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EFFICACY OF INTRAVENOUS LIPID EMULSION AS AN ADJUNCTIVE THERAPY FOR ACUTEALUMINUM PHOSPHIDE POISONING: A RANDOMIZED, OPEN-LABEL, PILOT CLINICAL TRIAL

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ABSTRACT – *Objective:* Aluminum phosphide poisoning, a leading cause of pesticide-related deaths, has a 70-100% mortality rate and no specific antidote. Intravenous lipid emulsion showed promise in case reports, possibly by sequestering phosphine. This pilot study evaluated the efficacy of intravenous lipid emulsion in reducing mortality and improving outcomes in acute aluminum phosphide poisoning.

Materials and Methods: This single-center, randomized, open-label trial enrolled 98 adults with confirmed aluminum phosphide poisoning. Patients received standard care plus intravenous lipid emulsion (20% emulsion, 250 ml bolus then 250 ml over 20 min) or normal saline placebo within 24 h. The primary outcome was all-cause mortality.

Results: Baseline characteristics were similar (N=98; 48 intravenous lipid emulsion, 50 control). Intravenous lipid emulsion group mortality [22.9% (11/48)] was significantly lower than control [62.0% (31/50); relative risk 0.493, 95% confidence interval 0.335-0.725; $p<0.001$]. Intravenous lipid emulsion led to greater lactate reduction (-2.3 *vs.* -0.6 mmol/l; $p<0.013$) and bicarbonate increase (7.0 *vs.* 2.0 mmol/l; $p<0.013$). Survival was higher with intravenous lipid emulsion in fresh celphos (71.4% *vs.* 0%; $p<0.001$) and shock (50% *vs.* 0%; $p=0.001$) subgroups.

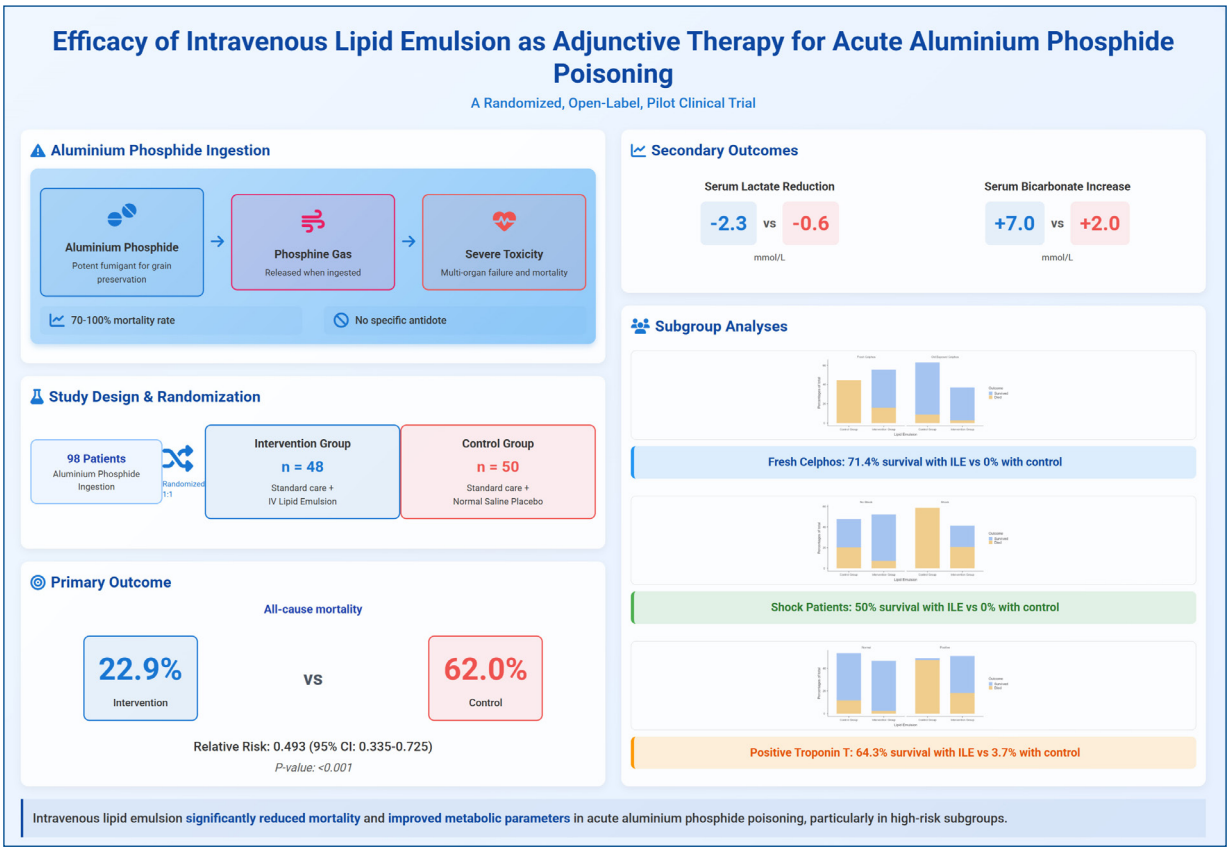
Conclusions: In this pilot trial, intravenous lipid emulsion as an adjunct to standard care significantly reduced mortality and improved metabolic parameters in acute aluminum phosphide poisoning, particularly in high-risk subgroups.

