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A RETROSPECTİVE STUDY ON METHYL ALCOHOL POISONING IN TURKEY: TREATMENT STRATEGY

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Abstract

Introduction: It is important to define the poison according to the symptoms of poisoning and intervene immediately.

Aim of this study was to evaluate the clinical and laboratory factors in patients with methanol poisoning and explain our treatment strategy.

Methods: In this study, all patients with methanol poisoning, who had presented to the emergency department of City Hospital, Ankara, Turkey. Methanol poisoning was diagnosed in all cases.

Results: Our results showed that low pH, nausea and, confusion were distinguishing findings for the diagnosis of methyl alcohol poisoning in our study. Furthermore, confusion was the determinant factor between whether or not to be admitted to the intensive care unit. Based on the findings of this study, delayed admission to hospital, death and high aminotransferases were identified in methanol poisoning.

Conclusion: Our treatment strategy was successful (about 80%) to save the poisoned patients.

Keywords: *Methyl alcohol, poisoning, treatment strategy, acidosis, antidote, coma, intensive care unit.*

Резюме

РЕТРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ ОТРАВЛЕНИЯ МЕТИЛОВЫМ СПИРТОМ В ТУРЦИИ: СТРАТЕГИЯ ЛЕЧЕНИЯ

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Актуальность: важно определить яд по симптомам отравления и немедленно принять меры.

Цель этого исследования состояла в том, чтобы оценить клинические и лабораторные факторы у пациентов с отравлением метанолом и объяснить нашу стратегию лечения.

Методы: В этом исследовании участвовали все пациенты с отравлением метанолом, обратившиеся в отделение неотложной помощи городской больницы Анкары, Турция. Во всех случаях диагностировано отравление метанолом.

Результаты: Наши результаты показали, что низкий уровень pH, тошнота и спутанность сознания были отличительными признаками для диагностики отравления метиловым спиртом в нашем исследовании. Кроме того, спутанность сознания была определяющим фактором при принятии решения о госпитализации в отделение интенсивной терапии. По результатам данного исследования при отравлении метанолом были выявлены поздняя госпитализация, летальный исход и высокие аминотрансферазы.

Заключение: Наша стратегия лечения была успешной в 80% случаев спасения отравленных пациентов.

Ключевые слова: *метиловый спирт, отравление, тактика лечения, ацидоз, антидот, кома, отделение реанимации.*

Түйіндеме

ТҮРКИЯДАҒЫ МЕТИЛ СПИРТІМЕН УЛАНУДЫ РЕТРОСПЕКТИВТІ ЗЕРТТЕУ: ЕМДЕУ СТРАТЕГИЯСЫ

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Өзектілігі: улануды улану белгілері бойынша анықтап, және дереу әрекет ету керек.

Бұл зерттеудің **мақсаты** метанолмен уланған науқастардағы клиникалық және зертханалық факторларды бағалау және емдеу стратегиямызды түсіндіру болды.

Әдістері: бұл зерттеуге Түркияның Анкара қалалық ауруханасының жедел жәрдем бөліміне жүгінген метанолмен уланған барлық науқастар қатысты. Барлық жағдайларда метанолмен улану диагнозы қойылған.

Нәтижелер: біздің нәтижелеріміз төмен pH, жүрек айну және шатасу біздің зерттеуімізде метил спиртімен улануды диагностикалаудың ерекше белгілері екенін көрсетті. Сонымен қатар, шатасу реанимация бөліміне жатқызу туралы шешім қабылдауда шешуші фактор болды. Осы зерттеудің нәтижелері бойынша метанолмен улану кезінде кеш госпитализация, өлім және жоғары аминотрансферазалар анықталды.

Қорытынды: біздің емдеу стратегиямыз уланған науқастарды құтқару жағдайларының 80% сәтті болды.

