

Role of clinical and paraclinical manifestations of methanol poisoning in outcome prediction

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Background: Methanol poisoning is one of the most important poisoning due to drinking of illegal and non-standard alcoholic beverage in some countries. Relatively limited studies have been carried out to identify the prognostic factors in methanol poisoning. **Materials and Methods:** We performed a retrospective study on acute methanol-intoxicated patients, which were admitted on the Loghman Hakim Hospital Poison Center (Tehran, Iran) over a 24-month period. The demographic data, clinical manifestations and paraclinical findings, therapeutic interventions and outcome (survivors with or without complications and non-survivors) were extracted. **Results:** We evaluated 30 patients with methanol poisoning during 2 years. All of the patients were male; with the median age of 25.5 years. Visual disturbances, respiratory manifestations, and loss of consciousness were the most common clinical manifestations on admission time. The results of paraclinical manifestations on admission time were as following: The median of blood methanol level was 20 mg/dL. The median of pH, PaCO₂ and HCO₃⁻ was 7.15, 22.35 mmHg and 7.2 mEq/L, respectively. Hyperglycemia was observed in 70% of the patients and the median of blood glucose was 184.5 mg/dL. In fourteen of the patients hemodialysis was performed. Median duration of hospitalization was 48 h. Nine of the patients died. There was a significant difference between survivors and non-survivors with regard to coma, blood methanol level, and PaCO₂ and blood glucose. Furthermore, we did not observe a significant difference between these two groups regarding to pH, HCO₃⁻ level, and time interval between alcohol ingestion to hospital admission and beginning of hemodialysis. **Conclusion:** Regarding the results of this study, it can be suggested that coma, PaCO₂ and hyperglycemia on admission time could be used as strong predictors of poor outcome.

Key words: Hyperglycemia, methanol, outcome, partial pressure of carbon dioxide, poisoning, prognostic factors

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INTRODUCTION

Methanol is a toxic alcohol, which is widely used as a solvent and to denature ethanol.^[1] Almost all cases of acute methanol toxicity result from ingestion. Rarely, poisoning follows inhalation or dermal absorption. Ingestion of as little as 30 mL of pure methanol has caused permanent blindness and 30-240 mL is potentially fatal, though individual susceptibility varies widely.^[2]

Methanol itself has a relatively low toxicity, but produces toxic metabolites as formaldehyde and formic acid. There is a direct correlation between formic acid concentration and morbidity and mortality.^[3] The acidosis appears to be caused by formic acid production and formic acid/formate is the principal cause of ocular toxicity.^[2]

As methanol is cheap and easily accessible, it has been used in the production of imitated spirits and wine, so cause the mortality and or morbidity in many people.^[4]

In Iran, according to legal and religious ban in production of alcoholic beverages, the use of illegal and non-standard alcoholic beverages is common and it may be a major role for an increase in the prevalence of methanol-intoxication among the alcohol abusers in the country.^[5,6]

There are relatively limited studies that reported the parameters such as respiratory arrest, coma, serum formate concentration, severe metabolic acidosis, blood methanol level as a criterion for the diagnosis and prognosis of acute methanol poisoning.^[6-8] The aim of this study was to assess the clinical manifestations and paraclinical findings in methanol intoxication and their role in the prediction of outcome.

METHODS

This was a retrospective study on acute methanol-intoxicated patients, which were admitted on the Loghman Hakim Hospital Poison Center (LHHPC) over a 24-month period.

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The diagnosis in all cases was based on the history of exposure, clinical manifestations and positive blood methanol level. Acute methanol-intoxicated patients with no history of diabetes, cardiovascular, respiratory, renal and hepatic failure, and no advanced medical management such as hemodialysis and antidote therapy for methanol poisoning in any medical center before admission in LHHPC, were included in the study. Furthermore, we exclude the cases with co-ingestion of other drugs and chemicals except ethanol based on the history and/or toxicological data.

The qualifying case records were extracted from the patients, medical files. We collected and abstracted patients, information regarding gender, age, history of chronic abuse of alcohol, type of alcoholic beverage, time between intake of alcohol to admission on hospital, signs and symptoms of intoxication on admission time, laboratory findings, therapeutic interventions, duration of hospitalization and outcome. Data were kept confidential in all stages of the study.