Clinical Trials Registry of India: CTRI/2021/06/034004

KEYWORDS: Celphos, Aluminum phosphide, Intralipid emulsion, Treatment, Critical care, Pesticide poisoning, Randomized trial.

INTRODUCTION

Aluminum phosphide is a solid fumigant widely used for grain preservation and rodent control and is among the most lethal toxicants encountered in clinical toxicology[1,2]. In agrarian regions of South Asia, the compound is inexpensive, readily available and frequently ingested in self-harm, leading to a disproportionate burden of pesticide-related deaths among young adults[3,4]. After ingestion, aluminum phosphide reacts with moisture and gastric acid to liberate phosphine gas, which is rapidly absorbed and distributed systemically. Phosphine inhibits mitochondrial cytochrome c oxidase, un-



Graphical Abstract. Effectiveness of intravenous lipid emulsion for the treatment of aluminium phosphide poisoning.

couples oxidative phosphorylation and generates reactive oxygen species, resulting in profound cellular hypoxia, lactic acidosis, cardiogenic shock and multi-organ failure[3-5]. Reported case-fatality rates in moderate-to-severe poisoning commonly range from 40% to more than 70%, despite aggressive supportive care[4,6].

Management of aluminum phosphide poisoning remains largely supportive. Standard measures include early gastric decontamination with non-aqueous solutions, hemodynamic resuscitation, correction of metabolic acidosis, magnesium supplementation, and organ support where available[7-9]. Various adjunctive therapies have been investigated, such as paraffin oil gastric lavage, N-acetylcysteine, insulin–glucose–potassium infusions, high-dose vasopressors and extracorporeal membrane oxygenation, with mixed and often inconclusive results[8-11]. No specific antidote has yet been validated, and mortality remains unacceptably high, particularly in resource-limited settings where access to advanced organ support is restricted.

Intravenous lipid emulsion (ILE), originally developed as a component of parenteral nutrition, has emerged over the past two decades as a rescue therapy for severe toxicity from local anesthetic and other lipophilic drugs[12]. Experimental and clinical data suggest several potential mechanisms of benefit, including the 'lipid sink' phenomenon (partitioning of lipophilic toxins into an expanded intravascular lipid phase), improved myocardial energy supply through provision of free fatty acids, and direct inotropic effects[12,13]. On this basis, ILE has been proposed as an adjunctive therapy in aluminum phosphide poisoning, where phosphine is highly lipid soluble and exerts prominent cardiotoxic and metabolic effects[3,4].

Evidence supporting ILE in aluminum phosphide poisoning has, until recently, been limited to case reports, small series, and observational studies. Baruah et al[14] reported successful use of ILE in two patients with severe aluminum phosphide poisoning, with rapid hemodynamic improvement and survival despite refractory shock. Subsequent non-randomized and randomized studies[15-18] from Egypt and other regions have suggested that ILE may prolong survival time, improve metabolic acidosis and increase mean arterial pressure, although most were underpowered to demonstrate a statistically significant reduction in mortality. A recent randomized controlled trial by Gheat et al[18] evaluated ILE as an adjuvant therapy in acute aluminum phosphide poisoning and found significant improvements in survival

time, arterial blood gases and serum lactate, with a non-significant trend towards lower mortality. These data, together with systematic reviews of therapeutic options in aluminum phosphide poisoning, have highlighted ILE as a promising but still incompletely evaluated intervention[10,11]. Given the high lethality of aluminum phosphide poisoning, the limited effectiveness of existing therapies and the biological plausibility of ILE, there is a compelling need for randomized clinical trials assessing its impact on clinically relevant outcomes. We therefore conducted a single-center, randomized, open-label, placebo-controlled pilot trial to evaluate whether adjunctive ILE, administered in addition to standard supportive care, reduces early mortality and improves metabolic recovery in adults with acute aluminum phosphide poisoning. This pilot study was designed to generate preliminary efficacy and safety data and to inform the design of future multicenter trials.

MATERIALS AND METHODS

Study design and setting

This was a single-center, randomized, open-label, placebo-controlled pilot trial conducted from July 2021 to July 2024 in the emergency medical ward of the Department of Internal Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. The protocol was approved by the Institutional Ethics Committee (INT/IEC/2021/SPL-83), and the trial was prospectively registered with the Clinical Trials Registry of India (CTRI/2021/06/034004; registration date 03 June 2021). As this was a pilot study, no formal power calculation was performed; the sample size was chosen pragmatically. Consecutive eligible patients were enrolled after trial registration during the predefined study period. No changes were made to the study protocol after trial commencement.

