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ORIGINAL ARTICLE

A potential prognostic indicator in methanol intoxication: Body temperature

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Received: 3 March 2024, Accepted: 21 May 2024,
Published online: 29 June 2024

ABSTRACT

Objective: Methanol intoxication is a type of poisoning with high mortality and morbidity. The current study aims to examine patients diagnosed with methanol intoxication and treated with standardized treatment to collect data that may be used to predict patient outcomes and mortality.

Materials and Methods: The current study was a retrospective study and included patients over 18 years of age diagnosed with methanol intoxication between 1st March, 2011 and 1st March, 2021. All patients were treated with the treatment protocol determined by the clinic in accordance with the guidelines. Sociocultural characteristics, vital and laboratory findings, and clinical outcomes of the patients were analyzed.

Results: Of the 28 patients included in the study, 80% were male, and the median age was 49. Patients were divided into two groups: survived and deceased. The median time since last alcohol intake was higher in surviving group (7 hours (Q1-Q3:6-12) vs 4 hours (Q1-Q3:2-17), p=0.005) and the amount of alcohol per kilogram of weight was lower in surviving group (3.13 ml/kg (Q1-Q3: 1.34-4.46) vs 8.81 ml/kg (Q1-Q3:5.22-9.49), p=0.002). The body temperature was lower in deceased group (35.40 °C (Q1-Q3:34.95-35.50) vs 36.40 °C (Q1-Q3:36.10-36.55), p=0.001). The current study showed that the other diagnostic factors of mortality in methanol intoxication are serum pH, lactate levels, bicarbonate levels, base deficit, anion deficit, the level of consciousness of the patient at admission, the time since the last alcohol consumption, and the amount of methanol ingested.

Conclusion: In this study, it was concluded that moderate hypothermia may be an indicator of mortality in addition to classical findings. Thus, it has been shown that hypothermia will be effective in methanol intoxication in addition to other early markers for early diagnosis and rapid initiation of treatment.

Keywords: methanol, toxicity, temperature, hypothermia, mortality.

INTRODUCTION

Methanol (methyl alcohol) is the simplest aliphatic alcohol, biochemically consisting of a methyl group attached to a hydroxyl group [1]. The primary chemical characteristics of the substance include being lightweight, volatile, flammable, and colorless [2]. It has a slightly alcoholic odor similar to ethanol. It is called wood spirit because it was first created by distilling wood at high temperatures in an airless environment. Today, it is used industrially as a precursor to many chemicals such as formaldehyde, acetic acid, and methyl benzoate and as a solvent for some chemicals.

The elimination half-life of methanol in intoxication is 24 hours [1]. It reaches its peak distributional concentration in 30-60 minutes [1]. Methanol undergoes primary elimination in the liver. It is converted to formaldehyde via hepatic alcohol dehydrogenase. Although formaldehyde is a toxic metabolite, it is metabolized rapidly via aldehyde dehydrogenase, so its effect is not apparent. Formaldehyde is metabolized to formic acid via aldehyde dehydrogenase. Formic acid is the primary metabolite that causes methanol-related toxic symptoms [1,3]. It is rapidly converted to its conjugated base formate and free hydrogen ion. Tetrahydrofolate synthetase breaks down formic acid into carbon dioxide and water in the final stage of metabolism. Folinic acid is the cofactor of the last step in metabolism (Figure 1).

Formic acid is the leading toxic agent in methanol metabolism [1,3]. Formaldehyde is rapidly metabolized to formic acid, which binds to the cytochrome oxidase enzyme at the end of the respiratory chain in mitochondria. The inhibition of the cytochrome oxidase enzyme disrupts oxidative metabolism. Simultaneously, the rapid dissociation of formic acid into formate and free hydrogen ions causes a decrease in serum pH and an increase in the inhibition rate of cytochrome oxidase with the resulting acidosis. All physiologic changes trigger an increase in serum lactate concentration. Due to the inhibition of aerobic metabolism by formic acid, cells activate anaerobic metabolism pathways. As a result of increased anaerobic metabolism, serum lactate concentration increases, pH decreases further, and acidosis deepens [1,4,5]. Due to increased acidosis, the conversion of formic acid to formate slows down, and the toxic activity of formic acid increases. Therefore, an increase in serum lactate concentration is triggered. A vicious cycle of formic acid and lactate occurs in methanol toxicity. As methanol is broken down, the osmolar gap decreases, and metabolic acidosis with increased anion gap occurs (Figure 1) [1,4,6].

Metabolic acidosis with increased anion gap is the leading cause of mortality in methanol intoxication [1,7,8]. Therefore, treatment should be initiated rapidly for suspected methanol intoxication. Sodium bicarbonate, fomepizole, ethanol, folinic acid, and hemodialysis treat methanol intoxication [1,4,9].