Түйінді сөздер: *метил спирті, улану, емдеу тактикасы, ацидоз, антидот, кома, реанимация бөлімі.*

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Introduction

Methanol is as a colorless fairly volatile liquid like that of ethyl alcohol and it is used in industry as a component of various household substance (National Center for Biotechnology Information, 2021; Rasamison, Besson, Berleur, Schicchi, & Megarbane, 2020). In our country, as a result of rising alcohol prices due to the increase in taxes on alcohol consumption, a serious increase is observed in the production of fake alcohol and admissions to the emergency department with methanol poisoning. Methanol poisoning often occurs when alcohol is produced illegally or as a result of an accidental intake or suicide attempt *(Güven et al.)*. Ingestion of methanol instead of ethanol causes serious problems, especially, for alcohol abusers, although the harmful effects of methanol are known. Toxic alcohol poisoning represents a concerning public health issue worldwide because the rates of mortality and morbidity (major sequelae) are high. The following adverse effects occur in those who drink methanol for suicide or alcoholic beverage adulterer with methanol *(Zakharov et al., 2014)*. These are gastrointestinal, ophthalmologic and neurological effects, and electrolyte imbalances. In severe cases, kidney failure, hematuria and rhabdomyolysis have been reported. Methanol itself is not harmful, it is slowly converted into metabolites by alcohol dehydrogenase enzyme. This transformation takes 12-24 hours. Therefore, following methanol intake, symptoms appear after 12-24 hours, when it is metabolized, 2 major metabolites namely formic acid and formaldehyde, are responsible for toxicity *(Ashurst & Nappe, 2021)*. High anion gap causes metabolic acidosis, basal ganglia damage, retinal damage, and optic nerve damage. In the early period, the patient may have visual symptoms, abdominal pain, vertigo, nausea, vomiting and headache *(Ashurst & Nappe, 2021)*. The most common finding is visual symptoms. During this period, if the patient is suspected of methanol poisoning and treatment is initiated, the symptoms may return. In fatal case, tachycardia or bradycardia and an increased respiration have been observed and with respiratory arrest, the patient is lost. Formic acid causes acidosis. Formaldehyde is related to ophthalmologic toxic effects, causes optic nerve degeneration that causes up to blindness (Centers for Disease Control and Prevention, 2011). Worldwide, methanol poisoning is not dependent on any time or season. However, even if there is no precise information and statistics in Turkey, it is thought that methanol poisoning is increased by more the consumption of alcoholic beverages such as, before the new year and in the spring-summer seasons. The reason is that ethanol is adulterated to alcoholic beverages since it is cheaper. This should not mean that methanol poisoning occurs only during these periods. In this retrospective study presented, poisonings occurred in different time periods, although most of them occurred due to this reason. The reason for the high mortality rate is that the person does not admit to the hospital or goes to the hospital late because of the suicidal intake of methanol or the person consuming alcoholic beverages mixed with methanol without realizing it. Especially, it is not to establish a relationship between the symptoms experienced and the adulterated alcoholic beverages and therefore the alcoholic beverages consumed is not blamed. According to the consumption types mentioned (above), methanol poisoning usually occurs orally, although inhalation or transdermal absorption may lead to poisoning. The symptoms of poisoning and the toxic effects of methanol vary between individuals. A small amount may cause very toxic effects in some individuals (Rakus, Kroczak, & Ruszkowski, 2005). Sometimes the diagnosis is delayed due to the weakness of the symptoms, which delays the initiation of treatment or without waiting for laboratory confirmation, but considering the high rate of mortality, treatment should be initiated before finalizing the

diagnosis (Çetinkaya, Sırakaya, & Aydın, 2021). Many case examples have failed due to methanol treatment management not being performed correctly and timely. It is important to apply both multidisciplinary and correct methanol treatment management (Barceloux, Bond, Krenzelok, Cooper, & Vale, 2002).

Materials and Methods

A single-center and retrospective study was conducted of all the patients admitted to Ministry of Health Ankara City Hospital with the diagnosis of methanol poisoning during period of February 2019 to April 2021.

The study was approved by Ankara City Hospital ethical committee (Ethical Number: E. Board-E1-21-1935). Medical records of all the admitted patients with the final diagnosis of methanol poisoning were reviewed and clinical and laboratory data of each case were recorded.

The records of hospital were reviewed retrospectively for all methyl alcohol poisonings. Patients with recent history of ingesting toxic amounts of methanol and inclusion criteria comprised of history of strong clinical suspicion of methanol poisoning and at least two of the following criteria: arterial pH< 7.3; serum bicarbonate < 20 meq/L (mmol/L); or osmolal gap >10 Osm/kg H_2O. Patients who were transferred out or left against medical advice were excluded from our study.