Participants and diagnostic criteria

We enrolled adult patients (aged ≥18 years) presenting with acute aluminum phosphide poisoning. The diagnosis of aluminum phosphide poisoning was based on a combination of the following criteria: (i) a clear history of ingestion of a commercial aluminum phosphide formulation (tablet or powder), with documentation of the brand and formulation when available; (ii) presence of the characteristic garlic- or decaying fish-like odor of phosphine gas on the patient's breath or gastric aspirate; and (iii) compatible clinical features such as vomiting, abdominal pain, hypotension, metabolic acidosis and/or arrhythmias. In cases where the history was unclear, the diagnosis was supported by detection of a phosphine odor in gastric aspirate, typical electrocardiographic abnormalities and exclusion of alternative causes of shock and metabolic acidosis. Patients with uncertain exposure and no supportive clinical or olfactory findings were not enrolled.

Inclusion criteria were age ≥18 years; presentation within 24 hours of ingestion; diagnosis of aluminum phosphide poisoning according to the above criteria; and informed consent from the patient or a legal representative. Exclusion criteria included known chronic renal or hepatic failure, pregnancy, known hypersensitivity to components of lipid emulsions (soybean oil, egg phospholipids) and refusal to participate.

Randomization and interventions

Eligible patients were randomized in a 1:1 ratio to the intervention (ILE) group or the control group using a computer-generated randomization list with concealed allocation. Because of the nature of the intervention, the trial was open-label; however, the primary outcome (mortality) is an objective endpoint.

All patients received standard supportive care, including airway protection when indicated, gastric lavage with non-aqueous solution, intravenous fluids, vasopressors and inotropes as required, magnesium sulphate, sodium bicarbonate infusion for severe metabolic acidosis, proton pump inhibitors and organ support according to the treating physician's judgement. Hemodynamic parameters, urine output, arterial blood pressure, electrocardiography and arterial blood gases were monitored regularly.

Patients in the intervention group received a 20% intravenous fat emulsion containing a mixture of medium-chain triglycerides and long-chain triglycerides (per 100 ml: soybean oil 10 g, medium-chain triglycerides 10 g, egg phospholipids 1.2 g and glycerol 2.5 g, in water for injection) administered as follows: an initial bolus of 250 ml infused over 5-10 minutes, followed by 250 ml over 20 minutes. The total dose was thus 500 ml (approximately 1 g/kg of lipid for a 50-kg adult), given within 24 hours of presentation. The emulsion was used as a generic parenteral nutrition lipid emulsion, and commercial product names were avoided in the protocol and case record forms. The control group received an equivalent volume of 0.9% normal saline over the same time frame in addition to standard supportive care.

To monitor for potential adverse effects of lipid emulsion, including fat overload syndrome, pancreatitis and acute respiratory distress syndrome, vital signs and oxygen saturation were recorded hourly for the first 24 hours, and serial clinical assessments and laboratory tests (including serum triglycerides when clinically indicated) were performed at the discretion of the treating team.

Outcomes

The prespecified primary outcome was all-cause mortality within 72 hours of admission. We chose this early time point because previous reports indicate that deaths from aluminum phosphide poisoning occur predominantly in the first 24-48 hours, and because our emergency ward functions as a short-stay high-dependency unit before transfer or discharge. In our cohort, all deaths occurred within the first 24 hours of admission. Secondary outcomes included: (i) changes in serum lactate, bicarbonate and creatinine between day 1 (at enrolment) and day 5 among survivors; (ii) development of shock (systolic blood pressure <90 mmHg or need for vasopressors despite adequate fluid resuscitation); (iii) occurrence of organ failure (cardiac, renal, hepatic, neurological or respiratory) as assessed by clinical and laboratory criteria; and (iv) length of hospital stay among survivors. Data were collected using a standardized case record form, including the number of tablets or amount of powder ingested, time from ingestion to presentation, type of formulation (fresh *vs*. previously exposed tablets), and intent (suicidal *vs.* accidental).

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables as counts and percentages. Baseline characteristics were compared between groups using the Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables, as appropriate. The primary outcome (72-hour mortality) was compared using the Chi-square test, and relative risk with 95% confidence intervals was calculated. Secondary outcomes were analyzed similarly; changes in lactate, bicarbonate and creatinine between day 1 and day 5 were compared using the Mann-Whitney U test among survivors with available paired data. All analyses followed the intention-to-treat principle. A two-sided p-value <0.05 was considered statistically significant.

Sample size considerations

Given the absence of prior randomized controlled trials of ILE in aluminum phosphide poisoning at the time of protocol development, this study was designed as a pilot trial to assess feasibility, safety signals, and preliminary efficacy. We aimed to enroll 100 patients (50 per group), which was considered feasible within the study period and sufficient to detect a large absolute difference in early mortality if present. No formal power calculation was performed.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and the national guidelines of the Indian Council of Medical Research and was approved by the Institutional Ethics Committee of the Postgraduate Institute of Medical Education and Research, Chandigarh with approval number INT/IEC/2021/SPL-83 dated 12/Jan/2021. Written informed consent was obtained from all participants or their legal representatives. Participation in the trial did not preclude any standard or rescue therapies deemed necessary by the treating physicians. In the event of trial-related injury, treatment was provided at PGIMER at no additional cost to the participants.

