxidative stress results in insulin resistance and hyperglycemia [45,46]. Hyperglycemia is also a poor prognostic factor in aluminum phosphide poisoning [51].

GIK infusion as a possible treatment of aluminum phosphide poisoning was first used in 2008 in a small number of patients [52]. Later, an Iranian study claimed a favorable outcome and prolongation of hospital stay [53]. On this basis, we conducted a prospective intervention study to determine whether adding GIK infusion to supportive care improves the outcome in adult patients with acute aluminum phosphide poisoning.

Methods

Study design

This is a prospective open-label pilot study, conducted at the adult medical emergency of the department of Internal Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India from July 2016 to December 2017. Ethical clearance was obtained from the Institutional Ethics Committee (No.: INT/IEC/2017/000312).

Study participants

Patients aged above 13 years were enrolled based on the history of ingestion of aluminum phosphide and clinical features (symptoms and signs) compatible with significant aluminum phosphide poisoning (such as garlic smell of the breath, hypotension, or metabolic acidosis) at the presentation during the study period. Hypotension was defined as a systolic blood pressure of $\leq$90 mmHg, and a bicarbonate level of $\leq$15 mEq/L was used to determine metabolic acidosis.

Written informed consent was obtained in all the cases from the patient or their relatives if the patients could not provide the consent. For the patients aged below 18 years, the consent was obtained from both the patients and their parents. Patients were not eligible to enter the study if there was a doubtful history of aluminum phosphide poisoning, the patient had the poisoning with an unknown compound, or more than one compounds were excluded. The patients who died within two hours of enrolment were also excluded mainly since the patients in the intervention group need to show the effects of GIK protocol.

Decontamination of the gastrointestinal tract with gastric lavage was performed within 1 to 2 h of ingestion. In patients with an altered mental state, gastric lavage was carried out only after adequately protecting the airway to avoid aspiration. All patients received primary emergency medical care addressing the airway, breathing, and circulation (ABCs) at admission. For the management of hypotension, norepinephrine was the initial vasopressor of choice.

Laboratory investigations

On enrolment, the patients underwent routine investigations, including plasma blood sugar levels, blood gas analysis, serum electrolytes, renal function tests, serum bilirubin, complete blood counts, 12-lead electrocardiogram, and chest radiograph. Further investigations (including liver chemistry, coagulation profile, cardiac biomarkers, toxicological screening for the other toxicants causing similar toxidrome, ultrasonography, etc.) were performed when judged to be appropriate.

Study groups and regimen

Patients were randomly divided into two groups – the intervention group and the conventional group. The sequence of randomization was computer generated. Because of a vast difference in the nature of the treatments and investigator-participant involvement, blinding to the treatment allocation was not possible. GIK infusion was initiated immediately after enrolment in the intervention group. The insulin preparation used in the study was insulin regular, which is short-acting human insulin, with the onset of action 30 to 45 min, peak at 2–3 h, and effective duration of action 3–6 h. Insulin regular was given as a loading dose of 0.1 to 0.2 IU/kg, followed by an infusion at a rate of 0.2 to 0.5 IU/kg/hr. A plasma glucose level between 150 to 200 mg/dL is maintained by administering intravenous glucose. The glucose infusion is titrated based on bedside blood glucose monitoring at every hour. We defined hyperglycemia as plasma glucose levels of more than 200 mg/dl and hypoglycemia as less than 70 mg/dl. Serum potassium was monitored every 8 h and was replaced to keep serum levels at 3.5 to 4.5 mEq/L. A serum level of less than 3.5 mEq/L was used to describe hypokalemia. GIK infusion was tapered or transiently discontinued when hypoglycemia or hypokalemia did not improve with simultaneous replacement.

After admission and randomization in the medical emergency, the patients were shifted to an emergency department observation unit or an intensive care unit according to the availability of the bed. All patients were under regular observation for their vital signs (systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse rate, respiratory rate, Glasgow coma scale score) and metabolic parameters (blood pH, bicarbonate level) for possible improvement in the hemodynamic and resolution of metabolic acidosis.