Sodium Bicarbonate: The level of metabolic acidosis on admission is a prognostic marker [10-12]. In cases of suspected methanol intoxication, it is recommended to start intravenous sodium bicarbonate infusion if the pH is <7.3 [1]. Early correction of acidosis increases the conversion rate of formic acid to formate.

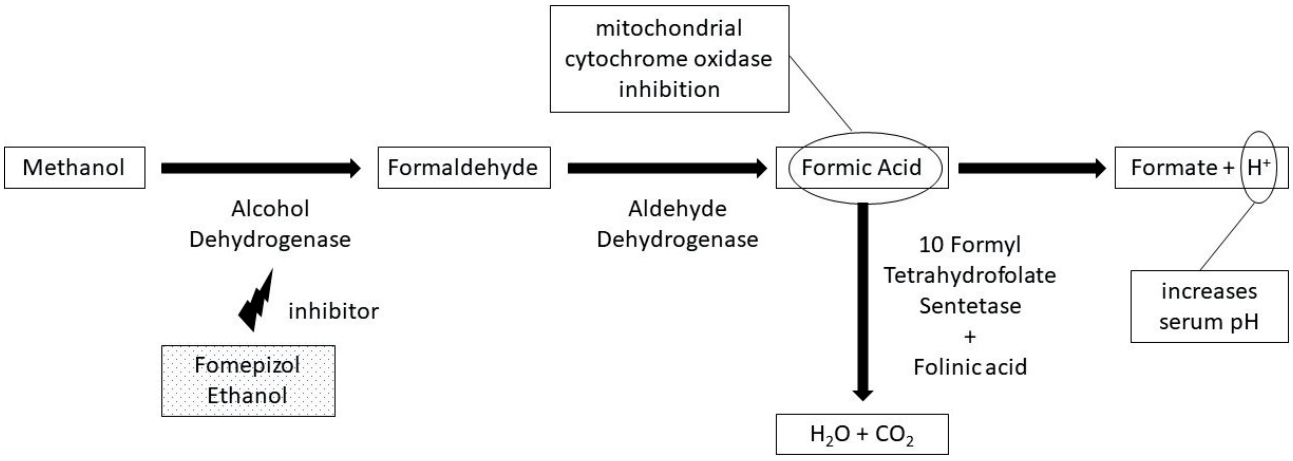

Figure 1. The metabolism of methanol

Fomepizole/Ethanol: It is a potent inhibitor of the alcohol dehydrogenase in the first step of metabolism. The affinity of ethanol for alcohol dehydrogenase is 20 times higher than methanol [13]. Therefore, it acts as a competitive inhibitor of alcohol dehydrogenase.

Hemodialysis: Removes methanol and its toxic metabolites from circulation and regulates serum pH [1,14]. The circulating half-life of methanol is prolonged in ethanol-treated patients. Hemodialysis should be started immediately to prevent prolonged methanol circulation and undesirable physiological effects.

The leading causes of methanol intoxication are accidental ingestion or inhalation of chemicals and oral ingestion due to using methanol to produce home-distilled alcohol. Although the rate of methanol intoxication in Turkey is not known, it is known that there was a relative increase in methanol intoxication cases in 2016 and 2020 [15].

The current study aims to examine patients diagnosed with methanol intoxication and treated with standardized treatment to obtain data that may be useful in predicting patient outcomes and mortality.

MATERIALS and METHODS

Approval for the study was obtained from the Clinical Research Ethics Committee of the Hacetttepe University (Project no: GO 21/494, decision no: 2021/08-29). The current study was planned as a single-center retrospective study. Patients over 18 years old diagnosed and treated for methanol intoxication in the emergency department were included in the study between 1st March, 2011 and 1st March, 2021. The data were scanned through the hospital information system and printed files.

Hospital records were retrospectively reviewed for cases reported as methanol poisoning. The American Academy of Clinical Toxicology criteria for fomepizole or ethanol treatment in methanol intoxication were used for the diagnose [1]. Patients who met at least one of the following criteria and received ethanol and folic acid treatment were included in the study. Patients had to fulfill the following criteria to be included. A total of 28 patients were included in the study.

1. Plasma methanol concentration > 20 mg/dl

or

2. Recent history of ingestion of methanol with serum osmol gap > 10 mOsm/L

or

3. History or strong clinical suspicion of methanol poisoning and at least two of the following criteria:

   a. Arterial pH <7.3

   b. Serum bicarbonate <20 meq/L (mmol/L)

   c. Osmolal gap >10 mOsm/kg L

All patients were treated with the treatment protocol determined by the clinic in accordance with the guidelines. Hemodialysis was performed immediately in patients who met the criteria determined by Extracorporeal Treatments in Poisoning as indications for hemodialysis in methanol intoxications [16] (Table 1).

Demographic characteristics such as age, gender, marital status, presence and duration of alcohol and smoking, laboratory results, and outcomes were recorded.