RESULTS

Study population

A total of 98 patients with acute aluminum phosphide poisoning were enrolled and randomized: 48 to the ILE group and 50 to the control group (Figure 1). Baseline characteristics were well balanced between groups (Table I). The mean age was 32.0 years (range 25.0-38.6) in the ILE group and 34.5 years (24.9-44.1) in the control group (p=0.443). The proportion of female patients was similar (33.3% *vs.* 32.0%; p=0.892). The median time from ingestion to presentation at the emergency department was 5.0 hours in both groups (p=0.393). The formulation ingested (tablet *vs*. powder), number of tablets, proportion ingesting previously exposed ('old') tablets, prior gastric lavage, prevalence of shock at admission, baseline Glasgow Coma Score, and need for intubation did not differ significantly between groups. Baseline arterial pH, serum bicarbonate and lactate levels were also comparable, as were most other laboratory and vital sign parameters (Supplementary Table I), with the exception of aspartate aminotransferase, which was modestly higher in the control group.

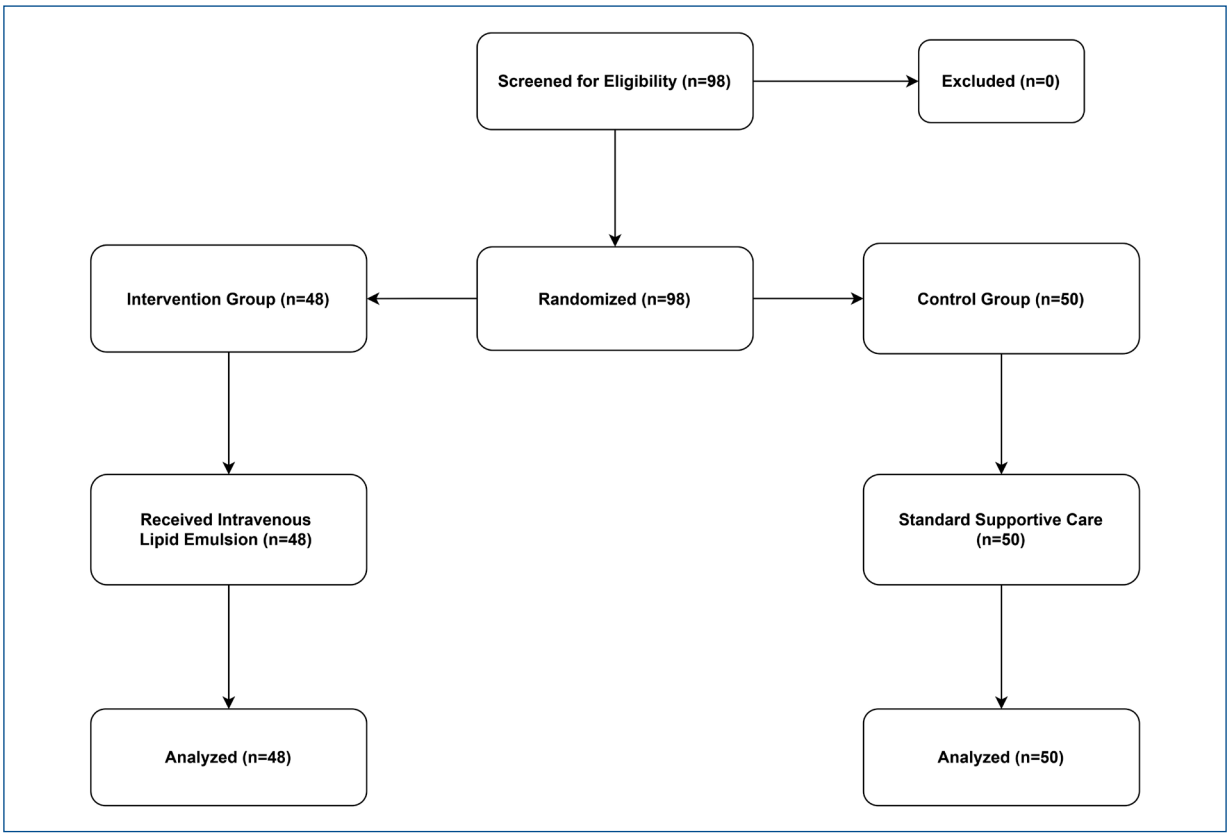


Figure 1. Consort flow diagram of study participants.

