Aluminum Phosphide Poisoning Mortality Rate in Iran; a Systematic Review and Meta-Analysis

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Abstract: Introduction: According to statistics provided by the forensic medicine facility of Iran, there are a high number of Aluminum phosphide (ALP) poisoning-related deaths in the country; while the mortality rate varies in different studies. This study aimed to determine a pooled estimate of ALP poisoning mortality rate in Iran. Methods: The present study was a systematic review and meta-analysis of the mortality rate of ALP poisoning in Iran. Through the quarry of Persian and English databases, using “aluminum phosphide”, “phosphine”, “rice pills”, “poisoning”, and “Iran” as keywords, and no time restrictions, studies reporting mortality rate in ALP poisoning cases were collected. The random-effects model was used to pool the proportions of mortality and age of survivors versus non-survivors. Results: 21 studies with 3432 cases of ALP poisoning were included in this meta-analysis. The pooled mortality rate of ALP poisoning in Iran was 39.6%, (95% CI: 31.5%-47.9%; I² = 95%). Since there was significant publication bias, the trim-and-fill correction was conducted and the corrected pooled mortality rate was estimated to be 27.3% (95% CI: 18.9%- 36.5%), which is the rate that should be considered for clinical guidance. Morality rate in male and female patients was 62.3% (95% CI: 53.5%-70.8%) and 37.7% (95% CI: 29.2%-46.5%), respectively (p < 0.01). Survivors had significantly lower mean age than non-survivors (SMD: -0.26 (95% CI: -0.37 to -0.15); p < 0.01; I²=0%). Conclusion: According to this report, the Mortality rate of ALP poisoning in Iranian population is about 27%, with men having a higher fatality rate than women. Poisoning at a younger age is associated with better results.

Keywords: Aluminum phosphide; Poisoning; phosphine; Mortality; Iran

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1. Introduction

Aluminum phosphide (ALP), known as rice pill in Iran, is a very effective pesticide for commercial and industrial use. The high lethality of ALP is due to phosphine gas (PH3), which is released when ALP reacts with water. The resulting gas is colorless and has a distinct odor of garlic or rotten fish (1). Phosphine gas released in the stomach of individuals who have devoured this pill intentionally or accidentally, quickly gets absorbed into body organs and disrupts enzymatic activities, causes cell death and disrupts the function of almost all vital organs, namely brain, lungs, and liver (2). Symptoms of poisoning are due to the involvement of the cardiovascular, gastrointestinal, nervous, and pulmonary systems. The most common clinical signs and symp-
toms of ALP poisoning are restlessness, irritability, dizziness, vertigo, tremors, diplopia, imbalance, cough, shortness of breath, abdominal colic, nausea, vomiting, in some cases black vomit, black stools, decreased cardiac output, irregu-
lar heartbeat, pulmonary edema, cyanosis, renal impair-
ment, jaundice, enlarged liver and spleen, intestinal paral-
ysis, seizure, and acute respiratory distress syndrome (1). Se-
vere hypotension and shock are the most common symp-
toms of severe poisoning (3). Delayed symptoms of intoxica-
tion include pulmonary edema, hypocalcemic tetany, cardio-
vascular arrhythmia, liver damage, bradycardia, metabolic
acidosis, thrombocytopenia, and methemoglobinemia (4). Treatment for ALP poisoning is only supportive treatment, as there is no known antidote available against it. The effective-
ness of these treatments in poisoned patients depends en-
tirely on the degree of poisoning and the time of arrival at the medical center; the mortality rate following ALP poison-
ing varies between different studies. Despite the ban on the public sale of rice pills since 2012, Iran has a high number of ALP poisoning cases (intentional or accidental). According to statistics provided by the forensic medicine facility of Iran, there is a high number of ALP poisoning-related deaths in the country (5). While many observational studies have reported the cases of ALP poisoning; there is no overall view about the mortality rate of ALP poisoning in the country. This study aimed to determine a pooled estimate of the ALP poisoning mortality rate in Iran.

