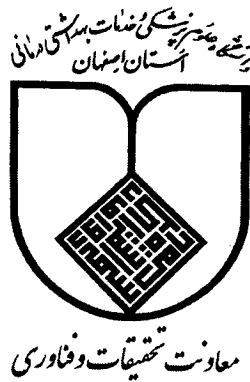


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**بررسی برخی فاکتورهای پیش گوئی کننده پیابند در بیماران مسموم با آفتامین ها
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Dear Professor Eizadi-Mood:

I am pleased to inform you that your manuscript # JRPP-14-528 with the title of: "**Outcome prediction in patients with Methamphetamine poisoning**" authored by: *Ms. Parva Paydar, Mr. Hooman Paydar and Professor Nastaran Eizadi-Mood*, is accepted for publication in the Journal of Research in Pharmacy Practice.

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Outcome prediction in patients with Methamphetamine poisoning

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Abstract:

Introduction

Methamphetamine (METH) is the most widely abused drug worldwide. Since there is a difference with respect to epidemiology of poisoning in the geographic distribution, we performed a study on the METH poisoning in a referral clinical toxicology department in Iran considering outcome prediction.

Methods:

This hospital based, analytical and descriptive study was carried out from 2012 to 2013 at referral clinical toxicology department. The inclusion criteria were all patients between 18 to 65 years of age admitted with diagnosis of METH poisoning. The information included gender, age, type and route of poisoning, clinical manifestations, duration of hospitalization, and outcome. ANOVA, chi-square and binary logistic regression were used for analysis.

Results:

During one year of study, 129 patients including 111(86%) males and 18(14%) females had been hospitalized and evaluated. The mean (SD) age was 30.70 ± 0.93 . Most of the patients had intentional poisoning (93.7%). In 42.6%, inhalation was the main route of exposure. Six patients had skin and 25 (19.37%) patients had pulmonary manifestations.

Most of the patients had complete improvement without any complication (89.1%). Age (OR, 1.05; 95% CI 1.006-1.099), suicide history (OR 30.33; 95% CI 3.11-295.24), route of poisoning [(ingestion: OR, 0.21; 95%CI 0.05-0.87), (inhalation: OR, 0.19; 95% CI 0.04-0.78)] and pulmonary system manifestations (OR 1.84; 95% CI 1.15-2.93) were predictive in patients outcome ($P < 0.05$).

Conclusion:

Methamphetamine poisoning was more common in males with intentional poisoning. Age, past history of suicide, route of poisoning and pulmonary manifestations on admission to hospital should be considered as important predictive factors in outcome patients.

Key words: Methamphetamine, Toxicity, Poisoning, abuse, suicide

Introduction

Methamphetamine (METH) is the most widely abused type of amphetamine, a class of stimulant drugs (1). Amphetamine or methamphetamine use was documented in many countries. Uses have been more prevalent in East and South East Asia, North America, South Africa, New Zealand, Australia and a number of European countries (2). Methamphetamine has contributed to a substantial number of deaths in Australia (3). Individuals with methamphetamine-use disorders had a higher mortality risk than those with diagnoses related to cannabis, cocaine, or alcohol. (4).

In a study evaluated the global prevalence of amphetamine dependence and the burden of disease attributable to these disorders, there were an estimated 24.1 million psychostimulant dependent people in 2010. There were significant differences between amphetamines in the geographic distribution of crude DALYs. Over half of amphetamine dependence DALYs was in Asian regions (52%) (5). In Alabama, cocaine and methamphetamine among fetuses/neonates was three- and fivefold greater than the general population (6). Also at least 84% of deaths were violent or drug-related (12% suicides) in Sweden population. (7). The data, presented for the Dresden region, Saxony, Germany, demonstrate the escalation of MA-related crime and fatalities between 2005 and 2011 (8).

METH has neurobiological effects on the nervous system; some of which are transitory and some longer lasting (9). Signs of toxicity include hot, flushed or very sweaty skin, headache; chest pain; changes in consciousness and mental status; tremor, spasm; agitation; difficulty breathing; seizures; and psychosis (10,11). Most cases of methamphetamine toxicity can be managed supportively. In the case of a severe overdose, immediate supportive care, including airway control, oxygenation and ventilation support, and appropriate monitoring is required. (12, 13, 14).

