Int J Clin Exp Med 2019;12(5):5938-5950
www.ijcem.com /ISSN:1940-5901/IJCEM0085245

Original Article

Clinical features, treatment, and prognosis of acute methanol poisoning: experiences in an outbreak

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Received September 8, 2018; Accepted February 12, 2019; Epub May 15, 2019; Published May 30, 2019

Abstract: Aims: The aim of this study was to examine the clinical features of acute methanol poisoning to better understand its pathophysiology. Methods: A retrospective study was performed in 52 patients with acute methanol poisoning. Patient characteristics and test results were collected and analyzed. Results: A total of 52 patients, ranging from 20-79 years of age, consumed between 5 and 500 mL of alcohol-based fuel, equivalent to 3.3-329.5 g of methanol. Of the 52 patients, 49 were discharged without sequelae, one patient experienced decreased visual acuity, and two patients died after comprehensive treatment. Central nervous system (CNS) disorders, visual disturbances, and gastrointestinal symptoms were found in 46 (88%), 20 (38%), and 34 (65%) patients upon admission, respectively. Univariate analysis showed that coma, dyspnea, pH, and anion gap (AG), along with calcium, potassium, creatinine, and blood sugar levels, were correlated with severity of methanol poisoning and associated with poor patient outcomes. Conclusion: Acute oral methanol poisoning can lead to nerve damage, metabolic acidosis, and gastrointestinal injuries. Most patients recovered after timely and effective comprehensive treatment.

Keywords: Methanol poisoning, methanol toxicity, clinical features, prognosis

Introduction

Methanol, also known as the wood alcohol or Columbian spirit, is a colorless liquid with a taste and smell similar to that of ethanol [1]. While methanol poisoning has been associated with ingestion, methanol exposure also occurs by inhalation and skin absorption. After being rapidly absorbed, methanol is oxidized, converted to formaldehyde by alcohol dehydrogenase, and subsequently metabolized into formic acid by aldehyde dehydrogenase in the liver [2]. It is a formic acid metabolite that is highly toxic to humans, as it functions as an inhibitor of mitochondrial cytochrome oxidase [3]. Formic acid is a weak inhibitor compared to cyanide, but it is strong enough to cause metabolic acidosis.

Incidence of methanol poisoning has been rising, worldwide, with a number of outbreaks occurring in the Czech Republic, Estonia, Iran, Kenya, Khartoum, Libya, Norway, and other countries [4-9]. From 2000-2012, there were more than 50 mass outbreaks of methanol poisoning, worldwide, resulting in approximately 5,000 acute cases of toxicity and more than 2,000 associated deaths [10]. Outbreaks often arise from the consumption of ethanol adulterated with methanol (i.e., methylated spirits) [11]. In addition, several recent examples of methanol poisoning have been linked to occupational exposure [12]. In rare cases, methanol may be used for attempted suicide. There have been several instances of accidental transdermal exposure [13-15]. In China, acute methanol poisoning most commonly results from the excessive consumption of liquor contaminated with methanol.

In addition to metabolic acidosis, methanol intoxication leads to central nervous system (CNS) depression, cardiovascular disease, visual disturbances, putamina hemorrhages, and even death. It has been reported that mortality rates for methanol poisoning range from 10 to 50% [6-9]. Previously, the rates of long-term visual sequelae and total sequelae (both vision and CNS) after methanol poisoning were 25-40% and 18-40%, respectively [7, 16]. When treatment is delayed or inadequate, the mortality rate increases to more than 40% and

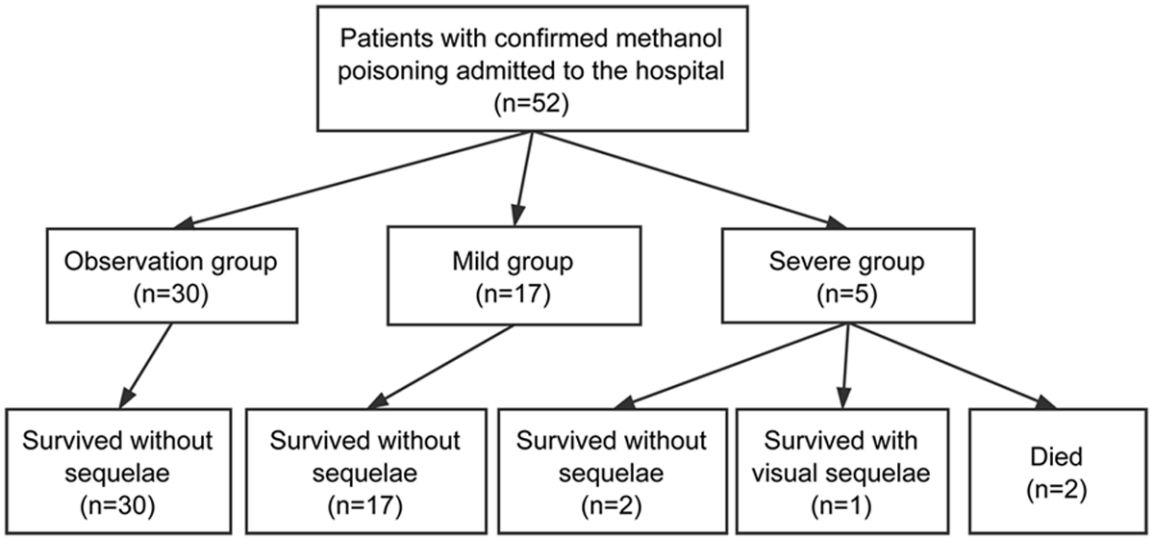

Figure 1. Classification and outcomes of patients with methanol poisoning.