Outcomes

Primary outcomes

The intervention group was compared with the control group for the in-hospital CFR.

Secondary outcomes

Duration of the hospital stay, the requirement of mechanical ventilation, and the change in hemodynamic parameters, i.e. systolic and diastolic blood pressure, mean arterial pressure and pulse rate, scores at Glasgow coma scale and metabolic acidosis parameters, i.e. blood pH and bicarbonate levels were the secondary outcomes.

Table 1. Baseline characteristics of the study population[a].

Variable	GIK ($N = 30$)	Control ($N = 30$)
Age (years) (mean ± SD)	31.6 ± 13.2	34.6 ± 16.5
Male sex – no. (%)	18 (60%)	21 (70%)
Time interval between exposure and hospitalization (hours) (median, IQR)	5.0 (0.3–17.0)	3.5 (0.45–48.0)
Systolic blood pressure (mmHg) (mean ± SD)	69.0 ± 8.2	67.2 ± 9.7
Diastolic blood pressure (mmHg) (mean ± SD)	46.1 ± 7.0	44.7 ± 5.1
Mean arterial pressure (mmHg) (mean ± SD)	54.7 ± 6.8	52.2 ± 5.6
Pulse rate (per minutes) (mean ± SD)	105.5 ± 21.2	95.4 ± 20.9
Respiratory rate (per minute) (mean ± SD)	24.8 ± 2.7	23.9 ± 3.4
Score on Glasgow coma scale[#] (mean ± SD)	13.3 ± 2.4	11.9 ± 4.5
Blood pH (mean ± SD)	7.13 ± 0.23	7.09 ± 0.21
Bicarbonate (mEq/L) (mean ± SD)	10.5 ± 6.1	10.5 ± 6.6
PCO_2 (mm Hg) (mean ± SD)	26.4 ± 10.3	29.2 ± 11.5
Hemoglobin (g/dL) (mean ± SD)	11.8 ± 2.2	12.7 ± 1.6
White blood cells (per μL) (mean ± SD)	14989 ± 5798	16579 ± 7780
Platelet counts (per μL) (mean ± SD)	212500 ± 107371	219241 ± 92651
Random plasma glucose (mg/dL) (mean ± SD)	145.7 ± 70.0	115.3 ± 59.5
Serum sodium (mEq/L) (mean ± SD)	139.5 ± 5.4	140.9 ± 7.1
Serum potassium (mEq/L) (mean ± SD)	3.9 ± 0.7	4.0 ± 0.5
Serum creatinine (mg/dL) (mean ± SD)	1.4 ± 0.9	1.3 ± 0.6

[#]Scores on the Glasgow Coma Scale range from 3 (worst) to 15 (best), with 13 or higher indicating only mild cerebral dysfunction.
PCO_2: Partial pressure of arterial carbon dioxide.
[a]No significant differences between the groups.

All clinical symptoms, signs, complications, and interventions (including invasive ventilation, if used) were recorded.

Statistical analysis

The data was fed into Microsoft excel and was analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 21.0. The normalcy of data was checked by the Kolmogorov-Smirnov test. The mean and median of the parameters were obtained. These were compared for any significant difference before and after treatment and at discharge or death. Categorical variables, including CFR, were presented in percentages and were tested for the difference using Chi-square test and Fisher's exact test. Continuous variables were analyzed, depending on whether data was normal in distribution. Unpaired student's t-test was used for parametric variables, whereas the paired t-test was used for comparing the change in hemodynamic and metabolic parameters before and after treatment. Kaplan-Meier survival analysis was done for the length of time after enrollment until the occurrence of the primary endpoint (CFR) for the intervention and control treatment group. The *p*-value for significance was set at ≤ 0.05.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the research data and had final responsibility for the decision to submit for publication.