Coma grade was calculated on admission time in the emergency department.^[9] All patients were followed until discharge from the hospital or death. According to the outcome, the patients were divided into survivors (with or without complications) and non-survivors.

All data were analyzed with SPSS software (version 12) and STATA software (version 11). The data were expressed as median or mean \pm SD for numeric variables and as frequency and percentage for categorical variables. Chi-square test was used for statistical comparison of qualitative variables. The fisher exact test was used if the number of cases was less than 5.

The normal distribution of quantitative variables was tested by Kolmogorov-Smirnov test. The statistical comparison was carried out with Mann-Whitney U-test for non-parametric variables and independent student *t*-test was used for parametric variables. We used the Pearson test for the analysis of correlation in the continuous variables and odds ratios was calculated for the binary variables. *P* values of 0.05 or less were considered to be statistically significant.

RESULTS

A total of 30 patients with acute methanol poisoning were included in the study. All of the patients were male; with the median age of 25.5 years (range 15-52 years) [Table 1].

In all of the patients, the route of exposure was oral ingestion. Only 9 (30%) of the patients had the history of chronic misuse of alcohol. In 24 (80%) of the patients, the type of alcohol was illegal hand-made alcoholic beverages.

Only 3 (10%) of the patients had a history of consumption of industrial alcohol (a kind of alcoholic product that used only as a household cleaner and not for a drink), and in 3 (10%) of the patients the type of alcohol source was unknown. The median time between intake of alcohol to admission on a hospital was 24 h (range 4-96 h) [Table 1].

Visual disturbances, respiratory manifestations, and loss of consciousness were the most common clinical manifestations 64% (95% confidence interval [CI]: 0.44-0.80), 47% (95% CI: 0.28-0.66) and 47% (95% CI: 0.28-0.66) respectively on admission time. 13 patients (43%) had mydriasis. In 5 (17%) of the patients, the pupils were unresponsive to light [Table 2].

The median of blood methanol level was 20 mg/dL (range 7-75 mg/dL) [Table 1]. A total of 11 patients (37%) had methanol level $20 \leq$ mg/dL to <50 mg/dL and seven patients (23%) had methanol level more than 50 mg/dL, one of them survived and the other six ones died. Only three patients (10%) had methanol level $5 \leq$ mg/dL to <10 mg/dL and in others, methanol level was $10 \leq$ mg/dL to <20 mg/dL.

Analyze of venous blood gas on admission showed that the median of pH was 7.15 with a range of 6.73-7.32 [Table 1]. Most of the patients (60%) had pH $7 <$ to ≤ 7.20 , 12 of them survived and six others died. Furthermore from seven patients who had pH $7.20 <$ to ≤ 7.30 , six patients survived and only one patient died. All of the three patients who had the pH above 7.30, survived and two patients who had the pH less than 7 died.

The median of PaCO₂ was 22.35 mmHg (range of 2.70-46.60 mmHg) [Table 1]. In most of the patients (80%), PaCO₂ was less than 35 mmHg. Only two patients (7%) had PaCO₂ $35 \leq$ mmHg to <45 mmHg, one of them survived and the other died [Figure 1]. Figure 2 shows the relationship between pH and PaCO₂ in survivors and non-survivors.

The median of HCO₃ was 7.2 mEq/L with a range of 1-20 mEq/L [Table 1]. In most of the patients (47%), HCO₃ level was $5 <$ mEq/L to ≤ 10 mEq/L. None of them had HCO₃ level more than 20 mEq/L, and only five patients (17%) had HCO₃ level $15 <$ mEq/L to ≤ 20 mEq/L, three of them survived and two others died.

Most of the patients (60%) had leukocytosis, and in others the numbers of white blood cells (WBC) were within normal range. The median number of WBC was 13400/ μ L with the range of 6000-26400/ μ L. 40% of the patients showed hyperkalemia and in others the level of potassium was in the normal range. Hyperglycemia was also observed in 21 (70%) of the patients and in others, the blood glucose level was in the normal range. The median of blood sugar was 184.5 mg/dL with the range of 70-540 mg/dL [Table 1].

