### **Original Article**

# Intoxication-Related Deaths in a Poisoning Center in Isfahan: Demographic and Other-Related Factors

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#### Abstract

**Background:** The aim of this study was to investigate the frequency of poisoning mortality in the 5-year period of 2014–2019 in Isfahan Khorshid Hospital, Iran.

**Materials and Methods:** This study is a cross-sectional descriptive analytical study, which was performed in 2020. The demographic and clinical data about the patients were extracted from the patients' files and were then analyzed.

**Results:** The number of deaths due to poisoning in the study period was 264, and the mean age of the deceased was  $42.33 \pm 20.097$ . One hundred and ninety-three (73.1%) patients were male. The frequency of deaths in the poisoning ward was 0.84%. The causes of death were accidental overdose (73, 26.9%), suicide (155, 63.2%), accidental use (18, 7.3%), and homicide in one patient. The mean age, time between exposure of toxin until death and history of addiction, substance use, and suicide in men patients was significantly higher than women (P < 0.05), however, such significant results were observed in married when compared with single patients. The differences between the two genders based on the type of toxic substance were statistically significant (P < 0.001). The most common causes of death were pesticides poisoning (n = 121), especially paraquat (n = 48) and Aluminum phosphide (n = 45), and multidrug poisoning (n = 48).

**Conclusion:** In this study, we showed that the death rate due to poisoning in our center was lower than other centers. The highest number of poisoning was in men as well as married patients. It is also recommended that more serious educational and preventive strategies should be used in this regard.

Keywords: Epidemiology, mortality, poisoning

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## INTRODUCTION

Poisoning is a serious problem and one of the most common causes of hospital emergencies in many countries.<sup>[1-3]</sup> According to the World Health Organization, suicide by chemicals annually accounts for nearly one million deaths worldwide due to pesticides.<sup>[4]</sup> The pattern of poisoning varies according to the socioeconomic, cultural, technological, and agricultural situation of countries.<sup>[5-7]</sup> Mortality rates due to poisoning have been varied in different parts of the world due to the introduction of new drugs and chemicals.<sup>[8]</sup>

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Poisoning is the third leading cause of death in developing countries, the fifth cause of referring to hospital and the second cause of death among inpatients.<sup>[9]</sup> Meanwhile, the mortality rate due to drug poisoning in underdeveloped countries is four times that of developed countries.<sup>[10]</sup> Insecticides are the most common cause in developing countries.<sup>[4]</sup>

In developing countries, we are encountering with increasing prevalence of intoxication due to weak pharmaceutical and chemical regulations, lack of monitoring systems, and easy access to toxic drugs and chemicals that could explain higher poisoning mortality rates.<sup>[8]</sup>

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In Iran, poisoning is one of the most common causes of hospitalization<sup>[11]</sup> and opioids are the most common cause of lethal poisoning.<sup>[12]</sup> Factors associated with probability increment in the lethality of poisoning are age over 60 years, suicidal ideation, similar previous manners, psychological and social stress, chronic or severe illness, drug addiction, psychosis, and lack of a supportive family system.<sup>[13]</sup>

Iran has the greatest increase in suicide-related deaths among the Eastern Mediterranean region and Islamic countries. Age, male gender, and somatic disorders were the most important predictors of death due to suicide.<sup>[14]</sup>

The aim of this study was to investigate the frequency of poisoning mortality in the period of 5 years. In addition, we aimed to determine the epidemiological and intoxication factors that could influence toxicity-related deaths.

## Materials and Methods

This is a descriptive-analytical cross-sectional study (ethical code: IR.MUI.MED.REC.1398.619) which was conducted in 2020 on all patients who were poisoned and died during the years 2014–2019 in Isfahan Clinical Toxicology Department of Khorshid Hospital. The inclusion criteria were the presence of any types of poisoning leading to death. When incomplete file information was more than 10%, it was considered as the exclusion criteria.