Results

Participants and baseline characteristics

A total of 60 patients were assigned to receive either GIK infusion (intervention group, 30 patients), and supportive care alone (conventional or control group, 30 patients). The baseline characteristics at enrolment were similar between the groups (Table 1). Most patients were young, and the age group 20–39 years constituted more than half of the patients ($N = 33$, 55%). Males were predominant in both groups.

All study patients had ingestion of aluminum phosphide. The median time interval between ingestion and hospitalization for the study was 4 h (IQR, 0.3–48.0). Median time interval to admission remained the same for both survivors and non-survivors (4 h with IQR 0.3–17.0 and 4 h with IQR 1.15–48.0, respectively), thus did not affect case fatality in this study.

All patients had clinical or laboratory features of acute aluminum phosphide poisoning at presentation. Hypotension was the most common clinical manifestation. It was present in all except one. The most frequent laboratory abnormality was metabolic acidosis, 48 out of 60 patients (80%) had it at presentation.

In the intervention group, the mean duration of insulin infusion was 29.13 (±13.04) hours, and the mean dose of insulin used was 379.3 (±164.5) IU.

Analysis of the primary outcomes

The primary outcome of this study was the CFR in the two groups, which was significantly low in the intervention group (46.7% versus 73.3%; *p*-value 0.03) (Table 2). The median cumulative survival time (survival times for the group as a whole) was statistically longer for the GIK-treated cases, i.e. 120 h (confidence interval, 0–240) as compared to 11 h (CI, 5.8–16.8) for the controls (*p*-value 0.01).

Analysis of the secondary outcomes

The median length of hospital stay was significantly higher in the intervention group than the conventional group, when the comparison was performed between the overall patients (p-value < 0.01), between the survivor of the groups (p-value < 0.001) or between the non-survivors (p-value < 0.001) (Table 2). Mechanical ventilation was required in 40% of the patients that received GIK, and in 63.3% of the

Table 2. Primary and secondary outcomes.

Outcome parameters	GIK ($N = 30$)	Control ($N = 30$)	p Value
In hospital mortality – no. (%)	14 (46.7%)	22 (73.3%)	**0.03**
Hospital stay (h) (median, IQR)			
Overall	35.0 (19.0–61.0)	10.6 (8.2–30.5)	**<0.01**
Among Survivors	50.0 (34.0–68.5)	35.5 (25.5–94.5)	**<0.001**
Among Non-survivors	18.0 (13.2–45.2)	9.0 (8.0–15.0)	**<0.001**
Mechanical ventilation – no. (%)	9 (40.9%)	15 (60.0%)	**<0.01**
Systolic blood pressure (mmHg) (mean ± SD)			
At 00 h (baseline)	69.0 ± 8.2	67.2 ± 9.7	0.43
At 12 h	86.0 ± 14.0	65.5 ± 24.8	**<0.001**
At 24 h	76.8 ± 46.7	38.3 ± 52.5	**<0.001**
At 48 h	72.1 ± 56.9	30.7 ± 50.4	**<0.001**
Diastolic blood pressure (mmHg) (mean ± SD)			
At 00 h (baseline)	46.1 ± 7.0	44.7 ± 5.1	0.14
At 12 h	55.0 ± 7.8	38.9 ± 21.6	**<0.001**
At 24 h	47.8 ± 34.0	21.7 ± 32.0	**<0.001**
At 48 h	45.3 ± 33.9	18.4 ± 31.9	**<0.001**
Mean arterial pressure (mmHg) (mean ± SD)			
At 00 h (baseline)	54.7 ± 6.8	52.2 ± 5.6	0.13
At 12 h	64.8 ± 9.4	43.4 ± 26.1	**<0.001**
At 24 h	57.2 ± 38.2	27.7 ± 39.5	**<0.001**
At 48 h	53.6 ± 42.7	22.6 ± 38.1	**<0.001**
Pulse rate (per minute) (mean ± SD)			
At 00 h (baseline)	105.5 ± 21.2	95.4 ± 20.9	0.11
At 12 h	88.3 ± 16.2	78.6 ± 18.4	0.06
At 24 h	90.4 ± 14.8	85.4 ± 9.4	0.32
At 48 h	91.8 ± 17.8	86.0 ± 28.0	0.66
Score on Glasgow coma scale (mean ± SD)			
At 00 h (baseline)	13.3 ± 2.4	11.9 ± 4.5	0.78
At 12 h	12.3 ± 3.6	8.7 ± 5.1	**<0.001**
At 24 h	12.0 ± 4.5	10.9 ± 5.7	0.81
At 48 h	12.9 ± 4.3	13.5 ± 4.2	0.32
Metabolic parameters Blood pH (mean ± SD)			
At 00 h (baseline)	7.13 ± 0.23	7.09 ± 0.21	0.49
At 12 h	7.20 ± 0.18	7.17 ± 0.22	0.69
At 24 h	7.29 ± 0.14	7.29 ± 0.13	0.96
At 48 h	7.39 ± 0.09	7.39 ± 0.20	0.41
Bicarbonate (mEq/L) (mean ± SD)			
At 00 h	10.5 ± 6.1	10.5 ± 6.6	0.98
At 12 h	12.0 ± 5.0	12.0 ± 7.0	0.98
At 24 h	16.1 ± 5.8	17.8 ± 6.2	0.55
At 48 h	16.8 ± 5.1	15.8 ± 0.6	0.78