Statistical analysis was performed using the IBM SPSS for Windows version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in median (Q1-Q3 values) for continuous variables and in number and frequency for categorical variables. The distribution of continuous variables was analyzed using the Shapiro-Wilk tests. For multiple group comparisons, the continuous variables were analyzed using the Kruskal-Wallis, and the categorical variables were analyzed using the Pearson chi-square test and Fisher exact test.

Table 1. Hemodialysis criteria

Hemodialysis criteria
1. Coma, Seizures, New Vision Deficits
2. Metabolic acidosis (blood pH ≤ 7.15)
3. Persistent metabolic acidosis despite adequate supportive measures and antidotes
4. Serum anion gap higher than 24 mmol/L
5. Serum methanol concentration:
a. greater than 70 mg/dL in the context of fomepizole therapy
b. greater than 60 mg/dL in the context of ethanol treatment
c. greater than 50 mg/dL in the absence of an alcohol dehydrogenase blocker
6. Renal Failure

The statistical analysis between two independent groups with non-normal distribution data was performed with the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was used to demonstrate the accuracy of characteristics in mortality of methanol intoxication. The Youden index was used to adjust the best cut-off point. The calculation of sensitivity and specificity was performed with the 95% confidence intervals. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 28 patients included in the study, 80% were male, and the median age was 49. Of all patients, 19 were treated with hemodialysis, and 8 (28.6%) died. Patients were divided into two groups: survived and deceased. The characteristics of the two groups were analyzed. The median time since last alcohol intake was 7 hours (Q1-Q3: 6 - 12) in the deceased group and 4 hours (Q1-Q3: 2 - 17) in the surviving group (p=0.005). The amount of alcohol per kilogram of weight consumed at the last drink in the deceased group (8.81 ml/kg (Q1-Q3: 5.22 - 9.49)) was higher than in the surviving group (3.13 ml/kg (Q1-Q3: 1.34 - 4.46)) (p=0.002) (Table 2).

Differences in vital signs between the two groups were analyzed. The median body temperature was 35.40 °C (Q1-Q3: 34.95 - 35.50) in the deceased group and 36.40 °C (Q1-Q3: 36.10 - 36.55) in the surviving group (p=0.001). Among vital signs, only body temperature significantly differed between the two groups (Table 2).

The blood gas analysis was analyzed. Median pH was 6.79 (Q1-Q3: 6.72 - 6.85), bicarbonate was 4.85 mmol/L (Q1-Q3: 4.40 - 5.75), and lactate was 46,50 mmol/L (Q1 Q3: 13.45 - 18.55) in the deceased group, while the median pH was 7.18 (Q1-Q3: 7.13 - 7.24), bicarbonate was 8.75 mmol/L (Q1-Q3: 6,55 - 16.30) and lactate was 2.85 mmol/L (Q1-Q3: 1.70 - 8.95) in surviving group (p<0.001, 0.003 and <0.001, respectively) (Table 2). The median base deficit was 23.70 (Q1-Q3: 17.20 - 27.90) and the median anion gap was 23.70 (Q1-Q3: 16.15 - 28.00) in survived group, while the median base deficit was 32.50 (Q1-Q3: 27.75 - 37.45) and the median anion gap was 32.50 (Q1-Q3: 27.67 - 37.62) in deceased group (p=0.002, p=0.002, respectively).

Differences between deceased and surviving groups were analyzed regarding sociocultural characteristics such as marital status, being a parent and educational status, comorbidities, and complaints on admission. The two groups had no significant differences regarding sociocultural characteristics and comorbidities. Significant differences were found in cooperation and orientation on admission (p=0.033, p=0.011, respectively) (Table 3). All (100%) of the deceased patients received hemodialysis. In the surviving group, 55% received hemodialysis (Table 3).

ROC analysis was performed, and thresholds were calculated for the characteristics with statistically significant differences between the deceased and surviving groups (Table 4). In the ROC curve diagram for serum pH predicting mortality, the AUC was 0.959 (95% CI= 0.905 - 1.000). The serum pH threshold for death was 6.97 (sensitivity= 100%, specificity= 95%). In the ROC curve diagram for serum lactate, AUC was 0.950 (95% CI= 0.875 - 1.000), and the threshold was 9.8 mmol/L (sensitivity= 100%, specificity= 80%). AUC for the anion gap was 0.872 (95% CI= 0.739 - 1.000), the threshold was 26.95 (sensitivity= 100%, specificity= 70%), AUC for temperature was 0.925 (95% CI= 0.821 - 1.000), the threshold was 35.95 0C (sensitivity= 100%, specificity= 85%) (Table 4).