Diagnosis Criteria of Methanol Poisoning

Methanol level should be checked for the diagnosis of methanol poisoning. This is not always possible. Methanol level is not measured in our hospital, either. If the blood methanol level cannot be studied in patients with high anion gap metabolic acidosis with a history of alcohol intake, ethanol level is requested. If ethanol level is zero in these patients, it supports the diagnosis of methanol poisoning.

Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 (IBM Corp, Armonk, NY). Median with interquartile range (IQR) were used for presentation of descriptive statistics of numeric variables, and frequency (n) and percentage (%) were used for categorical variables. Mann-Whitney U Test was used for comparing numeric variables and Fisher's Exact Test was used for comparing categorical variables among non-fatal and fatal patients, and patients not-admitted and admitted to intensive care unit. A value of $p<0.05$ was set as statistically significance level.

Results

The subject's age, gender, methyl alcohol blood levels, the source of methyl alcohol and accompanying laboratory results were recorded. Between the study period 30 patients, who met inclusion and exclusion criteria, were included in the study.

Approximately all patients were male and median age was 49.0 years with an interquartile range of 41.8-57.0 years. A total of 30 patients who admitted to the emergency department with alcohol abuse or suspected methanol poisoning, who were diagnosed with methanol poisoning were included in the study. Only one of 30 patients took orally methyl alcohol to commit suicide. Only one patient is female (her age is 31), the rest of them is male with mean age of 47.8±12.4 years. Patients' admission time to the hospital is a minimum of 2 hours and a maximum of 48 hours. In order for the intervention to be successful, the starting time of the treatment following the poisoning is important. 46.6% of the patients were admitted to the hospital in more than 10 hours. 60% (n=18) of patients are in coma when they admitted to the hospital. The two most common symptoms were confusion and nausea, respectively (Table 1). Most of the patients were symptomatic with 10 (33.3%) patients reporting nausea, making it the single most common clinical feature and the symptom with the second largest percentage was confusion (n=20, 66.7%). Out of these, 6 (20%), 3 (10.0%) and 3 (10%) patients presented with visual impairments, throat ache and chest pain, respectively. There is no data on the symptoms of a patient (n=1, 3.3%). Hemodialysis was applied to 63.3% of the patients at least once. 23% had no hemodialysis at all, and the remainder received 2-3 hemodialysis times. 60.0 % of the patients (n=18) were intubated. 70% (n = 21) were taken to intensive care unit, and after therapy they are discharged and 10% (n = 3) were treated and discharged without entering the intensive care unit. 50% patient (n=15) needed to take the vasopressor agent (Table 1). The victim's median APACHE II score was 25.5 and median GCS was 6.0. Of the patients, 28 admitted to intensive care unit and 7 patients died.

Table 1.

Demographics and clinical features of patients.

Demographics and clinical features	
Sex (Male/Female), n	29/1
Age (Years), Median (*IQR)	49.0 (41.8-57.0)
APACHE II score, Median (*IQR)	25.5 (11.5-42.0)
GCS, Median (*IQR)	6.0 (3.0-15.0)
Symptoms, n (%)	
Visual Impairments	6 (20.0)
Nausea	10 (33.3)
Throat Ache	3 (10.0)
Chest Pain	3 (10.0)
Confusion	20 (66.7)
Need For Mechanical Ventilation, n (%)	18 (60.0)
Need For The Vasopressor Agent, n (%)	15 (50.0)

**** IQR: Interquartile range; APACHE II: Acute Physiology and Chronic Health Evaluation II, GCS: Glasgow Coma Scale.***

Fatal patients had statistically significantly low GCS and high APACHE II scores (p=0.003 and p=0.016, respectively; Table 2), and they also had more base deficit and lactate levels than non-fatal patients (p=0.033; Table 2). Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Blood Pressure (MBP) were statistically significantly low in fatal patients (p=0.006, p=0.008 and p= 0.004, respectively; Table 2), their pH levels also were lower than non-fatal patients (p=0.014, Table 2). Serum ALT, AST, ALP and LDH levels of non-fatal patients were statistically significantly low when compared to non-fatal patients (p=0.019, p=0.048, p=0.006 and p=0.014, respectively). Among the symptoms, only confusion prevalence was statistically significantly low (median= 7.08 with IQR =6.70-7.20) and median 6.79 with 6.52-6.83 IQR, p=0.033, Table 2) but other symptoms were similar (Table 2).

