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Evaluation of clinical findings of acetaminophen poisoning and factors associated with its severity in poisoned patients

Hamid Mohammadi Kojidi [1], Haniye Sadat Fayazi [1], Amaneh Khalilzadeh [1], Mirsaeed Attarchi [1] *

[1] Razi Clinical Research Development Unit, Guilan University of Medical Sciences, Rasht, Iran

Abstract

Introduction: Acetaminophen poisoning is one of the most common types of suicide in Iran. Investigation and identification of factors affecting the severity of this poisoning can have a significant impact on optimal treatment management. The aim of this study was to evaluate the clinical findings of Acetaminophen poisoning and its associated factors.

Materials and Methods: In a cross-sectional study, the files of patients admitted due to acetaminophen poisoning in the years 2011-2015 in the poisoning ward of Razi Educational Center in Rasht have been reviewed. Demographic characteristics of the poisoned, acetaminophen use, number of days of hospitalization, poisoning outcome, history of addiction, previous suicide history, time spent from drug use to hospitalization, clinical findings, severity of poisoning and laboratory test results were extracted from patients' records and registrated. Independent t-test, chi-square and regression analysis were used to investigate the relationship between study variables and severity of intoxication.

Results: In this study, 244 cases of poisoning were investigated. The highest frequency of symptoms was related to nausea (25.9%) and then vomiting (22.1%). More than 99% of those poisoned recovered. Mean hospital stay (P = 0.015), mean hospital stay after acetaminophen (P = 0.001) and mean liver enzyme levels (P < 0.05) were significantly higher in the moderate to severe intoxication group compared to the asymptomatic group. In the logistic regression analysis, even after removing confounders, there was a statistically significant association between the duration of the patient's arrival at the hospital (P <0.001, OR = 15.44; 95% CI: 5.88-40.44) and the amount of acetaminophen consumption (P <0.001, OR = 4.62; 95% CI: 2.00- 10.68) with severe poisoning.

Conclusion: In this study, most of those poisoned were female and aged 21-30 years. Most of the poisoned recovered. The acetaminophen dose and the duration of drug intake until hospitalization were significantly associated with the severity of poisoning and the mean values of liver function tests were higher in the high poisoning group.

Keywords: Suicide, Poisoning, Acetaminophen, Prognosis

*Corresponding Author: Mirsaeed Attarchi

✉ Email: msattarchi@yahoo.com

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Introduction

Suicide is a major problem in the world today and the fifth leading cause of death among people aged 15-49 worldwide. Asian countries account for about 60% of global suicides (1). The choice of suicide type varies according to geographical, social and demographic characteristics (2). Poisoning is the most common type of suicide in Asian countries, accounting for more than 60% of all deaths. In developing countries, poisoning is more common due to weak regulations, lack of monitoring systems and easy access to toxic drugs or chemicals. In Iran, poisoning is the most common cause of hospitalization and the second leading cause of death (3). Acetaminophen is the most commonly used antipyretic and analgesic in the world. Due to the easy availability and widespread use of acetaminophen, drug intoxications from drug use and even drug abuse have always been a problem (4). In 2005, more than 165,000 cases of poisoning were reported in the USA, of which about 67,000 were from acetaminophen alone (5). In the United Kingdom, 50% of poisoning cases resulted in hospitalization due to acetaminophen poisoning (6). In previous studies, acetaminophen poisoning was considered one of the most common causes of poisoning in Iran (7,8). In Iran, acetaminophen is an over-the-counter drug that comes in different formulations and dosages. Overdose of this drug is often observed in suicidal behaviour.

Early manifestations of acetaminophen poisoning are usually mild and non-specific and include nausea, vomiting, abdominal pain and weakness. These symptoms may improve within the first 24 hours or lead to progressive liver and kidney damage. In severe poisoning, patients may experience signs and symptoms of liver damage, including metabolic acidosis, coagulopathy and hepatic encephalopathy. Renal damage occurs in less than 2% of poisoned individuals without hepatotoxicity and in 25% of poisoned individuals with severe hepatotoxicity (9,10).