DISCUSSION

Methanol is a solvent in cleaners, antifreeze, and paint solvents [9]. Although it frequently causes poisoning by ingestion, it may also cause poisoning by inhalation and dermal route [17]. Home-distilled alcohol is produced predominantly in countries where alcohol sales are illegal and in low-income countries due to high alcohol prices [18]. Methanol, cheaper than ethanol, is used in home-distilled alcohol production [19]. For this reason, methanol toxicity outbreaks have emerged in many low-income countries and countries where alcohol sales are illegal [20-23]. In 2019, a consensus of clinical toxicologists defined 3 cases occurring within 72 hours in the same region as a methanol toxicity outbreak [24]. In 2018, it was reported that 31 people were affected by a methanol outbreak in Malaysia; 30 were male (96.7%), the average age was 32 years, and the mortality rate was 61.3% [21]. In a 2014 outbreak of methanol toxicity in Kenya,

Table 2. The effect of variables on mortality

Characteristics (median/Q1-Q3)	Total (N=28)	Survived (n=20)	Deceased (n=8)	p*
Age (year)	**49.0 (36.0 – 56.0)**	**39.0 (33.5 – 51.5)**	**58.00 (50.00 – 62.50)**	**0.012**
Duration of alcohol consumption (year)	**21.00 (10.00 – 30.50)**	**17.5 (7.50 – 24.0)**	**30.50 (26.00 – 39.00)**	**0.009**
Time since last alcohol intake (hour)	**6.0 (2.0 – 12.0)**	**4.0 (2.0 – 17.0)**	**7.00 (6.00 – 12.00)**	**0.005**
Systolic Blood Pressure (mmHg)	130.50 (113.50 – 140.00)	132.00 (115.50 – 143.50)	126.00 (104.00 – 138.00)	0.387
Diastolic Blood Pressure (mmHg)	78.50 (68.50 – 89.00)	80.50 (71.50 – 89.00)	78.00 (54.00 – 84.00)	0.297
Pulse (beat/min)	83.50 (72.00 – 97.00)	83.50 (75.50 – 96.00)	74.50 (55.50 – 98.00)	0.445
Temperature (°C)	**36.10 (35.45 – 36.50)**	**36.40 (36.10 – 36.55)**	**35.40 (34.95 – 35.50)**	**0.001**
Glascow Coma Scale Score	**14.5 (5.0 – 15.0)**	**15.0 (10.5 – 15.0)**	**3.00 (3.00 – 7.00)**	**0.002**
Saturation (%)	95.00 (91.50 – 97.00)	96.50 (94.00 – 97.00)	90.00 (85.50 – 97.50)	0.118
Sodium (mEq/L)	133.50 (132.00 – 138.00)	133.50 (132.00 – 136.50)	134.00 (129.00 – 140.00)	0.818
Potassium (mEq/L)	4.69 (4.02 – 5.11)	4.18 (3.74 – 5.05)	5.20 (4.69 – 5.45)	0.033
Chloride (mEq/L)	101.50 (97.0 – 103.00)	102.00 (98.50 – 107.50)	98.00 (96.00 – 101.00)	0.058
Calcium (mg/dL)	9.15 (8.79 – 9.52)	9.03 (8.71 – 9.38)	9.53 (9.16 – 10.15)	0.056
Phosphorus (mg/dL)	**4.90 (4.15 – 6.83)**	**4.70 (3.71 – 5.06)**	**7.71 (6.31 – 9.12)**	**0.002**
Creatinine (mg/dL)	**1.12 (0.89 – 1.27)**	**1.02 (0.82 – 1.21)**	**1.30 (1.14 – 1.43)**	**0.008**
Urea (mg/dL)	12.22 (7.80 – 15.98)	12.15 (7.95 – 14.64)	14.40 (7.55 – 20.49)	0.445
Uric acid (mg/dL)	8.00 (6.87 – 9.02)	8.20 (6.79 – 9.02)	7.86 (7.61 – 10.08)	0.525
Albumin (g/dL)	4.26 (3.66 – 4.66)	4.37 (3.98 – 4.67)	3.66 (3.55 – 4.25)	0.104
ALT (U/L)	28.00 (19.50 – 73.00)	30.00 (14.00 – 75.00)	28.00 (23.50 – 66.50)	0.703
AST (U/L)	47.00 (30.00 – 86.00)	43.00 (23.00 – 79.50)	64.00 (43.00 – 94.00)	0.222
ALP (U/L)	85.50 (69.50 – 102.50)	83.00 (57.00 – 114.00)	91.00 (84.50 – 100.50)	0.309
GGT (U/L)	77.00 (46.00 – 153.00)	65.50 (32.00 – 153.00)	91.00 (74.00 – 495.00)	0.178
Total Bilirubin (mg/dL)	0.56 (0.35 – 1.04)	0.45 (0.33 – 0.90)	0.70 (0.37 – 1.57)	0.558
INR	1.21 (1.06 – 1.51)	1.19 (1.06 – 1.40)	1.38 (1.14 – 1.54)	0.373
Hemoglobin (g/dL)	14.65 (13.55 – 15.85)	14.90 (13.95 – 15.90)	13.65 (12.60 – 15.10)	0.186
Hematocrit (%)	45.00 (41.90 – 48.30)	45.60 (41.90 – 48.30)	43.75 (41.50 – 48.95)	0.799
Leukocyte (x10^3/µL)	9.90 (8.30 – 14.20)	10.40 (7.90 – 14.40)	9.55 (9.15 – 11.70)	0.780
Lymphocyte (%)	26.15 (13.99 – 34.18)	24.96 (13.27 – 34.18)	31.30 (21.07 – 38.52)	0.263
Neutrophile (%)	62.32 (51.49 – 77.40)	70.05 (51.49 – 79.11)	60.80 (53.20 – 68.73)	0.334
Thrombocyte (x10^3/µL)	239.00 (194.00 – 280.50)	250.50 (198.00 – 288.00)	209.00 (182.00 – 239.00)	0.170
Mean Corpuscular Volume (fL)	**97.00 (94.50 – 103.50)**	**95.70 (91.70 – 97.80)**	**104.65 (103.70 – 107.95)**	**<0.001**
pH	**7.15 (6.85 – 7.21)**	**7.18 (7.13 – 7.24)**	**6.79 (6.72 – 6.85)**	**<0.001**
Glucose (mg/dL)	**124.00 (106.50 – 219.50)**	**113.50 (104.00 – 194.00)**	**220.50 (133.50 – 275.50)**	**0.025**
Lactate (mmol/L)	**8.45 (2.05 – 14.45)**	**2.85 (1.70 – 8.95)**	**16.50 (13.45 – 18.55)**	**<0.001**
PO_2 (mmHg)	**65.90 (58.75 – 80.70)**	**62.85 (54.90 – 72.70)**	**89.00 (63.90 – 91.25)**	**0.015**
PCO_2 (mmHg)	25.20 (17.95 – 32.40)	27.75 (19.15 – 35.35)	22.40 (17.10 – 24.95)	0.079
HCO_3 (mmol/L)	**7.25 (4.82 – 11.05)**	**8.75 (6.55 – 16.30)**	**4.85 (4.40 – 5.75)**	**0.003**
Base deficit	**26.95 (20.00 – 29.70)**	**23.70 (17.20 – 27.90)**	**32.50 (27.75 – 37.45)**	**0.002**
Serum osmolarity	281.41 (275.11 – 291.92)	279.44 (275.11 – 289.04)	284.06 (277.48 – 297.58)	0.416
Anion Gap	**26.95 (19.90 – 30.20)**	**23.70 (16.15 – 28.00)**	**32.50 (27.67 – 37.62)**	**0.002**