Table 2.

Comparison of clinical and laboratory features between non-fatal and fatal patients.

	Non-fatal patients (n=23)	Fatal patients (n=7)	*p*
Glasgow Coma Scale (GCS), Median (IQR)	12.0 (5.0-15.0)	3.0 (3.0-3.0)	**0.003**
APACHE II score, Median (IQR)	12.0 (9.0-41.0)	42.0 (36.0-42.0)	**0.016**
Blood Urea Nitrogen (mg/dL), Median (IQR)	13.0 (8.0-19.0)	18.0 (10.0-33.0)	0.190
Base deficit (mmol/L), Median (IQR)	-21.0 (-27.0--14.0)	-28.0 (-34.0--27.0)	**0.033**
Creatinine (mg/dL), Median (IQR)	1.17 (0.91-1.60)	1.44 (1.20-2.02)	0.107
Lactate (mmol/L), Median (IQR)	2.74 (0.66-6.62)	7.74 (5.62-15.09)	**0.007**
Glucose (mg/dL), Median (IQR)	152.0 (103.0-256.0)	164.0 (149.0-241.0)	0.441
Systolic blood pressure (mm Hg), Median (IQR)	115.0 (90.0-126.0)	90.0 (74.0-92.0)	**0.006**
Diastolic blood pressure (mm Hg), Median (IQR)	74.0 (57.0-80.0)	50.0 (50.0-50.0)	**0.008**
Mean blood pressure (mm Hg), Median (IQR)	85.0 (70.0-96.0)	63.0 (57.0-70.0)	**0.004**
pH, Median (IQR)	7.08 (6.70-7.20)	6.79 (6.52-6.83)	**0.014**
HCO3 (mmol/L), Median (IQR)	7.30 (5.40-11.30)	5.70 (3.50-6.40)	0.061
pCO2 (mm Hg), Median (IQR)	32.0 (25.0-43.9)	39.6 (18.9-71.0)	0.288
Aspartate aminotransferase (U/L), Median (IQR)	63.0 (33.0-95.0)	330.0 (78.0-777.0)	**0.019**
Alanine aminotransferase (U/L), Median (IQR)	35.0 (25.0-66.0)	166.0 (27.0-307.0)	**0.048**
Gamma glutamyl transferase (U/L), Median (IQR)	82.0 (48.0-175.0)	69.0 (41.0-242.0)	0.886
Alkaline phosphatase (U/L), Median (IQR)	91.0 (73.0-129.0)	140.0 (114.0-200.0)	**0.006**
Lactate dehydrogenase (U/L), Median (IQR)	320.0 (257.0-370.0)	659.0 (318.0-937.0)	**0.014**
Hemodialysis time (hour), Median (IQR)	3.0 (3.0-5.0)	3.0 (0.0-6.0)	0.598
Visual impairments, n (%)	6 (26.1)	0 (0.0)	0.290
Nausea, n (%)	9 (39.1)	1 (14.3)	0.372
Throat Ache, n (%)	3 (13.0)	0 (0.0)	>0.999
Chest Pain, n (%)	3 (13.0)	0 (0.0)	>0.999
Confusion, n (%)	13 (56.5)	7 (100.0)	**0.033**
Bicarbonate treatment, n (%)	11 (47.8)	5 (71.4)	0.399

IQR: Interquartile range

Patients who did not admit to intensive care unit had statistically significantly high APACHE II scores (median= 7.0 with 6.0- IQR and median=31.0 with IQR=12.0-42.0); p=0.028; Table 3), and they also had lower DBP than intensive care unit patients (p=0.041; Table 3. Having confusion was another statistically significant difference between patients admitted and not-admitted to intensive care unit (p=0.038). All other clinical and laboratory findings were statistically similar (Table 3).

Table 3.

Comparison of clinical and laboratory features between patients not admitted and admitted to ICU.