In a cross-sectional and retrospective study, Pajoumand et al. reviewed the medical records of 185 patients with acetaminophen poisoning referred to Loghman Hakim Hospital. Demographic information, laboratory findings, incidence of toxic hepatitis and renal failure were compared between poisoned and non-poisoned patients. Most of the poisoned were discharged on the first day and there were no deaths. But three patients had liver intoxication. The severity of intoxication depended on the ascetic serum concentration of acetaminophen and the elapsed time after administration of the drug (11). In a study (12) over a two-year period from January 2005 to January 2007, 85 patients admitted to Sina Hospital with acute acetaminophen poisoning were followed up. About 64% of the patients were female. In adults, acceptance was due to suicidal ideation rather than accidental poisoning. Patients who took more than 150mg/kg of acetaminophen or had impaired liver function had a longer hospital stay. There were no deaths in this study. The timely use of N-acetylcysteine in these poisoners may justify the lack of mortality. A study (13) of 21 patients who had attempted suicide by overdose of paracetamol at Maharaj Nakorn Chiang Mai Hospital between 2002 and 2000 was examined. Most of those poisoned were women (76%), students (38%) and employees (33%). The average age of those poisoned was 22 years and most cases were single (86%). The number of paracetamol tablets taken (500 mg tablets) ranged from 10-90 tablets. The blood levels of paracetamol were 0.12-8.3g/l. Nausea and vomiting were present in all poisoning cases. In this study, several subjects suffered from liver involvement, but all survived and recovered completely.

Identifying the factors that influence the prognosis of this poisoning may be effective in the management of acetaminophen poisoners. In our studies abroad, a number of predictors of the course and severity of this poisoning, such as age, early administration of N-acetylcysteine and arterial lactate levels have been identified (14,15). However, few studies have been conducted in this field in Iran, so in this study, we investigated the clinical outcomes and factors related to the severity of acetaminophen poisoning.

Materials and Methods

Study Design and Subjects

This study is a cross-sectional study that examines the records of hospitalised patients due to poisoning from the consumption of different amounts of acetaminophen with suicidal intent during the years 2011-2015 in the poisoning ward of Razi Educational Center in Rasht. In this study, as a sample of the study,

the records of all patients who were referred to this hospital and admitted to this center with a diagnosis of acetaminophen poisoning from the beginning of 2011 to the end of 2015 were examined. All patient information, especially patient identity information, was kept confidential and the results of the study were presented in general. All provisions of the Helsinki Convention were followed in this study. This research was the dissertation of a medical student (Ameneh Khalilzadeh Sabet Masouleh) conducted to obtain a degree in general medicine (registration number: 188951012). This research was approved by the Research Ethics Committee of Guilan University of Medical Sciences and the code of ethics obtained from the Vice Chancellor for Research of Guilan University of Medical Sciences is IR.GUMS.REC.1396.7.

Inclusion criteria included all patients whose records included the use of acetaminophen. Patients whose medical records were incomplete or illegible or who had taken other medications in addition to acetaminophen were excluded from the study. It is noteworthy that none of the clients complained about taking acetaminophen due to the increased dose of this drug and all had used this drug with suicidal intent.

To conduct this study, a checklist was designed by the researchers and included patient demographic characteristics (age, sex, occupation, education), acetaminophen use (number and dose), number of hospitalization days, disease outcome (recovery or death), history of underlying diseases, history of drug dependence (type of substance and method of use), history of previous suicide, history of drug use (type and amount of drug), time interval between drug use and hospitalization , clinical findings (asymptomatic, headache, abdominal pain, nausea, vomiting, anorexia, sweating, drowsiness, decreased level of consciousness, seizures, shortness of breath, etc.), and the results of the laboratory tests and treatment (administration of activated charcoal and n-acetylcysteine) were extracted from the patient records and recorded.

Intensity of the poisoning:

Patients based on poisoning severity score (PSS) (16) in terms of severity and outcome into five groups

(0) None: No symptoms or signs related to poisoning

(1) Minor: Mild, transient and spontaneously resolving symptoms

(2)Moderate: Pronounced or prolonged symptoms

(3) Severe: Severe or life-threatening symptoms

(4) Fatal: Death

Have been classified.

Statistical analysis

After collecting the data by checklist, the information was entered into SPSS software version 16 and the necessary analyses were carried out. Percentage, mean and standard deviation were used to express descriptive variables.

