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Original Article

Outcome of patients supported by extracorporeal membrane oxygenation for aluminum phosphide poisoning: An observational study

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ABSTRACT

Introduction: Aluminum phosphide (AlP) poisoning has a high mortality rate despite intensive care management, primarily because it causes severe myocardial depression and severe acute respiratory distress syndrome. The purpose of this study was to evaluate the impact of the novel use of extracorporeal membrane oxygenation (ECMO), a modified ''heart-lung'' machine, in a specific subset of AlP poisoning patients who had profound myocardial dysfunction along with either severe metabolic acidosis and/or refractory cardiogenic shock.

Methods: Between January 2011 and September 2014, 83 patients with AlP poisoning were enrolled in this study; 45 patients were classified as high risk. The outcome of the patients who received ECMO ($n = 15$) was compared with that of patients who received conventional treatment ($n = 30$).

Results: In the high-risk group ($n = 45$), the mortality rate was significantly ($p < 0.001$) lower in patients who received ECMO (33.3%) compared to those who received conventional treatment (86.7%). Compared with the conventional group, the average hospital stay was longer in the ECMO group ($p < 0.0001$). In the ECMO group, non-survivors had a significantly ($p = 0.01$) lower baseline LV ejection fraction (EF) and a significantly longer delay in presentation ($p = 0.01$).

Conclusion: Veno-arterial ECMO has been shown to improve the short-term survival of patients with AlP poisoning having severe LV myocardial dysfunction. A low baseline LVEF and longer delay in hospital presentation were found to be predictors of mortality even after ECMO usage. Large, adequately controlled and standardized trials with long-term follow-up must be performed to confirm these findings.

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1. Introduction

Pesticide poisoning is a worldwide health problem that can occur intentionally for suicidal or homicidal purpose and unintentionally as the result of accidental or occupational causes. Furthermore, self-poisoning accounts for one-third of suicides throughout the world.[1] Aluminum phosphide (AlP) is a solid fumigant that is used for the fumigation of agricultural compounds, in animal feed, and for pest control in agricultural fields. In North India, AlP poisoning has been found to be the most common cause of suicidal death.[2] In India, the considerable time gap between the ingestion of the poison and the initiation of proper treatment has been found to be the major reason for the high mortality rate of AlP poisoning. AlP poisoning mortality rates vary from 40% to 80%.[3] Once refractory myocardial depression sets in, which is not uncommon, the mortality rate further increases to 77% (37–100%).[3,4] Reports in the literature have shown that resistant hypotension and metabolic acidosis are robust predictors of a poor prognosis after AlP poisoning.[5] Extracorporeal membrane oxygenation (ECMO) is a well documented therapy for improving survival in patients with severe respiratory failure.[6] Veno-venous ECMO is the preferred method in patients with isolated respiratory failure.[6] However, veno-arterial (VA) ECMO should be used in patients with combined cardio-vascular and respiratory failure.

In this study, we investigated the use of VA ECMO in a high-risk subgroup of AlP poisoning patients who were at a very risk of mortality with AlP poisoning. The high risk subgroup was identified by following two criteria: (1) severely reduced left ventricular ejection fraction (LVEF $\leq$ 35%) and (2) severe metabolic acidosis (pH $\leq$ 7.0) and/or refractory shock, i.e. systolic blood pressure <80 mmHg despite conventional medical therapies.

2. Material methods

2.1. Study population

This was a tertiary care, single-center prospective study. We enrolled 83 patients admitted to our center with AlP poisoning between January 2011 and September 2014. All patients had ingestion of the tablet form of AlP with suicidal intention. Forty-five patients were classified as high-risk group of AlP poisoning. The patients of AlP poisoning were classified as a high risk if they met the following criteria:

1. Left ventricular myocardial dysfunction i.e. EF of $\leq$35%
2. Severe metabolic acidosis (pH $\leq$ 7.0) and/or refractory shock i.e. systolic blood pressure <80 mmHg despite conventional medical therapies.

