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Prognostic markers of mortality in patients with methanol poisoning

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Abstract
Aim: Methanol is a kind of alcohol, which is used in industry in numerous different products. Methanol intoxication entails high mortality and morbidity rates. In this study, we aimed to investigate the effectiveness of laboratory parameters in determining the severity of exposure in patients presenting with methanol intoxication.
Material and Methods: The study was performed in the university hospital between January 1, 2015, and January 1, 2020. All data were obtained retrospectively from the hospital automation system. Receiver Operating Characteristic (ROC) curve was used to determine ideal cut-off values. A logistic regression model was used to perform univariate and multivariate analyses.
Results: The study included 49 patients and 3 of them were women. Thirty (61%) received both hemodialysis and intravenous ethanol for treatment. Univariate analysis revealed increased mortality in patients with pH below 7.00, HCO3 below 8.40 (mmol/L), lactate 4.35 (mmol/L), glucose 183 (mg/dl) and above, PCO2 42.7 (mmHg), high osmolarity, and a high anion gap. The results of multivariate logistic regression analysis for model 1 is (pH, bicarbonate, lactate, glucose, PCO2, osmolarity, and anion gap); pH <7.00 (OR:0.016, %95 CI <0.01-0.15, p<0.001) and for model 2 is (bicarbonate, lactate, glucose, PCO2, osmolarity, and anion gap); lactate ≥4.35 (OR:31.66, 95% CI 3.25-308.5, p=0.003) and PCO2 ≥42.7 (OR: 7.01, 95% CI 1.12-43.96, p=0.038).
Discussion: Laboratory parameters would predict mortality. PH emerged as a predictive mortality marker, while blood lactate and high partial carbon dioxide pressure were capable of predicting mortality if pH was excluded. Starting on the treatment with clinical diagnoses decreases mortality in methanol intoxication.

Keywords
Methanol, Emergency Department, Prognostic Markers

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Introduction

Methanol is a colorless type of alcohol whose odor and taste resemble those of ethanol. It is employed in industry in the manufacture of antifreeze, brake fluids, windshield washer fluids, wallpaper, and window washer fluids [1].

When methanol enters the circulatory system, it is metabolized in the liver by alcohol dehydrogenase (ADH) to formaldehyde, which is then metabolized to formic acid by aldehyde dehydrogenase (ALDH).

Although methanol is not itself toxic, the resulting metabolites can lead to permanent organ damage and death in humans [2]. Pathognomonic findings of formic acid intoxication include petechial bleeding in the occipital, temporal, and parietal cortex, basal ganglia, and pons. Hemorrhagic necrosis and edema are also seen in the thalamus, putamen, globus pallidus, basal ganglia, and cerebral cortex. It also causes visual disorders in association with mitochondrial deterioration and vacuolization in the retinal pigment epithelium, photoreceptor inner segment, and the optic nerve [3].

While methanol intoxications can be accidental, they are frequently observed as a result of the use of methyl alcohol instead of ethyl alcohol in beverage production. Many individuals are affected by the deliberate or accidental consumption of these products [4]. Intoxication is a global health problem, although it is more common in developing countries. Outbreaks involving large numbers of cases involving the consumption of alcohol containing methanol have been reported from Argentina, Norway, the Czech Republic, Libya, and Iran [5-7].

Due to its high mortality and morbidity rates, methanol intoxication requires rapid and effective treatment, which should be initiated in the emergency department [4]. It is difficult to diagnose and determine the severity of intoxication for reasons such as the inability to obtain adequate information due to impaired consciousness, difficulties in measuring blood methanol levels, or because gas chromatography used to measure methanol levels is not available in all hospitals [2-4].

This study investigated the value of laboratory parameters in determining the severity of exposure in patients presenting with methanol intoxication. Our aim was to be able to predict mortality using different models.

Material and Methods

Patients

The study was performed retrospectively in the emergency department of a university hospital in Turkey between January 1, 2015, and January 1, 2020. Forty-nine patients meeting the study criteria and definitely diagnosed by means of gas chromatography were included from the 67 patients presenting due to methanol exposure. Patient data were retrieved and analyzed from the hospital record system. Inclusion criteria were age over 18 and blood gas and biochemistry parameters recorded during presentation to the emergency department. Patients with no heart beat at presentation were excluded.

Approval for the study was granted by the university ethics committee (no. 1058). The study conformed to the provisions of the 1995 Declaration of Helsinki.

Data collection

The arrival symptoms, laboratory test results, treatment administered, and outcomes for the patients included in the study were recorded by examining data from the hospital automation system. Blood gas tests were performed on a RADIOMETER COPENHAGEN ABL 835 FLEX device, while biochemistry parameters were measured with an Abbott kit on an Abbott C 16000 device.

