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Evaluation of treatment outcomes in aluminum phosphide poisoning patients supported by extracorporeal membrane oxygenation

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Abstract

Background: Aluminum phosphide (AlP) is a highly toxic poison which directly affects cardiovascular system and results in death. Thus, this study was performed with the aim to evaluate the effect of venoarterial extracorporeal membrane oxygenation (VA-ECMO) on treatment outcomes in these patients.
Materials and Methods: This was a prospective study carried out for a duration of two and a half years at a tertiary care hospital in Gujarat, India. The patients who were exposed to AlP poison and were classified as high risk based on presence of myocarditis, reduced left ventricular ejection fraction (LVEF) < 30% and severe metabolic acidosis were included in the study after receiving their written informed consent. VA-ECMO was performed in these patients using femoral-femoral route. Heparin was continuously infused intravenously. The patients were weaned off of ECMO when LVEF > 35% and acidosis resolved. The data was analysed using SPSS v 19.0. $P < 0.05$ was considered significant.
Results: A total of 124 patients were enrolled during the study duration. The mean age of the patients was 35.74 ± 6.83 years and majority were males (75%). The average time of reaching the hospital was 160.85 ± 21.75 minutes and the average time of putting the patient on ECMO was 206.85 ± 18.21 minutes. The ECMO initiation time reduced from 180 minutes to approximately 30 minutes with average time being 60 minutes. There was a significant reduction in serum lactate levels and increase in LVEF at 24 hours, which predicted better outcomes ($P = 0.001$). The average ECMO run was 76 hours. Out of 124 patients, 109 were successfully discharged, while 22 developed complications and 11 patients died while on ECMO. The time of initiation of ECMO treatment was key factor involved in predicting the outcome ($P = 0.01$). The most common complication was bleeding at cannula site which occurred in seven patients.
Conclusion: In conclusion, VA ECMO can be used as treatment modality to improve survival outcomes in the patients with AlP poisoning. It improves LVEF and metabolic acidosis. Time of initiation of therapy plays a crucial role as an outcome predictor.

Keywords: Cardiorespiratory failure, ECMO, phosphine

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Introduction

Aluminum phosphide (AlP) is a highly toxic inorganic compound which is used as insecticide, rodenticide and fumigant in grain preservation. Poisoning by insecticides is a growing worldwide problem which could be accidental, suicidal or sometimes homicidal. It is observed that one-third of suicides throughout the world are due to pesticide self-poisoning [1]. AlP is a cheap and easily available poison with no specific antidote; which makes it a suicidal 'agent of choice' [2]. In India, it is one of the most common suicidal poison in rural areas of North India and Gujarat regions; especially in adult male patients belonging to lower socio-economic strata [3]. Overall mortality in AlP poisoning ranges from 40% to 100% [4]. It is available as tablets and pellets. Even 1-3 tablets of AlP have proved to be fatal [2]. The toxicity is due to the release of phosphine gas upon reaction of AlP with water or hydrochloric acid in stomach, which is a cardiac, respiratory and gastrointestinal toxin. It inhibits the electron transport chain, respiratory enzymes and cytochrome oxidase enzyme [5]. This is associated with various systemic dysfunctions especially respiratory and cardiac abnormalities. There is reduction in ejection fraction, arrhythmias, pleural and pericardial effusions, metabolic acidosis and refractory shock [6].

Extracorporeal membrane oxygenation (ECMO), a technique which provides prolonged respiratory and cardiac support to the patients who are in respiratory and cardiac failure, has emerged as a very effective mode of treatment for such patients. There are two main modalities of ECMO: veno-venous (VV), in which the blood drained is returned to venous system [7] and veno-arterial (VA), in which the blood is returned to the arterial system [8]. VA-ECMO has been used effectively in patients with combined cardio-respiratory failure. In the literature, there are a few case reports where VA-ECMO has been used successfully for the management of patients with AlP poisoning [9, 10]. But, there is a dearth of prospective studies with more number of patients for the same. Hence, this study was conducted to evaluate the treatment outcomes of VA-ECMO in high risk AlP patients.