All 45 patients were given the option for ECMO but 30 patients refused primarily due to economical issues. Thereby, 30 patients received the conventional mode of treatment (conventional group) while 15 patients received ECMO in addition to conventional treatment (ECMO group). The outcome of patients in the high-risk group that were treated with ECMO and those of patients in the conventional treatment group was compared. Fig. 1 demonstrates the study design. Conventional treatment for AlP poisoning included gastric lavage with coconut oil, early resuscitation with fluid and vasoactive agent, intravenous magnesium sulfate, and intensive care management. Various vasoactive agents included dopamine, epinephrine, and nor-epinepherine. Intra-aortic balloon pumping was not used as a cardiac support in any of the patient. All patients in ECMO group and majority of the patients in conventional group received ventilator support at the time of admission or during the course of hospitalization.

2.2. ECMO indications and procedure

VA ECMO was considered for patients with AlP poisoning who were classified as high-risk group as mentioned above.

The cannulation site was determined based on patient status. The majority of patients underwent percutaneous cannulation through femoral vessels. The ECMO cannulation was done in intensive care unit. A venous cannula was placed in the inferior vena cava or right atrium for drainage infusion. The usual size of venous cannula ranges from 21 to 25 F. The return cannula is a short arterial cannula inserted via the common femoral artery. This cannula is fully inserted to the taper, with the tip lying in the common iliac artery or lower aorta. The usual size of arterial cannula ranges from 17 to 21 F. Additional distal perfusion 9 F return cannula (''backflow cannula'') is inserted antegradely into the common femoral artery and directed into the superficial femoral artery.

The patients were maintained on a continuous heparin infusion to achieve an activated clotting time between 180 and 200 s. The goal for the activated clotting time was adjusted if there were issues with bleeding or coagulation. To maintain a hemoglobin level of $\geq$10 g/dL and a platelet count of $\geq$100,000 dL^{-1}, patients received a transfusion during the ECMO treatment. The patients were continuously monitored in terms of hemodynamic improvement, reversal of metabolic acidosis, and adequate oxygenation. Once these parameters are satisfactory, the ECMO weaning protocols were initiated. The circuit flow was reduced to assess the native cardiac function in the setting of an increased venous return. Flow was reduced from 2.5 L/min in a series of 0.5 L/min increments while hemodynamic and echocardiographic evaluations were done. Decannulation was performed once the patient had improvement in LVEF to >35%, maintaining systolic blood pressure of >90 mmHg without any inotropic support and acidosis had recovered.

2.3. Statistical analysis

Continuous variables are presented as the mean ± standard deviations. Categorical variables are expressed as percentages. Continuous variables were compared using Student's *t* test if the data followed a normal distribution and using the Wilcoxon test if the data were skewed. Categorical variables were compared using the chi-square test or Fisher's exact test as indicated. All probability values were 2-sided, and difference with *p* values of <0.05 was considered statistically significant.

