



Prevalence and Life-Threatening Electrocardiographic Changes in Aluminum Phosphide Poisoned Patients

Faezeh Ghalavand¹, Elnaz Javanshir², Maryam Zaare Nahandi³ and Ali Banagozar Mohammadi^{4*}

1. School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

2. Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

3. Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

4. Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

* Corresponding author

Ali Banagozar Mohammadi, MD, FMMT, FCT

Department of Internal Medicine,
School of Medicine, Tabriz University of
Medical Sciences, Tabriz, Iran

Tel: +98 41 3549 8260

Fax: +98 41 3549 8406

Email: alibanagozar@gmail.com;
alibanagozar@tbzmed.ac.ir

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Abstract

Background: According to World Health Organization report, poisoning with phosphides is the most common fatal poisoning in most of the world, especially developing countries. One of the leading causes of morbidity and mortality in these patients is cardiovascular complications; therefore, the researchers aimed to study the prevalence and type of electrocardiographic changes, especially life-threatening electrocardiographic changes observed in poisoned patients with aluminum phosphide.

Methods: This retrospective cohort study was carried out on all the individuals poisoned with aluminum phosphide tablet and were admitted to the toxicology center in northwest Iran and met the inclusion criteria and no exclusion criteria. After categorization, the data were entered into SPSS (SPSS Inc, Chicago, USA) software, and appropriate statistical analyses were done. In all the tests, $p < 0.05$ was considered statistically significant.

Results: Our findings pointed out that the majority of the patients were in the 20-40 age group and male-to-female ratio was 2.00. Electrocardiographic changes were prevalent in 86.1 percent of the patients who consumed aluminum phosphide. The most common change was sinus bradycardia. The mean consumed aluminum phosphide was 1.93 ± 1.88 tablets, and the mean interval from consumption to medical care was 3.67 ± 2.05 hr which did not have significant correlations with electrocardiographic changes.

Conclusion: The most common electrocardiographic change is bradycardia, but the most lethal is ventricular tachycardia; therefore, taking repeated electrocardiograms and echocardiography could help the decision making in the process of patient management. Definitive conclusions need further studies.

Keywords: Aluminum phosphide, Electrocardiogram, Poisoning, Toxicology

Introduction

Extensive use of pesticides in agriculture, in addition to its benefits for the economy and agriculture, can cause many problems in the field of public health (1); Hundreds of thousands of people around the world die each year from pesticide poisoning or suffer from health-threatening complications, which in most cases occur intentionally and are rarely reported as accidental (2,3).

Aluminum Phosphide (ALP) was easily marketed in India, where about 15,000 poisonings occur annually, two-thirds of which result in death (4). According to the World Health Organization, phosphide poisoning is one of the most common causes of death in poisoned patients, especially in developing countries (5). This poison is very lethal, and it does not have an antidote, since it is out of reach of people in most parts of the world, but in Iran, people can still easily buy this lethal poison, and it still causes death (6). The most common causes of death include cardiac arrhythmias, refractory hypotension, Acute Respiratory Distress Syndrome (ARDS), end-organ damage, and acidosis (7). Previous studies have recorded different cardiovascular changes in these patients (8-13).

Yadav et al. examined the clinical profile of aluminum phosphide poisoning and reported that nearly eighty percent of poisoning cases are in their 20 to 40s; the most common clinical manifestations were shock, metabolic acidosis, and electrocardiogram changes, respectively. The most common organs involved were the gastrointestinal tract and the heart. 38% of people died within 6 hours of hospitalization, and total mortality of 62% was reported (14). Sultannejad *et al*, in a study, examined the electrocardiographic findings of aluminum phosphide poisoning; the most common change in the electrocardiogram was ST segment elevation, which was present in 45% of the cases (15). Khodabandeh *et al* (16), in the study of complications leading to death in aluminum phosphide poisoning, considered cardiac arrhythmias as the most common complication leading to death. Bradycardia, followed by atrial fibrillation, is the most common presentation of arrhythmia; cardiac complications are the most common causes of death in less than 6 hours after poisoning (16). Mathai *et al* suggested that cardiac arrhythmias may predict mortality (17).

In a study that determined the main predictors of mortality in aluminum phosphide poisoning, Louriz *et al* found that in addition to electrical changes in the heart, the presence of shock and the use of vasoactive drugs were significantly associated with mortality (18).

