Fresh-Packed RBC Infusion Diminishes Acute AlP Poisoned-Patients' Mortality Rate: A Clinical Trial

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Abstract- Accidental or intentional poisoning with Aluminum phosphide (AlP) is associated with severe complications such as metabolic acidosis, cardiac failure, and death. Previous animal experiments demonstrated that fresh-packed RBC is protective in an experimental model of AlP poisoning. The aim of this study was to assess the effect of fresh-packed RBC on survival in patients admitted to a referral hospital due to AlP poisoning in a randomized clinical trial. Eighty-two patients were admitted to Clinical Toxicology Unit at Baharloo Hospital due to acute AlP poisoning after approval by the Iranian Registry of Clinical Trials (registration reference: IRCT20180428039443N1). All patients received standard treatment, and forty-one of them received fresh-packed RBC. There was no significant difference between groups in the underlying characteristics, including vital signs and laboratory investigations. But interestingly, the mortality rate was meaningfully decreased (difference: 31.7%, 95% CI: 0.10-0.52) in patients receiving fresh-packed RBC (10 deaths/31 survived; 24.4% mortality) in comparison to standard treatment patients (23 deaths/18 survived; 56.1% mortality). Furthermore, fresh-packed RBC substantially improved the GCS, systolic/diastolic blood pressure, ST changes, and pH 12- and- 24 hours after admission. This study showed that fresh-packed RBC infusion alongside standard supportive treatment leads to a decrease in mortality rate; also, it provided evidence for a protective role of fresh-packed RBC in the management of patients with acute AlP poisoning.

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Introduction

Aluminum phosphide (AlP) tablets have been used for agricultural purposes-storage and transportation- as a fumigant or rodenticide from the 1950s in Europe and the USA and the 1970s in Asia (1,2). After exposure accidentally or intentionally, AlP poisoning leads to severe complications with a very high mortality rate (30-80%) within 24-48 hours following intensive care unit admission (3-8). Its harmful impact initiates from the early moments of exposure, as phosphine (a gas released from AlP under the aqueous and acidic condition in the air and gastric acid) is absorbed easily and quickly via the respiratory and gastrointestinal system, leading to systemic effects, including respiratory distress, severe metabolic acidosis, circulatory shock, cardiac failure and

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death (9-11). The treatment of phosphine-poisoned patients remains supportive since no antidote is known (8,12-17). But, the mortality rate and adverse effects of poisoned patients with phosphine gas continue to be a challenging issues.

In our previous animal study, infusion of fresh-packed red blood cells (RBCs) to AlP-poisoned rats demonstrated that fresh-packed RBCs infusion during the first 4 hours after exposure to AlP decreased the mortality rate of poisoned animals (18). Fresh-packed RBCs treatment was also associated with improved cardiac function and balanced arterial blood gas profile, plasma electrolytes, and cardiac troponin levels (18). We proposed that an increased pool of RBCs can potentially chelate AlP-related toxic intermediates via phosphine-hemoglobin interaction. Moreover, several studies report that RBC transfusion can also normalize the body's buffering capacity, which is essential in acid-base disturbances, improve the oxygen carrying-capacity and intravascular volume (19-21). This is particularly important in AlP poisoning as resistance metabolic acidosis plays a crucial role in the pathogenesis of cardiac failure during AlP poisoning.

There has been an increase in the number of individuals who commit suicide by ingesting AlP tablets in Iran in the past few years (4,22,23). These unfortunate incidents motivated us to develop an antidote to reduce mortality and complications of AlP poisoning. Further to our preclinical report on experimental animals (18), in the present study, we hypothesized that fresh-packed RBC transfusion, besides supportive care, would decrease the death rate in patients who were referred to a referral medical center due to ingestion of AlP tablets.

Materials and Methods

Study design and setting; and time period

This is a randomized clinical trial which is carried out in the Clinical Toxicology Unit at Baharloo Hospital (Affiliated to Tehran University of Medical Sciences, Tehran, Iran) from January of 2019 till March of 2020 after approval by the Tehran University of Medical Sciences Ethics committee (registration number: IR.TUMS.MEDICINE.REC.1397.589), and approval of Iranian Registry of Clinical Trials (registration reference: IRCT20180428039443N1) in accordance with the Helsinki Declaration as revised in 2013. The written informed consent obtained from the patient or their families where the patients could not arrange for the approval.