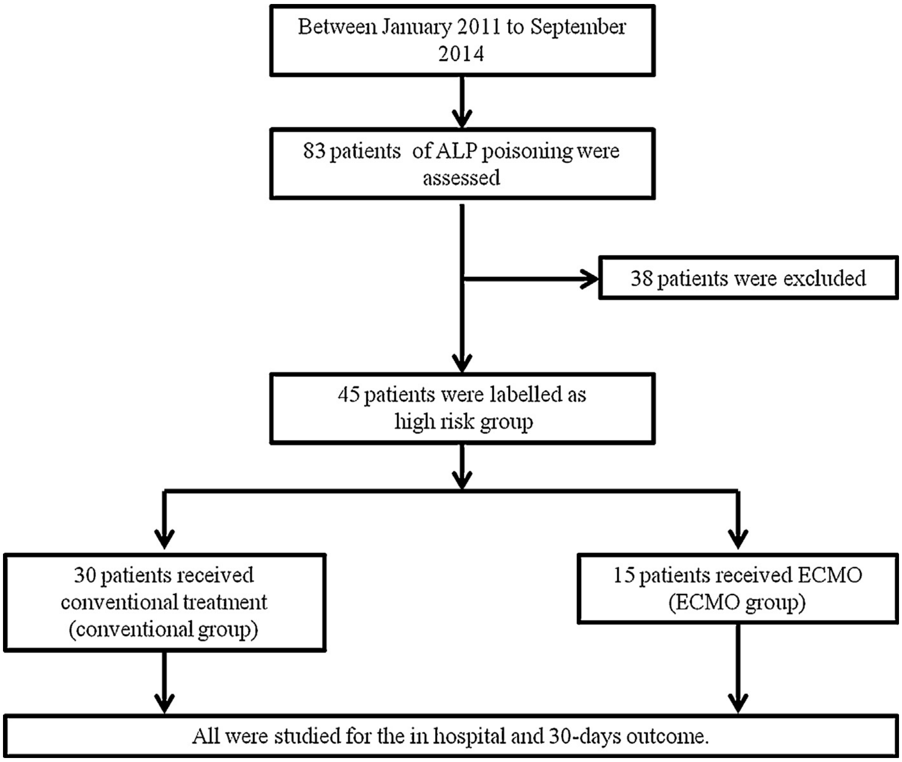

Fig. 1 – Flow chart showing the study design. ALP: aluminum phosphide, ECMO: extracorporeal membrane oxygenation. * Patients were categorized in high risk group if the met the following criteria: (1) Left ventricular myocardial dysfunction i.e. ejection fraction of $\leq$35%. (2) Severe metabolic acidosis ($pH \leq 7.0$) and/or refractory shock i.e. systolic blood pressure $<$80 mmHg despite conventional medical therapies.

2.4. *Follow-up*

Detailed information regarding the occurrence of adverse events and any related symptoms was obtained during routine follow-up at 30 days and 6 months from the time of procedure. Patients were either interviewed by phone or seen by their physician. Those with significant complaints like dyspnea, fatigue, pedal edema, etc. underwent complete clinical, electrocardiographic, and laboratory examinations.

3. Results

Between January 2011 and September 2014, 45 of 83 patients with AlP poisoning at our center were classified as high risk as mentioned above. In this high-risk group, 15 patients received ECMO as a therapeutic modality along with standard management, while 30 patients received conventional management.

3.1. *Baseline characteristics*

The mean age of the ECMO group was 34 ± 8.9 years (73.3% male), while the mean age of the conventional group was 29.1 ± 12.7 years (60% males). The ECMO group was significantly older than the conventional group. The clinical characteristics of both groups are listed in Table 1.

Among AlP poisoning patients in the high-risk subgroup, the mortality rate was significantly lower in those treated with ECMO. The in-hospital mortality rate was 86.7% ($n = 26$) in the conventional group and 33.3% ($n = 5$) in the ECMO group (p value 0.001). The average delay in reaching the hospital after exposure to AlP was higher, although not significant, in the

Table 1 – Baseline characteristics of patients in high-risk group of aluminum phosphide poisoning.

Parameters	Conventional group ($n = 30$)	ECMO group ($n = 15$)	p Value
Age (in years)	29.1 ± 12.7	34 ± 8.9	0.03
Sex (male)	18 (60%)	11 (73.3%)	0.37
Average delay in presentation (in hours)	7.6 ± 5	8.9 ± 3.4	0.06
Number of tablets of Aluminum phosphide	2.1 ± 1.5	2.1 ± 0.9	0.43
Heart rate at the time of presentation >100 bpm	16 (53.3%)	15 (100%)	–
Systolic blood pressure at the time of presentation <90 mmHg	22 (73.3%)	15 (100%)	–
Patients with GFR <60 ml/min	13 (43.3%)	8 (53.3%)	0.52
ECG abnormality	10 (33.3%)	12 (80%)	0.01

ECMO: extracorporeal membrane oxygenation.

Table 2 – Results of patients in high-risk group of aluminum phosphide poisoning.

Parameters	Conventional group ($n = 30$)	ECMO group ($n = 15$)	p Value
Average hospital stay (in days)	6.8 ± 10	16.1 ± 12.9	<0.0001
pH <7.0	8 (26.7%)	15 (100%)	–
LVEF (%)	27.2 ± 4.0	27.1 ± 2.9	0.7
Systolic blood pressure (<90 mmHg)	22	15 (100%)	–
In-hospital mortality	86.7% (26)	33.3% (5)	0.001

ECMO: extracorporeal membrane oxygenation.

Table 3 – Demonstrating the temporal trends in improvement of left ventricular myocardial function among the survivors.

Average LVEF (%)	Conventional group ($n = 4$)	ECMO group ($n = 10$)	p Value
At the time of discharge	50.5 ± 2.4	50 ± 2.1	0.7
At six months of follow up	60.8 ± 1.7	62 ± 2.4	0.3

LVEF: left ventricular ejection fraction; ECMO: extracorporeal membrane oxygenation.

Table 4 – Comparison of survivors with non-survivors in ECMO group.