Due to the knowledge gap in the ECG patterns and predictive factors of ALP poisoning in northwest of Iran, and also because knowing the prevalence and type of electrocardiographic changes in aluminum phosphide can effectively prevent the complications of poisoning and control and accelerate the treatment process in these patients, we decided to investigate the prevalence and type of electrocardiographic changes, especially life-threatening electrocardiographic changes observed in poisoned patients with aluminum phosphide and also prognostic factors of these patients admitted to Tabriz Sina Hospital, a teaching hospital in northwest Iran, for four years during 2014-2017.

Materials and Methods

Type of study

The present study is a retrospective cohort study. The target population includes all individuals (male and female of all ages) poisoned with aluminum phosphide poison in East Azerbaijan province and admitted to Sina Hospital in Tabriz, Iran, for four years during 2014-2017 (Inclusion criteria). The diagnosis of aluminum phosphide poisoning was determined based on the history of ingestion, signs, symptoms and paraclinical findings.

Patients with incomplete medical recording, discharge from the hospital with personal consent, history of cardiovascular disease, poisoning with other drugs or toxins at the same time, and history of medications that affect the ECG were excluded from the study (exclusion criteria). Patients' information was accessed by referring to the medical records and documents. All ECG (12 leads) changes observed since admission to discharge or death (at the time of entry and every day during hospitalization, also each time that any electrocardiographic changes were observed in continuous cardiac monitoring) were reviewed. A cardiologist recorded and evaluated all these changes. The ECG parameters during patients' assessment were mentioned from arrhythmias to ST-T changes and even the presence of an abnormal heartbeat such

as sinus tachycardia, Sinus Bradycardia, Ventricular tachycardia, Ventricular Fibrillation, Left Bundle Branch Block (LBBB), Right Bundle Branch Block (RBBB), ST segment changes, and Asystole.

SPSS (SPSS Inc, Chicago, USA) software version 16 was used for analysis. The descriptive statistics section used the mean and standard deviation or frequency and percent to describe the data. In the analytical statistics section, chi-square test (accurate test, in small samples) for qualitative data and independent t-test (Mann-Whitney, if one does not meet the assumptions of one-way independent t-test) and one-way analysis of variance (Kruskal-Wallis, if failure to establish the premises of one-way analysis of variance) was used for quantitative data. Pearson correlation coefficient (Spearman correlation coefficient, if normality is not confirmed) was used to investigate the relationship between quantitative variables. Logistic regression was used to investigate the effectiveness of relationships and find any appropriate statistical correlation. The significant p-value in all tests was considered 0.05%.

Ethical clearance was obtained from the Research

Ethics Committees of Tabriz University of Medical Sciences; Approval ID (code): IR.TBZMED.REC.1398.081. (Approval Date:2019-04-22). During all the stages of the study, the patients' privacy was considered.

Results

Medical records of 150 patients with aluminum phosphide poisoning who were hospitalized in Sina Hospital from the beginning of 2014 to the end of 2017 were provided to the researcher, and 114 cases were excluded due to concurrent poisoning, history of heart disease, and defects in the patients' files.

Of the remaining 36 cases, 24 were male, 12 were female, and the sex ratio was 2.00. Twenty-one people (58.3%) were single, and the rest were married. Their mean age was 28.24 ± 12.54 years, and 41.7% of them were in the age group of 20 to 40 years (Figure 1). 66.7% of the patients resided in Tabriz (Figure 2). 18 patients (50%) passed away due to aluminum phosphide toxicity.

The most commonly observed chief complaint was nausea and vomiting, which was not different