Primary outcome

All 42 deaths (42.9% of the total cohort) occurred within the first 24 hours of admission. Seventy-two-hour mortality was significantly lower in the ILE group than in the control group: 22.9% (11 of 48 patients) *vs.* 62.0% (31 of 50 patients), corresponding to a relative risk of 0.49 (95% confidence interval 0.34-0.73; $p<0.001$) (Table II and Supplementary File). Because no additional deaths occurred after the first 24 hours, 72-hour mortality in this setting closely reflected very early in-hospital mortality.

Table I. Baseline characteristics of study participants.

	Intervention group (N=48)	Control group (N=50)	*p*-value
Age (Years)	32.0 (25.0-38.6)	34.5 (24.9-44.1)	*p*=0.44
Sex: Female	16/48	16/50	*p*=0.89
Time taken to reach emergency (hours since ingestion)	5.0 (3.7-8.6)	5.0 (3.0-8.0)	*p*=0.39
Tablet or powder: tablet celphos	43/48	49/50	*p*=0.08
Amount ingested - No. of tablets/packets	1.0 (1.0-2.0)	1.0 (1.0-1.0)	*p*=0.02
Fresh/old: old exposed celphos	13/48	22/50	*p*=0.08
Gastric lavage before hospitalization: Yes	44/48	45/50	*p*=0.78
Shock: Yes	12/48	17/50	*p*=0.33
Glasgow Coma Score	15.0 (15.0-15.0)	15.0 (12.0-15.0)	*p*=0.06
Intubated: Yes	8/48	15/50	*p*=0.12
Serum bicarbonate (mmol/L) - day 1	15.0 (8.7-18.0)	12.2 (6.5-21.0)	*p*=0.71
Serum lactate (mmol/L) - day 1	4.4 (1.8-8.0)	5.9 (1.4-9.9)	*p*=0.72
Tropnin T: Positive	28/48	27/50	*p*=0.67

Table II. Primary and secondary outcome data.

	N	Intervention group (N=48)	Control group (N=50)	Relative risk	*p*-value
Primary outcome: all-cause mortality	98	11/48	31/50	0.493 (0.335 - 0.725)	*p*<0.01
Serum lactate (mmol/L) - change from day 1 to day 5	56	-2.3 (-4.4 - -0.7)	-0.6 (-1.0 - -0.5)		*p*<0.01
Serum lactate (mmol/L) - day 1	98	5.9 (1.4 - 9.9)	4.4 (1.8 - 8.0)		*p*=0.72
Serum lactate (mmol/L) - day 5	56	0.6 (0.4 - 0.9)	0.9 (0.7 - 1.2)		*p*<0.01
Serum bicarbonate (mmol/L) - change from day 1 to day 5	56	7.0 (3.8 - 10.3)	2.0 (1.2 - 4.8)		*p*<0.01
Serum bicarbonate (mmol/L) - day 1	98	12.2 (6.5 - 21.0)	15.0 (8.7 - 18.0)		*p*=0.71
Serum bicarbonate (mmol/L) - day 5	56	24.0 (24.0 - 24.0)	23.0 (22.0 - 24.0)		*p*=0.01
Creatinine (mg/dL) - change from day 1 to day 5	56	-0.2 (-0.3 - -0.1)	-0.2 (-0.2 - -0.0)		*p*=0.65
Creatinine (mg/dL) - day 1	98	1.1 (0.8 - 1.8)	0.9 (0.7 - 1.3)		*p*=0.11
Creatinine (mg/dL) - day 5	56	0.7 (0.4 - 0.8)	0.7 (0.5 - 0.9)		*p*=0.14

Secondary outcomes

Among the 56 patients who survived to day 5 with available paired measurements, treatment with ILE was associated with greater improvement in metabolic parameters. The median reduction in serum lactate between day 1 and day 5 was -2.3 mmol/L (IQR -4.4 to -0.7) in the ILE group compared with -0.6 mmol/L (IQR -1.0 to -0.5) in the control group (p=0.013). The median increase in serum bicarbonate over the same period was 7.0 mmol/L (IQR 3.8-10.3) *vs.* 2.0 mmol/L (IQR 1.2-4.8), respectively (p=0.013). Changes in serum creatinine between day 1 and day 5 did not differ significantly between groups (p=0.653). Day 1 and day 5 absolute values for these parameters are presented in Table II.

Subgroup analyses

Prespecified subgroup analyses demonstrated consistent treatment effects across several high-risk strata (Figure 2). Among patients ingesting fresh (non-exposed) tablets, survival in the ILE group was 71.4%, whereas no patient in the control group survived (0%; p<0.001). In patients presenting with shock at admission, survival was 50.0% in the ILE group compared with 0% in the control group (p=0.001). Among those with positive troponin T, survival was 64.3% *vs.* 3.7% (p<0.001). In the subgroup of non-intubated patients at enrolment, survival in the ILE group was 87.5% compared with 54.3% in the control group (p=0.001).