Materials and Methods

This was a prospective, single-center study carried out for a duration of 2 years and 6 months from September 2017 to March 2020 at a tertiary care hospital in Surat, Gujarat, India.

Study population

As shown in Figure 1, during the study duration, 146 patients were admitted to hospital with AlP poisoning. Out of them, 124 high risk patients were put on ECMO. The categorization of AlP toxicity patients into high risk was done at the time of admission according to the following criteria:

- Presence of myocarditis.
- Reduction in Left Ventricular Ejection Fraction (LVEF) < 30%.
- Presence of severe metabolic acidosis with Serum lactate > 4 mmol/L, serum Bicarbonate < 15 mEq/L and pH < 7.2.

Based on the above severity criteria, 19 patients had mild toxicity and were treated conservatively. The conservative treatment included inotropes and hemodialysis without ECMO. Out of the remaining 127 patients, 3 patients denied to be put on ECMO primarily due to financial reasons. So, finally 124 patients were put on ECMO who had severe disease and were also willing to be put on ECMO. Before starting the study, written informed consent was obtained from all the study participants after thoroughly explaining them entire procedure.

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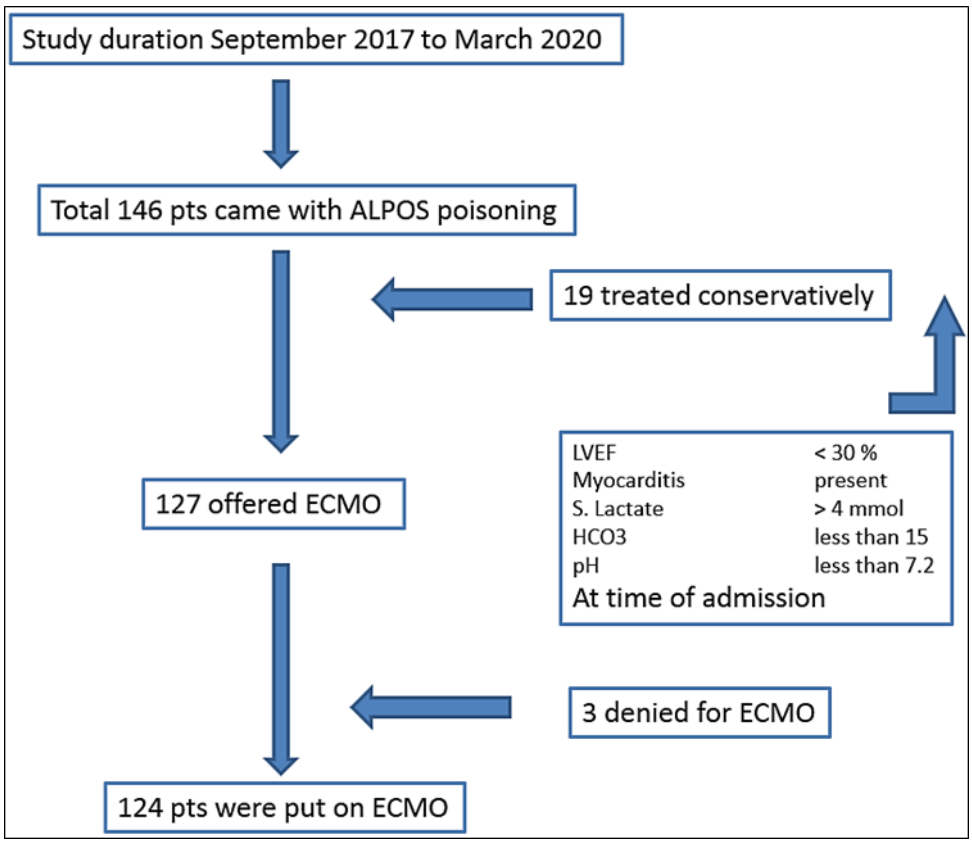

Fig 1: Flow chart of patient inclusion. ALPOS-Aluminum phosphide, ECMO-Extracorporeal Membrane Oxygenation