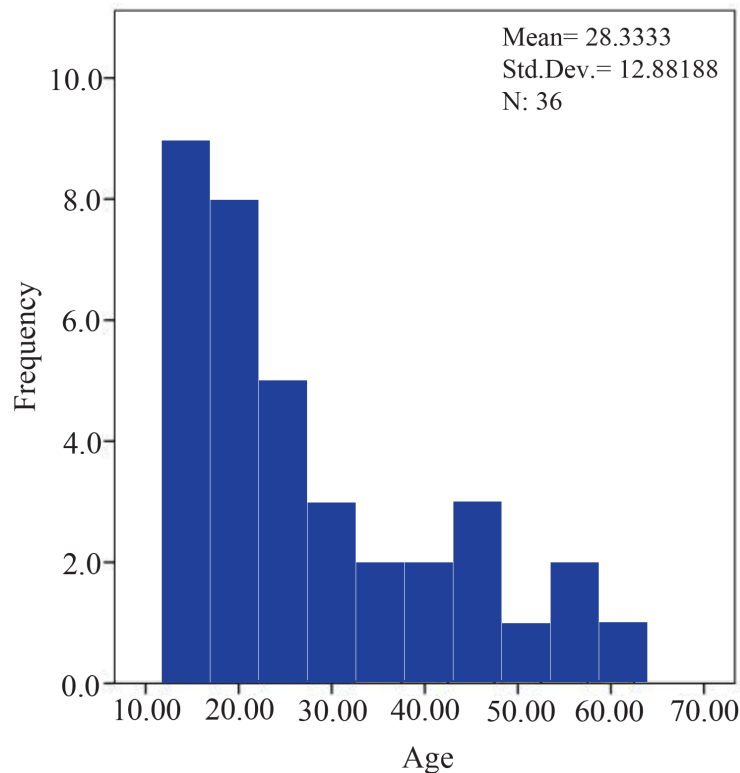


Figure 1. Age distribution of patients with aluminum phosphide poisoning.

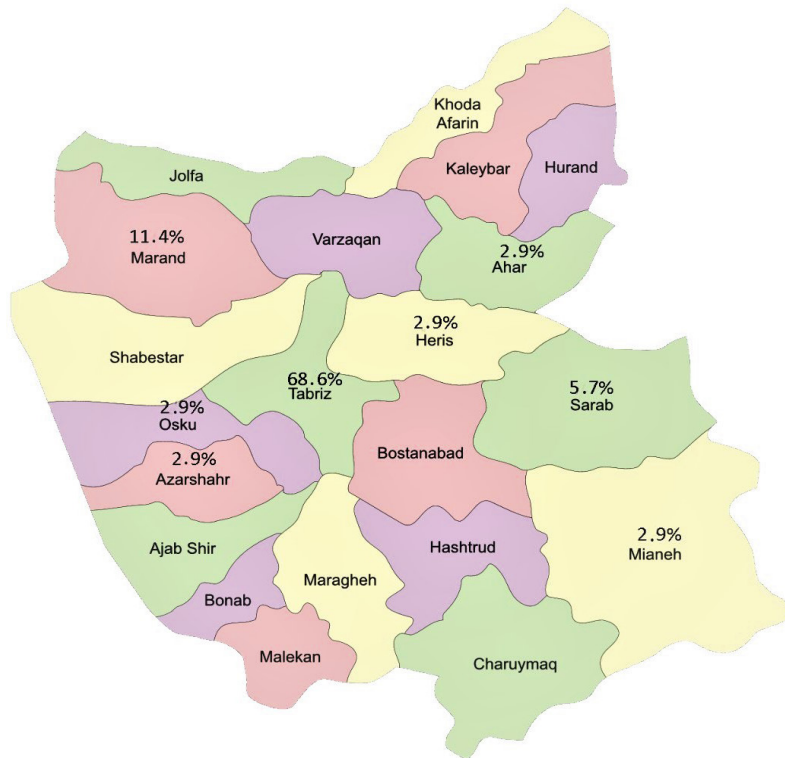


Figure 2. Distribution of the patients with aluminum phosphide poisoning based on township of residence in East Azerbaijan-Iran.

in patients with electrocardiographic changes ($p=0.482$); however, the rate of nausea and vomiting at the time of admission was significantly higher in the recovered patients ($p=0.046$) (Tables 1 and 2). It was also observed that the incidence of loss of consciousness at the time of admission was higher in patients who died ($p<0.001$).

Electrocardiographic changes were present during hospitalization in 31 patients (86.1%). These changes include: Sinus Bradycardia, Ventricular tachycardia, Ventricular Fibrillation, Sinus tachycardia, left bundle LBBB, RBBB, ST depression in precordial leads, and Asystole [during hospitalization and before death, with primary response to Cardiopulmonary Resuscitation (CPR)].