Based on the objectives of the study and the research questions, a checklist was prepared and all the required information was extracted from the patients' records and entered into the checklist. These data included sex, age, marital status, nationality, place of residence, cause of poisoning (substance use,<sup>[15]</sup> suicide, accidental suicide), type of poisoning agent, manner of poisoning (gastrointestinal, cutaneous, inhaled, or injected), the time interval between exposure to the toxic substance and admission to the hospital, the time interval between poisoning and death, length of hospitalization, history of suicide, and substance use. Due to the unavailability of toxicological screen in autopsy specimen, the probable cause of death is recorded in the mentioned cases.

The collected data were analyzed using SPSS-26 software (SPSS Inc., Chicago, IL, USA). At the level of descriptive statistics, the indicators of mean, standard deviation, and frequency were used. The means were analyzed based on Mann–Whitney and Chi-square tests. Progressive analysis was performed with independent *t*-test, ANOVA, and Kruskal–Wallis test. If the data did not show a normal distribution, nonparametric tests were used. P < 0.05 was considered as significant differences.

# RESULTS

The number of died patients due to poisoning was 280; 16 cases were excluded from the study due to incomplete records. From the years 2014 to 2019, about 54, 52, 55, 61, and 58 patients died in the poisoning service, respectively. Considering that

7288, 7416, 6401, 6467 and 6615 patients have been admitted to the poisoning ward in these 5 years; The frequency of deaths was 0.7%, 0.85%, 0.89%, 0.86%, 0.92% and 0.84% in total, respectively. About 41.8% died in the ward and 58.2% in the intensive care unit. The mean age of the subjects was  $42.33 \pm 20.097$  (with minimum age of 7 and maximum age of 90 years). Most of them were Iranians 257 (97.3%) and only 7 (2.7%) non-Iranians.

The causes of death were as accidental overdose subsequent to substance use (73, 26.9%), suicide (155, 63.2%), accidental use (18, 7.3%), and homicide (one patient). One hundred and seventy-five of these patients lived in Isfahan. Of these, 93 had a history of substance use disorder, 90 had a history of opioid use, 12 had a history of stimulant use, and 17 had a history of alcohol use. The mean time from intoxication to admission to emergency department (ED) was  $6.25 \pm 7.51$  h, the mean time for hospitalization was  $287.50 \pm 116.53$  h, and the mean time from consumption to death was  $163.6 \pm 103.34$  h. The mean time for hospitalization was  $116.53 \pm 287.5$  hours and the mean time from consumption to death was  $103.34 \pm 166.57$  hours.

As shown in Table 1, the mean age of married patients was significantly higher than single patient, and the mean age of men who died of poisoning was higher than women (P < 0.001). In addition, the mean time between exposure of toxin and death was higher in married subjects than single subjects (P = 0.02) and was more in men than women (P = 0.004). The results showed that the mean time of hospitalization in men was significantly higher, compared to women (P = 0.006). A comparison of the cause of death due to poisoning among men and women showed that the main cause in men was related to use and suicide manner, but in women, the important cause was suicide (P = 0.004). Moreover, the suicide rate was higher in married patients than the single ones (P = 0.03) and more in men than women (P = 0.001).

The analysis of the type of toxic substance based on sex and marital status is shown in Table 2. The differences between the two genders based on the type of toxic substance were statistically significant (P < 0.001). However, in a more detailed analysis, this difference was significant for pesticides (P = 0.004), paraquat (P = 0.001), and aluminum phosphide (P = 0.03).

The most common causes of death were pesticides poisoning (n = 121), especially paraquat (n = 48) and Aluminum phosphide (n = 45), and multidrug poisoning (n = 48).

Table 2 lists the frequency of deaths due to poisoning with paraquat and aluminum phosphide alone and in combination with other pesticides, as well as deaths due to each drug alone or in the form of multidrugs. Opioids have been implicated in the deaths of 77 patients, either directly or in combination with other drugs and toxins. The type of toxic substance based on the age groups (under 10 years, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and over 70 years old) was analyzed, and nonsignificant difference was observed (P = 0.258).