	Survivors ($n = 10$)	Non-survivors ($n = 5$)	p Value
LVEF at admission (%)	26.2 ± 4.8	19.6 ± 1.7	0.01
Delay in presentation (hours)	7.3 ± 2.6	12.0 ± 2.6	0.01
Hospital stay (days)	22.8 ± 10.3	2.6 ± 0.5	0.002
Poison exposure to ECMO (hours)	10.8 ± 4.2	15.8 ± 3.1	0.01
Admission to ECMO (hours)	3.5 ± 3.2	3.8 ± 0.8	0.2
Duration of ECMO (hours)	60 ± 35	62.4 ± 13.1	0.1

LVEF: left ventricular ejection fraction; ECMO: extracorporeal membrane oxygenation.

Table 5 – Demonstrating the complications related to ECMO usage.

Complication related to ECMO use	
Vascular access site haematomas	53.3% ($n = 8$)
Need for vascular access site surgical correction	20% ($n = 3$)
Persistent thrombocytopenia (<50,000 mm^{-3})	66.7% ($n = 10$)
Worsening of renal failure	60% ($n = 9$)

ECMO: extracorporeal membrane oxygenation.

ECMO group. Compared with the conventional group, the average hospital stay was significantly longer in the ECMO group ($p < 0.0001$). Table 2 demonstrates the results from this study. Among the survivors, the hospital stay in ECMO group (22.8 ± 12.3 days) was significantly longer than the conventional group (9.8 ± 4.5 days) with p-value of 0.02. No mortality was noted at six months of follow-up. Among the survivors, there was significant improvement in LVEF during the hospital stay. At the time of discharge, the mean LVEF was 50.5 ± 2.4% and 50 ± 2.1% in the conventional and ECMO groups, respectively. At the 6-month follow-up, LV function had completely normalized, with average LVEF of 60.8 ± 1.7% and 62 ± 2.4% in the conventional and ECMO groups, respectively. Table 3 shows the temporal trends in improvement of LV functions among survivors.

In the ECMO group, the baseline LVEF obtained at admission was significantly lower in non-survivors (19.6 ± 1.7%) than survivors (26.2 ± 4.8%) with p-value of <0.01. In the ECMO group, the average delay in the initiation of ECMO treatment after hospital admission was 3.6 ± 2.6 h, and this delay was similar between survivors and non-survivors. The duration of ECMO usage during the hospital stay was similar between the non-survivors (62.4 ± 13.1 h) and survivors (60 ± 35 h) with the p-value of 0.1. Table 4 shows a comparison between the survivors and non-survivors in the ECMO group.

Two patients died within 3 days of admission, both of whom had multi-organ dysfunction prior to initiation of ECMO. Three patients succumbed to disseminated intravascular coagulopathy and acute renal failure. All of these five patients received ECMO in addition to conventional treatment.

Vascular access site haematomas were found the major complication in the ECMO group and was seen in 53% ($n = 8$) of cases, and in three patients, this complication necessitated surgical correction. Limb ischemia was not observed in those who received ECMO. Another observed complication was persistent thrombocytopenia (<50,000 mm^{-3}) that required multiple platelet transfusions. Sudden worsening of renal function was noted in 60% ($n = 9$) of patients, and six of those patients required continuous renal replacement therapy (CRRT). Lung injury was not observed in any of the patients in either group. Table 5 highlights the complications related to ECMO use.

4. Discussion

AlP is an insecticide that is commonly used in developing countries, including the Indian subcontinent. The mortality rate of AlP poisoning is approximately 70%.[3] After exposure to hydrochloric acid and water in the stomach, AlP releases phosphine gas, which is rapidly absorbed gastro-intestinal contact. Each tablet of AlP weighs about 3 g and contains two compounds: AlP and aluminum carbonate in a ratio of 54:46. Each 3 g tablet releases 1 g of phosphine gas. The LD50 dose of AlP is 10 mg/kg of body weight. The specified fatal dose is 0.15–0.5 g. However, most of the patients present with ingestion of three or more tablets, which invariably results in death.

Phosphine gas causes the release of oxidant-free radicals and the inhibition of metabolic enzymes, such as mitochondrial cytochrome C oxidase, and thereby interferes with cellular oxygen utilization.[7] Enzymatic inhibition causes conformational changes to mitochondria and a 70% reduction in oxidative respiration. These effects cause a significant decrease in mitochondrial membrane potential.[8]

Other pathogenic mechanisms of AlP poisoning include the following:

1. Generation of highly reactive hydroxyl radicals due to the interaction between phosphine and hydrogen peroxide.
2. Inhibition of catalase and peroxidase enzymes by phosphine.