We found that ventricular tachycardia had a significant correlation with the dose of Aluminum phosphide ($r=0.490$, $p=0.003$) (Table 3) and could be a life-threatening electrocardiographic change in these patients. There was no significant relationship between the interval between consumption and the start of treatment with electrocardiographic changes ($p=0.758$ and $r=0.053$), and also between various

ECG changes and time from use to treatment (Table 3). We also found that on average, 14.27 ± 9.1 hr after consuming aluminum phosphide, electrographic changes appear in patients. We couldn't find any correlation between vomiting and epigastric pain with ventricular tachycardia or electrocardiographic changes ($p>0.05$).

It was found that the dose, form of use, duration of hospitalization, and prevalence of abdominal pain were significantly different between individuals who had ECG changes and the group who had a normal electrocardiogram (Table 1). As observed in table 1, ECG changes occur more in greater doses ($p=0.004$), ingestion of fresh tablet ($p=0.027$), delay in onset of the symptoms ($p>0.05$), and delay in arrival to medical care center ($p>0.05$). Therefore, logistic regression was performed, and no statistical correlation was found between these findings and the creation of electrocardiographic changes ($p>0.05$). However, in the path analysis, it was observed that only abdominal pain as a chief complaint (beta: 0.400, $p:0.012$) was predictive of electrocardiographic changes. In the correlation study, the duration of

Table 1. Clinical and demographical characteristics of the patients with regard to presence of ECG changes

Variable	Level/Unit	ECG change+(Pos)		ECG change-(Neg)		p
		n/Mean	%/SD	n/Mean	%/SD	
Gender	Male	20	64.5%	4	80.0%	0.496
	Female	11	35.5%	1	20.0%	
Dosage	Tablet	2.08(M)	1.95(SD)	0.81(M)	0.37(SD)	0.004
Tablet form	Fresh tablet	29	93.5%	3	60.0%	0.027
	Water solution	2	6.5%	2	40.0%	
Ingestion to onset of symptoms	Hour	2.87(M)	2.01(SD)	1.80(M)	0.76(SD)	0.252
Ingestion to treatment	Hour	3.71(M)	2.16(SD)	3.40(M)	1.19(SD)	0.650
Admission duration	Day	2.71(M)	2.95(SD)	7.40(M)	3.44(SD)	0.034
Chief complaint	Abdominal pain	2	6.5%	1	20.0%	0.006
	Chest pain	0	0%	2	40.0%	0.552
	Vomiting	15	48.4%	3	60.0%	0.630
	Loss of consciousness	14	45.2%	1	20.0%	0.290
History of depression	Yes	5	16.1%	2	40.0%	0.211
	No	26	83.9%	3	60%	
History of suicide	Yes	7	22.6%	0	0%	0.236
	No	24	77.4%	5	100%	
Outcome	Death	18	58.1%	0	0%	0.016
	Discharge	13	41.9%	5	100%	

hospitalization, abdominal pain in admission time, and the form of pill had a significant correlation with electrocardiographic changes ($r=-0.485$, $p=0.003$, $r=0.460$, $p=0.006$, $r=0.369$ and $p=0.027$, respectively). As shown in table 1, in patients who consumed unfresh ALP or water solution of ALP; or in patients without abdominal pain in admission time electrocardiographic changes were less common; and patients without electrocardiographic changes had a better survival and discharge after being hospitalized for a longer period of time.

In examining the pattern of electrocardiographic changes, we found that all patients who died had electrocardiographic changes, and all the patients

who had normal electrocardiograms were discharged, and this difference was also statistically significant ($p=0.016$). It is noteworthy that not all those who had electrocardiographic changes died. These nonlethal ECG changes were Bradycardia, Sinus tachycardia, LBBB, RBBB, and ST depression in precordial leads (Table 2).

As seen in table 2, in the study of factors affecting the outcome of hospitalization, we found the dose, form of use (fresh, old, or dissolved in water tablets), time from use to the onset of the symptoms, time from use to treatment, duration of hospitalization, the prevalence of nausea and vomiting and loss of consciousness, and electrocardiographic changes,

Table 2. Electrocardiographic changes, and clinical, as well as demographical characteristics of the patients with regard to outcome of admission