Table 3. The characteristics of study group

Characteristics (n,%)	Alive (n=20)	Exitus (n=8)	p*
Gender			
Male	16 (80)	8 (100)	0.295
Female	4 (20)	0 (0)	
Marital status			
Single	7 (35)	1 (12.5)	0.380
Married	11 (55)	5 (62.5)	
Divorced	2 (10)	2 (25)	
Being parent			
Yes	12 (63.7)	7 (87.5)	0.214
No	8 (33.3)	1 (12.5)	
Educational status			
Primary	11(55)	2 (25)	0.067
Secondary	5 (25)	6 (75)	
Higher	4 (20)	0 (0)	
Diabetes mellitus			
Yes	8 (40)	0 (0)	0.063
No	12 (60)	8 (100)	
Hypertension			
Yes	5 (25)	2 (25)	
No	15 (75)	6 (75)	>0.999
Coronary artery diseases			
Yes	4 8 (20)	0 (0)	0.295
No	16 (80)	8 (100)	
Cirrhosis			
Yes	2 (10)	2 (25)	0.555
No	18 (90)	6 (75)	
Chronic alcoholism			
Yes	17 (85)	8 (100)	0.536
No	3 (15)	0 (0)	
Home distilled alcohol			
Yes	7 (35)	4 (50)	0.671
No	13 (65)	4 (50)	
Blurred vision			
Yes	7 (35)	3 (37.5)	>0.999
No	13 (65)	5 (62.5)	
Headache			
Yes	9 (45)	4 (50)	>0.999
No	11 (55)	4 (50)	
Loss of vision			
Yes	3 (15)	1 (12.5)	>0.999
No	17 (85)	7 (87.5)	
Nausea			
Yes	12 (60)	5 (62.5)	>0.999
No	8 (40)	3 (37.5)	
Vomiting			
Yes	10 (50)	2 (25)	0.401
No	10 (50)	6 (75)	
Cooperation			
Yes	**13 (65)**	**1 (12.5)**	**0.033**
No	**7 (35)**	**7 (87.5)**	
Orientation			
Yes	**14 (70)**	**1 (12.5)**	**0.011**
No	**6 (30)**	**7 (87.5)**	

58 of 62 patients were reported to be male (93%), 13 patients died (21%), and the median age was 30 years [20]. In the current study, 26 of 28 patients were male (92.85%). The median age was 49, and the mortality rate was 28.57% (n=8). Similar results were obtained with the literature. The observed median age in the present study could potentially be attributed to middle-aged individuals of low socioeconomic position who engage in the utilization of methanol for the manufacturing of home-distilled alcohol. Mortality rates are similar to the literature.