Statistical Analysis

Ideal cut-off values with high sensitivity and specificity in predicting mortality after methanol intoxication were determined using a Receiver Operating Characteristic (ROC) curve. Univariate and multivariate analyses were performed using a logistic regression model. Odds ratios (OR) were reported with corresponding 95% confidence intervals (95% CI), and a p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 24 software (SPSS Inc., Chicago, IL, USA).

Results

Forty-nine patients with a mean age of 50.5±14.1 and a median age of 53 (min 16, max 72) years were included in the study. Ninety-four percent (n=46) of the participants were men and 6% (n=3) were women. The median age of the female patients was 39 (min 31, max. 59) years, and the median age of the male patients was 53 (min 16, max 72).

Analysis showed that 46.9% (n:23) of patients arrived in their own vehicles, while 53.2% (n:26) were brought by ambulance.

Table 1. Demographic Characteristics of Patients Presenting with Methanol Toxicity

	n	%
Gender		
Male	46	94%
Female	3	6%
History		
DM	3	6%
HT	2	4%
CAD	3	6%
Psychiatric disease	2	4%
Gastritis	2	4%
None	37	76%
Neurological Symptoms		
Blurred vision	15	31%
Clouded consciousness	17	35%
None	17	35%
Treatment Administered		
Hemodialysis	11	22%
Ethanol (iv)	8	16%
Hemodialysis + Ethanol (iv)	30	61%
Final Status in the Emergency Department		
Treated in the ED	5	10%
Treated in intensive care	31	63%
Treated in the ward	7	14%
Discharged	6	12%
Final Status		
Exitus	14	29%
Survived	35	71%

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Artery Disease

Eleven patients (16%) received hemodialysis only, eight (22%) received intravenous ethanol only, and 30 (61%) received both hemodialysis and intravenous ethanol. Methanol intoxication-related mortality occurred in 14 (29%) patients following emergency department and subsequent stage treatment (Table 1).

Cut-off values predicting mortality for laboratory parameters were determined separately using ROC analysis. Cut-off values were not determined for age (p=0.199), BUN (p=0.382), potassium (p=0.163), chloride (p=0.054), calcium (p=0.765), INR (p=0.982), or ethanol (p=0.974). Other parameters are shown in Table 2.

Univariate analysis revealed greater mortality in patients with PH<7.00 (OR: 0.02 95% CI <0.01-0.15, p<0.001), bicarbonate <8.40 mmol/L (OR: 0.06 95% CI 0.01-0.31, p=0.001), lactate ≥4.35 mmol/L (OR: 52.0 95% CI 5.78-467.48, p<0.001), serum glucose ≥183 mg/dl (OR: 10.59 95% CI 2.40-46.75, p=0.002), PCO2 ≥42.7 mmHg (OR: 14.67 95% CI 3.20-67.18, p=0.001), serum osmolarity ≥293.5 mOsm/kg (OR: 5.46 95% CI 1.40-21.29, p=0.015), and anion gap ≥24.4 mmol/L (OR: 12.38 95% CI 2.76-55.50, p=0.001). No association was observed between mortality and age (p=0.083), type of treatment (p=0.155), or troponin (p=0.147), creatine (p=0.067), or sodium (p=0.091) levels (Table 3).

Modeling established by including pH, bicarbonate, lactate, glucose, PCO2, osmolarity, and anion gap at multivariate logistic regression analysis (model 1) identified pH <7.00 (OR:0.016, %95 CI <0.01-0.15, p<0.001) as a powerful significant predictor in diagnosis for methanol intoxication. Modeling without pH but in which bicarbonate, lactate, glucose, PCO2, osmolarity, and the anion gap were included (model 2) revealed increased mortality in patients with lactate ≥4.35 (OR: 31.66, 95% CI 3.25-308.5, p=0.003) and PCO2 ≥42.7 (OR: 7.01, 95% CI 1.12-43.96, p=0.038)

Univariate analysis of the relationship between mortality and blood and clinical parameters in patients with suspected methanol intoxication revealed an increase in mortality in patients with PH below 7.00 at presentation, HCO3 below 8.40 (mmol/L), lactate above 4.35 (mmol/L), glucose levels of 183 (mg/dl) or above, PCO2 above 42.7 (mmHg), high molarity, and a high anion gap. Mortality was approximately six times higher in patients who started treatment following the determination of blood methanol levels compared to those who started treatment with clinical diagnoses (OR: 6.21 95% CI:1.46-26.43, p=0.014). The multivariate model identified pH below 7.00 alone as a predictive marker, while when pH was excluded, lactate of 4.35 (mmol/L) and above together with PCO2 above 42.7 (mmHg) constituted a predictive model.