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Variables		Sex		Marriage			
	Female ( <i>n</i> =71), <i>n</i> (%)	Male ( <i>n</i> =193), <i>n</i> (%)	Р	Married ( <i>n</i> =174), <i>n</i> (%)	Single ( <i>n</i> =90), <i>n</i> (%)	Р	
Age (years), mean±SD	33.65±16.53	45.53±20.38	< 0.001	50.27±19.30	26.99±10.39	< 0.001	
Time between consumption and admission to hospital (h), mean±SD	6.03±7.81	6.34±7.43	0.79	6.93±7.88	4.95±6.63	0.07	
Time between consumption until death (h), mean±SD	62.66±107.05	117.73±181.18	0.004	122.20±192.31	67±90.54	0.02	
Hospitalization period (h), mean±SD	58.05±99.25	138.05±328.48	0.006	118.06±230.37	113.59±375.16	0.90	
Type of poisoning							
Misuse (73)	8 (11)	65 (89)	0.004	55 (75.3)	18 (24.7)	0.135	
Suicide (156)	51 (32.7)	105 (67.3)		98 (62.8)	58 (37.2)		
Accidental (18)	5 (27.8)	13 (72.2)		12 (66.79)	6 (33.3)		
Route of poisoning							
Ingestion (246)	69 (28)	177 (70)	0.29	164 (66.7)	82 (33.3)	0.70	
Injection (6)	0	6		2 (33.3)	4 (66.7)		
Inhalant (10)	2 (20)	8 (80)		7 (70)	3 (30)		
History of suicide							
Yes (42)	20 (47.6)	22 (52.4)	0.001	22 (52.4)	20 (47.6)	0.03	
History of addiction							
Yes (93)	10 (89.2)	83 (10.2)	< 0.001	68 (73.1)	25 (26.9)	0.09	
SD: Standard deviation							

Table 1: Comparison of demographic and poisoning factors based on gender and marital status in poisoning-related deaths

#### Table 2: Frequency of the type of toxic substance based on sex and marital status in poisoning-related deaths

Type of toxic substance (n)	Marriage			Sex		
	Married (total=232), <i>n</i> (%)	Single (total=42), <i>n</i> (%)	Р	Female (total=116), <i>n</i> (%)	Male (total=244), <i>n</i> (%)	Р
Multidrug (48)	26 (54.2)	22 (45.8)	0.154	24 (50.0)	24 (50.0)	0.001
Antianxiolytics (30)	20 (66.7)	10 (33.3)		16 (53.3)	14 (46.7)	
Atypical antidepressants (3)	2 (66.7)	1 (33.3)		2 (66.7)	1 (33.3)	
Beta blockers (9)	7 (77.8)	2 (22.2)		6 (66.7)	3 (33.3)	
Anticonvulsants (6)	4 (66.7)	2 (33.3)		3 (50.0)	3 (50.0)	
Antipsychotics (9)	5 (55.6)	4 (44.4)		4 (44.4)	5 (55.6)	
Tricyclic antidepressant (9)	6 (66.7)	3 (33.3)		4 (44.4)	5 (55.6)	
Selective serotonin reuptake inhibitor (6)	4 (66.7)	2 (33.3)		2 (33.3)	4 (66.7)	
Nonsteroidal anti-inflammatory drugs (3)	1 (33.3)	2 (66.7)		1 (33.3)	2 (66.7)	
Antihyperglycemic agents (3)	2 (66.7)	1 (33.3)		1 (33.3)	2 (66.7)	
Simple analgesics (2)	2 (100.0)	0 (0.0)		2 (100.0)	0 (0.0)	
Calcium channel blockers (3)	2 (66.7)	1 (33.3)		1 (33.3)	2 (66.7)	
Anticholinergics (2)	2 (100.0)	0		1 (50.0)	1 (50.0)	
Pesticides (121)	78 (64.5)	43 (35.5)		28 (23.1)	93 (76.9)	
Paraquat (48)	35 (72.9)	13 (27.1)		4 (8.3)	44 (91.7)	
Aluminum phosphide (45)	22 (48.9)	23 (51.1)		17 (37.8)	28 (62.2)	
Lead (2)	2 (100.0)	0		0 (0.0)	2 (100.0)	
Cyanide (2)	1 (50.0)	1 (50.0)		1 (50.0)	1 (50.0)	
Gases (2)	1 (50.0)	1 (50.0)		1 (50.0)	1 (50.0)	
Opioids (77)	56 (72.7%)	21 (27.3%)		16 (20.8%)	61 (79.2%)	