ECMO Procedure

All the patients classified as high risk were put on VA ECMO. FEM-FEM route was used in all of the patients. Majority of the patients were cannulated percutaneously by intensivist I intensive care unit using Seldinger technique of venous catheterization. Seven patients had to be cannulated using open technique by vascular surgeon. For drainage infusions, a venous cannula was placed in right atrium or inferior vena cava. All the venous cannula used were of size 25 F. A short arterial cannula was inserted through the common femoral artery for return. The tip of the cannula was inserted up to the lower aorta or common iliac artery. The size of the arterial cannula used was 16 F. A distal cannula was put into right radial artery to measure the pulse pressure. To avoid clot formation, a continuous heparin infusion was started and activated clotting time was maintained between 160 to 180 seconds. If the patient had any coagulopathy, the clotting time goals were adjusted. The patients received blood transfusion during the ECMO, to maintain their hemoglobin level above 10 g/dL and platelet count above 1 lakh/dL. In view of the severe acidosis, all the patients were also put on sustained low-efficiency dialysis.

Metabolic acidosis reversal, hemodynamic improvement and adequate oxygenation of patients were continuously monitored. ECMO weaning protocols were started once these parameters came within satisfactory range. To assess the native cardiac function, circuit flow was reduced intermittently. From 2.5L/min, it was reduced in 0.5/L increments with continuous monitoring of echocardiographic and hemodynamic functions. Once the patient attained LVEF > 35% and metabolic acidosis was reversed, decannulation was performed.

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Follow up

The patients were followed up for a period of up to 6 months from the time of procedure routinely. All the details regarding the occurrence of adverse events was noted. Complete detailed clinical, hematological and radiological examination was done for patients who complained of fatigue or dyspnea.

Data analysis

All the data was recorded on a pre-validated patient data sheet. After data collection, it was analyzed using SPSS v 19.0. Continuous and categorical variables were described using mean, standard deviation and percentages. Paired t-test was used to determine the effectiveness of ECMO in the treatment. $P < 0.05$ was considered significant.

Results

A total of 124 AlP poisoning patients were successfully put on ECMO out of the 146 patients who were admitted during the study duration of two and half years. The average of the patients was 35.74 ± 6.83 years with the youngest being 18 years of age and oldest being 58 years old. Majority of patients were males (75%, n = 93). Table 1 gives the baseline characteristics of patients who were enrolled in the study. 67.74% (n = 84) patients took tablets and remaining (32.26%, n = 40) consumed powder of AlP for poisoning. The average time of reaching the hospital after consuming poison was 160.85 ± 21.75 minutes with 90 minutes being earliest and 540 minutes being longest. After complete evaluation and patient and relatives counselling, the average time of putting the patient on ECMO was 206.85 ± 18.21 minutes with 140 minutes being earliest and 640 minutes being longest. As the doctors got well versed with putting patients on ECMO, the ECMO initiation time reduced from 180 minutes to approximately 30 minutes with average time being 60 minutes.

Table 1: Baseline characteristics of AlP patients started on ECMO (n = 124)

Characteristic	Minimum	Maximum	Mean ± SD
Age (years)	18	58	35.74 ± 6.83
Tablets taken	1 Tablet lowest	10 Tablets highest	2.7 ± 1.8 Tablets
Powder taken	10 gm lowest	80 gm highest	45.67 ± 9.5 gm
Time to hospital	90 min earliest	540 min longest	160.85 ± 21.75 min
Time to ECMO (min)	140 min earliest	640 min longest	206.85 ± 18.21 min
ECMO initiation time	30 min fastest	180 min longest	60.58 ± 12.37 min
Heart rate	120 per min	180 per min	
Blood pressure	60 mm Hg systolic	140/80 mm Hg	
ECMO: Extracorporeal membrane oxygenation. AlP: Aluminum Phosphide.			

The heart rate of the patients ranged from 120 to 180 beats per min. Table 2 gives the electrocardiographic (ECG) pattern of patients as evaluated at the time of admission. The most common presentation was sinus tachycardia in 78 (62.90%) patients followed by wide complex or ventricular tachycardia in 21 (16.94%) patients. Seven patients required the use of defibrillator.