many of these patients will experience serious long-term visual and CNS impairment [17-19]. Fomepizole, an alcohol dehydrogenase inhibitor, is an effective antidote for methanol poisoning. However, this medication is currently unavailable in China. The mortality rate is 3.3% for those patients effectively treated, suggesting there is still room for improvement concerning therapies available for methanol intoxication [20]. Currently, early diagnosis and rapid therapeutic intervention are essential steps for successfully treating methanol poisoning in patients. However, late onset of clinical symptoms often delays diagnosis. In addition, some hospitals located in rural areas do not have direct access to the equipment required for methanol testing. This can also delay diagnosis and effective treatment planning for some patients.

In the current study, clinical data were collected and summarized from 52 patients treated for methanol poisoning. The aim was to better understand the pathophysiology and provide a basis for clinical diagnosis and treatment. All patients suffered acute methanol poisoning resulting from the ingestion of alcohol-based fuel, which was mistakenly served as ethanol at a party on February 3-4, 2017.

Materials and methods

Patients

Patients with methanol poisoning were included in this study (**Figure 1**). All patients felt discomfort from having mistakenly consumed different quantities of alcohol-based fuel on the day of admission or up to two days prior to admission. Diagnostic and degree criteria were based on the National Occupational Health Standards of the People's Republic of China and related research [21]: (1) The observation group included the following: 1) A history of public poisoning; 2) Epidemiologic evidence of a history of drinking alcohol-based fuel containing a very high concentration of methanol after toxicological identification; and 3) Patients were asymptomatic or felt some discomfort, such as a headache, dizziness, decreased strength, blurred vision, nausea, vomiting, abdominal pain, and diarrhea, yet recovered in a short time; (2) Mild acute intoxication (mild group) included cases that complied with observation case diagnostic criteria, in addition to one of the following: 1) Mild disorder of consciousness; 2) Optic disc congestion or edema, retinal edema, or black spots in the visual field; and 3) Mild metabolic acidosis; (3) Severe acute intoxication cases (severe group) included one of the following symptoms: 1) Serious disorder of consciousness; 2) A sharp decline in visual acuity, optic atrophy, and blindness; and 3) Serious metabolic acidosis. Diagnoses were confirmed by three or more physicians.

Patients were then divided into three groups, in accordance with the severity of methanol poisoning: 30 cases of observation-only, 17 cases of mild acute intoxication patients, and 5 cases

of severe acute intoxication (**Figure 1**). Medical histories of the patients in this study included a history of previous surgeries (n = 10), hepatitis (n = 3), and lung disease (n = 2). One patient each had hypertension, coronary heart disease, cerebral infarction, or cataracts. The remaining 34 patients had no prior medical history to report.

Collection of patient data

Patient data, including demographics, general information, and test results, were collected via an electronic medical history system. Data included hematological and biochemical testing, vision testing, stereoscopic fundus examination, visual evoked potential (VEP) testing, electrocardiogram (ECG), computed tomography (CT) imaging, and abdominal ultrasound (US) imaging. Written informed consent was obtained from patients or families and patients did not experience increased pain or hospitalization costs due to the study. The remaining alcohol-based fuel was sent to the National Supervision and Inspection Center of Liquor and Processed Food Quality for analysis. In the fuel, the detected methanol concentration was 659 g/L.

Treatments

Treatment protocols were formulated via discussion by a multidisciplinary medical team, consisting of physicians from the Departments of Emergency Medicine, Hemopathology, Nephrology, Urology, Endocrinology, Gastroenterology, and Gerontology. There were six treatment options, including: (1) Folic acid to enhance the metabolism of formate; (2) Sodium bicarbonate for correction of metabolic acidosis; (3) Methylprednisolone for patients with fundus or optic nerve damage for 2-3 days, followed by maintenance therapy with prednisone and precautionary steps to prevent direct stimulation of the fundus and/or optic nerve (i.e., eye guards); 4) Panax notoginseng saponins for reduction of oxidative stress and carithamine as an anticoagulant, along with vitamins B1, B6, and decavitamin for nerve recovery; (5) Blood purification to eliminate methanol and methanol metabolites (in serious cases), which included continuous renal replacement treatment (CRRT), hemodialysis (HD) [22] and plasmapheresis (PE) [23], along with continued treatment for acidosis; (6) Symptomatic supportive treatment, including treatment to protect the organs, maintain electrolyte balance, and reduce risks of infection, along with consciousness-promoting drugs and others. Endotracheal intubation and mechanical ventilation were used in severe cases, as required, with enhanced monitoring and nursing. Other treatment options are available but they were not used in this study. For example, gastrolavage was not conducted in this study due to the length of time between the ingestion of methanol and hospital admission. Also, fomepizole and ethanol, which can inhibit the alcohol dehydrogenase (ADH) enzyme, were not administered to patients in this study, as they are not yet approved in China.