Exploratory analyses

Figure 3 illustrates the relationship between time to presentation, admission lactate levels and mortality. In the control group, non-survivors had a longer median time from ingestion to presentation (6.0 hours, IQR 4.5-10.0) and higher median lactate (8.8 mmol/L, IQR 6.3-11.9) than survivors (3.0 hours, IQR 2.75-4.0; lactate 1.16 mmol/L, IQR 0.93-1.78). In the ILE group, these differences were more pronounced: non-survivors presented after a median of 16.0 hours (IQR 8.0-18.0) with a median lactate of 11.0 mmol/L (IQR 9.3-12.0), whereas survivors presented earlier (4.0 hours, IQR 3.0-6.0) with lower lactate (3.0 mmol/L, IQR 1.6-5.3). These observations underscore the importance of early presentation and the potential benefit of timely ILE administration.

Thirty-day mortality

Because this pilot trial was conducted in an emergency ward functioning as a short-stay high-dependency unit, systematic follow-up beyond discharge was not incorporated into the original protocol. As all deaths occurred within the first 24 hours and survivors were typically discharged or transferred once hemodynamically stable, 30-day mortality data were not prospectively collected and are therefore unavailable. We have highlighted this as a limitation of the study. No adverse events related to intravenous lipid emulsion were observed.

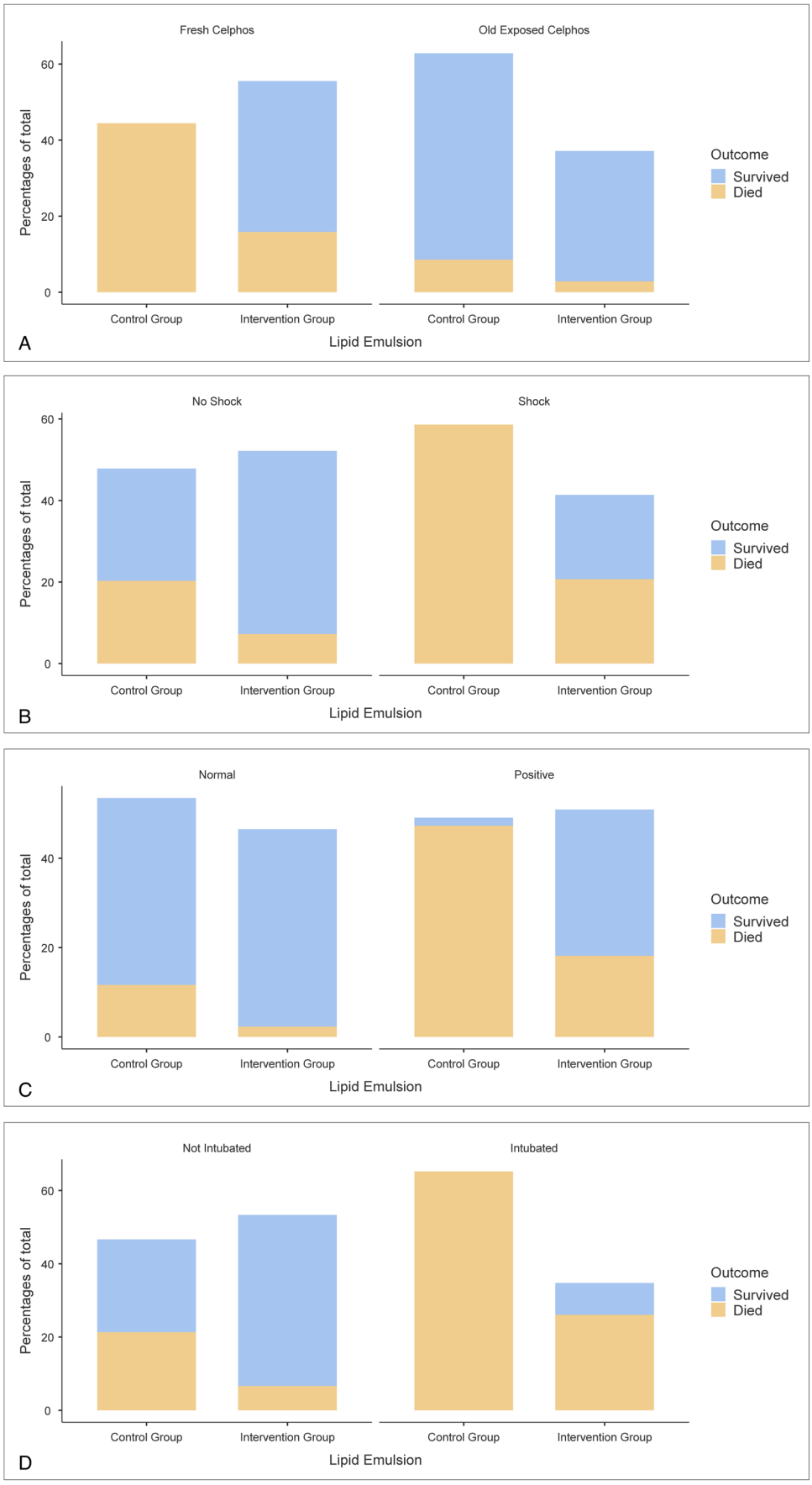


Figure 2. Mortality in the control and intervention arms in various participant subgroups. **A**, ingestion of fresh *vs.* old exposed celphos. **B**, shock *vs.* no shock at admission. **C**, Troponin T normal *vs.* positive at admission. **D**, intubated *vs.* not intubated at the time of enrolment.