Variable	Level/Unit	Death		Discharge		p
		n/Mean	%/SD	n/Mean	%/SD	
Gender	Male	10	55.6%	14	77.8%	0.157
	Female	8	44.4%	4	22.2%	
Dosage	Tablet	2.88(M)	2.26(SD)	0.99(M)	0.49(SD)	0.002
Form	Fresh tablet	18	100%	14	77.8%	0.034
	Water solution	0	0%	4	22/2%	
Ingestion to onset of symptoms	Hour	3.53(M)	2.03(SD)	1.92(M)	1.44(SD)	0.010
Ingestion to treatment	Hour	4.58(M)	1.91(SD)	2.75(M)	1.78(SD)	0.005
Admission duration	Day	0.72(M)	0.61(SD)	6.11(M)	2.68(SD)	<0.001
Chief complaint	Abdominal pain	0	0%	3	16.7%	0.070
	Chest pain	0	0%	2	11.1%	0.157
	Vomiting	5	27.8%	13	72.2%	0.046
	Loss of consciousness	13	72.2%	2	11.1%	<0.001
History of depression	Yes	2	11.1%	5	27.8%	0.206
	No	16	88.9%	13	72.2%	
History of suicide	Yes	3	16.7%	4	22.2%	0.674
	No	15	83.3%	14	77.8%	
Various ECG findings	Bradycardia	7	38.9%	8	44.4%	0.735
	Ventricular tachycardia	8	44.4%	0	0%	0.001
	Ventricular Fibrillation	3	16.7%	0	0%	0.070
	Sinus tachycardia	1	5.5%	4	55.2%	0.206
	Asystole	2	11.1%	0	0%	0.146
	LBBB	1	5.6%	1	5.6%	1.000
	RBBB	0	0%	1	5.6%	0.310
ST depression in precordial leads	2	11.1%	1	5.6%	0.546	

Left Bundle Branch Block (LBBB), Right Bundle Branch Block (RBBB).

Table 3. Matrix of correlation between various electrocardiographic changes, and clinical factors with outcome, dose, and time to receive care

Variable	Dose		Ingestion to treatment		Admission outcome	
	r	p	r	p	r	p
Bradycardia	-0.160	0.365	-0.098	0.571	0.054	0.748
Ventricular tachycardia	0.490	0.003	0.138	0.422	0.535	0.001
Ventricular Fibrillation	0.123	0.487	0.274	0.106	0.302	0.074
Sinus tachycardia	-0.001	0.994	-0.110	0.522	-0.211	0.218
Asystole	-0.059	0.742	0.311	0.065	0.243	0.154
LBBB	0.110	0.534	0.070	0.684	0.00	1.00
RBBB	-0.088	0.621	-0.223	0.190	-0.169	0.324
ST depression in precordial leads	0.067	0.706	0.149	0.384	0.101	0.560
Vomiting	-0.193	0.274	-0.468	0.005	-0.333	0.047
Loss of consciousness	0.454	0.007	0.531	0.001	0.620	<0.001
Abdominal pain	0.247	0.114	0.125	0.388	0.086	0.547
Tablet form	-0.197	0.265	-0.336	0.045	-0.354	0.034
Ingestion to onset of symptoms	0.281	0.104	0.885	<0.001	0.426	0.010
Ingestion to discharge	-0.452	0.007	-0.457	0.005	-0.822	<0.001

Left Bundle Branch Block (LBBB), Right Bundle Branch Block (RBBB).

especially ventricular tachycardia were significantly different in patients who recovered and the patients who passed away (Table 2). As seen in table 3, ingestion of greater doses, or fresh tablets; delay in onset of the symptoms, delay in arrival to medical care center, loss of consciousness during admission, and absence of vomiting after ingestion of tablet could increase the mortality and worsen the prognosis. We found that all of these factors have a significant correlation with the outcome of hospitalization (Table 3). According to table 3, with increasing the ingested dose of poison, the probability of decreasing the level of consciousness and the occurrence of Ventricular Tachycardia (VT) increases, and on the other hand, the probability of short hospitalization time and early death increases. Therefore, logistic

regression was performed, and despite the increased risk of death following the creation of VT in these patients but we found no statistical correlation between these findings and the probability of death ($p>0.05$). However, in path analysis, it was observed that ventricular tachycardia (beta: 0.416, $p=0.002$) and decreased level of consciousness ($p<0.001$, beta: 0.526) were only two independent and impact factors in prognosis, and these two prognostic factors had no effect on each other ($p=0.185$).