Table 2. Variables Predicting Mortality in ROC Analysis

Variable	AUC (95% interval)	Cut-off Value	Sensitivity (Cut-off)	Specificity (Cut-off)	p
pH	0.895 (0.806-0.984)	7.00	92.9%	82.9%	<0.001
HCO3 (mmol/L)	0.817 (0.697-0.938)	1.40	74.3%	85.7%	0.001
Lactate (mmol/L)	0.883 (0.789-0.976)	4.35	92.9%	80.0%	<0.001
Troponin (ng/mL)	0.685 (0.517-0.852)	0.060	71.4%	54.3%	0.045
Glucose (mg/dl)	0.764 (0.607-0.921)	183	78.6%	74.3%	0.004
Creatine (mg/dl)	0.729 (0.585-0.872)	1.30	57.1%	68.6%	0.013
Sodium (mEq/L)	0.681 (0.503-0.858)	137.5	64.3%	62.9%	0.050
PCO2 (mmHg)	0.776 (0.619-0.932)	42.7	78.6%	80.0%	0.003
Osmolarity (mOsm/kg)	0.696 (0.540-0.852)	293.5	71.4%	68.6%	0.034
Anion gap (mmol/L)	0.803 (0.655-0.951)	24.4	78.6%	77.1%	0.001

HCO3: Bicarbonate, PCO2 : Partial oxygen pressure

Table 3. Univariate Regression Analysis of Mortality from Methanol Intoxication

Variable	Category	OR (95% CI)	p
Age	Continuous	1.05 (0.99-1.12)	0.083
Type of treatment	Singe*/double*	1.59 (0.84-3.03)	0.155
Initiation of treatment	Delayed /Immediate	6.21 (1.46-26.43)	0.014
pH	<7.00/ ≥7.00	0.02 (<0.01-0.15)	<0.001
Bicarbonate	<8.40 / ≥8.40	0.06 (0.01-0.31)	0.001
Lactate	<4.35/ ≥4.35	52.0 (5.78-467.48)	<0.001
Troponin	<0.060/ ≥0.060	2.556 (0.72-9.08)	0.147
Glucose	<183/ ≥183	10.59 (2.40-46.75)	0.002
Creatine	<1.30/ ≥1.30	3.33 (0.92-12.08)	0.067
Sodium	<137.5/ ≥137.5	3.046 (0.84-11.07)	0.091
PCO2	<42.7/ ≥42.7	14.67 (3.20-67.18)	0.001
Osmolarity	<293.5 / ≥293.5	5.46 (1.40-21.29)	0.015
Anion gap	<24.4/ ≥24.4	12.38 (2.76-55.50)	0.001

*single: iv ethanol or hemodialysis. double: iv ethanol and hemodialysis

Discussion

Despite being a rare cause of presentation to the emergency department, methanol intoxications are a chaotic condition that can lead to significant mortality. Clinical symptoms emerge within approximately four hours after oral intake and can persist for 24-72 hours [1]. Presentations generally involve large numbers of patients arriving within a similar time frame [8]. Delays in the diagnosis of methanol intoxications may occur due to non-specific symptoms being observed, such as severe nausea and vomiting. Late blood methanol level results and delays in diagnosis are associated with increased mortality [9]. In the present study, mortality was approximately six times higher in patients who started treatment as a result of determination of blood methanol levels compared to those who started treatment based on clinical findings and histories (i.v. ethanol and hemodialysis) (OR: 6.21 95% CI:1.46-26.43, p=0.014).

Altered consciousness and vision disorders are symptoms frequently observed following exposure to methanol. Patients generally describe blurred and cloudy vision, double vision, or altered color perception. Narrowing of the visual field may occur, or vision may even be lost entirely. Petechial bleeding in the basal ganglia and pons in autopsy series is pathognomonic. Formic acid has been held responsible for mitochondrial impairment and vacuolization in the retinal pigment epithelium, photoreceptor inner segments, and optic nerve [1,3]. Hovda et al.

also reported significant numbers of patients with neurological symptoms and observed higher mortality in the patient groups with accompanying neuropathologies [5]. Shokoohi M et al. described blurred and cloudy vision as the most common presentation symptom, and reported that neurological symptoms, including visual findings, were correlated with the severity of the toxicity [7]. Similarly, in the present study, the most frequent presentations were seen in patients with neurological findings (67%).