In studies about methanol intoxications, medical history and complaints on admission were evaluated [18,25,26]. It was observed that patients admitted to the emergency department had dizziness, GI symptoms, visual symptoms, and dyspnea. However, no study was found in which these findings were analyzed as an indicator of mortality. The current study analyzed the patients' sociocultural and socioeconomic characteristics and presented complaints to predict mortality. Contrary to expectations, parameters such as marital status, having children, and educational status did not significantly affect mortality.

In the methanol outbreak in Taiwan, it was found that the Glasgow Coma Scale score (GCS) could be used to predict mortality (OR: 0.816, 95% CI: 0.682-0.976) [26]. Mahdavi et al. found that median GCS was lower in deceased patients than in survivors (5 vs. 15, respectively, p=0.001) [11]. In the current study, only GCS and impaired consciousness significantly predicted mortality among the complaints and symptoms on admission. These results can be explained by central nervous system depression caused by increased methanol metabolites.

In a study involving 795 patients examining the methanol outbreak in Iran in 2020, , the time elapsed after the last alcohol intake was 24 hours in patients who died and 48 hours in survivors (p=0.014) [11]. In the current study, the time since the last alcohol consumption was higher in the deceased group. The current result was accepted as a predicted situation. As the duration of methanol consumption increases, the severity of metabolic acidosis induced by methanol metabolism and formic acid will deepen. Increased metabolic acidosis and formate concentration are correlated with mortality [1]. Delays in hospital admission and medical intervention after methanol consumption

Table 4. The ROC analysis of the characteristics

Diagnostic Test	AUC	Standard error	P	95% CI		Threshold	Sensitivity	Specificity
				Lower Bound	Upper Bound			
pH	0.959	0.033	<0.001	0.905	1.000	≤6.97	100	95
MCV (fL)	0.991	0.013	<0.001	0.965	1.000	≥102.95	100	90
Temperature (°C)	0.925	0.053	0.001	0.821	1.000	≤35.95	100	85
Lactate (mmol/L)	0.950	0.038	<0.001	0.875	1.000	≥9.8	100	80
HCO_3 (mmol/L)	0.866	0.068	0.003	0.733	0.999	≤6.8	100	75
Base deficit	0.872	0.068	0.002	0.739	1.000	≥26.95	100	70
Anion gap	0.872	0.068	0.002	0.739	1.000	≥26.95	100	70
Phosphorus (mg/dL)	0.872	0.080	0.002	0.715	1.000	≥5.90	87.5	85
Glascow coma								
scale	0.847	0.089	0.005	0.672	1.000	≤8	87.5	80
Glucose (mg/dL)	0.775	0.102	0.025	0.574	0.976	≥130	87.5	70
Age (year)	0.890	0.083	0.012	0.647	0.972	≥46.5	87.5	60
Last alcohol intake (mL/kg)	0.888	0.076	0.002	0.738	1.000	≥5.01	85	87.5

are associated with increased mortality. Therefore, although the result obtained differs from previous studies, it should be considered that mortality increases as the time elapsed after methanol consumption increases.

Patients who died in the methanol outbreak in Norway were found to have lower serum pH levels (6.57 vs. 7.25, respectively, p=0.001) and higher base deficit (28 mmol/L vs. 18 mmol/L respectively, p=0.001) than the group who survived without sequelae [18]. In 2012, in the methanol outbreak in the Czech Republic (n=101), serum lactate level (6.75 mmol/L) was found to be more acidic in patients who died compared to patients who survived without and with sequelae (7.31 mmol/L vs 7.02 mmol/L respectively, p<0.001). The same study found median bicarbonate levels were lower in deceased patients than in survivors without sequelae (5.2 mmol/L vs. 17.8 mmol/L, p<0.001). The median base deficit (29.0 mmol/L vs 6.1 mmol/L, p<0.001) and the median anion gap (39 mmol/L vs 22 mmol/L, p<0.001) were higher in deceased patients [25]. In the current study, median pH and bicarbonate levels were lower in the deceased group than in the surviving group. Median lactate, median PO2, median base deficit, and median anion gap were higher in the deceased group. The data obtained were similar to the previous studies in the literature.