Ninety-three (35.2%) patients had the history of substance use; the frequency of the type of substance used by died patients based on gender and marital status is shown in Table 3. It was shown that the history of substance use was more in men and married patients when compared with women (P = 0.009) and single patient (P = 0.026).

### DISCUSSION

Early diagnosis and appropriate treatment of poisoning are vital and it can save the lives of these patients. Therefore, understanding the general pattern of poisoning in different parts of countries is of great importance. Dorooshi, et al.: Intoxication-related deaths

Substance type	Marriage			Sex			
	Married (total=92), <i>n</i> (%)	Single (total=48), <i>n</i> (%)	Р	Female (total=10), <i>n</i> (%)	Male (total=130), <i>n</i> (%)	Р	
Opium (50)	41 (82.0)	9 (18.0)	0.026	4 (8.0)	46 (92.0)	0.009	
Methadone (28)	20 (71.4)	8 (28.6)		0	28 (100.0)		
Heroin (10)	4 (40.0)	6 (60.0)		0	10 (100.0)		
Tramadol (2)	2 (100.0)	0		1 (50.0)	1 (50.0)		
Methamphetamine (10)	5 (50.0)	5 (50.0)		2 (20.0)	8 (80.0)		
Cannabis (2)	1 (50.0)	1 (50.0)		1 (50.0)	1 (50.0)		
Alcohol (17)	8 (47.1)	9 (52.9)		2 (11.8)	15 (88.2)		
Polysubstance abuse (21)	11 (52.4)	10 (47.6)		0	21 (100.0)		

In this study, about 63.2% causes of deaths were due to suicide and 26.9% were due to accidentally overdose. In addition, 35.2% of the dead had a history of substance use. The difference in poisoning between men and women could be partly explained by social differences, including improved literacy and increased life expectancy for women in Iran.

Churruca and Mitchell<sup>[16]</sup> reported that during 2001–2013, there were 17,895 deaths from drug poisoning in Australia. The number of deaths due to drug poisoning has increased during this 13-year period. Nearly two-third of the deaths were male, with the highest mortality rate occurring in adults aged 30-49 which is consistent with our study, but unintentional way in this study was 48.3%-66.3% while in our study, 7.3% of the cases were accidental poisoning.

In China, the main risk factors for unintentional poisoning were the men Chinese, villagers, and the elderly patients, use of alcohol, drugs, and occupational hazards.<sup>[17,18]</sup> This gender difference wsa similar to our study and could be explained that men are more involved in social communication than women.

The highest mortality rate was due to pesticides and suicide among people over 15-year old, although this poisoning has been declining. This is consistent with our study that the highest mortality rate was due to pesticides.

According to a study in the United States,<sup>[19]</sup> from 1999 to 2017, deaths by drug overdose in both urban and rural regions have increased. The mortality rate due to overdose of heroin was higher in major cities than rural areas. In our study, according to this point that most our patients lived in Isfahan not rural area, we did not separate these areas. We can describe this similarity to opioid-related deaths in two population.