Another factor associated with mortality is age, with advanced age and decreased physiological capacity being linked to mortality [5-8]. Chung JY et al. reported that mortality increased in line with age, and implicated age-related impairment of physiological resistance mechanisms and chronic damage resulting comorbid diseases [10]. However, no statistically significant relationship was observed between increasing age and mortality in the present study (OR: 1.05 95CI%: 0.99-1.12, p=0.083).

Cellular and tissue damage due to formic acid results in an increase in breakdown products. Depending on the severity of toxicity, products and waste materials cause remarkable precursor changes in blood gas parameters, without yet causing significant alterations in conventional biochemical markers. The first indications of cellular breakdown are observed in pH, HCO3, PCO2, and lactate, which accumulate with an increase in breakdown with impairment of glucose balance, osmolarity, and an increased anion gap. Methanol is metabolized to formaldehyde by alcohol dehydrogenase (ADH), and formaldehyde is metabolized to the toxic agent formic acid by aldehyde dehydrogenase (ALDH). The accumulation of formic acid results in metabolic acidosis and hypoxia with cytochrome inhibition in mitochondria. Methanol intoxication is therefore essentially linked to metabolic acidosis and hypoxia [11,12]. Coulter C et al. examined laboratory parameters and blood gas in victims of methanol exposure and reported that the evaluation of metabolic acid and hypoxia alone could be used in the prediction of mortality, while other parameters were insufficient in terms of predicting mortality. Those authors reported that pH was the most powerful predictor of mortality, and that mortality increased in case of pH <6.7 [13]. Raido Paasma also emphasized the importance of blood gas analysis and reported that a high osmolar gap and anion gap metabolic acidosis were associated with mortality. pH <6.98 was described as a cut-off value for mortality [4]. Consistent with previous literature, the most powerful determinant of mortality in the present study was also pH, with high mortality being observed at pH values lower than 7.00.

Partial carbon dioxide and bicarbonate are directly linked to pH. An increase in PH resulting from increased anaerobic respiration mechanisms due to mitochondrial damage developing in association with accelerated anaerobic respiration and formaldehyde production in the early period and formic acid leads to a decrease in carbon dioxide and bicarbonate [11,12]. Kadam DB et al. reported pH below 7.3 and HCO3 lower than 20 mEq/L in methanol intoxications. Those authors emphasized that pH and HCO3 decreased in line with the severity of toxicity. Similarly in the present study, and consistent with the previous literature, low HCO3 indicated the severity of toxicity and was one of the early markers [14].

Increased catabolic breakdown with anaerobic respiration, together with acidosis and hypoxia, results in the production of lactate and pyruvate from glucose and alanine without oxygen consumption. The lactate and pyruvate cause lactic acidosis at the cellular level and acidosis and hypercarbia with increased lactate accumulation in tissues. In addition, increasing formic acid and lactate also result in an anion gap [11,12]. Kraut JA emphasized the methanol-induced anaerobic respiration steps and compensation mechanisms, and reported that increased lactic acidosis and hypercarbia, and therefore, an increased anion gap osmolarity, are compatible with the severity of toxicity. Glucose also increased in line with energy production. Those authors also reported that the severity of the anion gap and osmolarity will increase with exacerbation of tissue hypoxia [15]. Although the sensitivity and specificity were low in the present study, PCO2, anion gap, glucose and osmolarity were moderately-highly compatible with methanol toxicity.

This study investigated the clinical and laboratory parameters of patients who presented to the emergency department with methanol intoxication and determined cases that would result in mortality. Univariate analysis revealed increased mortality in patients with low pH, high lactate, high glucose, high PCO2, increased serum osmolality, and an increased anion gap. Multivariate analysis revealed that pH<7 or lactate ≥4.35 mmol/L together with CO2 ≥42.7 mmHg at the time of presentation may represent a predictive marker of mortality.

One of the most important findings of this study is the value of blood gas measurements. Changes in blood glucose levels, liver function tests, electrolytes, and electrocardiograms will be observed with an increase in tissue hypoxia and end-organ damage. However, reactions commencing at the cellular level did not alter the laboratory results in the early period, although blood gas analysis constitutes an earlier response compared to other laboratory parameters.

Limitations

The principle limitation of this study is its retrospective nature. Another limitation lies in the heterogeneous nature of the treatments applied. We do not know which patients achieved idea ethanol levels with ethanol therapy. We recommend that further studies with larger patient numbers be performed investigating factors capable of reducing mortality.

Conclusion

In conclusion, mortality decreased in patients who started treatment based on clinical diagnosis. In addition, our findings show that pH is a predictive marker of mortality, and that if pH is excluded, then high lactate and high partial carbon dioxide pressure can predict mortality in patients presenting with methanol intoxication.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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