The T-test was used to compare these variables among the groups. The $\chi 2$ was used to compare the qualitative variables. Logistic regression analysis was used to eliminate the confounding variables and test the correlation between prognostic factors and severity of poisoning.

In the regression model, patients were divided into the mild to low intensity group (group one: None and Minor) and the moderate to severe intensity group (group two: Moderate, Severe, Fatal) according to the severity of poisoning using the POISONING SEVERITY SCORE and in the regression model in the form of these two groups were analysed and compared.

Furthermore, the patients were divided into two groups according to the toxic dose of acetaminophen Acetaminophen less than 7.5g and equal to or greater than 7.5g were classified (17) and compared in a regression analysis.

P values less than 0.05 were considered statistically significant. The results of statistical analysis are expressed as odds ratio (OR) with 95% confidence intervals (95% CI).

Results

In this study, all 244 cases of medical records in a given period were examined, of which all poisoned persons had taken acetaminophen to commit suicide. In terms of gender, 31.1% (76 subjects) were poisoned and 68.9% (168 subjects) were female. The average age of the subjects was 25.17 (±10.04) years, with the

youngest poisoned being 14 years old and the oldest 80 years old.

The mean length of hospital stay for the patients studied was 2.1 (±1.64) days, with a minimum length of hospital stay of one day and a maximum length of hospital stay of 22 days. The mean duration of acetaminophen use until the patient arrived at the hospital and was admitted to the hospital was 4.1 (±4.27) hours with a range of 30 minutes to 48 hours. 18.6% of patients had an underlying medical condition, 11.9% had a history of addiction, 12.3% had a history of suicide and 81.6% had a history of drug use. Of the 244 subjects, 42 (17.2%) had no symptoms and 202 had symptoms. The highest frequency of symptoms related to nausea (25.9%), followed by vomiting (22.1%), drowsiness (16.9%), headache (10.4%), abdominal pain (9%) and decreased consciousness (6.7%). The mean values of the liver function tests, namely AST, ALT, ALKP, were 23.2, 23.1 and 190.1 U/L, respectively. The mean values of the kidney tests, namely BUN and Cr, were 10.91 and 0.90 mg/dl, respectively. 93.4% of patients were prescribed activated charcoal and gastric lavage and 62.3% of patients were prescribed acetylcysteine. In the end, more than 99% of patients recovered and only 0.8% of cases ended in death. Patients were divided into two groups based on the mean time of arrival at the hospital after taking acetaminophen, such that 86 patients (35.2%) were admitted to the hospital three hours or less or 158 patients (64.8%) were admitted more than three hours after taking acetaminophen. Based on the dose of acetaminophen, those poisoned were divided into two groups with a dose of less than 7.5g (100 people or 41.0%) or a dose of 7.5 or more (144 people or 59.0%). According to the PSS criteria, the poisoned persons were divided into 5 groups according to the severity of poisoning: 42 persons (17.2%) None, 71 persons (29.1%) Minors, 98 persons (40.2%) Moderate, 31 persons (12.7%) Severe and 2 persons (0.8%) Fatal have been classified. Finally, we classified those poisoned into two groups according to the severity of the disease. The first group, i.e. asymptomatic patients to mild symptoms (None to Minors), were 113 (46.3 %) and the second group, i.e. moderate severity to death (Modarate to Fatal), were 131 (53.7 %).

Table 1 examines and compares the mean values of demographic and clinical variables and laboratory test results in the patient groups by disease severity. As the results from Table 1 show, the mean length of hospital stay (P = 0.015) and the mean time to hospitalization after acetaminophen ingestion (P = 0.001) were significantly larger number of moderate to death (Moderate to Fatal) poisonings occurred than in the group of asymptomatic to mild (None to Minors) poisonings. The mean values of liver enzymes in the moderate to fatal intoxication group were higher and this difference was statistically significant (P < 0.05).

Table 1. Comparison of mean values of clinical, demographic and laboratory variables by severity of acetaminophen poisoning.