Statistical analysis

All statistical analyses were performed using SPSS Version 23.0 (IBM, Chicago, IL, USA). Data are expressed as median with a range and mean ± standard deviation (mean ± SD), as appropriate. For comparisons of quantitative data between groups, common statistical tests were employed, such as *t*-test, one-way analysis of variance (ANOVA), Kruskal-Wallis H-test, and Mann-Whitney U-test. Chi-squared test and Fisher's exact test were used for qualitative data. Correlation analyses between two variances were conducted using Spearman's rank correlation analysis. *P*-values less than 0.05 are considered statistically significant.

Results

Demographics and general patient information

Fifty-two patients with accidental methanol poisoning were included in the study. The mean age of all subjects was 47.67 ± 12.13 years of age (range: 20-79 years), as shown in **Table 1**. From the 52 recruited patients, 45 were male and seven were female. All females were classified into the observation group. The average alcohol-based fuel intake was 91.73 ± 81.24 mL (range: 5-500 mL), with 1 mL of fuel containing 0.659 g of methanol. There was a significant difference in the average alcohol-based fuel intake between the observation group and mild toxicity group ($P < 0.02$), along with the observation group and severe toxicity group ($P < 0.02$). Symptoms appeared in all patients within 12-24 hours after ingestion of the methanol. The amount of time between ingestion and appearance of symptoms was not signifi-

Table 1. Demographics and general characteristics of patients with acute methanol poisoning

Characteristics	Observation (n = 30)	Mild (n = 17)	Severe (n = 5)	Total (n = 52)	*p*
Age (mean ± SD)	49.20 ± 10.87	45.76 ± 14.23	45.00 ± 12.96	47.67 ± 12.13	NS
Gender					
Male	23 (76.7)	17 (100.0)	5 (100.0)	45 (86.5)	-
Female	7 (23.3)	0	0	7 (13.5)	
Drinking					
Daily	5 (16.7)	6 (35.3)	0	11 (21.2)	NS
Not or occasionally	25 (83.3)	11 (64.7)	5 (100.0)	41 (78.8)	
Smoking	14 (46.7)	7 (41.2)	2 (40.0)	23 (44.2)	NS
Intake (range)	5-150	15-200	100-500	5-500	< 0.02#,**
Latency (median; h)	12-24	12-24	12-24	12-24	NS
Time from intake to admission (d)	1.84 ± 0.78	1.55 ± 0.61	1.40 ± 0.37	1.70 ± 0.71	NS
Symptoms					
Dizzy	25 (83.3)	15 (88.2)	2 (40.0)	42 (80.8)	NS
Headache	5 (16.7)	4 (23.5)	1 (20.0)	10 (19.2)	NS
Weak	11 (36.7)	5 (29.4)	1 (20.0)	17 (32.7)	NS
Nausea	9 (30.0)	7 (41.2)	0	16 (30.8)	NS
Vomiting	3 (10.0)	4 (23.5)	2 (40.0)	9 (17.3)	NS
Abdominal pain	11 (36.7)	7 (41.2)	1 (20.0)	21 (40.4)	NS
Abdominal distension	10 (33.3)	3(17.6)	0	13 (25.0)	NS
Diarrhea	6 (20.0)	2 (11.8)	0	8 (15.4)	NS
Blurred vision	10 (33.3)	4 (23.5)	3 (60.0)	17 (32.7)	NS
Chest stuffiness	1 (3.3)	2 (11.8)	1 (20.0)	4 (7.7)	NS
Palpitation	6 (20.0)	2 (11.8)	3 (60.0)	11 (21.2)	NS
Dyspnea	1 (3.3)	1 (5.9)	3 (60.0)	5 (9.6)	0.006**
Disturbance of consciousness	0	3 (17.6)	4 (80.0)	7 (13.5)	< 0.001**

#Observation group vs Mild group; **Observation group VS Severe group; *Mild group VS Severe group.

cantly different between the groups. There were no significant differences in age, history of alcohol consumption, history of cigarette smoking, or the time from intake to hospital admission between the three groups.