Among the studies examining methanol intoxications, a limited number of studies analyzed data on body temperature. Many external and patient-related factors determine body temperature. However, the typical features of methanol outbreaks are that patients from the same geographical region and with the same climatic characteristics present to the emergency department. A study involving 32 patients diagnosed with methanol intoxication in Taiwan found that hypothermia developed in 50% of the patients [26]. Cox regression analysis in the same study showed that hypothermia was associated with mortality (OR: 168.686, 95% CI: 2.685-10595.977, p=0.015) [26]. The current study found lower body temperature in the deceased group than in the surviving group. In a study conducted by Mohler et al., it was observed that hypothermia occurred within 1 to 2 hours in rats given methanol compared to those given saline, and behavioral responses that could be exhibited to get away from hypothermia were disrupted [27]. Thus, it was experimentally proven that methanol intoxication has a negative effect on thermoregulation. Since methanol metabolism is clearly explained, metabolic changes that may occur can be predicted. The severity of these metabolic changes may be associated with mortality. However, using an easily measurable and simultaneous assessment, such as body temperature as a possible marker of mortality, is valuable data.

A multivariate regression analysis was performed in a study of the methanol outbreak in the Czech Republic. In this study, serum pH level <7.0 (OR 0.04 (0.01-0.16), p < 0.001), patient presenting with coma (OR 29.4 (10.2-84.6), p < 0.001) and negative

serum ethanol (OR 0.08 (0.02-0.37), p < 0.001) were found to be independent parameters that could be used to predict mortality [25]. In the Cox regression analysis performed in the study analyzing methanol intoxications in Taiwan, GCS (OR: 0.816, 95% CI: 0.682-0.976, p= 0.026), hypothermia (OR: 168. 686, 95% CI: 2.685-10,595.977, p= 0.015) and serum creatinine level (OR: 4.799, 95% CI: 1.321-17.440, p= 0.017) were associated with mortality [26]. In the current study, regression analysis could not be performed due to insufficient patients. However, ROC analysis was performed for the variables in which a statistical difference was found between the deceased and surviving groups. As expected, serum pH, lactate, bicarbonate, base deficit, and anion gap had thresholds with high sensitivity and specificity. After serum pH and lactate, body temperature was the parameter with the highest AUC value and high sensitivity and specificity. It was concluded that hypothermia caused by methanol suppression of the thermoregulation system in the central nervous system is a parameter that can be used to predict mortality.

CONCLUSION

Methanol intoxication has a high mortality rate. However, early diagnosis and treatment will reduce possible mortality and morbidity rates. The diagnostic factors of mortality in methanol intoxication are serum pH, lactate levels, bicarbonate levels, base deficit, anion deficit, the level of consciousness of the patient at admission, the time since the last alcohol consumption, and the amount of methanol ingested. In methanol intoxications resulting in death, the presence of central nervous system and metabolic disorders, as well as moderate hypothermia, was observed. If the patient's history suggests methanol intoxication, investigating the presence of hypothermia before obtaining laboratory results may help predict mortality. Especially in patients with a preliminary diagnosis of methanol intoxication, hypothermia on initial physical examination should lead to immediate initiation of methanol intoxication treatment. Thus, mortality due to methanol intoxication can be reduced.

Limitation

Since the current study was conducted in a single center with a limited number of patients, the targeted regression analysis models could not be created. Although standardized treatment protocols were carried out in the center where the study was conducted, the lack of fomepizole might have a negative effect on mortality.

Author contribution

Study conception and design: AB, GK, OAU; data collection: AB, GK; analysis and interpretation of results: AB, OAU, MA; draft manuscript preparation: AB, MA. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Hacettepe University (Protocol no: GO 21-494/06.04.2021).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA, American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning . American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol 2002;40(4):415-46. https://doi.org/10.1081/clt-120006745

[2] Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol 2008;3(1):208-25. https://doi.org/10.2215/CJN.03220807

[3] Jangjou A, Moqadas M, Mohsenian L, et al. Awareness raising and dealing with methanol poisoning based on effective strategies. Environ Res 2023;228:115886. https://doi.org/10.1016/j.envres.2023.115886

[4] Nekoukar Z, Zakariaei Z, Taghizadeh F, et al. Methanol poisoning as a new world challenge: A review. Ann Med Surg (Lond) 2021;66:102445. https://doi.org/10.1016/j.amsu.2021.102445

[5] Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. Mayo Clin Proc 2013;88(10):1127-40. https://doi.org/10.1016/j.mayocp.2013.06.012

[6] Ng PCY, Long BJ, Davis WT, Sessions DJ, Koyfman A. Toxic alcohol diagnosis and management: an emergency medicine review. Intern Emerg Med 2018;13(3):375-83. https://doi.org/10.1007/s11739-018-1799-9

[7] Gallagher N, Edwards FJ. The Diagnosis and Management of Toxic Alcohol Poisoning in the Emergency Department: A Review Article. Adv J Emerg Med 2019;3(3):e28. https://doi.org/10.22114/ajem.v0i0.153

[8] Sanaei-Zadeh H, Esfeh SK, Zamani N, Jamshidi F, Shadnia S. Hyperglycemia is a strong prognostic factor of lethality in methanol poisoning. J Med Toxicol 2011;7(3):189-94. https://doi.org/10.1007/s13181-011-0142-x

[9] Rietjens SJ, de Lange DW, Meulenbelt J. Ethylene glycol or methanol intoxication: which antidote should be used, fomepizole or ethanol? Neth J Med 2014;72(2):73-9.