Kordrostami et al., [20] from 2011 to 2015, it was stated that 1667 of suicides were investigated by Tehran Forensic Medicine Organization in Iran, of which 674 (40.43%) had positive results for drugs and pesticides in postmortem samples. Of these, 68.55% were men and 31.45% were women. The mean age of the dead patients was  $32.61 \pm 13.7$  years. Poisoning was the most important method of suicide in the young subjects. Aluminum phosphide was the most toxic substance detected in postmortem samples, followed by opioids, methamphetamine, organophosphates, cyanide, and strychnine. Comparing the results of that study with ours, although the mean age of deceased patients in Tehran was lower than Isfahan, the type of poisoning leading to death and the gender of the deceased patients were similar. Considering the easy access to prescription drugs as well as pesticides, it seems that people have chosen these two available methods for suicide.

Khodabandeh et al.<sup>[21]</sup> presented that, multiple drug toxicity and opioid poisoning were the most common causes of acute poisoning (27.5% and 27.1%, respectively). Like to our results, the mean time interval between acute poisoning until ED admission and duration of hospitalization until death were  $5.6\pm1.2$  and  $8.3\pm0.7$  h, respectively. There was a significant relationship between death due to acute poisoning and gender and age group, place of referral, type of toxic substance, and time interval from consumption to admission. As in our study, a history of suicide and self-harm was less common among the deceased patients.

In a study by Gheshlaghi et al.,<sup>[22]</sup> the poisonings cases leading to death who referred to the forensic organization in Isfahan in the period of 2010-2014 were investigated. In this study, 1590 patients died due to poisoning during this period and it was shown that the most common cause of death was drug poisoning (48%). About 60.1% of deaths were due to suicide. However, the mortality rate due to poisoning in our study has been constantly declining, and the type of poisoning leading to death has changed from drugs to pesticides. Another explanation is that the study population between ours and Gheshlaghi et al.<sup>[22]</sup> is different. In addition, it should be considered that a number of opiate poisoning patients have been referred directly to forensic medicine due to death at home and have not been recorded in the hospital statistics.

The increased prevalence of psychiatric illnesses, low price, and easy access to a variety of drugs and drug use leads to the spread of poisoning with these drugs and substances. However, reducing the percentage of fatal poisoning with these drugs could be explained by closer monitoring of the drug supply chain and strengthening treatment and care management in the poisoned ED with increasing the public awareness and paying more attention to poisonings in the society.

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## CONCLUSION

Pesticides were the main cause of fatal poisoning in our study. Increased access to toxic agents by victims, inadequate monitoring of the distribution of pesticides, and insufficient attention to educational programs in the community are the major causes. The results of our study reveal the importance of poisoning as a cause of mortality and reduction of life expectancy due to affecting young people. It is suggested that more preventive measures should be taken by the relevant agencies in the field of increasing and raising the level of public awareness in this regard.

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#### **Conflicts of interest**

There are no conflicts of interest.

## REFERENCES

- Alikhani B, Soleymanpour A, Sabzghabaee AM, Eizadi-Mood N. Demographic, clinical, and forensics findings in deceased cases of acute methadone poisoning. J Isfahan Med Sch 2017;35:1343-51.
- Mew EJ, Padmanathan P, Konradsen F, Eddleston M, Chang SS, Phillips MR, *et al.* The global burden of fatal self-poisoning with pesticides 2006-15: Systematic review. JAffect Disord 2017;219:93-104.
- Pillans PI, Page CB, Ilango S, Kashchuk A, Isbister GK. Self-poisoning by older Australians: A cohort study. Med J Aust 2017;206:164-9.
- Mehrpour O, Akbari A, Jahani F, Amirabadizadeh A, Allahyari E, Mansouri B, *et al.* Epidemiological and clinical profiles of acute poisoning in patients admitted to the intensive care unit in eastern Iran (2010 to 2017). BMC Emerg Med 2018;18:30.
- Jailkhani S, Naik J, Thakur M, Langare S, Pandey V. Retrospective analysis of poisoning cases admitted in a tertiary care hospital. IJRTSAT 2014;10:365-8.
- Jalali A, Savari M, Dehdardargahi S, Azarpanah A. The pattern of poisoning in southwestern region of Iran: Envenoming as the major cause. Jundishapur J Nat Pharm Prod 2012;7:100-5.
- 7. Moharani B, Vijayakumari N. Profle of poisoning cases in a tertiary care

hospital, Tamil Nadu, India. JAPS 2013;3:91-4.