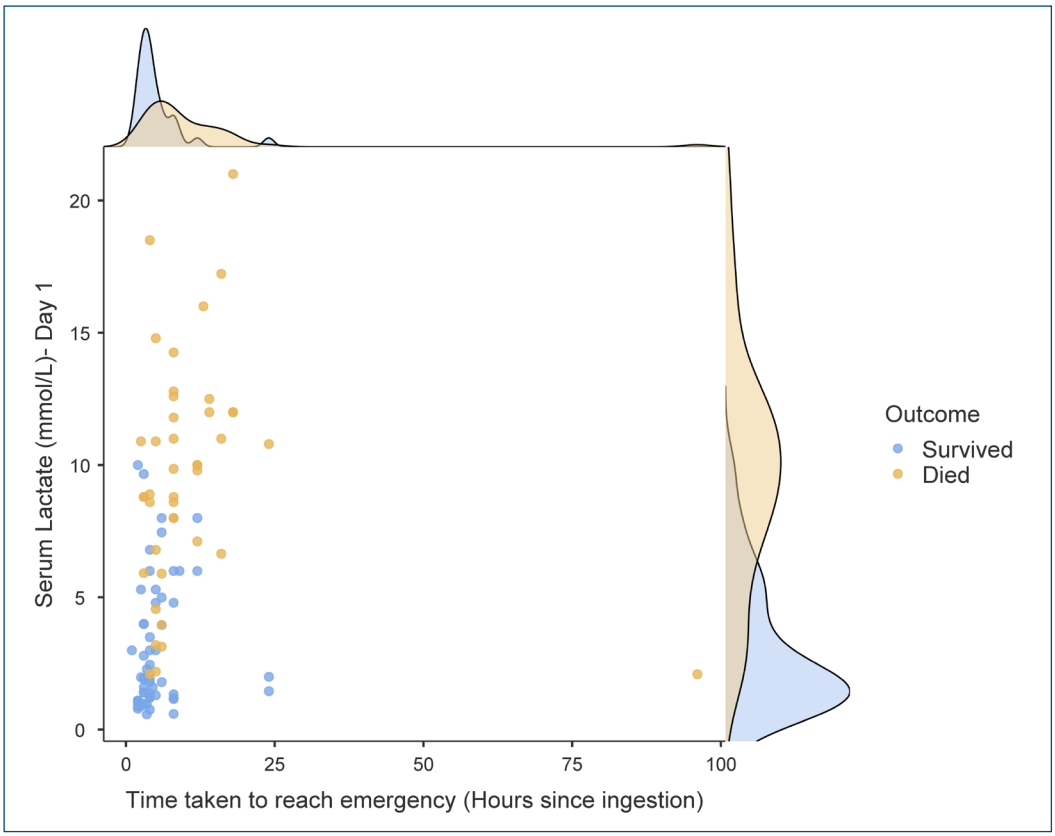


Figure 3. Scatterplot of the effect of time to reach the emergency (hours since ingestion) and lactate at admission on mortality.

DISCUSSION

In this single-center randomized pilot trial, adjunctive ILE therapy was associated with a substantial reduction in early mortality among adults with acute aluminum phosphide poisoning, together with improvements in metabolic parameters indicative of recovery from severe lactic acidosis. Compared with standard care alone, ILE reduced 72-hour mortality from 62.0% to 22.9%, with a relative risk of 0.49 (95% confidence interval 0.34-0.73). The magnitude of this effect is notable in the context of aluminum phosphide poisoning, a condition historically associated with very high case-fatality rates and limited therapeutic options.

Our findings extend the growing body of evidence supporting the potential role of ILE in aluminum phosphide poisoning. Earlier reports, including case reports and observational studies[14-17], suggested that ILE could improve hemodynamics, metabolic acidosis and survival time, but were underpowered to demonstrate statistically significant reductions in mortality. The recent randomized trial by Gheat et al[18] found that ILE significantly prolonged survival time, improved arterial blood gases and reduced serum lactate levels, although the reduction in mortality did not reach statistical significance, possibly because of sample size and illness severity. In our trial, ILE similarly improved lactate and bicarbonate trajectories and, importantly, was associated with a marked reduction in early mortality.