Discussion

Our results showed that the most prevalent age group is 20-40 years old, and men were twice as likely as women to be exposed to aluminum phosphide. This is consistent with the results of Khurana *et al* (19),

Kalawat *et al* (9), and Khosla *et al* (20) studies. The most common age group in the present study was the age group of 20-40 years, and men were twice as likely as women. In the study of Rahbar Taromsari *et al* (21) and Aziz *et al* (22), the most common age group was 15-25 years, and just like our study, two-thirds of the patients were men. Shadnia *et al* (23) obtained similar results in terms of age as ours, but the proportion of men and women was the same. Unfortunately, in all studies, patients were young; this highlights the importance of monitoring the trade of poisons and resolving problems leading to suicide in these individuals.

Electrocardiographic changes are present in 86.1% of patients with aluminum phosphide poisoning. The ECG changes in our study were more prevalent than the study of Soltaninejad *et al* (15), Shadnia *et al* (23), Kalawat *et al* (9), and Taromsari *et al* (21), and was less than the study of Hosseinian *et al* (24), Khosla *et al* (20); and was similar to the findings of Aziz *et al* (22). The different classification of ECG changes in these studies could contribute to the differences observed so that in some studies, tachy/brady arrhythmias were not considered as electrocardiographic changes.

The most common changes in ECG included bradycardia which was observed in 41.7% of the patients, followed by ventricular tachycardia with 22.2% incidence and sinus tachycardia with 13.9% incidence. Contrary to our study, the most common finding in Louriz *et al* (18), Khosla *et al* (20), and Kalawat *et al* (9) studies was sinus tachycardia. In the study of Soltaninejad *et al* (15), Aziz *et al* (22), and Rahbar Taromsari *et al* (21), atrial fibrillation was also the most common finding. Similar to the current study, Khodabandeh *et al* (16) demonstrated that the most common finding was bradycardia, less common than ours. Contrary to our findings, in the study of Shadnia *et al* (23) and Khurana *et al* (19), the most common findings consisted of ST-segment depression and tachycardia. The observed differences in the prevalence of ECG changes can be linked to the characteristics of patients; or subclinical or undiagnosed previous heart disease. In the present study, all changes from the beginning to the end of hospitalization were examined.

The most common complaints of patients were vomiting in 50.0% and loss of consciousness in 41.7%

of the cases; on the other hand, Khurana *et al* showed that the most common complaints were restlessness and palpitations (19). They also demonstrated in another study that, the most common clinical finding was nausea and vomiting, with a prevalence of 96% (25). In the study of Kalawat *et al* (9), there was nausea and vomiting in all the patients. In the study of Shadnia *et al* (23), the most common finding was that epigastric pain; and nausea, and vomiting were present in 40% of the cases, and chest pain was present in 17% of the cases. Nausea, vomiting, or epigastric pain can be caused by aluminum phosphide's gastrointestinal or cardiac complications. The differences observed here could also be due to differences in the timing of getting patients history and filing complaints. In the present study, the chief complaint with which the patient was referred was recorded.

Nausea and vomiting were more common in patients who recovered but were not considered a factor influencing hospital outcome in logistic regression; similar to our study, in Shadnia *et al*'s study (23), nausea and vomiting did not affect hospital outcome. For this reason, nausea and vomiting appear to be more due to gastrointestinal side effects of the aluminum phosphide pills. Loss of consciousness in hospital admission was more prevalent in patients who had died than those who achieved recovery, which was also observed in the study of Khodabandeh *et al* (16). In the present study, half of the patients died, and half of them were discharged from the hospital, which was less than the study of Khurana *et al* and Aziz *et al* (22) and more than the study of Hosseinian *et al* (24), Shadnia *et al* (23), and Kalawat *et al* (9). In this study, 114 patients were excluded from the study due to concomitant poisoning with other drugs or a history of heart disease. Then, statistical differences may be due to this. In this study, all the patients without ECG changes improved, and more than 50% of patients with ECG changes died.

The mean time interval between consumption and the start of treatment in this study was 3.67 ± 2.5 hr, which was not associated with electrocardiographic changes, but associated with mortality. Although it was correlated with hospital outcomes, but in logistic regression it was not considered an influencing factor. In the study of Khurana *et al* (25) and Khodabandeh *et al* (16), most of the patients who died had been

referred to the medical center between 2-4 hr (mean 3.02 hr and 3.2 hr) from the time of consumption. However, in the study of Khodabandeh *et al* (16), the time factor had a significant difference in the outcome of hospitalization. Contrary to our study, in Hosseinian *et al*'s study (24) and Shadnia *et al* (23), the time interval between consumption and admission to the medical center did not show a significant difference between those who died and those who were discharged. According to the studies mentioned above, hospitalization time affects patients' survival, which requires additional studies with a larger sample size to investigate this matter.