2. Methods

2.1. Study design and setting

The present study was conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist. Scientific sources were searched by two independent researchers from 2000 to 2021. Search for ar-
ticles and dissertations in Iranian sources were performed in the University Jihad Scientific Information Center (SID) database, and PubMed / MEDLINE, Scopus, EMBASE, and Web of Science databases with the keywords of “aluminum phosphide”, “phosphine”, “rice pills”, “poisoning”, and “Iran”. English and Persian articles were quarried. The reference list of all articles identified in the early stages was reviewed in or-
der to access cited articles that were not found via electronic searches.

The studies that reported cases of aluminum phosphide poi-
soning in Iran were selected in two stages. First, the ab-
stracts of articles obtained in electronic searches were thor-
oughly reviewed, and irrelevant or duplicate studies were eliminated. In the second stage, the decision on the final in-
clusion of studies was made after reviewing the full text of the studies (Table 1). Information on study characteristics, qual-
ity, and results were extracted from each selected article.

The criteria for inclusion in the study was to evaluate patients with aluminum phosphide poisoning and present their mor-
tality rate. Studies that only looked at the decedents were not included in this study. All articles that met the selection cri-
tera were evaluated in terms of methodological quality.

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ity, and results were extracted from each selected article.

2.2. Data extraction

A pilot evaluation of the final full texts was performed to
ensure inclusion of all data needed for final data synthesis to answer the study questions. Based on this evaluation, a
checklist was provided for data extraction. This checklist in-
cluded study ID, study design, province of study, duration of observation, the total number of cases (n), number of male and female cases, total mortality rate and mortality rate in each gender, and mean age of all participants, survivors, and non-survivors. A checklist of each study was filled by a single reviewer. Randomly, 5 studies were refilled by a second reviewer to ensure Inter-Rater reliability of checklists.

2.3. Data synthesis

We quantitatively examined the mortality rates of aluminum phosphide poisoning, the gender ratio of mortality, and the age of individuals. Mean age was pooled using the random

effect model through calculation of Standard Mean Differ-
ence (SMD). The possibility of publication bias was checked
using freeman-Tukey double arcsine transformation and Eg-
ger's test in case of the binomial outcome of mortality. In case
of publication bias, the trim-and-fill approach was used to
tackle the issue. All statistical analyzes were performed using R statistical packages.

3. Results

As shown in the PRISMA flowchart (figure 1), finally, 21 stud-
ies with 3432 cases of ALP poisoning were included in this
meta-analysis. There were about 1637 male and 1732 female
poisoning cases (one study, Shadnia et al., 2007, did not re-
port gender). Cases were evaluated from 2000 to 2021 (table
1).

3.1. Overall mortality rate

The pooled mortality rate of ALP poisoning in Iran was 39.6%
(95% CI: 31.5% to 47.9%); with 95% heterogeneity (p <0.01; figure 2).

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3.2. Gender and mortality rate

The male and female mortality rates were pooled from 12 studies listed in figure 3a and 3b. Proportion of mortality in male patients was 62.3% (95% CI: 53.5% to 70.8%); with 80% heterogeneity (p < 0.01). The proportion of mortality in female patients was 37.7% (95% CI: 29.2% to 46.5%); with 80% heterogeneity (p < 0.01).

As shown in the funnel plot in figure 4, freeman-Tukey double arcsine transformation and Egger's test revealed significant funnel plot asymmetry, indicating the possibility of publication bias or small-study effects, P<0.01. It reveals that studies are shifted to the right. Linear regression test of funnel plot asymmetry also confirmed asymmetry (t = 2.23, df = 21, p = 0.0369).

To address the publication bias, we utilized the trim-and-fill approach to look at the effect on the pooled estimate. After applying the trim-and-fill approach to account for missing studies, the result was a symmetrical Egger funnel plot, which is shown in figure 5, where the linear regression test of funnel plot asymmetry was not significant (t = 0.17, df = 32, p = 0.8673). The mortality rate that should be considered for therapeutic purposes is 27.3% (95% CI: 18.9% to 36.5%) as shown in the new forest plot in figure 6, with the pooled proportion corrected for publication bias.

3.3. Mean age and mortality rate

In a comparison of mean age of survivors versus non-survivors, a random effect model showed a significant difference between survivors versus non-survivors, where survivors had significantly lower age (SMD: -0.26, 95% CI: -0.37 to -0.15; p< 0.01; figure 7). Heterogeneity was not observed in the case of age comparison (I2=0%).