CNS symptoms were most common in patients, followed by gastrointestinal (GI) symptoms and visual disturbances. These were observed in 46 (88%), 34 (65%), and 17 (32.7%) of patients, respectively. Among CNS symptoms, dizziness was seen in 42 (80.8%) patients, cephalalgia in 10 (19.2%) patients, and a disturbance of consciousness in 7 (13.5%) patients. Disturbance of consciousness was only observed in patients with mild or severe methanol poisoning. Somnolence was only noted in patients with mild methanol poisoning. More serious consciousness disorders were apparent in patients with severe methanol poisoning, including somnolence, confusion, stupor, delirium, and comas. GI symptoms, such as nausea, vomiting, abdominal pain, abdominal distension, and diarrhea, were found in 16 (30.8%), 9 (17.3%), 21 (40.4%), 13 (25.0%), and 8 (15.4%) patients, respectively. Other symptoms, including chest stuffiness, palpitations, dyspnea, and general weakness, were observed in 4 (7.7%), 11 (21.2%), 5 (9.6%), and 17 (32.7%) patients, respectively (**Table 1**). Incidence of dyspnea and disturbances of consciousness were significantly different between the observation group and severe methanol poisoning group ($P = 0.006$ and $P < 0.001$, respectively). However, incidence of other symptoms was not significantly different between the groups. There were several clinical manifestations of methanol poisoning that occurred at low frequencies, not listed in **Table 1**, including orbital and periorbital pain (n = 6), acanthesthesia of the throat (n = 3), numbness of limbs (n = 2), burning sensation of the face (n = 2), the feeling of stepping

on cotton (n = 1), photophobia and tearing (n = 1), ocular foreign-body sensation (n = 1), amaurosis (n = 1), hoarseness (n = 1), odynophagia (n = 1), and fevers (n = 1).

Interestingly, 31 of the 52 (59.62%) patients showed no distinctly positive clinical signs of methanol poisoning. Abdominal tenderness was confirmed in 13 patients, though only one patient experienced rebound tenderness. Three patients were found to have a flushed face during intake and two patients displayed pharyngeal hyperemia. Coma, cyanosis, rapid and shallow breathing, Kussmaul breathing, crackling in the lungs, arrhythmias, and weak pulse or pulselessness were found among individual patients with severe methanol poisoning.

Blood testing and evaluation parameters

Blood gas analysis was performed in 42 patients. There were 21 in the observation group, 16 in the mild toxicity group, and 5 in the severe toxicity group. Among the 21 patients in the observation group that received blood work, one patient had respiratory acidosis and another patient had respiratory alkalosis. Among the 16 patients with mild poisoning, 3 had increased AG metabolic acidosis, and 13 had normal AG metabolic acidosis. Increased AG metabolic acidosis was observed in four patients with severe poisoning, one of which also had respiratory acidosis. One patient with severe poisoning had normal AG metabolic acidosis. Furthermore, patients with severe poisoning had lower carbon dioxide combining power (CO_2CP), pH, bicarbonate, base excess levels, and higher AG levels than patients in the observation and mild poisoning groups, as illustrated in **Table 2**. There were no significant differences in $PaCO_2$ between the three groups. However, PaO_2 in the observation group was notably lower in mild and severe toxicity groups. In addition, sodium, potassium, and calcium levels were significantly different, while there was no difference in chloride levels among the three groups. After hospital admission, one patient had mild hyponatremia, four had hyperkalemia, and four had hypokalemia. It is worth noting that 10 patients became hypokalemic during treatment, with three of the 10 patients being hyperkalemic prior to admission. The other seven patients had normal potassium levels at admission.

Despite some differences in hemoglobin and platelet levels between the groups, there were no apparent abnormalities in any patients from the three groups. However, WBC and hematocrit levels were higher in severe cases of methanol poisoning, compared with observation and mild toxicity groups. Abnormal liver function, as indicated by increased transaminase without a change in bilirubin, was detected in varying degrees among the patients. Patients with severe poisoning had significantly elevated levels of creatinine, compared to patients from the observation and mild toxicity groups. Uric acid levels were increased in 20 patients and were remarkably different between the severe toxicity group and other groups (observation and mild toxicity). Urea levels were within the normal range in all patients and were not significantly different between any of the three groups. Patients with severe poisoning suffered from myocardial damage, evidenced by highly increased Troponin I levels and abnormal coagulation functioning, as indicated by the prolonged prothrombin time and decreased prothrombin activity. There was no difference in amylopsin between the three groups. In addition, random blood sugar levels were higher in the severe group, compared with the observation group. Routine feces examinations and fecal occult blood tests were performed in 31 of the patients. Of these, one patient had a positive fecal occult blood test. In addition, urine tests were conducted in 41 of the patients, Three patients were positive for urine occult blood and one patient was positive for urine protein.