[10] Meyer RJ, Beard ME, Ardagh MW, Henderson S. Methanol poisoning. N Z Med J 2000;113(1102):11-3.

[11] Mahdavi SA, Zamani N, McDonald R, et al. A cross-sectional multicenter linkage study of hospital admissions and mortality due to methanol poisoning in Iranian adults during the COVID-19 pandemic. Sci Rep 2022;12(1):9741. https://doi.org/10.1038/s41598-022-14007-1

[12] Liu JJ, Daya MR, Carrasquillo O, Kales SN. Prognostic factors in patients with methanol poisoning. J Toxicol Clin Toxicol 1998;36(3):175-81. https://doi.org/10.3109/15563659809028937

[13] Paine A, Davan AD. Defining a tolerable concentration of methanol in alcoholic drinks. Hum Exp Toxicol 2001;20(11):563-8. https://doi.org/10.1191/096032701718620864

[14] Banagozar Mohammadi A, Delirrad M. Problems with Methanol Poisoning Outbreaks in Iran. Alcohol Alcohol 2019;54(3):338. https://doi.org/10.1093/alcalc/agz028

[15] Gulen M, Satar S, Avci A, Acehan S, Orhan U, Nazik H. Methanol poisoning in Turkey: Two outbreaks, a single center experience. Alcohol 2020;88:83-90. https://doi.org/10.1016/j.alcohol.2020.07.002

[16] Roberts DM, Yates C, Megarbane B, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med 2015;43(2):461-72. https://doi.org/10.1097/CCM.0000000000000708

[17] Mojica CV, Pasol EA, Dizon ML, et al. Chronic methanol toxicity through topical and inhalational routes presenting as vision loss and restricted diffusion of the optic nerves on MRI: A case report and literature review. eNeurologicalSci 2020;20:100258. https://doi.org/10.1016/j.ensci.2020.100258

[18] Hovda KE, Hunderi OH, Tafjord AB, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. J Intern Med 2005;258(2):181-90. https://doi.org/10.1111/j.1365-2796.2005.01521.x

[19] Anseeuw K, Sabbe MB, Legrand A. Methanol poisoning: the duality between 'fast and cheap' and 'slow and expensive'. Eur J Emerg Med 2008;15(2):107-9. https://doi.org/10.1097/MEJ.0b013e3282f3c13b

[20] Rostrup M, Edwards JK, Abukalish M, et al. The Methanol Poisoning Outbreaks in Libya 2013 and Kenya 2014. PLoS One 2016;11(3):e0152676. https://doi.org/10.1371/journal.pone.0152676

[21] Md Noor J, Hawari R, Mokhtar MF, et al. Methanol outbreak: a Malaysian tertiary hospital experience. Int J Emerg Med 2020;13(1):6. https://doi.org/10.1186/s12245-020-0264-5

[22] Kabli AO, Felemban AM, Nasri AK, et al. Outcome of Methanol Toxicity Outbreak In Saudi Arabia: Case Series Study. Cureus 2023;15(6):e41108. https://doi.org/10.7759/cureus.41108

[23] Collister D, Duff G, Palatnick W, Komenda P, Tangri N, Hingwala J. A Methanol Intoxication Outbreak From Recreational Ingestion of Fracking Fluid. Am J Kidney Dis 2017;69(5):696-700. https://doi.org/10.1053/j.ajkd.2016.10.029

[24] Hassanian-Moghaddam H, Zamani N, Roberts DM, et al. Consensus statements on the approach to patients in a methanol poisoning outbreak. Clin Toxicol (Phila) 2019;57(12):1129-36. https://doi.org/10.1080/15563650.2019.1636992

[25] Zakharov S, Pelclova D, Urban P, et al. Czech mass methanol outbreak 2012: epidemiology, challenges and clinical features. Clin Toxicol (Phila) 2014;52(10):1013-24. https://doi.org/10.3109/15563650.2014.974106

[26] Lee CY, Chang EK, Lin JL, et al. Risk factors for mortality in Asian Taiwanese patients with methanol poisoning. Ther Clin Risk Manag 2014;10:61-7. https://doi.org/10.2147/TCRM.S51985

[27] Mohler FS, Gordon CJ. Thermoregulatory effects of methanol in Fischer and Long Evans rats. Neurotoxicol Teratol 1990;12(1):41-5. https://doi.org/10.1016/0892-0362(90)90111-o