- Alinejad S, Zamani N, Abdollahi M, Mehrpour O. A narrative review of acute adult poisoning in Iran. Iran J Med Sci 2017;42:327-46.
- Rabiul H, Robed A, Ahmed-Riyadh H, Azizul K, Fazle Rabbi C. Clinico-epidemiological study of poisoning in a teriary care hospital in Bangladesh. J Emerg Pract Trauma 2017;3:4-10.
- Ghodsi Z, Moghaddam SS, Saadat S, Yoosefi M, Rezaei N, Ostadrahimi H, *et al.* Trend of fatal poisoning at national and provincial levels in Iran from 1990 to 2015. Public Health 2019;170:78-88.
- Manouchehrifar M, Derakhshandeh N, Shojaee M, Sabzghabaei A, Farnaghi F. An Epidemiologic study of pediatric poisoning; a six-month cross-sectional study. Emerg (Tehran) 2016;4:21-4.
- Shokrzadeh M, Hoseinpoor R, Hajimohammadi A, Delaram A, Shayeste Y. Epidemiological survey of suicide attempt by drug poisoning in Gorgan, Iran, 2008 to 2015. J Mazandaran Univ Med Sci 2016;26:201-10.
- Kurani S, McCoy RG, Inselman J, Jeffery MM, Chawla S, Finney Rutten LJ, et al. Place, poverty and prescriptions: A cross-sectional study using Area Deprivation Index to assess opioid use and drug-poisoning mortality in the USA from 2012 to 2017. BMJ Open 2020;10:e035376.
- Delam H, Zarebi K, Kavi E, Shokrpour N, Bazrafshan MR. Epidemiology of suicide attempts and deaths: A population-based study in the South of Iran (2012–2017). J Health Sci Surveill Syst 2020;8:115-20.
- Connors NJ, Hamilton RJ. Withdrawal principles. In: Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS, editors. Goldfrank's Toxicologic Emergencies. 11<sup>th</sup> ed. New York: McGraw-Hill Education; 2019. p. 236.
- Churruca K, Mitchell R. Exploring coronial determination of intent for poisoning-related deaths in Australia, 2001-2013. BMC Public Health 2017;18:83.
- Tang Y, Zhang L, Pan J, Zhang Q, He T, Wu Z, *et al.* Unintentional poisoning in China, 1990 to 2015: The global burden of disease study 2015. Am J Public Health 2017;107:1311-5.
- Wang L, Wu Y, Yin P, Cheng P, Liu Y, Schwebel DC, et al. Poisoning deaths in China, 2006–2016. Bull World Health Organ 2018;96:314-26A.
- Hedegaard H, Miniño AM, Warner M. Urban–Rural Differences in Drug Overdose Death Rates, by Sex, Age, and Type of Drugs Involved, 2017. NCHS Data Brief, No 345. Hyattsville, MD: National Center for Health Statistics; 2019.
- Kordrostami R, Akhgari M, Ameri M, Ghadipasha M, Aghakhani K. Forensic toxicology analysis of selfpoisoning suicidal deaths in Tehran, Iran; trends between 2011-2015. DARU J Pharm Sci 2017;25:15.
- Khodabandeh F, Emamhadi MA, Mostafazadeh B. Epidemiological assessment of acute poisoning death – one year survey. Int J Med Toxicol Forensic Med 2012;2:103-9.
- Gheshlaghi F, Eizadi-Moud N, Soleimanpoor A, Montazeri G, Rahmani-Jouybari M. Investigating the 5-years trend of poisoning led to death in Isfahan province, Iran, during 2010-2014. J Isfahan Med Sch 2015;33:1718-29.