Bold values are statistically significant ($p < 0.05$).

patients in the control group, which was significantly different (p-value < 0.01).

In the intervention group, blood pressure, including systolic, diastolic, and mean arterial pressure improved with GIK, and the measurements at 12, 24 and 48 h of the treatment were significantly higher than the baseline (Table 3). The difference between the blood pressures of the two groups was significant at these time intervals. GIK infusion did not affect the pulse rate, and it remained comparable between the groups at various time intervals.

After the initiation of GIK infusion, there was an improvement in the score of GCS at 12 h, and the difference was statistically significant between the groups (p-value 0.009); however, it was transient, and values were comparable after 12 h.

Regarding metabolic acidosis, no significant change was noted in pH or bicarbonate levels after GIK infusion, as well as between the groups throughout the hospital stay.

Adverse events

The incidence of hyperglycemia was 53.3% among patients in the GIK group compared to 3.3% among the controls (p-value < 0.01). Hypoglycemia was also more common in the intervention group, but there was no statistically significant difference (20% versus 10%, p-value 0.47).

Discussion

The results of this study show that GIK improved outcomes in patients with acute aluminum phosphide poisoning. The addition of GIK to the standard supportive treatment reduced both CFR and severity of the toxicity. GIK prolonged the hospital stay of the patients, both the survivors and non-survivors. Because of the rapid development of severe toxidrome that results in death within 24 to 48 h in most of the patients with acute exposure, prolonging survival beyond the first 48 h is vital for the management of these patients and overall outcome.

We demonstrated the beneficial effect of GIK on the severity of the toxidrome by the improvement in the blood pressure and reduced requirement of mechanical ventilation. Cardiovascular toxicity with circulatory failure or profound shock is a major risk, and mainly arises from myocardial injury due to inhibition of oxidative phosphorylation and enhanced oxidative stress of myocytes by phosphine [17–24]. We noted that blood pressure measurements (systolic, diastolic, and mean arterial) showed improvement after the GIK

Table 3. Hemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse rate), score on Glasgow coma scale and metabolic acidosis parameters (blood pH and bicarbonate levels) in the intervention group at baseline (00 h), and at 12 h, 24 h and 48 h after treatment with GIK infusion.