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Table 2: Electrocardiographic rhythm at the time of presentation (n = 124)

Electrocardiographic Rhythm	Number (%)
Sinus tachycardia	78 (62.90%)
Sinus bradycardia	6 (4.83%)
Atrial fibrillation	14 (11.29%)
Wide complex tachycardia/ventricular tachycardia	21 (16.94%)
Ventricular fibrillation	5 (4.03%)

The various parameters that were evaluated on examination to determine the high risk patients for putting up on ECMO were pH, Serum bicarbonate and lactate, partial pressure of oxygen and carbon dioxide in blood and left ventricular ejection fraction. These parameters were then again evaluated after 24 hours of ECMO treatment and also at the time of ECMO wean off. Table 3 gives the values of these parameters at the different intervals. There has been improvement in all the parameters on ECMO treatment. The pH improved from 7.1 on admission to 7.3 at weaning off. Similarly, partial pressures of oxygen and carbon dioxide in blood also improved with ECMO treatment. Also, there was improvement in serum bicarbonate levels but it was not statistically significant. Statistically significant improvement was seen in levels of serum lactate and LVEF ($P < 0.05$). Lactate decreased from 13.2 ± 7.3 mEq/L to 3 ± 3.4 mEq/L at the time of weaning off suggesting resolution of metabolic acidosis. LVEF improved to 35.4 ± 6.4 % as compared to 15.2 ± 5.0 % at the time of admission. All the patients who survived on ECMO had normal cardiac function on follow up with an average LVEF of 55.8 ± 5.1 which was statistically significant ($P = 0.04$) (Table 4).

Table 3: Comparison of various parameters before starting, at 24 hours and at weaning off of ECMO

Parameter	At the time of admission	After 24 hours on ECMO	At the time of weaning from ECMO
pH	7. 10 ± 0.2	7. 25 ± 0.3	7. 34 ± 1.5
Serum bicarbonate (mEq/L)	9.20 ± 3.0	19.20 ± 2.7	21.20 ± 3.7
PaO_2	81 ± 22	100 ± 10	90 ± 4.2
$PaCO_2$	25 ± 3.7	40 ± 2.2	37.3 ± 1.2
Serum Lactate (mmol/L)	13.2 ± 7.3	8 ± 6.2*	3 ± 3.4*
Left Ventricular Ejection Fraction (%)	15.2 ± 5.0	20 .2 ± 7.8*	35.4 ± 6.4*
ECMO: Extracorporeal membrane oxygenation. *P value statistically significant ($P < 0.05$).			

Table 4: Timeline of improvement in LVEF in patients who survived on ECMO (n = 113)

	On admission	At the time of wean off	During follow up
Left Ventricular Ejection Fraction (%)	15 .2 ± 5.0	35.4 ± 6.4*	55.8 ± 5.1*
ECMO: Extracorporeal membrane oxygenation. LVEF: Left Ventricular Ejection Fraction. *P value statistically significant ($P < 0.05$).			

Table 5 gives the outcomes of the patients who were undergoing ECMO treatment. 113 patients out of 124 were successfully weaned off of ECMO. But four of them developed complications of sepsis (n = 3) and pulmonary embolism (n = 1) post weaning which were fatal. So, total 109 patients were successfully discharged. Total eleven deaths were reported; out of which ten patients died while on ECMO and one had to be weaned off forcefully because of severe cerebral edema which lead to brain death in the patient.

Table 5: Outcome of patients on ECMO

Outcome	Number of Patients
Survived to home	109

Successful weaning	113
Forceful weaning	1
Death on ECMO	10
ECMO-Extracorporeal membrane oxygenation	

Figure 2 shows the complications which occurred during the ECMO treatment. Total 22 (17.74%) patients suffered from complications. The most common complication was cannulation site bleed which occurred in seven patients. Five patients developed distal limb ischemia on ECMO; surgical interventions were needed to manage it in all of them. Gastrointestinal bleed occurred in 4 patients which was managed conservatively. In two patients arterial cannula was dislodged accidentally and emergency arterial repair was performed. One patient recovered very well with normal myocardium but developed severe cerebral edema with absent brainstem activity so he was declared brain dead and ECMO was removed.