Demographic and hematologic findings were compared between the survivors and patients that died. Incidence of dyspnea and coma was higher in patients that died, compared to those individuals that survived (P = 0.008 and P = 0.001, respectively), as shown in **Table 3**. Similarly, WBC count, ALT, AST, random blood sugar, creatinine, cystatin C, potassium, anion gap, PaO_2, troponin I, myoglobin, LDH, amylase, and PT levels were higher in patients that died, while levels of calcium, CO_2CP, pH, bicarbonate, base excess, and PTA were lower in patients that died when, compared with survivors. However, there was no difference in age, gender, amount of methanol intake, time between intake to hospital admission, drinking history, latency, hematocrit, uric acid, or $PaCO_2$ levels

Table 2. Laboratory findings from the 52 patients with methanol poisoning (range)

Parameters	Observation (n = 30)	Mild (n = 17)	Severe (n = 5)	*p*	*p* Obs. - Mild	*p* Obs. - Severe	*p* Mild - Severe
WBC (× 10^9/L)	4.67-13.99	5.14-11.51	8.03-20.28	< 0.01	NS	0.01	0.01
Hemoglobin (g/L)	120-164	128-176	134-195	0.01	NS	0.02	NS
Hematocrit (%)	34.8-47.6	38.3-51.6	43.7-61	< 0.01	NS	< 0.01	NS
Platelet (× 10^9/L)	157-358	92-288	216-402	< 0.01	0.03	0.03	< 0.01
ALT (U/L)	7.5-72.7	16.9-164.1	16.5-131.8	NS	NS	NS	NS
AST (U/L)	16.6-33.6	17.8-73.9	19.7-346.3	0.03	0.03	NS	NS
TBIL (μmol/L)	6.5-28.4	18.2-29.4	5.4-11.5	NS	NS	0.03	0.02
Urea (mmol/L)	3.06-6.86	3.06-6.77	2.86-8.23	NS	NS	NS	NS
Uric acid (μmol/L)	191.9-553.5	293.4-667.0	473.4-717.8	< 0.001	< 0.001	< 0.01	NS
Creatinine (μmol/L)	47.6-81.9	48.1-107.9	74.6-165.7	< 0.01	NS	< 0.01	0.04
Cystatin C (mg/L)	0.66-1.02	0.74-1.21	0.88-1.32	0.03	NS	0.02	NS
Blood sugar (mmol/L)	3.84-8.2	5.28-11.37 [3]	7.24-20.67	< 0.01	NS	< 0.01	NS
Sodium (mmol/L)	136.8-147.0	134.2-145.3	137.1-149.0	0.02	< 0.01	NS	NS
Potassium (mmol/L)	3.31-4.78	3.54-5.86	4.4-6.11	< 0.01	0.04	< 0.01	NS
Chloride (mmol/L)	103.0-116.3	104.5-118.9	101.0-115.0	NS	NS	NS	NS
Calcium (mmol/L)	1.96-2.43	2.06-2.37	1.07-2.19	0.01	NS	< 0.01	0.03
CO_2CP (mmol/L)	19.6-32.5	7.5-27.4	4.9-8.7	< 0.001	< 0.01	< 0.001	NS
AG (mmol/L)	3.4-13.6	6.1-22.2	15.3-41.6	< 0.001	< 0.01	< 0.001	NS
pH	7.32-7.62 [9]	7.21-7.43 [1]	6.69-7.26	< 0.001	< 0.001	< 0.001	NS
$PaCO_2$ (mmHg)	13.9-54.7 [9]	21.7-58.4 [1]	14.4-78.6	NS	NS	NS	NS
PaO_2 (mmHg)	59.5-136 [9]	53.1-153.2 [1]	111.7-198.0	< 0.001	NS	< 0.001	< 0.001
Bicarbonate (mmol/L)	14-31.9 [9]	8.7-30.7 [1]	2.6-7.0	< 0.001	0.03	< 0.001	NS
Excess Base (mmol/L)	-4.33-6.06 [10]	-16.7-3.78 [3]	-32.8-18.0	< 0.001	0.01	< 0.001	NS
PT (s)	10.1-14.8 [1]	9.6-14.7	12.8-18.4	< 0.001	NS	< 0.001	< 0.001
PTA (%)	80-119 [1]	82-130.1	54-100	< 0.001	NS	< 0.001	< 0.001
Troponin I (ng/ml)	0.001-0.015	0.001 [1]	0.001-0.213	NS	NS	NS	NS
LDH (U/L)	133.6-212.2 [19]	154.4-244.0 [8]	117.1-530.7 [2]	NS	NS	NS	NS
Amylase (U/L)	32.5-108.9 [7]	50.7-143.0 [2]	78.9-529.5	NS	NS	NS	NS

WBC: White blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; PT: prothrombin time; PTA: prothrombin activity; LDH: lactic dehydrogenase; The digits in square brackets means the number of cases not examined.

between patients that died and those that survived.

Ophthalmologic examination

Mydriasis occurred in three patients (D ≥ 4 mm) and sluggish or nonreactive pupils were detected in two patients with severe methanol poisoning (**Table 4**). Lens opacity was found in 13 patients (mean age 49.8 ± 2.4; range: 34-69) from the observation group, six patients (mean age 54.0 ± 5.0; range: 34-65) from the mild toxicity group, and two patients (mean age 45.0 ± 3.0; range: 42-48) from the severe toxicity group. Vitreous opacities were found in four patients (mean age 49.0 ± 7.3; range: 29-61) from the mild toxicity group and four patients (mean age 46.0 ± 4.1; range: 34-52) from the severe toxicity group. One patient was found to have optic disc hyperemia. There were no cases of retinal hyperemia or hemorrhages in the 29 patients that underwent fundus examinations. Of the 14 patients that underwent VEP testing, five had abnormalities in both eyes and one had abnormalities limited to the left eye.