The clustering of deaths within the first 24 hours in both groups has important implications for interpreting treatment efficacy. Aluminum phosphide poisoning typically leads to rapid cardiovascular collapse driven by phosphine-induced mitochondrial dysfunction and severe oxidative stress[3-5]. In this context, therapies that modulate very early hemodynamic and metabolic responses are most likely to influence survival. The fact that all deaths occurred within 24 hours and that 72-hour mortality mirrored in-hospital mortality suggests that the observed benefit of ILE primarily reflects early pathophysiological effects rather than differences in downstream ICU care or late complications. Conversely, the absence of later deaths limits our ability to assess any long-term impact of ILE beyond the acute phase.

Several mechanisms may underlie the observed benefits of ILE. The 'lipid sink' hypothesis posits that an expanded intravascular lipid phase can sequester lipophilic toxins, thereby reducing their free concentration at target tissues[12]. Although the exact lipophilicity profile of phosphine

is complex, experimental data indicate that aluminum phosphide formulations and phosphine gas can partition into lipid phases and cell membranes, potentially rendering them amenable to lipid sequestration[3,4]. Additionally, ILE provides a concentrated source of free fatty acids that can serve as an energy substrate for the myocardium, improve cardiac output and stabilize cell membranes, effects that have been demonstrated in local anesthetic and other drug toxicities[12,13]. The greater correction of lactic acidosis and bicarbonate levels in the ILE group in our trial is consistent with amelioration of mitochondrial dysfunction and improved tissue perfusion.

Subgroup analyses in our study further suggest that ILE may be particularly beneficial in patients with high-risk features. Among patients ingesting fresh tablets, who are expected to have greater phosphine release, survival was markedly higher in the ILE group than in controls. Similarly, patients presenting with shock or positive troponin T, markers of severe cardiotoxicity, experienced substantial survival gains with ILE. These findings align with the concept that lipid therapy may be most effective when administered early in the course of severe poisoning, before irreversible myocardial and multi-organ damage has occurred.

Our study has limitations. First, as a pilot trial with a relatively small sample size, the precision of effect estimates is limited, and the findings should be interpreted cautiously. Larger, multicenter, preferably blinded randomized trials are needed to confirm the mortality benefit and to define patient subgroups most likely to benefit. Second, the open-label design may introduce bias, although the primary endpoint of mortality is objective, and baseline characteristics were balanced between groups. Third, this was a single-center study conducted in a region with a high burden of aluminum phosphide poisoning and particular patterns of exposure, which may limit generalizability to other settings.

Fourth, we did not collect systematic 30-day follow-up data, as the study was designed around early in-hospital outcomes in a short-stay emergency ward, and all deaths occurred within 24 hours. Although this limits conclusions regarding longer-term outcomes, it is unlikely that substantial late mortality was missed, given the typical clinical course of aluminum phosphide poisoning in our setting and the practice of discharging or transferring patients once hemodynamically stable. Finally, while no major adverse events attributable to ILE were observed in this cohort, the study was not powered to detect infrequent complications such as pancreatitis or acute respiratory distress syndrome; ongoing pharmacovigilance is therefore warranted.

Despite these limitations, our findings have important clinical implications. ILE is widely available, relatively inexpensive and simple to administer, making it an attractive adjunctive therapy in resource-limited settings where aluminum phosphide poisoning remains an important cause of preventable mortality. If confirmed in larger trials, early administration of ILE, alongside optimized supportive care and other emerging therapies, could substantially improve outcomes for patients with this otherwise highly lethal poisoning.

Future research should focus on confirming the mortality benefit in adequately powered multicenter randomized trials, exploring optimal dosing regimens and timing, and more clearly delineating the mechanistic basis of ILE's effects in aluminum phosphide poisoning. Comparative effectiveness studies integrating ILE with other promising interventions, such as insulin–glucose–potassium therapy, N-acetylcysteine and extracorporeal life support, may also be informative.

CONCLUSIONS

In this randomized, open-label pilot trial, adjunctive intravenous lipid emulsion significantly reduced early mortality and improved metabolic recovery in adults with acute aluminum phosphide poisoning. The benefits were most pronounced in patients with high-risk features such as shock, positive troponin T and ingestion of fresh tablets. Although these findings require confirmation in larger, multicenter trials, they provide encouraging evidence that intravenous lipid emulsion may represent a practical, readily deployable adjunct to supportive care in a poisoning syndrome that currently lacks an effective antidote.

Ethics Approval

The study was approved by the Institutional Ethics Committee of the Postgraduate Institute of Medical Education and Research, Chandigarh with approval number INT/IEC/2021/SPL-83 dated 12/Jan/2021.

Informed Consent

Written informed consent was obtained from all participants or their legal representatives.

Conflict of Interest

The authors have no competing interests to declare.

Data Availability

The data that support the findings of this study are available from the corresponding author, SCS, upon reasonable request.

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Authors' Contributions
MSB - conceptualization, data curation, funding acquisition, methodology, project administration and writing – original draft. RA - methodology, validation and writing – review and editing. AS - investigation, project administration and writing – review and editing. AKP - investigation, resources, and writing – review and editing. NS - investigation, supervision, and writing – review and editing. SCS - data curation, formal analysis, methodology, visualization and writing – original draft.

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