Methamphetamine poisoning has become common in our poisoning referral center these years (15). As there is a difference with respect to epidemiology of poisoning in the geographic distribution, we performed a study on the Metamphetamine poisoning in central part of Iran during 2012-2013.

Materials and Methods:

This hospital based, cross sectional, analytical and descriptive study was carried out from April 2012 to April 2013 at referral clinical toxicology department of the Noor Hospital, Isfahan University of medical Sciences, Isfahan, Iran, with a population of 4,815,000.

The inclusion criteria were all patients between 18 to 65 years of age admitted to the mentioned hospital with a diagnosis of acute methamphetamine poisoning. The exclusion criterion was discharge of patient by his own consent.

After primary assessments and therapeutic management's patients different information recorded in a check list. Data was extracted from the medical record (ICD 10 codes files). The information included sex, age, type of poisoning (accidental or intentional), route of poisoning (oral, inhalation, intravenous, intramuscular, subcutaneous, mixed), clinical manifestations, duration of hospitalization, and clinical outcome (survived with or without complication and death).

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS, Inc., Chicago, IL, USA). P value less than 0.05 was assumed significant. To compare mean values between groups independent T Test or ANOVA were used. Comparing frequency distribution of qualitative factors was performed using chi-square or Fisher Exact tests where appropriate. Predictive factors for clinical outcome were evaluated by the binary logistic regression analysis.

Results:

During one year of study, 129 patients including 111(86%) males and 18(14%) females presented to the clinical toxicology department. The mean age was 30.70 ± 0.93 (range: 1- 80 years). 18.6 % had a history of psychological disorders and 10.1% had a history of suicide. Most of the patients had intentional poisoning (93.7%). Inhalation was the main route of exposure (42.6%). 40 cases used only Methamphetamine and the others (89 cases) ingested other drugs with METH. Six patients had skin and 25 (19.37%) patients had pulmonary manifestations. The

most present cardiovascular sign was tachycardia in 23 patients (17.82%). Most of the patients survived without any complication (89.1%).

Time from usage to hospital admission was 11.9 ± 1.02 hours. The length of hospital stay was 18.86 ± 2.24 hours. Patients were divided based on outcome in two groups [survived with or without complication (N=115); and death (N=14)]. The results comparing the different variables based on outcome has been shown in Table 1.

Table 1: Different variables in patients with Methamphetamine poisoning respect to outcome

Variables	Outcome		P value
	Survived without complication	complications or death	
Age (year)	30.01± 0.90	37.14± 3.97	0.01
Gender			
Male	98 (85.2)	13 (92.9)	0.69
Female	17 (14.8)	1 (7.1)	
Drugs			
Methamphetamine	36 (31.3)	4 (28.6)	0.59
Alcohol	1 (0.9)	0 (0)	
Hashish	5 (4.3)	0 (0)	
opioids	58 (50.5)	7 (50)	
Benzodiazepines	6 (5.2)	0 (0)	
Antidepressants	7 (6.1)	2 (14.3)	
Analgesics	2 (1.7)	1 (7.1)	
Route of exposure			
Inhalation	51 (44.3)	4 (28.6)	0.07
Oral	46 (40)	4 (28.6)	
Injection	3 (2.6)	0 (0)	
mixed	15 (13)	6 (42.9)	
Type of exposure			
Suicide	36 (31.3)	6 (42.9)	0.64
Accidental	8 (7)	0 (0)	
Abuse	71 (61.7)	8 (57.1)	
History of psychiatric disease			
+	19 (16.5)	5 (35.7)	0.13
-	96 (83.5)	9 (64.3)	
History of suicide			
+	6 (5.2)	7 (50)	0.0001
-	83 (72.2)	6 (42.9)	
Unknown	26 (22.6)	1 (7.1)	
History of Addiction			
+	98 (85.2)	14 (100)	0.0001
-	17 (14.8)	0 (0)	
Time from usage to admission (Hours)	11.77 ± 1.12	13 ± 2.24	0.71

The results are presented as mean ± SE or n (%)

Coma, agitation, hypotension, tachycardia, bradycardia and pulmonary manifestations were more common in patients dead or survived with complications (Table 2). Creatinine phosphokinase (CPK) was high only in two patients (6100 and 2061 U/L). There were no significant differences in lab tests performed on admission between two groups ($P > 0.05$). Data with respect to clinical manifestations and outcome has been shown in Table 3.