Other adjunctive examinations

One patient had an abnormal ECG with ventricular fibrillation, accompanied by moderate ST-segment depression after cardiopulmonary resuscitation upon admission to the hospital. ECGs of the other patients were normal. Three patients underwent an abdominal ultrasound examination. Results showed no apparent liver, gallbladder, pancreas, kidney, or spleen abnormalities, with the exception of a left renal cal-

Table 3. Demographic and hematologic findings in the survivors and deceased patients

Evaluated factors	Survivors (n = 50)	Deceased (n = 2)	*p*
Age (years)	47.74 ± 11.82	46.0 ± 25.45	NS
Gender (male/female; n)	43/7	2/0	NS
Intake (mL)	88.50 ± 82.15	150.0 ± 70.71	NS
Time from intake to admission (d)	1.73 ± 0.72	1.17 ± 0.23	NS
Daily drinking (n)	11	0	NS
Symptoms (n)			
Dyspnea	3	2	0.008
Coma	0	2	0.001
Latency (median; h)	12-24	12-24	NS
WBC (× 10^9/L)	8.10 ± 2.70	18.02 ± 3.20	0.02
Hematocrit (%)	43.27 ± 4.13	52.35 ± 12.23	NS
ALT (U/L)	27.49 ± 23.24	91.3 ± 57.28	0.029
AST (U/L)	26.54 ± 10.09	192.35 ± 217.12	0.029
Blood sugar (mmol/L)	6.33 ± 1.64	15.68 ± 7.05	0.023
Uric acid (μmol/L)	395.71 ± 132.39	583.3 ± 112.57	NS
Creatinine (μmol/L)	67.14 ± 15.19	150.45 ± 21.57	0.017
Cystatin C (mg/L)	0.83 ± 0.11	1.21 ± 0.16	0.021
Sodium (mmol/L)	142.12 ± 2.82	143.05 ± 8.41	NS
Potassium (mmol/L)	4.31 ± 0.54	6.01 ± 0.14	0.017
Chloride (mmol/L)	110.24 ± 3.12	103.05 ± 2.90	0.002
Calcium (mmol/L)	2.23 ± 0.1	1.60 ± 0.74	0.032
CO_2CP (mmol/L)	22.22 ± 6.75	6.30 ± 1.98	0.02
AG (mmol/L)	9.66 ± 4.93	34.35 ± 10.25	0.017
pH	7.34 ± 0.11	6.72 ± 0.04	0.018
PaO_2 (mmHg)	95.17 ± 23.52	173.6 ± 34.5	< 0.001
$PaCO_2$ (mmHg)	39.86 ± 10.31	48.85 ± 42.07	NS
Bicarbonate (mmol/L)	21.64 ± 6.88	4.45 ± 2.62	0.02
Base excess (mmol/L)	-3.85 ± 7.44	-31.84 ± 1.32	0.018
Troponin I (ng/ml)	0.001 ± 0.002	0.11 ± 0.15	0.001
Myoglobin (ng/ml)	41.79 ± 16.92	219.02 ± 64.66	0.017
LDH (U/L)	1777.72 ± 29.0	388.85 ± 200.61	0.022
Amylase (U/L)	74.94 ± 23.98	318.25 ± 298.75	0.033
PT (s)	12.36 ± 1.55	17.2 ± 1.70	< 0.001
PTA (%)	100.29 ± 10.39	62.0 ± 11.31	< 0.001

culi in one patient. Cerebral CT imaging was performed in five patients. There were no abnormalities observed by CT imaging, except for a lacunar infarction of the left thalamus in one patient.

Correlation analysis

Correlation between characteristics and test results of patients with the magnitude of methanol poisoning was analyzed (**Table 5**). The amount of methanol ingested was positively correlated with severity of intoxication (r_s = 0.49, $P < 0.001$). In addition, there was a small correlation between gender and severity of poisoning (r_s = 0.33, $P = 0.017$). However, the degree of intoxication was not related to age, alcohol consumption, cigarette smoking, time between intake and hospital admission, or latency. Severity of poisoning was positively correlated with levels of hemoglobin, hematocrit, AST, creatinine, uric acid, potassium, AG, CK-MB, myoglobin, random blood sugar, and PT, and negatively correlated with pH, bicarbonate, base excess, CO_2CP, sodium, and PTA (**Table 5**).