Time	At 00 h (mean ± SD)	At 12 h (mean ± SD)	*p* Value	24 h (mean ± SD)	*p* Value	At 48 h (mean ± SD)	*p* Value
SBP (mmHg)	69.0 ± 8.2	86.0 ± 14.0	**<0.001**	76.8 ± 46.7	**<0.001**	72.1 ± 56.9	**<0.001**
DBP (mmHg)	46.1 ± 7.0	55.0 ± 7.8	**<0.001**	47.8 ± 34.0	**<0.001**	45.3 ± 33.9	**<0.001**
MAP (mmHg)	54.7 ± 6.8	64.8 ± 9.4	**<0.001**	57.2 ± 38.2	**<0.001**	53.6 ± 42.7	**<0.001**
Pulse rate	105.5 ± 21.2	88.3 ± 16.2	0.18	90.4 ± 14.8	0.32	91.8 ± 17.8	0.66
GCS score	13.3 ± 2.4	12.3 ± 3.6	**<0.001**	12.0 ± 4.5	0.81	12.9 ± 4.3	0.32
Blood pH	7.13 ± 0.23	7.20 ± 0.18	0.67	7.29 ± 0.14	0.96	7.39 ± 0.09	0.41
Bicarbonate	10.5 ± 6.1	12.0 ± 5.0	0.98	16.1 ± 5.8	0.98	16.8 ± 5.1	0.55

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PR: pulse rate; GCS: Glasgow coma scale; SD: standard deviation.
Bold values are statistically significant ($p < 0.05$).

administration in the interventional group, and the values at various time intervals were significantly better than the conventional group. Previous studies of GIK for toxicant-induced cardiovascular failure in calcium channel blockers, beta-blockers, as well as in aluminum phosphide poisoning have reported similar findings [39–43,47–49]. In circulatory shock, the cellular uptake or metabolism of glucose becomes impaired in the critical tissues like myocardium, resulting in a metabolic starvation state, which further worsens an already present toxin-induced myocardial depression. The proposed mechanism of hemodynamic action of GIK is that it maximizes myocardial glucose uptake, promotes energy production from carbohydrates, and restores calcium flux [38–50].

Patients with severe aluminum phosphide poisoning often require endotracheal intubation and invasive positive pressure ventilation because of pulmonary edema, acute respiratory distress syndrome, refractory shock, or coma. There was a significant reduction in the need for mechanical ventilation with GIK infusion. This finding might also negate a theoretical possibility of severe cardiorespiratory failure secondary to volume overload and cardiogenic pulmonary edema with GIK infusion in patients with already having toxin-induced cardiac dysfunction. The benefit of ventilator-free management is always significant in any life-threatening pesticide toxidrome as ventilators, and intensive care unit facilities are not readily available in rural regions of the developing world where pesticide poisoning is a major concern.

Our study provided some clinical evidence that GIK infusion increased survival through its good cardiodynamic and hemodynamic response. However, the treatment did not affect the parameters of metabolic acidosis (pH and bicarbonate) and heart rate, which are also considered as clinical or physiological markers of tissue perfusion. Nonetheless, it was challenging to demonstrate the effect of single treatment intervention on all these multisystem parameters in a small-scale study.

Concurring with the other studies, adverse events with GIK were predictable and did not require discontinuation of GIK infusion [43,50]. Hyperglycemia was the common adverse effect but was treated with increasing the infusion rate of insulin. Hypoglycemia was infrequent and was managed by the administration of additional dextrose.

Limitations of the study

Because this study has the small sample size and high CFR, the difference between the groups as well as within the GIK treated group beyond 12 h was difficult to determine with adequate sample size and power, which might explain why the benefit in the GCS score seen at 12 h was not present at 24 or 48 h. However, for the other outcomes, the differences noticed in the first 12 h persisted further.

The lack of difference in the mean-time interval to admission between the survivors and non-survivors may also reflect the inherent limitation of a small-scale study.

Given the study was unblinded, it was subjected to ascertainment or detection bias.

Conclusions

In conclusion, in this small single-center study, we report a survival benefit from the addition of GIK infusion to the high-quality supportive care in the management of acute aluminum phosphide poisoning in patients with a hypodynamic myocardium. Such a therapy could provide an inexpensive, widely available, safe intervention in the resource constraint rural agricultural communities. A further larger multicenter double-blinded clinical trial will be needed to confirm and clarify the magnitude of GIK infusion benefit in aluminum phosphide poisoning.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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