Variable	Severity of the poisoning		
Clinical and demographic variables	None to Minors (mean - standard deviation)	Moderate to Fatal (Mean - Standard deviation)	The significance level
Age (years)	25.30 (9.97)	25.06 (10.14)	0.848
Length of hospital stay (days)	1.83 (0.96)	2.34 (2.02)	0.015
Duration of drug use until hospitalization (hours)	2.90 (1.59)	5.13 (5.43)	0.001
Laboratory variable			

Hb (g/dl)	12.30 (2.10)	12.49 (1.45)	0.575
AST(U/L)	20.13 (13.06)	25.68 (16.11)	0.047
ALT(U/L)	19.82 (14.15)	26.54 (32.78)	0.044
ALKP(U/L)	179.07 (62.67)	200.35 (75.94)	0.019
BUN (mg/dl)	12.85 (10.27)	13.65 (11.46)	0.585
Cr (mg/dl)	0.86 (0.35)	0.96 (1.07)	0.344

Table 2 examines the association between the qualitative variables of the study and the severity of intoxication. As the results of this table show, there was no statistically significant association between gender, history of addiction and history of underlying disease with the severity of intoxication (P > 0.05). However, there was a statistically significant association between the duration of poisoning from suicide to hospitalization, the amount of acetaminophen and a history of suicide with the severity of poisoning (P <0.05). The group of patients who came to the hospital more than three hours after the suicide with acetaminophen, the group of patients who received a dose of 7.5g or more of acetaminophen had a suicide attempt and had a history of suicide, respectively 7, 7 and 2.6 times higher than the group of patients admitted to hospital 3 or less hours after suicide with acetaminophen, groups of patients who committed suicide with a dose of less than 7.5g of acetaminophen and Groups of patients who had attempted suicide with a dose of less than 7.5g acetaminophen and groups with no history of suicide had a moderate to fatal risk of poisoning (Table 2).

Table 2. Assessment of the association between qualitative variables of the study with the severity of acetaminophen poisoning.

Variable	Severity of the poisoning			The significance level
	None to Minors (number)	moderate to fatal (number)	OR (95%CI)	
Acetaminophen dosage (g)				
Less than 7.5	73	27	7.03 (3.96-12.46)	0.0001>
7.5 and higher	40	104		
Duration of drug use until hospitalization (hours)				
Three and less	65	21	)12.89-3.90(7.09	0.0001>
More than three	48	110		
Gender				
Male	36	40	)1.37-0.77(1.03	0.890
Female	77	91		

History of addiction				
Yes	15	14	)2.78-0.58(1.27	0.557
No	98	117		
Suicide story				
Yes	10	20		
No	93	121	)5.82-1.16(2.60	0.019
History of the underlying disease				
Yes	24	19		
No	89	112	)3.08-0.81(1.59	0.181

Liver function test values were assessed according to the amount of acetaminophen used. The values of AST, ALT and ALKP were statistically significantly higher in the group consuming 7.5g and more than acetaminophen than in the group consuming less than 7.5g (P < 0.05) (Table 3).

Table 3. Assessment of the relationship between the levels of functional liver enzymes in relation to the dose of acetaminophen.

Liver function test	Acetaminophen dosage (g)		The significance level
	Less than 7.5 (mean - standard deviation)	7.5 and higher (mean - standard deviation)	
AST(U/L)	19.95 (10.81)	25.97 (16.63)	0.002
ALT(U/L)	18.88 (15.71)	26.59 (30.94)	0.023
ALKP(U/L)	164.10 (57.16)	208.83 (73.64)	0.0001

Logistic regression analysis was used to eliminate confounding factors and examine the more precise association between the variables of patient arrival time at the hospital and the amount of acetaminophen consumption with the severity and outcome of the illness (table 4). As the results of this analysis show, even after removing confounding factors, there is a statistically significant association between the time of the patient's arrival at the hospital (P <0.001, OR = 15.44; 95% CI: 5.88-40.44) and the amount of acetaminophen (P <0.001, OR = 4.62; 95% CI: 2.00-10.68) with severe poisoning. In this analysis, no correlation was found between age, sex, history of addiction, history of suicide and history of underlying disease with the outcome of poisoning (P> 0.05).

Table 4. Investigation of the association between factors related to the outcome of poisoning by logistic regression analysis*.