Table 2: clinical manifestations of the patients with Methamphetamine poisoning with respect to outcome

Variables	Outcome		P value
	Survived without complication	with complications or death	
Gastrointestinal Decontamination +	33 (28.7) 82 (71.3)	4 (28.6) 10 (71.4)	0.90
Glasgow Coma Scale (GCS)	14.07 ± 0.16	13.21 ± 0.74	0.28
Level of consciousness			0.058
Alert	28 (24.3)	2 (14.3)	
Lethargic	49 (42.6)	3 (21.4)	
Stupor	4 (3.5)	2 (14.3)	
Coma	1 (0.9)	2 (14.3)	
Agitation	33 (28.6)	5 (35.7)	
Cardiovascular system (CVS)			0.03
Without CV toxicity	90 (78.3)	7 (50)	
Tachycardia	19 (16.5)	4 (28.6)	
Bradycardia	3 (2.6)	1 (7.1)	
Chest pain	1 (0.9)	0 (0)	
Arrhythmia	1 (0.9)	0 (0)	
Hypotension	1 (0.9)	2 (14.3)	
Gastrointestinal manifestations			0.10
-	94 (81.7)	12 (93.2)	
+	21 (18.2)	2 (6.8)	
Skin manifestations			0.002
-	113 (98.3)	10 (76.9)	
+	2 (1.7)	4 (24.1)	
Pulmonary manifestations			0.001
-	97 (84.3)	7 (50)	
+	18 (15.7)	7 (50)	
Pupil size			0.4
Normal size	50 (43.5)	4 (28.6)	
Miosis	31 (27)	6 (42.9)	
Midriyasis	34 (29.6)	4 (28.6)	
Respiratory rate (/min)	17.52 ± 0.26	18.21 ± 1.45	0.44
Heart rate (/min)	88.13 ± 1.96	91.07 ± 3.39	0.61
Systolic Blood pressure (mmHg)	130.25 ± 9.7	119.4 ± 4.69	0.69
Diastolic blood pressure (mmHg)	75.73 ± 1.15	71.07 ± 2.78	0.18
Temperature (°C)	36.66 ± 0.1	37.06 ± 0.19	0.22
Length of hospital stay (hours)	16.99 ± 1.76	34.21 ± 14.6	0.26

Table 3: Para-clinical tests on admission of the patients with Methamphetamine poisoning with respect to outcome

Variables	Outcome		P value
	Survived without complication	Survived with complications or death	
BS (mg/dl)	116.11 ± 9.35	107.25 ± 3.59	0.66
Na (mEq/L)	140 ± 0.70	144.33 ± 4.39	0.37
K (mEq/L)	7.22 ± 3.20	4.41 ± 0.36	0.40
BUN (mg/dl)	18.68 ± 2.69	28.33 ± 15.18	0.55
CR (mg/dl)	1 ± 0.06	1.42 ± 0.32	0.24
PTT	34.12 ± 1.89	38.12 ± 3.84	0.30
PT	15.28 ± 0.31	15.71 ± 0.28	0.40
INR	1.35 ± 0.04	1.34 ± 0.052	0.89
WBC (x 1000)	11.98 ± 0.70	10.76 ± 2.41	0.64
HB (mg/dl)	14.88 ± 0.32	14.52 ± 1.10	0.67
HCT	43.86 ± 0.73	43.25 ± 2.24	0.74
PLT (x1000)	252.46 ± 11.57	193.57 ± 37.72	0.054
Venous PH	7.08 ± 0.12	7.13 ± 0.31	0.84
PCO ₂ (mmHg)	42 ± 0.7	47.65 ± 2.58	0.30
HCO ₃ (mol/L)	23.13 ± 1.04	27.94 ± 2.62	0.056
PO ₂ (mmol/L)	43.76 ± 4.15	48.76 ± 12.96	0.63
O ₂ saturation	89.88 ± 2.08	78.06 ± 14.57	0.50