Table 1: Comparison of demographic, clinical and para-clinical manifestations in survival and non-survival groups

Parameter	All patients (n=30) (%)	Survivors (n=21) (%)	Non-survivors (n=9) (%)	P value	
	Mean±SD (range), (median)	Mean±SD (range), (median)	Mean±SD (range), (median)		
Age (year)	28.43±10.42 (15-52), (25.5)	30.10±10.87 (18-52), (27)	24.56±8.60 (15-42), (23)	0.15*	
Place of admission	Intensive care unit	8 (27)	2 (10)	6 (67)	0.003**
Duration of hospitalization (hour)	60.13±51.77 (3-240), (48)	46.90±25.76 (24-96), (48)	91±80.78 (3-240), (48)	0.27*	
History of alcohol misuse	First time	10 (33)	8 (38)	2 (22)	0.67
	Recreational	11 (37)	8 (38)	3 (33)	
	Chronic	9 (30)	5 (24)	4 (45)	
	Alcohol type	Illegal hand-made spirits	24 (80)	17 (81)	
Industrial alcohol	3 (10)	2 (9.5)	1 (11)		
Unknown	3 (10)	2 (9.5)	1 (11)		
^s TIAMHA (hour)	29.83±21.29 (4-96), (24)	32±20.95 (4-96), (24)	24.78±22.49 (4-72), (24)	0.34*	
Methanol level (<10 mg/dL)	28.89±20.06 (7-75), (20)	23.17±16.55 (7-70.5), (20)	42.22±22.10 (10-75), (50)	0.02**	
pH (7.35-7.45)	7.15±0.14 (6.73-7.32), (7.15)	7.18±0.09 (7.03-7.32), (7.16)	7.06±0.18 (6.73-7.24), (7.13)	0.07**	
PaCO ₂ (35-45 mmHg)	22.30±13.32 (2.70-46.60), (22.35)	18.63±11.41 (2.70-45), (19.80)	30.86±14.16 (7.50-46.60), (24.10)	0.02***	
HCO ₃ (22-26 mEq/L)	8.73±5.66 (1-20), (7.2)	8.49±5.41 (1-20), (7.5)	9.30±6.50 (2.6-20), (6.80)	0.73**	
White blood cell count (6000-10000/μL)	13427±5081 (6000-26400), (13400)	12100±3918 (6000-20600), (13100)	16522±6309 (8000-26400), (16500)	0.03***	
Potassium level (3.5-5 mEq/L)	6.28±1.12 (5.20-9.10), (5.90)	5.86±0.56 (5.20-7), (5.70)	6.86±1.5 (5.20-9.10), (6.50)	0.14*	
Blood sugar (70-110 mg/dL)	194.07±104.84 (70-540), (184.5)	153.43±58.71 (70-258), (152)	288.89±129.52 (149-540), (245)	0.003***	
Total bicarbonate dose (mEq)	504±471 (75-2100), (425)	441±400 (75-1250), (250)	650±609 (100-2100), (500)	0.25*	
Duration of ethanol treatment (day)	1.47±0.82 (0-4), (1)	1.38±0.59 (0-2), (1)	1.67±1.22 (0-4), (1)	0.73*	
Number of hemodialysis	No hemodialysis	16 (54)	12 (57)	4 (45)	0.17
	1 time	12 (40)	9 (43)	3 (33)	
	2 times	1 (3)	0	1 (11)	
	3 times	1 (3)	0	1 (11)	
^{ss} TIHABH (hour)	6.64±5.02 (0-17), (4)	6.78±6.18 (0-17), (4)	6.40±2.30 (4-9), (7)	0.54*	

*The nonparametric test was used for statistical analysis; **The parametric test was used for statistical analysis; ^sTime interval between alcohol use and hospital admission; ^{ss}Time interval between hospital admission and beginning of hemodialysis; Data are mean±SD The difference between survival and non-survival groups is significant at *P<0.05 and **P<0.005