Table 4. Ophthalmologic examination results of patients with acute methanol poisoning

Examination	Observation (n = 30)	Mild (n = 17)	Severe (n = 5)	Total (n = 52)	*p*
Mydriasis (D ≥ 4 mm)	0/30	0/17	3/5	3/52	-
Sluggish or Nonreactive pupil	0/30	0/17	2/5	2/52	-
Lens opacity	13/15	6/10	2/2	21/27	NS
Vitreous opacity	4/15	4/10	0/0	8/27	NS
Hyperemia of optic disc	0/17	1/9	0/3	1/29	-
Decreased visual acuity	0/15	0/12	1/3	1/30	-
Visual evoked potential (VEP)	0/5	4/7	2/2	6/14	-

The former data out of parentheses indicated as the cases of abnormality and the latter is representative the numbers of patients performed the examination. NS: not statistically significant.

However, there was no correlation between WBC count, platelet, $PaCO_2$, blood oxygen saturation, chloride, calcium, ALT, TBIL, LDH, urea, cystatin C, and Troponin I levels. In addition, there was no correlation between biomarkers of pancreatic injury and severity of methanol poisoning. Interestingly, pH was positively correlated with CO_2CP (r_s = 0.659, P < 0.001), bicarbonate (r_s = 0.623, P < 0.001), and excess base (r_s = 0.748, P < 0.001), as well as negatively correlated with anion gap (r_s = -0.605, P < 0.001) and potassium (r_s = -0.59, P < 0.001). In addition, pH was weakly correlated with the amount of intake (r_s = -0.31, P = 0.049). It was not correlated with $PaCO_2$. Furthermore, optic nerve damage was not correlated with amount of intake or the pH.

Outcomes

After treatment by a multidisciplinary team, 50 of the 52 patients in the study recovered and were discharged without sequelae. The two patients that did not recover were from the severe toxicity group. However, one of the patients with severe poisoning suffered from decreased visual acuity after discharge. Two patients with severe poisoning died in the hospital. The mortality rate in this study was 3.8%.

Discussion

Alcohol-based fuel is a new type of liquid fuel that is cleaner and more environment-friendly. These fuels are primarily composed of various alcohols, such as methanol, ethanol, and butanol. The outbreak of methanol poisoning examined in the current study was caused by a group of individuals mistaking the fuel for ethanol. The methanol concentration in this fuel was very high, at approximately 659 g/L. It has been reported that the minimum lethal dose of methanol in adults is 0.3-1 g/kg of body weight. Even smaller doses of methanol can harm adults. Studies have shown that 10 mL can cause blindness [24] and 15 mL can result in death [2]. In this study, the two deceased patients had ingested 100 and 200 mL of the alcohol-based fuel, equivalent to 65.9 g and 131.8 g of methanol, respectively. None of the patients in the current study suffered from acute blindness. Variability between patients in the lethal minimal dose and dosage that induces blinding may be attributed to individual variations in their susceptibility to methanol. In addition, the simultaneous ingestion of other substances, such as ethanol, could impact the way patients respond to varying dosages of methanol.

Methanol poisoning is extremely harmful to both patients and society. Compared with the 1.1% to 48% mortality rate reported in previous studies [5, 6, 25-28], the mortality rate in this outbreak of methanol poisoning was only 3.8%. In addition, only one patient had decreased visual acuity and no patients had CNS sequelae. These results are lower, in terms of the number of patients with visual acuity and CNS problems, than those reported in previous studies. This may be due to racial differences, the concomitant ingestion of ethanol, emergency measures actively taken by the government, and timely hospitalization and treatment of patients after outbreaks. As pointed out by an international working group, it may not be feasible to accurately compare the rates or severity of disease among countries, as there is a lack of consistency in the type of data collected from cases of methanol poisoning [29]. As found in previous studies, the average incubation period after oral ingestion of methanol is 12-24 hours, which may be prolonged if ethanol was ingested simultaneously [30, 31]. For this reason, most patients are not diagnosed

Table 5. Correlation between the clinical parameters and magnitude of methanol poisoning

Factors	r_s	*p*	Factors	r_s	*p*	Factors	r_s	*p*
Age (years)	-0.13	NS	pH	-0.81	< 0.001	ALT	0.19	NS
Gender	0.33	0.017	Bicarbonate	-0.7	< 0.001	AST	0.36	0.009
Drinking	0.07	NS	Base excess	-0.71	< 0.001	TBIL	-0.1	NS
Smoking	-0.06	NS	$PaCO_2$	-0.28	NS	LDH	0.1	NS
Intake	0.49	< 0.001	Oxygen Saturation	0.01	NS	Urea	0.09	NS
Time from intake to admission	-0.19	NS	CO_2CP	-0.68	< 0.001	Uric acid	0.69	< 0.001
Latency	-0.02	NS	AG	0.62	< 0.001	Creatinine	0.48	< 0.001
WBC	0.22	NS	Sodium	-0.5	< 0.001	Cystatin C	0.31	NS
Hemoglobin	0.39	0.004	Potassium	0.49	< 0.001	Troponin I	0.1	NS
Hematocrit	0.43	0.001	Chloride	0.12	NS	Amylase	0.19	NS
Platelet	-0.03	NS	Calcium	-0.23	NS	PT	0.35	0.012
Blood sugar	0.47	< 0.001	VEP	0.53	NS	PTA	-0.31	0.025

r_s: Spearman's rank correlation coefficient; NS: not statistically significant.

until more than 24 hours after consuming the poison.