Both the above-mentioned mechanisms result in lipid peroxidation due to the production of reactive hydroxyl radicals.[9–11] Post-mortem studies have suggested a strong correlation between increased levels of superoxide dismutase, malonyldialdehyde, and catalase and mortality. Excessive oxidative stress results in an increase in glutathione reduction and, thus, a decrease in glutathione concentration in various tissues; this results in cellular injury because glutathione is a protective factor against oxidation that acts by catalyzing the reduction of oxygen peroxide into oxygen and water.[12]

Cardiac myocytes are directly injured by the toxic effects of phosphine gas and as a result of the profound circulatory collapse that occurs secondary to excessive fluid loss and adrenal gland damage in cases of AlP poisoning.[13] Major pathological changes observed in muscle biopsy of non-survivor patients include myocyte vacuolation, areas of myocytolysis and myocyte degeneration.[14]

The presentation of AlP poisoning depends on the amount of toxin ingested, its route of entry, and the duration between exposure to the poison and hospital admission. In this study, the average delays in hospital admission after AlP exposure were 7.6 ± 5 h and 8.9 ± 3.4 h in the conventional and ECMO groups, respectively. Patients with severe inhalation toxicity may develop acute respiratory distress syndrome, cardiac complications (e.g. heart failure and dysrhythmias), and neurological complications (e.g., convulsion and coma); furthermore, late manifestations of hepatotoxicity and nephrotoxicity can also occur.[15–17] Both hypo- and hypermagnesaemia can occur in cases of AlP poisoning, although their mechanism of action is not clear.[18] In our study, all patients had hypomagnesaemia. Other uncommon complications of AlP poisoning include intravascular hemolysis, acute adrenocortical insufficiency, hepatitis, pancreatitis, hypo- or hyperglycemia, meth-hemoglobinemia, microangiopathic hemolytic anemia, and disseminated intravascular coagulation.[13,19] In our study, four patients experienced acute renal failure, two of whom were placed on CRRT.

Clinically, cardiac complications of AlP poisoning are secondary to phosphine-induced myocardial damage; acute cardiovascular collapse is the most common presentation of AlP poisoning (60–100% of cases).[20] Bhasin et al.[21] demonstrated a similar pattern of global hypokinesia of the LV walls in 80% of their cases. Non-specific ST-T wave changes and intraventricular conduction defects are commonly observed on electrocardiograms (ECGs) of AlP poisoning patients and are most likely due to focal myocardial necrosis and changes in membrane action potentials.[22]

There is no specific antidote for phosphine or metal phosphide poisoning. Many different modalities have been used to treat AlP poisoning with varying degrees of success, including magnesium sulfate, N-acetyl cysteine, and decontamination with vegetable oils.[13] None of these agents have been shown to decrease mortality or have significant impacts on patient outcomes, but they may be used in addition to cardiovascular support. The majority of patients die despite intensive medical care. Aggressive support remains the management of choice for AlP poisoning. Similar to other poisons, AlP has a definite elimination time; therefore early arrival, resuscitation and intensive supportive therapy can result in a good outcome. Notably, the half-life of phosphine gas is 5–24 h, depending on various factors.[23]

The mortality rate of AlP poisoning is highly variable, ranging from 37% to 100% and can reach more than 60% even in patients treated by experienced clinicians at well-equipped hospitals.[24] Singh et al.[25] and Bogle et al.[4] showed that the outcome of these patients is primarily determined by the presence or absence of severe resistant hypotension and metabolic acidosis.