4. Discussion

This study showed a mortality rate of about 40% along with a publication bias. When we used trim-and-fill correction, mortality rate decreased to about 27%, which seems to be far from the reality. There is no proper official data available to facilitate reaching a final decision on mortality rate and in our knowledge, and this is the first study in Iran giving a comprehensive mortality rate for ALP poisoning. Also, there is a wide distance between the mortality rates of males and females, and averaging to find the overall mortality rate of ALP poisoning does not seem reliable.

Other studies have reported a 70–100% mortality rate, as reviewed by Meena et al. (26). A 59.3% mortality rate was reported in Mathai and Bhanu study in 2010 (27). But Iranian studies have reported a wider range of mortality rates as Abdollahi and Mehrpour (28) reported the mortality rate to vary

Table 1: Studies included in the meta-analysis

| Study ID | Year** | N | Gender (n) | Age (year; mean ± SD) | Survivors | Died |
|----------|--------|---|-----------|----------------------|----------|------|
| Majidi et al., 2021; (6); Urmia | 2015–2019 | 134 | Male 96 Female 38 | 40 28.6±11.5 | NA | NA |
| Navabi et al., 2018 (7); Kermanshah | 2014–2015 | 77 | Male 48 Female 29 | 41 28.7±10.2 | 31.3±10.7 |
| Shadnia et al., 2007 (8); Tehran | 2003 | 63 | NA Male 24 Female 32 | 16 27.3±11.5 | NA | NA |
| Ataei et al., 2021 (9); Mashhad | 2019–2021 | 41 | Male 23 Female 18 | 8 27.6±7.69 | NA | NA |
| Mehrpour et al., 2008 (10); Tehran | 2006 | 45 | Male 24 Female 21 | 16 27.3±11.5 | NA | NA |
| Rahbar et al., 2006 (11); Rasht | 2006–2003 | 116 | Male 63 Female 53 | 68 29.47±14.79 | NA | NA |
| Montazer et al., 2016 (12); Sari | 2013–2014 | 52 | Male 14 Female 38 | 16 23.4±9.2 | NA | NA |
| Rahbar et al., 2013 (13); Rasht | 2008–2009 | 104 | Male 66 Female 38 | 93 33.8±14.69 | NA | NA |
| Rahbar et al., 2011 (14); Rasht | 2005–2006 | 102 | Male 68 Female 34 | 77 29.75±14.34 | NA | NA |
| Soltaninejad et al., 2012 (15); Tehran | 2007–2010 | 956 | NA | 230 24.5±6.19 | 27.32±11.31 |
| Hassanian-Moghaddam et al. 2007 (16); Tehran | 2005–2007 | 340 | Male 162 Female 178 | 100 25.7±9.2 | NA | NA |
| Hoseinian et al., 2011 (17); Mazandaran | 2007–2008 | 102 | Male 46 Female 56 | 19 28.5±12.4 | 28.6±12.75 | 24.92±9.51 |
| Shokrzadeh et al., 2017 (18); Gorgan | 2008–2015 | 53 | Male 37 Female 16 | 16 26.1±11.6 | NA | NA |
| Farzaneh et al., 2015 (19); Ardabil | 2006–2012 | 386 | Male 72 Female 314 | 95 NA | NA | NA |
| Navabi et al., 2018 (7); Kermanshah | 2014–2015 | 118 | Male 75 Female 43 | 41 NA | 28.7±10.2 | 31.3±10.7 |
| Shadnia et al., 2009 (20); Tehran | 2000–2007 | 471 | Male 246 Female 225 | 146 NA | 24.38±8.81 | 30.87±14.80 |
| Mehrpour et al., 2009 (21); Tehran | 2006–2007 | 45 | Male 24 Female 21 | 32 NA | NA | NA |
| Erfantalab et al., 2017 (22); Tehran | 2014–2015 | 39 | Male 27 Female 12 | 15 31.0±11.3 | 30.5±11.7 | 31.8±11.1 |
| Mostafazadeh et al., 2011 (23) Tehran | 2009 | 48 | Male 24 Female 24 | 9 25.5±9.5 | NA | NA |
| Tavakoli-Far et al., 2018 (24); Karaj | 2006–2011 | 67 | Male 36 Female 31 | 30 NA | NA | NA |
| Shayeste et al., 2017 (25); Gorgan | 2009–2016 | 73 | Male 53 Female 20 | 25 27.4±16.75 | NA | NA |

* All study types were cross-sectional. ** Duration of observation. NA, not addressed.
from 30 to 100%. But other factors, as well as the amount of consumed ALP, affect the results.