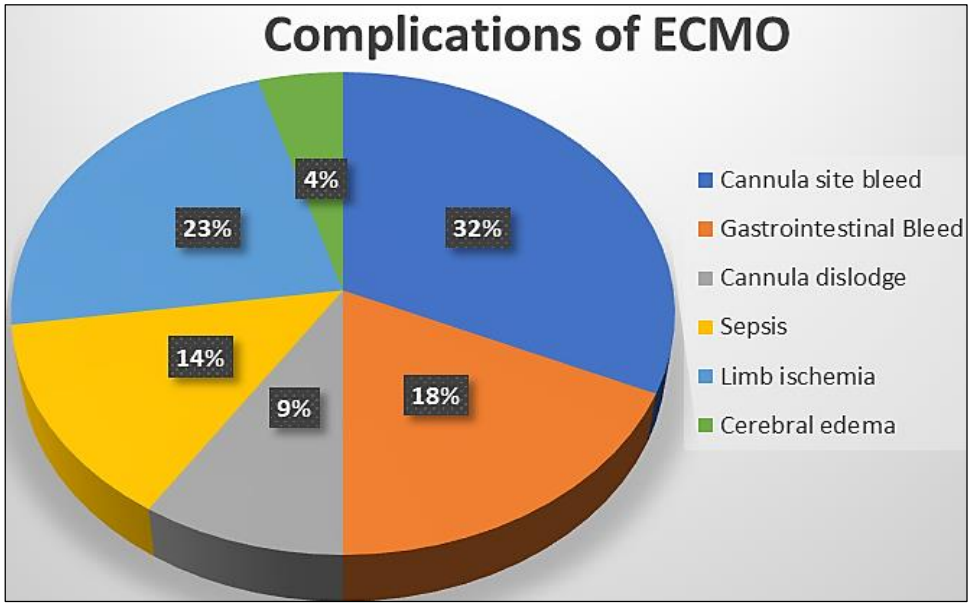

Fig 2: Complications of ECMO. (n = 22). ECMO-Extracorporeal membrane oxygenation

Table 6 gives the comparison between the survivors (n = 113) and non-survivors (n = 11) on ECMO. All survived patients required ECMO support for an average of 76 hours (shortest run was 48 hours and longest was 284 hours). Time to reach hospital and time to initiate ECMO treatment were statistically significant parameters in predicting the outcome of ECMO treatment. Patients who came early for treatment had better outcome as compared to late presenters. Patients with persistence high lactate and low EF after 24 hours on ECMO had poor outcomes which were statistically significant.

Table 6: Comparison between survivors and non-survivors on ECMO (n = 124)

Parameter	ECMO survival (n = 113)	ECMO non-survival (n = 11)	P value
pH	7. 13 ± 0.3	7. 10 ± 0.4	0.7
Serum bicarbonate (mEq/L)	10.20 ± 3.0	9.0 ± 2.4	-
Serum lactate (mmol/L)	12.2 ± 7.3	14.2 ± 7.3	-
Tablets taken	2.8 ± 2	2.7 ± 1.8	0.4
Time to hospital (mins)	100 ± 20.5	310 ± 40	0.01*
Time to ECMO (mins)	145 ± 10.5	430 ± 50	0.01*
LVEF on admission (%)	15.2 ± 5	10 ± 4.5	0.7
Serum lactate at 24 hrs	6.2 ± 7.3	12.2 ± 7.3	0.001*

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LVEF at 24 hrs (%)	20 ± 5	12 ± 5	0.002*
Rhythm at 24 hrs	Improved	Same or worsen	

ECMO: Extracorporeal membrane oxygenation.
LVEF: Left ventricular ejection fraction.
*P value statistically significant (P < 0.05).

Discussion

Aluminum phosphide is a very commonly used poison for suicide purposes in developing countries. Overall mortality in AlP poisoning ranges from 40% to 100% [4]. It is available as tablets as well as powder. Phosphine gas which is released from AlP on exposure to water and hydrochloric acid in stomach, is the causative agent of the toxicity. A 3-gram tablet of AlP releases 1 g of phosphine gas. Phosphine gas is highly toxic to the body, and ingestion of even three tablets can be fatal. There is no available antidote to Phosphine poisoning. Thus aggressive symptomatic treatment remains the only option. Phosphine causes a direct injury to cardiac myocytes as well as indirectly by resulting in a circulatory collapse due to excessive fluid loss and damage to adrenal gland [11]. Myocyte degeneration, myocytolysis and vacuoles in myocytes are common histopathological findings in fatal AlP poisoning cases [12].