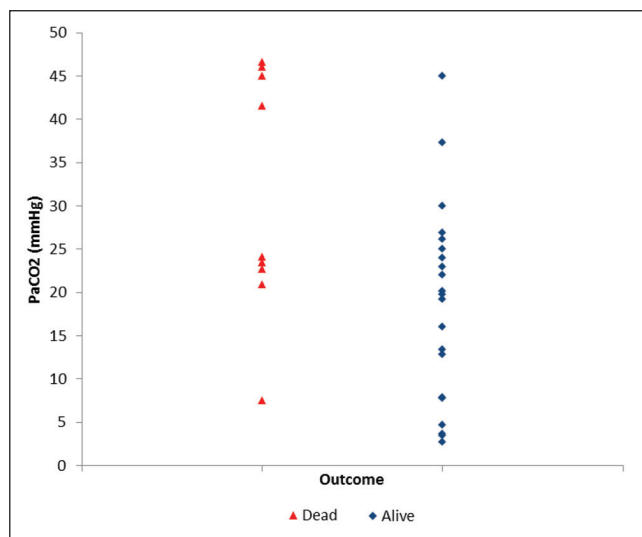


Figure 1: Distribution of patients regarding to their PaCO₂ and outcome

All patients were given sodium bicarbonate and folic acid. The median of total dose of sodium bicarbonate, which was administered in patients, was 425 mEq/L with a range of

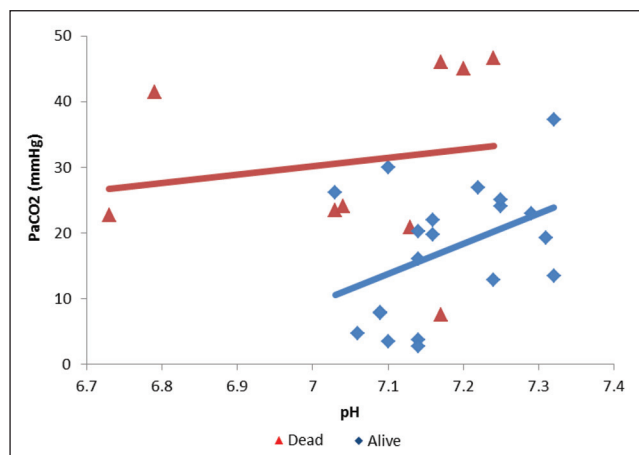


Figure 2: Relationship of pH with PaCO₂ in survivors and non-survivors

75-2100 mEq/L. Except for two patients; all of them were treated with oral ethanol solution 10% as an antidote. The median duration of ethanol therapy was 1 day with the range of 0-4 days. In 14 (46%) of the patients hemodialysis was performed. 4 from 16 patients who received no

Table 2: Distribution of patients according to clinical manifestations on admission time

Clinical manifestations	All patients (n=30) (%)	Survivors (n=21) (%)	Non-survivors (n=9) (%)	P value
Visual disturbances				
Blurred vision	15 (50)	12 (57)	3 (33)	0.23
Blindness	2 (7)	1 (5)	1 (11)	
Photophobia	2 (7)	2 (10)	0 (0)	
Pupil size				
Mydriasis	13 (43)	10 (48)	3 (33)	0.6 9
Miosis	0	0	0	
Pupil reactivity				
Non-reactive	5 (17)	2 (10)	3 (33)	0.14
Coma grade				
I	8 (27)	7 (33)	1 (11)	0.04*
II	1 (3)	0	1(11)	
III	5 (17)	0	5 (56)	
IV	0	0	0	
Respiratory manifestations				
Depression	5 (17)	1 (5)	4 (45)	0.02*
Dyspnea	9 (30)	7 (33)	2 (22)	0.68
GI symptoms				
Nausea and vomiting	10 (34)	7 (33)	3 (33)	1
GI Bleeding	1 (3)	0	1 (11)	
Epigastric pain	1 (3)	1 (5)	0	

GI=Gastrointestinal; The difference between survival and non-survival groups is significant at * $P < 0.05$

hemodialysis died. The median time interval between hospital admission and beginning of hemodialysis was 4 h with the range of 0-17 h [Table 1].

A total of 8 (27%) of the patients were admitted in intensive care unit. The median duration of hospitalization was 48 h (range 3-240 h) [Table 1]. Total 9 (30%) of the patients died; while two of the remaining survivors became blind.