Population

In this study, eighty-two patients who had been poisoned with aluminum phosphide (AlP), referred to Baharloo Hospital, and admitted to the ICU were randomly divided into two groups of standard treatment and fresh-packed RBC treatment. Inclusion criteria were acutely poisoned patients over the age of 18 years who took more than ¼ of rice tablets (the equivalent of 750 mg AlP-each pill weighs 3 grams) and were admitted during the first four h after exposure, with clinical manifestations such as garlic smell, hypotension (blood pressure less than 100/60 mmHg), gastrointestinal symptoms (e.g., vomiting); finally, whether or not the patient had agreed to trial entry. Exclusion criteria were patients with a history of underlying chronic disease (renal failure, hepatic failure, or congestive heart failure), pregnant women, lactating women, history of adverse reaction to blood transfusion, patients with hemoglobin above 16 grams per deciliter, and patients with incomplete hospital records. The enrolled patients were randomly allocated to the intervention (Fresh-packed RBC treatment)- or comparison (Standard treatment)- group using an online randomization program (http://sealedenvelope.com) in a 1:1 allocation ratio with a block size of 4 by the research coordinator.

In the initial protocol, we introduced a pH of less than 7.2 as the inclusion criteria for entering the study. If there are higher pH levels in the admission of patients, the reason for this is that some patients are referred to the hospital before the onset of symptoms. They report that they have been exposed to significant amounts of aluminum phosphide and have other symptoms such as pain in the gastrointestinal tract, nausea, the smell of garlic, etc. And delays in patient treatment may lead to patient loss. In one case, the patients in this study, who presented half an hour after taking 4 rice pills and with normal physiological symptoms, died after 12 hours, despite receiving all the care and speed of treatment.

Interventions

Standard treatment: Patients underwent standard treatment and did not receive fresh-packed RBC; they were given sodium bicarbonate (44 mEq), permanganate potassium (1: 10,000), and activated charcoal (1 g/kg) for gastric decontamination in the first 6 h after exposure; if patients needed intubation, mechanical ventilation, or intensive monitoring they were transferred to the ICU. They were treated with the same protocol (magnesium sulfate 4-6 g by IV infusion daily, calcium gluconate 4 g by IV infusion daily, adequate hydration, and norepinephrine 10 µg/min as vasopressor) according to

the hospital guideline.

Fresh-packed RBC treatment: Patients who received fresh-packed RBC transfusion in addition to standard treatment received fresh-packed RBC (according to their blood type and if the patient had agreed to the trial entry) in addition to standard treatment. The dose of fresh-packed RBC was 2 units (250-300 ml per unit) that were infused for 60-90 minutes with sixty minutes intervals. Tehran Blood Transfusion Services provided fresh-packed RBCs daily. To provide fresh-packed RBC, blood from donors in Tehran Blood Transfusion Center was processed according to the standard protocols for preparation and safety checks. Fresh-packed RBC was delivered to the hospital up to 48 hours after collecting from voluntary donors.

Outcome measures

For each case, the following data were collected: age, gender, route of exposure and consumption time; clinical data including vital signs (pulse rate, blood pressure, temperature, and respiratory rate), level of consciousness by Glasgow Coma Scale (GCS), electrocardiographic (ECG) monitoring; laboratory investigations including arterial blood gases (ABG), serum sodium and potassium, serum aspartate transaminase (AST), alanine transaminase (ALT) activities, and blood sugar.

The mortality rate is considered the primary outcome of our investigation. Blood biochemical factors and physiological parameters, and ECG parameters were considered secondary outcomes.

The sample size statistical expected for the study was 140 patients, which included 70 patients in each group. In the study process, after the presence of 40 patients in each group, a significant difference was observed in the mortality rate of the two groups, so the project report was done with the 41 patients in each group.

Sample size

Group sample sizes of 40 in group 1 and 40 in group 2 achieve 80% power to detect a significant difference between the group proportions. The proportion in group 1 (Fresh-packed RBC treatment) is assumed to be 0.40 under the null hypothesis and 0.70 under the alternative hypothesis (25,26). The significance level of the test is 0.05.

Statistical analysis

The data were recorded in Microsoft Excel and analyzed by Statistical Package for the Social Sciences (SPSS), version 22, and Graphpad Prism, version 8. Mean and standard deviation for continuous variables, Median and IQR for non-parametric variables, and percentages for categorical variables were reported accordingly. Kaplan-Meier graph followed by Mantel-Cox analysis and Fisher exact test was used to visualize the effect of fresh packed RBC transfusion on survival. Independent Student's t-test and Paired sample t-test were used for parametric variables using the Kolmogorov-Smirnov test for the equality of two distributions. *P* of 0.05 or less was considered statistically significant.