Because the AlP poisoning causes reversible myocardial depression and lung injury/ARDS, and does not tend to have major effects on smooth muscle vasculature, VA-ECMO was used as a bridge therapy in this subset of patients. Various other temporary percutaneous support devices being used in cardiogenic shocks from other causes include tandem heart, intra-aortic balloon support (IABP), Impella, etc. IABP had been used in AlP-related cardiogenic shock in few anecdotal case reports. VA-ECMO takes deoxygenated blood from a central vein or the right atrium, pumps it through an oxygenator, and then returns the oxygenated blood, under pressure, to the arterial side of circulation (typically to the aorta). This form of ECMO partially supports CO because the flow through the ECMO circuit is in addition to normal CO. ECMO is a complex, risky, and expensive life support measure that is usually reserved for patients whose underlying disease process is associated with a mortality rate >80% and is not responding to conventional ventilatory support or medical therapies but is still potentially reversible.[26] ECMO has rapidly gained importance as a support measure for both cardiovascular failure and acute respiratory distress.[27] Although ECMO is a candidate therapy for life-threatening cardiorespiratory failure, it has never been implemented in cases of AlP-induced severe myocardial dysfunction with hemodynamic and respiratory compromise. Our institutional experience of over ten years suggests that in patients with AlP poisoning, presenting late to the emergency department with severe LV dysfunction and resistant hypotension or severe metabolic acidosis, regardless of the provision of inotropic support for circulatory failure and ventilatory support for respiratory failure, the mortality rate is almost 100%. So, VA-ECMO seems to be a promising modality as a cardiorespiratory assist device in AlP poisoning.

In our study, in addition to conventional and supportive care, treatment with ECMO reduced the in-hospital mortality of AlP poisoning from 86.7% to 33.3% ($p = 0.001$). At the time of discharge, all patients in both groups had nearly normal LV myocardial function and this was found to have completely normalized at follow-up. This result suggests that the myocardial dysfunction secondary to the AlP poisoning is reversible. Elabbassi et al.[28] demonstrated a similar finding of reversible myocardial dysfunction in his case report. Average duration of ECMO support was 60 ± 35 h among the survivors and the half life of phosphine gas is 5–24 h as mentioned above, thereby suggesting that the cardio-respiratory failure is temporary and correlates with the half life of phosphine gas effect.

Our study demonstrated that low baseline LVEF is an important predictor of mortality in AlP poisoning patients who receive ECMO therapy. Additionally, the length of time of the ECMO treatment was significantly longer in non-survivors. Probably, the prolonged use of ECMO leads to additional complications beyond those of AlP toxicity itself, thus further compromising the patient.

ECMO is associated with several complications. In our study, we encountered the following complications: vascular access site haematomas requiring multiple blood transfusions, the need for surgical correction of vascular complications, profound thrombocytopenia and acute renal failure with or without the need for renal replacement therapy. In the initial few cases, the vascular access site complications were noted in almost all the patients and this was reduced in subsequent patients. It is probably considered to be due to the learning curve for the procedure at our institute in addition to its emergent nature.

This study demonstrates the novel use of ECMO in the management of a specific subset of AlP poisoning patients with a very high risk of mortality. The use of ECMO for this indication has been previously reported as anecdotal case reports only.[29] However, further studies with large numbers of patients and long-term follow-up are needed.

5. Limitations

Our study had certain limitations. First, because data were collected at a single center, the findings may not be representative of the general population. Second, the number of included patients was low; thus, a large prospective study is necessary to confirm our results. Third, ECMO itself is associated with various complications, as previously discussed, that are more prevalent during the learning phase of this procedure at an institution.

6. Conclusion

AlP poisoning carries a very high mortality rate. Venoarterial ECMO has shown promising improvement in the short-term survival of adults with AlP poisoning associated with LV dysfunction and severe metabolic acidosis and/or refractory shock. However, ECMO is also associated with significant complication rates, which must be incorporated into the risk–benefit analysis when determining the best treatment course. Another important highlight is the early presentation to the hospital and immediate referral to the tertiary care center with facility and experience to use ECMO. The decision to start ECMO should be prompt. Future studies may further refine the clinical criteria for its indications.

What is already known?

AlP poisoning carries nearly 100% mortality if patient has left ventricular dysfunction, shock, and severe metabolic acidosis.

As the myocardial dysfunction associated with the AlP poisoning is reversible, this high-risk subset of patients with AlP poisoning might be benefited by a cardio-respiratory assist device (as abridge therapy) which might tide over the crises in initial few days and thereby tend to improve the outcome.

What this study adds?

From this study, it is evident that in high-risk subset of AlP poisoning patients, who carry almost 100% mortality, the use of ECMO as a cardio-respiratory assist device has shown to significantly improve the outcome in term of mortality reduction.

In this study, among the high-risk group ($n = 45$), the mortality rate was significantly ($p < 0.001$) lower in patients who received ECMO (33.3%) compared to those who received conventional treatment (86.7%).

Conflicts of interest

The authors have none to declare.

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