	Not admitted to ICU (n=2)	Admitted to ICU (n=28)	*p*
Glasgow Coma Scale, Median (IQR)	15.0 (15.0-)	5.5 (3.0-15.0)	0.138
APACHE II score, Median (IQR)	7.0 (6.0-)	31.0 (12.0-42.0)	**0.028**
Blood Urea Nitrogen (mg/dL), Median (IQR)	13.5 (10.0-)	14.0 (8.3-22.0)	>0.999
Base deficit (mmol/L), Median (IQR)	-14.8 (-20.0-)	-23.5 (-31.0--16.5)	0.257
Creatinine (mg/dL), Median (IQR)	1.09 (0.81-)	1.24 (1.00-1.61)	0.556
Lactate (mmol/L), Median (IQR)	2.30 (1.71-)	4.11 (0.82-8.60)	0.556
Glucose (mg/dL), Median (IQR)	134.0 (103.0-)	152.5 (112.5-252.3)	0.607
Systolic blood pressure (mm Hg), Median (IQR)	128.0 (126.0-)	103.0 (81.0-117.5)	0.092
Diastolic blood pressure (mm Hg), Median (IQR)	85.0 (80.0)	60.0 (50.0-78.0)	**0.041**

Continuation of table 3.

	Not admitted to ICU (n=2)	Admitted to ICU (n=28)	*p*
Mean blood pressure (mm Hg), Median (IQR)	99.0 (95.0-)	74.0 (60.8-90.3)	0.092
pH, Median (IQR)	7.18 (7.08-)	6.90 (6.69-7.16)	0.225
HCO3 (mmol/L), Median (IQR)	11.95 (7.90-)	6.20 (5.03-8.70)	0.193
pCO2 (mm Hg), Median (IQR)	31.0 (27.0-)	32.8 (24.9-45.7)	0.837
Aspartate aminotransferase (U/L), Median (IQR)	27.0 (20.0-)	74.5 (36.5-170.5)	0.092
Alanine aminotransferase (U/L), Median (IQR)	54.0 (27.0-)	43.0 (25.5-118.0)	>0.999
Gamma glutamyl transferase (U/L), Median (IQR)	62.5 (40.0-)	78.5 (48.8-225.3)	0.460
Alkaline phosphatase (U/L), Median (IQR)	75.0 (60.0-)	110.5 (82.0-147.3)	0.193
Lactate dehydrogenase (U/L), Median (IQR)	236.5 (216.0-)	341.5 (281.8-532.8)	0.074
Hemodialysis time (hour), Median (IQR)	3.0 (0.0-)	3.0 (3.0-5.0)	>0.999
Visual impairments, n (%)	1 (50.0)	5 (17.9)	0.366
Nausea, n (%)	2 (100.0)	8 (28.6)	0.103
Throat Ache, n (%)	1 (50.0)	2 (7.1)	0.193
Chest Pain, n (%)	0 (0.0)	3 (10.7)	>0.999
Confusion, n (%)	0 (0.0)	20 (71.4)	**0.038**
Bicarbonate treatment, n (%)	0 (0.0)	16 (57.1)	0.209

ICU: Intensive care unit; IQR: Interquartile range.

Treatment Strategy

The aim of the treatment strategy of patients admitted to the hospital or brought to the hospital with methanol poisoning is to correct metabolic acidosis, to prevent toxic metabolite formation and to apply hemodialysis to remove the metabolites from the blood.

There are 3 treatment strategies applied in our hospital. These strategies are applied according to the severity of the poisoning and the symptoms of the patient.

1. Ethanol application: Ethanol competes with methanol, which uses the same enzyme (alcohol dehydrogenase) to metabolize. Ethyl alcohol prevents the formation of toxic metabolites by inhibiting alcohol dehydrogenase. Thus, the visual symptoms are improved.

2. Fomepizole application: It is a specific antidote. Its affinity for alcohol dehydrogenase is much higher. There are studies showing that it reduces the need for hemodialysis.

3. Hemodialysis is applied.

4. Folinic acid application: It is applied to increase formaldehyde metabolism. Folinic acid given to a patient will accelerate the conversion to carbon dioxide (CO_2) and water (H_2O).

5. (i)Patients with severe acidosis that formic acid is the primary toxic metabolite associated with anion gap metabolic acidosis and end-organ damage, and (ii)patients with renal damage until the patient was on dialysis, NAHCO3 was infused at a dose of 1 mEq per kg. Therefore, NaHCO3 was administered since the deep acidosis found in the blood to be able to correct.