Results

A total of 82 poisoned patients were assigned to this investigation, 41 patients in the fresh-packed RBC group and 41 patients in the standard treatment group. There were 60 male (28 fresh-packed RBC group; 32 standard treatment group) and 22 female (13 fresh-packed RBC group; 9 standard treatment group) patients. The general characteristic of the groups is shown in table 1 and figure 1.

The mortality rate of patients

The results revealed that 23 of the 41 patients who received standard treatment with no fresh RBC died during 48 hours; the mortality rate was 56.1%. On the contrary, 10 patients of the 41 patients who received fresh-packed RBC died during 48 hours of follow-up, so the mortality rate was 24.4%. As shown in figure 2, the Kaplan-Meier analysis indicates that fresh-packed cells could significantly reduce the mortality in comparison with the standard treatment; the mortality difference between these two groups is 31.7 percent with 95% CI: 0.10-0.52 substantially (Chi-square=8.76, *P*=0.003).

Table 1. The general characteristics of groups

	Standard treatment group	Fresh-packed RBC group	Total
Number	41	41	82
Gender (female/male)	9/32	13/28	22/60
Age (Median±IQR)	36.5±21	31±17	34±21
Time interval from exposure till admission (min; Median±IQR)	60±60	120±110	60±60

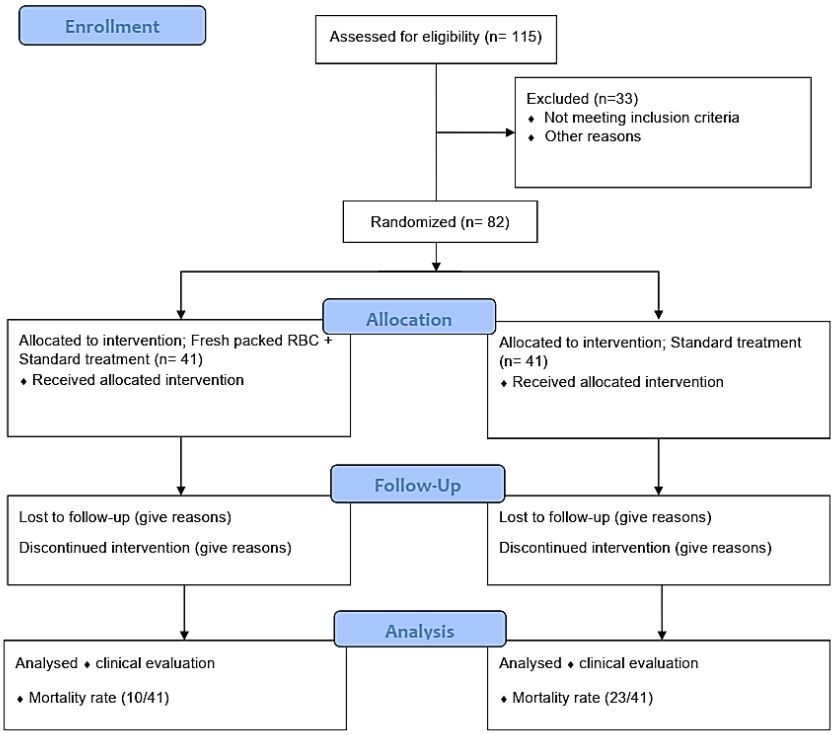

Figure 1. CONSORT 2010 flow diagram

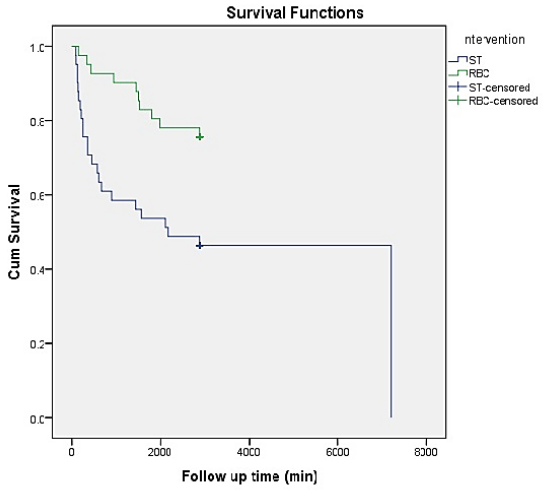

Figure 2. Caption. Kaplan–Meier analysis illustrating that fresh packed RBC (green line) administration could reduce mortality in patients with AlP poisoning in comparison with patients who received standard care (blue line) difference: 31.7 %, 95% CI: 0.10-0.52

The underlying characteristics

As shown in table 2, the study groups are compared according to biochemical parameters (i.e., pH, serum bicarbonate, sodium, and potassium) as well as physiological indexes (i.e., SpO2, heart rate, respiratory rate, systolic and diastolic blood pressure) at admission time using independent t-test. The analysis revealed there was no significant difference between the groups at the admission time.