Mortality rate in comatose and non-comatose cases was 50% versus 12.5%, respectively with odds ratio 7 (1.14-42.97, 95% CI). The mortality rate in patients with respiratory depression was 80% in compare to 20% in patients without depression of respiration, with odds ratio 16 (1.45-176.45, 95% CI). There was a correlation between methanol level ($r = 0.44$, $P = 0.01$), PaCO_2 ($r = 0.43$, $P = 0.02$), leukocytosis ($r = 0.41$, $P = 0.03$), blood sugar ($r = 0.60$, $P = 0.000$) and death.

DISCUSSION

The present study shows that the oral ingestion of illegal hand-made spirits is a most common cause of acute methanol poisoning in Tehran. This result is similar to our previous finding and other researchers.^[6,7,10] In Iran, according to national regulations, selling, buying, and consumption of alcoholic drinks is a punishable crime. Therefore, the use of homemade, illegal and non-standard alcoholic beverages can cause acute methanol intoxication.

The present results show that the young men are the major patients suffer from methanol poisoning. This is in concordance with our previous studies about general pattern of acute chemical and pharmaceutical poisoning in Tehran.^[5] In this study, the median time interval between methanol intakes to admission on a hospital was 24 h. It can be due to this fact that methanol is not toxic by itself and it must be metabolized to toxic metabolites like as formate. Methanol is oxidized by alcohol dehydrogenase to formaldehyde, which is oxidized to formic acid by formaldehyde dehydrogenase. Then, formic acid is converted to carbon dioxide and water. This process is time consuming and from this view, the clinical presentations in methanol poisoning appear after a latent period.^[11]

The mortality in our study was 30%. It is similar to our previous finding about mortality in acute methanol poisoning and other researchers.^[6,7,12]

The ophthalmic, respiratory, and central nervous system involvements were the most common clinical manifestations. These results supported by previous studies.^[6,8,13]

Although, in the present study, the mean blood methanol level in our patients is lower than other studies,^[8] but it is similar to our previous result.^[6] This may be related to the delay of admission of the patients in the hospital.^[6]

The treatment, including duration of ethanol therapy, total dose of bicarbonate and time interval between hospital admission and beginning of hemodialysis was similar in both survivor and non-survivor groups; so the difference

in the outcome of the patients could be related to their clinical and paraclinical status on admission time. In the present study, we found a significant difference between survivors and non-survivors with regard to coma grade, depression of respiration, PaCO₂, blood methanol level, leukocytosis, and blood sugar. Furthermore, there was a correlation between coma grade, depression of respiration, PaCO₂, blood methanol level, leukocytosis, blood sugar and death, which is the same as previous published data.^[6-8,11,12]

Respiratory arrest and increased PaCO₂ in the severely acidotic methanol-intoxicated cases have been suggested as a new marker.^[7,8] The current study confirms earlier studies showing mortality correlating with the lack of compensatory hyperventilation in spite of and only when there is a profound metabolic acidosis.

Hyperglycemia is recently shown as a prognostic marker^[12] and the same finding in this study is thus very interesting. The exact mechanism of hyperglycemia is not clear but it has been supposed that methanol poisoning can be associated with acute pancreatitis and this can be suggestive in creating hyperglycemia.^[14] Furthermore increased counter regulatory hormones from the acute stress of methanol poisoning could be another suggestive mechanism.^[15]

In spite of the results of previous studies, which showed a correlation between blood pH and poor prognosis,^[6-8,11] we did not find any significant difference in blood pH between survivor and non-survivor groups. One of the explanations is that the blood H⁺ concentration is regulated by PCO₂ and level of blood HCO₃⁻, so it will not necessarily be found in all patient populations depending on the their compensatory situations. The other reasons could be the fact that this study is retrospective and the number of patients is relatively small, which could be considered as a limitation of this study.

CONCLUSION

According to the results of this study, it could be concluded that coma, respiratory depression, PaCO₂ and hyperglycemia are strong predictors of poor outcome.

Furthermore, hyperglycemia might be a new prognostic factor in methanol poisoning, but further studies are needed to determine whether controlling hyperglycemia has therapeutic consequences.

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