The average number of aluminum phosphide tablets consumed in this study was 1.99 ± 1.90 tablets, which was less than the study of Khodabandeh *et al* (16) and more than the studies of Rahbar Taromsari *et al* (21), Shadnia *et al* (23), and Hosseinian *et al* (24). The number of pills used in the present study is higher than most of the studies, making it clear that our population uses more pills than in previous years and other regions due to solid intentions to die.

A significant relationship between ventricular tachycardia and the dose of aluminum phosphide consumed was observed. Higher consumption of aluminum phosphide, as in Hosseinian *et al* (24) and in contrast to the study of Shadnia *et al* (23), was associated with worse outcomes. In the study of Rahbar Taromsari *et al* (21), the dose of more than one pill resulted in the death of patients, and as in our study, higher consumption of aluminum phosphide was associated with an increase in the rate of arrhythmia (primarily ventricular tachycardia).

In the present study, electrocardiographic changes, especially ventricular tachycardia, were correlated with the outcome of hospitalization. As in our study, in Aziz *et al* (22), Taghaddosi Nejad (6), and Shadnia *et al* (23), there was a significant difference in the prevalence of electrocardiographic changes between those who died and those who were discharged. Based on upper findings and studies, it seems that higher doses of aluminum phosphide can lead to life-threatening dysrhythmias, and these electrocardiographic changes lead to death, but logistic regression indicated that this correlation was probably due to correlation with poison dose; and higher doses of aluminum phosphide through factors

like cardiac arrhythmias, refractory hypotension, ARDS, end-organ damage, and acidosis alone or with each other increase mortality.

Limitations and suggestions

Due to the high prevalence of electrocardiographic changes in patients with aluminum phosphide poisoning, it can be suggested that obtaining possible preventive therapeutic interventions, consecutive ECGs and echocardiography and further cardiac examinations can be effective in patients' management.

In the present study, the electrocardiograms of two patients became unreadable due to the passage of time (who were excluded from the study), thus making decisions to preserve patients' medical records and, if possible, creating electronically data bank or poisoning registry can be of great help in conducting such studies.

As one of the study limitations, the number of excluded patients was too large. Therefore, the sample size was small, therefore, multicentral and supra-regional investigations might provide better knowledge in this area.

Since the observed results as well as the published results of previous studies are a bit different from each other, and due to the different manifestations and complications of aluminum phosphide (and phosphine) poisoning, also the fact that more detailed study of factors affecting the outcome of hospitalization, or electrocardiographic changes requires a high sample size, multicentral and supra-regional investigations can provide better knowledge in this regard.

It is clear that paying attention to cardiac changes and controlling and preventing them may reduce patients' mortality. Furthermore, considering that the patients are mostly young and the patients who survived in this study had complete recovery without any complications, it is vivid that in case of reduced mortality, these patients can be returned to everyday life with psychiatric and social support and could be of profit for themselves and the society in the future.

Conclusion

Our results demonstrated that 20-40 years is the most prevalent age group, and men were twice as likely

as women to be exposed to aluminum phosphide. Electrocardiographic changes were present in 86.1% of patients who had consumed aluminum phosphide. The most common electrocardiogram (ECG) change in patients was sinus bradycardia, followed by ventricular tachycardia (the most lethal). we excluded all patients with history of cardiovascular disease, or history of medications that affect the ECG before analysis, and after this exclusion, in examining the pattern of ECG changes, we found that all people who died had ECG changes, and all people who had a normal electrocardiogram (5 people) were discharged (the advantages of this study over previous studies because of more accurate exclusion criteria). This difference was statistically significant, and not all people with electrocardiographic changes died. No association was found between the time interval between consumption and treatment and electrocardiographic changes in this study.

Ethical Considerations

Compliance with ethical guidelines: Ethical clearance was obtained from the Regional Ethics Committee (Research Ethics Committees of Tabriz

University of Medical Sciences; Approval ID (code): IR.TBZMED.REC.1398.081; Approval Date:2019-04-22). Also, the patients' information remained confidential in this study.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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