Table 2. Comparison of underlying characteristics between the groups

	Standard treatment group (Mean±S.D)	Fresh-packed RBC group (Mean±S.D)	*P*
pH	7.18 ± 0.16 (n=41)	7.19 ± 0.08 (n=41)	0.91
PCO2	41.27 ± 16.55 (n=41)	35.98 ± 11.86 (n=41)	0.10
HCO3-	17.72 ± 8.69 (n=41)	17.58 ± 6.05 (n=41)	0.93
PO2	70.10 ± 32.86 (n=41)	77.00 ± 39.87 (n=41)	0.41
Heart rate	84.15 ± 17.38 (n=41)	87.63 ± 17.50 (n=41)	0.36
Respiratory rate	18.10 ± 5.88 (n=40)	20.27 ± 5.97 (n=41)	0.10
Glasgow coma scale (GCS)	14.05 ± 1.16 (n=38)	13.60 ± 2.02 (n=40)	0.23
Systolic blood pressure (SBS)	92.73 ± 9.35 (n=41)	90.12 ± 8.87 (n=41)	0.20
Diastolic blood pressure (DBS)	56.78 ± 7.13 (n=41)	58.51 ± 6.28 (n=41)	0.25
White blood cell	10.65 ± 3.17 (n=38)	11.03 ± 3.07 (n=41)	0.59
Platelets	242.20 ± 55.02 (n=40)	250.93 ± 64.06 (n=41)	0.51
Hemoglobin (Hb)	13.09 ± 2.15 (n=41)	12.84 ± 2.01 (n=41)	0.59
Oxygen saturation (SpO2)	91.39 ± 10.92 (n=41)	92.79 ± 5.19 (n=38)	0.47
Glucose	165.46 ± 88.53 (n=37)	159.18 ± 98.48 (n=40)	0.77
Potassium (K+)	3.73 ± 0.44 (n=41)	3.76 ± 0.29 (n=41)	0.06
Sodium (Na+)	144.50 ± 6.22 (n=38)	142.37 ± 3.17 (n=41)	0.56
Magnesium (Mg++)	2.58 ± 2.47 (n=41)	2.19 ± 0.27 (n=41)	0.31
Calcium (Ca++)	9.07 ± 0.80 (n=40)	9.33 ± 0.86 (n=41)	0.17
Serum aspartate transaminase (AST)	19.15 ± 8.18 (n=41)	18.71 ± 7.11 (n=41)	0.79
Serum alanine transaminase (ALT)	20.93 ± 12.22 (n=41)	20.83 ± 16.42 (n=41)	0.97

Note: Data are expressed as mean±S.D.; *P* in comparison with the standard treatment group

Impact of treatments on physiological parameters

Table 3 displays the effect of fresh-packed RBC and standard treatment 12 and -24 hours after admission in surviving AlP-poisoned patients. Treatments were performed immediately after admission and registration in the study. Unfortunately, due to the death of a number of patients before the scheduled time for the test, the number of people in each test varies.

The levels of pH changed significantly in both the standard treatment group 12 ($P<0.05$; n=24) - and - 24 ($P<0.001$; n=22) hours after admission and in fresh-packed RBC group ($P<0.001$; n=38) 12-and- 24 hours ($P<0.001$; n=38) after admission in comparison with their admission time. As previously mentioned, these pH numbers were for survivors, and in the first 12 hours after admission, a large number of patients died. This may be due to the lack of improvement in pH and metabolic acidosis in these patients.

Glasgow coma scale and diastolic blood pressure did not change in patients who received standard treatment 12 and 24 hours after admission. In contrast, both the Glasgow coma scale and diastolic blood pressure improved substantially in patients who received fresh-packed RBC ($P<0.01$; n=38, and $P<0.001$; n=36, respectively) 24 hours after admission in comparison with the time of admission.