Discussion

Methanol is volatile at room temperature and by itself it is harmless, but its metabolites, formic acid and formaldehyde, are extremely toxic. Metabolism of methanol, methyl ethers, esters and amides increase to formic acid. Poisoning with methyl alcohol may be the result of either accidental or intentional ingestion. Formic acid causes acidosis, and other clinical symptoms. Formic acid is a mitochondrial cytochrome oxidase inhibitor, a weaker inhibitor than cyanide and hydrosulphide anions. an inhibitor of the causing histotoxic hypoxia *(Brandis, 2021)*. It is important to define the poison according to the symptoms of poisoning and intervene immediately. For this reason, accurate and detailed anamnesis from the poisoned individual or, if the individual is not himself/herself, from the person who brought him/her to the emergency room. Poisonings occur widely in summer in Turkey, especially due to the inclusion of methyl alcohol as ethanol in alcoholic beverages. In Turkey, there is a regulation to prevent it. This regulation is state that Ethyl alcohol must be used in alcoholic drinks and methyl alcohol not be used in alcoholic beverages named Raki, a drink unique to Turkey *(Türk Gıda Kodeksi Distile Alkollü İçkiler Tebliği, 2005)* (Communiqué No: 2005/11. Ministry of Agriculture and Rural Affairs, Turkish Food Codex, Distilled Alcoholic Beverages Communiqué). Raki is very popular and is preferred more than other alcoholic beverages and adulteration with methyl alcohol is very common and causes serious poisoning *(Cabaroglu & Yilmaztekin, 2011)*. Identification of the cause of poisoning is essential for quick diagnosis and decide the right treatments and apply accurate strategy, thereby preventing death and improving the outcome. The aim of this study was to evaluate the clinical and laboratory factors in patients with methanol poisoning. Methanol is absorbed rapidly via the gastrointestinal tract and absorption time is very short, in less than 10 minutes. It is not protein-bound and is absorbed directly into body and volume of distribution is about 0.7 L/kg. Metabolism takes place mainly in the liver through serial oxidation via alcohol and aldehyde dehydrogenase, respectively. Lethal dose of methanol is about 30 to 240 mL or 1 g/kg. Permanent visual damage may occur with 30 ml orally (Jones, 2019).

Methanol poisoning is difficult to diagnose in some cases. Methanol poisoning should definitely be considered in every patient with nausea, vomiting, vision problems and unexplained high anion gap metabolic acidosis (attention should be paid to pH and HCO3 values). In our study, fatal patients had statistically significantly low pH levels than non-fatal patients and also had more base deficit and lactate levels than non-fatal patients (p=0.033). Decreased pH and HCO3 due to increased lactate production causes increased diffusion of formic acid across all cell membranes. This further increases lactate dehydrogenase and causes hypotension and central nervous system depression *(Barceloux et al., 2002)*.

In patients in whom methanol poisoning is not noticed, coma, blindness, gastrointestinal bleeding, severe impairment in renal functions and renal damage, hemorrhage in the basal ganglia and death are observed in the late period. Methanol causes histotoxic hypoxia with this inhibitory effect. Acidosis causes loss of lysosomal latency, facilitation of the entry of calcium ions into cells, and deranged production of ATP, dilatation of cerebral vessel *(Liesivuori & Savolainen, 1991)*. In the presenting study, we also observed some visual problems but not observed blindness. Short-term or long-term exposure to methanol may result in dizziness, headache, nausea blurred vision. No information is about carcinogenic and reproductive effects of methanol. Environmental Protection Agency (EPA) has not classified methanol with respect to carcinogenicity.

Gulen et al observed that there were 18 patients who had coma (GCS < 8) at the time of admission, 14 of whom died. They found that the relationship between coma and poor outcome was statistically significant (p < 0.001) (Gulen et al., 2020). In our study, median of GCS was 12 in non-fatal patients and 3 was in fatal patients.

In a conclusion, clinical and laboratory findings (low pH, nausea which is not a specific symptom of poisoning) and, confusion are distinguishing findings for the diagnosis of methyl alcohol poisoning in our study. Furthermore, confusion was the determining factor between whether or not to be admitted to the intensive care unit. Our treatment strategy was successful to save the poisoned patients (about 80% healed without sequel).

Conflict of interest statement

The authors declare that there is no conflict of interest.

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