Unfortunately, due to factors such as high toxicity and high lethality of this substance and ease of access to this toxin, based on official reports a relatively high rate of poisoning is seen in the country, especially in some provinces such as Tehran, Gilan, Mazandaran, Golestan, and Lorestan, (5). Our meta-analysis also showed that most published studies are performed in these provinces.

Our study showed that the mortality rate of ALP poisoning in Iran was 39.6% with the proportion mortality being 62.3% in males and 37.7% in female patients. In the comparison of mean age of survivors versus non-survivors, there was a significant difference between survivors versus non-survivors, where survivors had a significantly lower age.

Based on the reports by forensic medicine facility of Iran, most of the ALP-poisoning-related deaths were in the age group of 20-40 years, and most of them intended to commit suicide. Statistics from 2008 to 2011 show that death from rice pills were on the rise. There were 214 individual cases of mortality (105 women / 109 men) in 2008, 228 cases (104 women / 124 men) in 2009, 406 cases (202 women / 204 men) in 2010, and 463 cases (204 women / 259 men) in 2011 (5).

In a comparison of studies performed outside Iran, according to El-Sarnagawy’s study, there was a strong link between mortality risk and young age, rural location, suicidal ingestion, increased toxic dose, and prehospitalization duration. They reported 44.7% deaths with ALP in 5 years (29). A study by Sheta showed that 43.3 percent of cases died (30). Compared to our study, better survival in Iranian poisoning cases could be due to the higher experience of Iranian health care providers in the management of ALP poisoning, as most case reports of successful treatment of ALP are being published by Iranians (31-33).

In a study by Alnasser et al., they evaluated ALP poisoning in Saudi Arabia over a nine-year period, the highest rate of death from ALP poisoning belonged to children, and it occurred most frequently during household fumigation. Delays in medical treatment and diagnosis may have had a role in the patients’ death (34).

Poisoning due to the use of rice pills in Iran has led to the responsible organizations and institutions in the country taking measures to ban the import and restrict the sale of rice pills. Having comprehensive data on ALP poisoning mortality rate in our country could help us in policymaking regarding public sale of ALP for industrial purposes.

5. Limitations

A concern in this study was the possibility of publication bias. As a result, the findings of this study should be interpreted with caution, bearing the limitations in mind. Although our article search was limited to Iran, there was a low possibility of biased study retrieval due to the high number of studies; however, there might be a possibility of incomplete study retrieval as we did not find studies performed in the south of the country and medical dissertations and official and unofficial reports were not included. Reporting bias might also have affected our results as datasets with high mortality rates might have not be reported.

6. Conclusion

According to this report, the mortality rate of ALP poisoning in Iranian population is about 27%, with men having a higher fatality rate than women. Poisoning at a younger age is associated with better results.

7. Declarations

7.1. Acknowledgments

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7.2. Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

7.3. Conflict of interest statement

The authors have declared that no competing interests exist.

7.4. Author contribution

FB and NK conceptualized the study questions and performed revisions. FR and SA performed the searches. NH and NJM conducted the statistical analyses. Other authors provided the draft manuscript.

7.5. Ethical Considerations

All ethical principles are considered in this article.

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Figure 1: PRISMA flow chart of study.
Figure 2: Forest plot of mortality rate.

Figure 3: Forest plot of mortality rate based on gender, (a) male, (b) female.
Figure 4: Funnel plot of included studies.

Figure 5: Trim-and-fill corrected Funnel plot of included studies.
Figure 6: Trim-and-fill corrected Forest plot of mortality rate.
Figure 7: Forest plot of mean age of survivors versus non-survivors.