Systolic Blood Pressure showed significant improvements in the standard treatment group ($P<0.01$) 24 hours after admission, whereas this parameter in the fresh-packed RBC group changed significantly ($P<0.001$) 12-and- 24 hours after admission in comparison with the time of admission.

As shown in Table 3, both groups did not illustrate significant differences in heart rate, respiratory rate, and hemoglobin levels 12 and 24 hours after admission in comparison with the admission time. Other characteristics did not show any significant changes (data not shown).

ECG parameters

Since there is a significant difference in the number of patients who survived between the two groups (standard treatment versus fresh-packed RBC), it is challenging to compare laboratory and electrocardiographic parameters during the follow-up. However, to shed some light on the effect of fresh RBC on ECG parameters in AlP-intoxicated patients, the electrophysiological parameters were compared during the first 24 hours of admission (Table 4). Among ECG parameters, there was a significant difference in ST changes in 12 and 24 h after admission between the two treatment groups ($P<0.05$ and $P<0.01$, respectively). Statistical analysis for other parameters, including QRS and QT intervals, did not show any significant changes between the two treatment groups (Table 4).

Table 3. Comparison of treatments' effect on pH, heart rate, respiratory rate, glasgow coma scale, systolic blood pressure, diastolic blood pressure, and hemoglobin level after 12 and 24 hours from admission with the related group level at admission time

	Admission time (0 h)	12 Hours after admission	24 Hours after admission
pH			
Standard treatment group	7.24 ± 0.16	7.33 ± 0.15 (n=24) *	7.38 ± 0.08 (n=22) ***
Fresh-packed RBC group	7.19 ± .089	7.36 ± 0.13 (n=38) ***	7.41 ± .071 (n=36) ***
Heart Rate			
Standard treatment group	87.50 ± 16.99	84.04 ± 17.92 (n=24)	81.00 ± 22.13 (n=22)
Fresh-packed RBC group	85.78 ± 16.69	94.08 ± 28.33 (n=37)	86.53 ± 25.81 (n=34)
Respiratory Rate			
Standard treatment group	20.08 ± 13.39	17.39 ± 6.07 (n=23)	17.63 ± 3.99 (n=22)
Fresh packed RBC group	20.24 ± 6.015	20.16 ± 5.330 (n=38)	20.00 ± 6.93 (n=36)
Glasgow Coma Scale (GCS)			
Standard treatment group	14.31 ± 0.99	13.31 ± 3.34 (n=22)	13.66 ± 3.21 (n=22)
Fresh packed RBC group	13.61 ± 2.04	12.18 ± 3.875 (n=38) *	12.39 ± 4.08 (n=36) **
Systolic blood pressure (SBS)			
Standard treatment group	95.58 ± 5.05	105.29 ± 27.63 (n=24)	107.47 ± 21.50 (n=22) **
Fresh packed RBC group	90.22 ± 9.32	108.92 ± 16.49 (n=37) ***	114.97 ± 14.94 (n=35) ***
Diastolic Blood Pressure (DBS)			
Standard treatment group	59.42 ± 4.83	68.17 ± 16.55 (n=24)	68.043 ± 17.58 (n=22)
Fresh packed RBC group	58.41 ± 6.55	62.81 ± 13.23 (n=37)	68.26 ± 12.28 (n=35) ***
Hemoglobin (Hb)		6 hours after admission	
Standard treatment group	13.17 ± 2.18	13.51 ± 2.82 (n=20)	13.20 ± 2.36 (n=22)
Fresh packed RBC group	12.68 ± 1.97	12.82 ± 1.93 (n=34)	13.07 ± 1.79 (n=33)

Note: Data represented as Mean±S.D. * P<0.05, ** P<0.01, *** P<0.001 compared with the related group at the admission time

Table 4. ECG parameters in treatment groups

Treatment Group	ECG parameter	Admission	6 Hours	12 Hours	24 Hours
standard treatment group	QRS (ms)	85.55±24.55	90.00±21.21	84.28±19.88	85.00±25.63
	QT (ms)	417.50±50.93	407.89±42.75	439.57±67.40	418.50±27.23
	ST (mv)	-0.11±0.96	-0.50±0.92	-0.28±1.38	0.12±1.55
Fresh-packed RBC group	QRS (ms)	88.00±26.66	94.35±29.36	92.67±28.03	85.51±28.73
	QT (ms)	433.08±47.20	434.00±40.32	427.93±47.65	424.55±37.65
	ST (mv)	-0.57±0.34	0.04±0.77	-0.067±0.86*	0.0±0.0**

Note: *P<0.05, **P<0.01 in comparison with the related group in the standard treatment group

Discussion

We studied the impact of fresh-packed RBCs alongside the standard supportive treatment in patients with AlP poisoning. Our findings demonstrated that fresh-packed RBC infusion leads to substantially less mortality than the standard treatment group. There are various mechanisms involved in the toxicity of AlP, including metabolic acidosis and hypoxemia. Our results indicated that treatment with fresh-packed PBCs ameliorates both systolic and diastolic blood pressure. In addition, the fresh-packed RBC treatment group illustrated significantly less ST-T changes in AlP-poisoned patients.