Variable	Condition	β	OR	95%CI	P-value
Fixed coefficient	---------	- 6.50	0. 001	----------	0.0001>
Acetaminophen dosage (g)	Less than 7.5	1.53	1.00	----------	0.0001>
	7.5 and higher		4.62	2.00 -10.68	

Duration of drug use until hospitalization (hours)	Three and less	2.73	1.00	----------	0.0001>
	More than three		15.44	40.44-5.89	

*Intensity and consequence of poisoning: reference group - None to Minors, comparison group - moderate to fatal.

Discussion

Acetaminophen is one of the most commonly used drugs in patients with drug intoxication. Acetaminophen is the second most commonly used drug for self-medication after tricyclic antidepressants (18). In Iran, acetaminophen is an over-the-counter drug available in several formulations and in different dosages. Acetaminophen is a dose-dependent hepatotoxin found in many products on the market and can cause acute liver damage when taken in doses of more than 6 to 10 grams per day (19). In our study, 244 patients with acetaminophen poisoning who had attempted suicide were examined. In the present study, most of the patients were aged 21-30 years and the mean age of the subjects was 25.17 years. Previous studies have reported that most acetaminophen poisonings are observed in young and early adulthood, but most poisonings resulting in death are observed in older age (20). In the study, the mean age of acetaminophen poisoning patients was 21.81 years and in both the male and female age groups, the most common age of acetaminophen poisoning was 20 years (20). A study of 1,019 patients with acetaminophen poisoning in Denmark from 1994 to 2003 found that age 15 to 24 years was the most common age for poisoning and that females outnumbered males. However, deaths from paracetamol poisoning occur more frequently in patients aged 40 years and older (14). Similar to other studies where women were the majority of acetaminophen poisoners, in our study women were the highest percentage of patients consuming varying amounts of acetaminophen for suicide and hospitalization (68.9%). In the study by Zyoud et al, acetaminophen suicide was higher among women than men in Malaysia, but men used higher toxic doses of the drug (21). In another study of 1,543 patients with acetaminophen poisoning in Canada between 1995 and 2004, the prevalence of cases was about three times higher in those aged 10-29 years than in those over 30 years, and 68% of patients were women with acetaminophen poisoning. (22). Of the 244 people we studied, 202 had symptoms. Among 202 symptomatic patients, the highest symptom frequency was associated with nausea (25.9%), vomiting (22.1%), drowsiness (16.9%) and only 0.8% of those poisoned died. During the study by Badsar et al (8), 31.2% of patients had no significant clinical manifestations. In other patients, the most common clinical symptom was nausea (50.4 %). After ingestion of acetaminophen, the drug is rapidly absorbed from the gastrointestinal tract and reaches therapeutic levels within 30 minutes to 2 hours. Overdose peaks within 4 hours (23). Toxicity of acetaminophen occurs at a dose of 7.5 to 10 grams per day. The mortality rate due to paracetamol overdose is currently about 0.4% (24). The toxicity of paracetamol is divided into four stages (24). The first stage The first 24 hours after consumption: This stage is the most critical stage and is characterised by vague findings such as nausea, weakness, vomiting and lethargy. Laboratory findings are usually normal. Second stage 24 to 72 hours after use: Initially, the signs and symptoms of the first stage disappear and patients appear clinically improved, while hepatic aminotransferases, serum prothrombin time and total bilirubin levels increase and renal dysfunction may occur. Third stage 72 to 96 hours after consumption: In this stage, symptoms become more prominent. Systemic findings, including weakness, nausea and vomiting, reappear and may be associated with central nervous system involvement such as confusion, drowsiness and possible coma. Jaundice may occur, as well as damage to the pancreas, kidneys and heart. Fourth stage 4 days to 2 weeks after consumption (recovery phase): During this period, liver problems are resolved. In this stage, clinical symptoms disappear and laboratory values normalise, and permanent damage rarely occurs. The course of acetaminophen poisoning can range from complete uncomplicated recovery to sometimes extensive liver necrosis to severe liver failure with bleeding complications, renal failure, hepatic encephalopathy and death in the next few days (25). In our study, the laboratory index of liver enzymes was statistically significant between groups