The sign and symptoms of toxicity usually depend on the route of entry, dose ingested and duration between exposure and initiation of treatment. In our study the average reported time to hospital admission and initiation of ECMO treatment were 160 minutes and 206 minutes respectively. From the outcomes on ECMO, it was clear that early initiation of treatment with ECMO improved survival chances in these patients. Similar findings were reported in a previous similar study by Mohan *et al*. in AlP poisoning patients [13]. A study by Bosarge *et al*. reports the same in patients with severe adult respiratory distress syndrome (ARDS) [14]. This could be due to the reason that as there is delay in starting treatment, phosphine gas causes more and more damage in the patient. It has been observed that patients who develop inhalation toxicity, suffer from severe complications, such as ARDS, heart failure, arrhythmia followed by convulsion and coma which becomes very difficult to treat and is almost always fatal. Nephrotoxicity and hepatotoxicity can also occur as late manifestations [15, 16].

It was observed that all of the patients presented with abnormal ECG rhythm. The most commonly reported was sinus tachycardia with the heart rate ranging from 120 to 180 beats per min as observed on ECG. Deepak Jain also reported similar changes in ECG in AlP poisoning patients [17]. ECG changes such as intraventricular conduction defects and non-specific ECG changes have been reported frequently in AlP poisoning patients [18].

It was observed that LVEF was significantly reduced in AlP poisoning patients. The study reported a significant improvement in LVEF in survivors which was almost normal during the follow up. When the EF did not improve within 24 hours of ECMO treatment, prognosis was poor in such cases. Thus, LVEF is statistically significant in improving the outcomes in AlP toxicity. Similar findings were recently reported by Sheta *et al*. who observed that the median value of LVEF in survivors was double that of non-survivors [19]. This results suggests a reversible myocardial damage in AlP poisoning. A case report published by Elabbassi *et al*. corroborates similar findings [20]. The average duration of ECMO treatment was 76 hours in the survivors. This is similar to the findings by Mohan *et al*. which reported an average time of 60 ± 35 hours of ECMO support in AlP poisoning [13]. Since the half-life of phosphine gas is 6-24 hours, the recovery from cardiorespiratory failure corroborates with the same. As the ECMO itself has many complications, the use should be precisely timed.

The study reported several complications with ECMO. The most common of which was bleeding at cannula site in seven patients. These were more common initially and gradually reduced in following patients. This could be due to the learning curve of the procedure as the staff got used to performing more and more ECMO in emergency situations, such

complications started minimizing.

This study demonstrates a novel indication of ECMO in management of high risk AlP poisoning patient. The cardiorespiratory support provided by ECMO to such patients is often enough to tide over the critical time of phosphine toxicity. This study is one of its kind as to the best of our knowledge, there have been no research studies carried out solely to evaluate the use of ECMO in more number of AlP poisoning cases. There have been a few case reports only [10, 20]. There are certain limitations in our study. First, as this was a single center study, the data may not represent general population. Secondly, the effect of ECMO has not been compared with conventional management, so it is difficult to hypothesize that the improvement is solely because of ECMO. Further such studies are required to effectively use ECMO in such patients.

Conclusion

It can be concluded that venoarterial ECMO can play a major role in the survival of AlP poisoning patients. It significantly decreases the metabolic acidosis and improves the LVEF. The main predictors of the survival on ECMO are early presentation to the hospital and a quick initiation of ECMO treatment. However, ECMO itself has certain complications which should be kept in mind and the decision to start as well as duration of ECMO treatment should be taken with due consideration. Further studies are required to evaluate the benefits of ECMO over the conventional supportive treatment in more number of patients. That will help in incorporating ECMO as a routine measure in high risk AlP poisoning cases.

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