It is well known that AlP toxicity is related to phosphine liberation, a highly toxic gas that causes high mortality (30% to 80%) after exposure. In a series of 195 patients admitted to a hospital in northern India, there were 115 deaths (59%) (24). In a clinical study reported by Kordrostami *et al*., (25), 619 deaths in 764 cases (81%) occurred due to AlP poisoning between 2011 and 2015 in Tehran. The results of our study showed a mortality rate of 56.1 % in the standard treatment group.

Our previous animal study revealed that oral administration of AlP (12 mg/kg) in rats caused 80% mortality, but the infusion of fresh-packed RBC (1.5 ml) significantly reduced the mortality rate to 0% and ~ 24% when RBCs were infused 60 and 90 minutes after exposure to AlP, respectively (18). Further experiments clarified that fresh-packed RBC infusion improved the imbalance of blood pH, HCO3-, Na+, and Ca2+ levels, and the ECG parameters (18). We assumed that the

beneficial effect of fresh-packed RBC infusion might be related to the chelation of phosphine and/or buffering capacity of the RBCs. In a previous animal study, infusion of 1-week-old stored packed RBC did not reduce the mortality rate of AlP-poisoned rats (18). Several studies indicated that RBC storage leads to structural and biochemical changes, including accumulation of lactic acid and reduction of 2,3-diphosphoglycerate (DPG) level (26-28), which has a major impact on erythrocytes' diverse functions. This was why we used fresh-packed RBC in our trial. In the present clinical study, infusion of fresh-packed RBC substantially reduced the mortality rate in AlP-poisoned patients: 23 patients out of 41 patients who received standard supportive treatment lost their lives, while only 10 patients out of 41 patients in the fresh RBC group died. RBCs possess many functions alongside their classical role in tissue oxygenation.

We also investigated the survivors up to 2 weeks after admission for possible side effects of fresh RBC perfusion. There was no report of adverse effects related to fresh-packed RBC infusion. Packed RBC infusion is usually a safe procedure when there is no contraindication (29). In a study by Müller *et al*., there was only one case report of severe side effects following packed RBC transfusion in Germany from 1999 to 2015 (29). In our project, no side effects of fresh-packed RBC transfusion were reported based on our follow-up investigation.

Our study also revealed that ST-segment deviation from baseline occurred more frequently in the standard supportive treatment group 12- and 24-hour following hospital admission. Khosla *et al*. have also reported ST-elevation in 8% and ST depression in 12% of cases with AlP poisoning (26). ST-T changes could be due to ischemia (26,27), myocarditis (28-30), and electrolyte abnormalities (31). In our study, 24 hours after admission, ST elevation developed in 25% and ST depression in 12.5% of cases with standard treatment. As expected, ST deviation was significantly improved in the group with fresh RBC treatment. Moreover, ST changes depict impaired oxygenation in cardiac muscle and ischemia, and improvement of ST changes by fresh RBC infusion may indicate that fresh RBC may enhance tissue oxygenation and mitochondrial function. Mitochondrial dysfunction and impaired oxygenation as a leading mechanism in ALP-induced cardiac toxicity has been discussed in our previous study (28).

Our study provides evidence for the possible beneficial effect of fresh-packed RBCs administration in AlP-poisoned patients despite some limitations. The data in the present study were collected from a single referral center. Future multi-central randomized clinical trials with larger sample sizes will provide solid evidence for the efficacy of fresh RBC transfusion in AlP poisoning. AlP poisoning is known as poisoning with high mortality with no known antidote, whereas fresh-packed RBC is an inexpensive and safe product that is available widely. We hope that this preliminary report provides a glimpse of hope for patients, their relatives, and healthcare staff.

To conclude, this single-center study demonstrated that fresh-packed RBC infusion plus supportive treatment decreased the mortality rate in AlP-poisoned patients; and improved the physiological factors and ECG parameters changes.

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