with different severity of poisoning. Identifying the unfavourable prognostic markers at the onset of the patient after acetaminophen poisoning is crucial for assessing the necessary interventions in clinical care. The results of one study (15) showed that advanced age, higher ALT, bilirubin and lactate levels, and lower levels of factor V and arterial pH were significantly associated with a poor prognosis of acetaminophen poisoning. In the study by Taghadosi Nejad and colleagues, careful examination of the medical history and simultaneous monitoring of plasma levels of acetaminophen were used to investigate the effective factors in causing severe poisoning in order to better select treatment priorities with N-acetylcysteine. This study was conducted in 2007 on 170 patients at Loghman Hospital who had taken more than 7.5 grams of acetaminophen based on their clinical history. The average age of those poisoned was 21.81 years, 55.3% were female. The prevalence of poisoning was higher in the third decade of life. The mean plasma level of the drug was 18.7 μg / ml. Variables such as the number of suicide attempts, the number of tablets taken and the time interval between drug intake and hospitalization had an influence on the severity of poisoning. In this study, in cases where it was not possible to quickly determine the plasma level of acetaminophen to determine the need for N-acetylcysteine, some biographical factors such as medication overdose, suicidal ideation and delayed hospitalisation are known risk factors, which can be used in designing the treatment process (20). In our study, charcoal was prescribed and gastric lavage was performed in 93.4% of patients and acetylcysteine was prescribed in 62.3% of patients. The mean value of liver function tests in the moderate to severe poisoning group was also higher and statistically significant ($P < 0.05$). In our study, the mean length of hospital stay ($P = 0.015$) and mean time to hospitalization after acetaminophen ($P = 0.001$) were significantly higher in the moderate-to-severe poisoning group than in the asymptomatic-to-mild group. Even after adjusting for confounding factors, there was a statistically significant association between the duration of the suicide attempt until hospitalization, the amount of acetaminophen consumed and the suicide history with the severity of poisoning ($P < 0.05$). The group of patients who arrived at the hospital more than three hours after attempting suicide with acetaminophen had a higher risk of moderate to severe poisoning than those who attempted suicide with a dose of 7.5g or more of acetaminophen. . In our study, the levels of AST, ALT, ALKP were statistically significantly higher in the group with 7.5 and more acetaminophen than in the group with less than 7.5g ($P <0.05$). In a retrospective cohort study over a 5-year period from 1 January 2004 to 31 December 2008, patients admitted to the emergency department within 24 hours of taking acetaminophen were included in the study. The frequency of vomiting in these poisoned patients was 65.3% at the time of admission. Multiple logistic regression analysis showed that there was a significant risk of vomiting in patients who reported a acetaminophen dose of 10g or more ($p < 0.001$) and a delay of more than 8 hours ($p = 0.030$). The increase in the frequency of vomiting episodes at first hospitalization appears to be an important indicator of the risk of renal and hepatic involvement in the near future after acetaminophen poisoning (26). The strongest predictor of severe hepatotoxicity in patients with acetaminophen poisoning is delayed treatment with N-acetylcysteine or no antidote in patients with more than 10 g of paracetamol or with toxic serum levels (27). One study (28) investigated the association between renal function at first hospitalization and the outcome of severe paracetamol poisoning. In this study, it was found that creatinine level at first admission predicted poor outcome in paracetamol overdose.

One of the limitations of our study was the lack of access to acetaminophen serum levels. The establishment and organisation of advanced laboratories to measure drug levels, including paracetamol serum levels, is recommended for optimal treatment of poison poisoners. Also, this study was a cross-sectional study in which, of course, the statement on the correlation of variables was not conclusive and it is recommended to conduct a prospective cohort study.

Conclusions

In the present study, acetaminophen poisoning was observed in patients with suicidal ideation mainly in women and aged 21-30 years. None of our patients died. Most of them seem to have suicidal thoughts and behaviour rather than making real efforts to end their lives. However, we recommend that you take steps to

limit the dose of this medicine without a prescription. The acetaminophen dose and the duration of drug administration until hospitalisation were also associated with the severity of intoxication, and the mean values of the liver function tests were higher in the high-severity intoxication group.

Author contribution

Conflict of interest

No potential conflict of interest was reported by the authors.

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