BS, Blood Sugar; Na, serum sodium; K, serum potassium; BUN, blood urea nitrogen; CR, creatinine; WBC, white blood cell; HB, hemoglobulin; HCT, hematocrite; PLT, platelet; PCO₂, carbon dioxide pressure; HCO₃, Bicarbonate; PO₂, oxygen pressure; O₂, oxygen

To find predictive variables in patients' outcome, the backward step binary regression was used. Age, suicide history, route of poisoning, and pulmonary system manifestations were predictive in outcome. (Table 4)

Table 4: Predictive factors of outcome in patients with Methamphetamine poisoning

Variables	P value	OR (95 % CI)
Age	0.027	1.05 (1.006 – 1.099)
Suicide history	0.003	30.33 (3.11 – 295.24)
Route of poisoning		
Ingestion	0.032	0.21 (0.05 – 0.87)
Inhalation	0.220	0.19 (0.04 – 0.78)
Pulmonary system manifestations	0.01	1.84 (1.15 -2.93)

The cost of hospitalization was 931490 ± 874564 (Rials). The cost with respect to outcome was 718830 ± 85716 (Rials) in patients survived without complications and 2774500 ± 937551 (Rials) in patients survived with complications or death. (P < 0.0001)

Discussion:

As METH poisoning has become common in our poisoning referral center these years (15), the purpose of the study was to evaluate different factors in METH poisoning.

METH Methamphetamine use varies geographically, but overall, amphetamine-type stimulants, which include methamphetamine, are the fastest rising drug of abuse worldwide (16).

In our study most of the cases were men and in young age. In a study performed in 2007 the highest proportion of meth/amphetamine users were also men and those in the 20–29-year age group (10).

In 42.6% of the patients inhalation was the main route of exposure. Routes of administration that produce rapid onset of the drug effects (i.e., smoking and injection) are likely to lead to more medical and psychiatric effects (9).

40 cases used only Methamphetamine and the others (89 cases) ingested other drugs with METH. Although we couldn't find difference between patients survived or death regarding co-ingestion, co-ingestants increase the risk of morbidity and mortality (9).

History of psychiatric disorder (35.7%) and suicide (50%) was observed in patients with worse outcome. Depression has been reported commonly occurs among methamphetamine users. And symptoms of depression may persist for weeks, months or in some cases even several years after stopping methamphetamine use (10). Most of our patients had history of addiction. Chronic use of METH can produce significant neurological damage as well as damage to cardiovascular, pulmonary, and other organ systems. (9) Chronic exposure to methamphetamine may cause the personality changes, psychotic syndrome, and ulcers of the lips and tongue (11).

Coma, agitation, hypotension, tachycardia and pulmonary manifestations was more in patients found complications or dead compared to patients survived without any complications. All clinical manifestations were compatible with METH poisoning which has been reported in different studies (9). Methamphetamine hydrochloride poisoning may ultimately result in collapse, shock, systemic acidosis (accumulation of acid in the body), coma, and convulsions (11).

We could not find any significant difference in lab tests data between two groups with respect to outcome. However, hypokalemia from direct sympathomimetic effects of methamphetamine; hyperkalemia indirectly due to hyperthermia, rhabdomyolysis, or renal failure has been reported previously(17). Also hypernatremia from dehydration; and hyponatremia has been reported in METH overdose (17).

In conclusion methamphetamine poisoning was more common in males with intentional poisoning. Age, past history of suicide, route of poisoning and pulmonary manifestations on admission to hospital should be considered as important predictive factors in outcome patients

Conflict of interest: There is no conflict of interest

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