Adverse effects most commonly associated with acute methanol poisoning include CNS damage, metabolic acidosis, and vision problems. In this study, methanol poisoning mostly manifested as dizziness, cephalalgia, and fatigue, though some patients suffered from numbness of limbs, disturbances of consciousness, and even death in two cases. The latter effects are closely related to the degree of CNS damage induced by methanol. Methanol toxicity results in the transient inhibition of the CNS and is highly toxic to nerves and blood vessels. This results in inebriation, similar to that of ethanol intoxication [2]. Furthermore, formic acid inhibits mitochondrial cytochrome C oxidase, resulting in the suppression of oxidative phosphorylation and destruction of oxygen utilization in neurocytes. This can lead to severe hypoxia and necrosis of brain cells [32]. Formic acid can also cause some secondary adverse effects, including edema, ischemia, hemorrhages, impairment of the blood-brain barrier, reactive oxidative damage, axonal demyelination, neuronal degeneration, and cell death [16]. In this study, both patients in comas upon admission or shortly after admission died. Incidence of comas was significantly different between survivors and deaths. Mortality rates among the comatose patients in previous studies ranged from 50-67%, demonstrating that comas are associated with a poor prognosis after methanol poisoning [6, 7, 33].

Most patients suffered from metabolic acidosis, as indicated by the lab results, but did not have obvious symptoms. Patients with severe acidemia presented with cephalalgia, chest congestion, palpitations, dyspnea, and disturbances in consciousness. In this study, 21 patients with acute methanol poisoning had metabolic acidosis and seven patients had an elevated anion gap. These are typical features of methanol poisoning. Nazir et al. stated that unexplained metabolic acidosis with an elevated anion gap and osmol gap is an important clue when diagnosing suspected methanol poisoning [34]. Moreover, it was found that the anion gap was negatively correlated with pH and that patients with severe poisoning had increased levels of lactic acid. The main reason for the increase in lactic acid is the accumulation of formic acid, which is the metabolite of methanol. Formic acid metabolizes slowly in the human body, with a half-life of about 20 hours. In addition, methanol inhibits some oxidase systems, such as cytochrome c oxidase, and formic acid affects the normal metabolism of tissue cells. This subsequently results in tissue hypoxia and the accumulation of lactic acid, further increasing the degree of acidemia.

In the current study, pH was lower and the anion gap was higher in patients that died than in patients that survived. Correlation analysis showed that the severity of methanol poisoning was inversely related to pH levels and positively related to the anion gap. This is in accord with results of previous studies, in which the pH of patients with visual and CNS sequelae was significantly lower, compared with patients that fully recovered. This was also found to be true for patients that died as a result of methanol poisoning. These studies also reported a cor-

relation between anion gap, levels of formic acid, and levels of lactic acid, finding that severe metabolic acidosis, with an increased anion gap, was an indicator of poor prognoses after methanol poisoning. Also, they suggested that pH may serve as an independent predictor of death in patients with methanol poisoning [8, 35]. Hovda et al. discovered that $PaCO_2$ decreased when pH decreased among the survivors, but the opposite was true for deceased patients. This suggests that higher $PaCO_2$ may reflect insufficient respiratory compensation and CNS respiration depression [6]. However, there was no difference in $PaCO_2$ levels between the patients that survived and patients that died in the current study. In contrast, PaO_2 was higher in patients that died than in those that survived. One explanation for this may be the oxygen therapy administered via mechanical ventilation or nasal catheter oxygen inhalation to patients after admission.

Electrolyte metabolic disorders, particularly those affecting potassium, occur in most patients with methanol poisoning. In this study, some patients suffered from hyperkalemia. Hyperkalemia may be caused by a compensatory mechanism used to restore the acid-base balance in cases like metabolic acidosis and hypokalemia. This may be attributed to the decreased intake and increased loss of nutrients caused by gastrointestinal problems caused by methanol poisoning, such as nausea and vomiting. Levels of blood calcium among patients with severe toxicity and deceased patients were lower than in individuals in the observation and mild toxicity groups, suggesting that calcium levels are significantly correlated with severity of poisoning. Although detailed mechanisms related to hypocalcemia remain to be elucidated, it is often seen in critically ill patients. It was previously shown that hypocalcemia (0.81-0.90 mmol/L) is positively associated with increased mortality in critically ill patients and that it is independently associated with persistent organ failure in patients with acute pancreatitis [36, 37].

Ophthalmologic symptoms observed in this study included blurred vision, decreased visual acuity, photophobia, tearing, dilated pupils, nonreactive pupils, hyperemia of the optic disc, and lens or vitreous opacity. Moreover, VEP was abnormal in 6 of the 14 (43%) patients. Formic acid or formate can inhibit oxidative phosphorylation of the retina and optic nerves, resulting in optic atrophy and toxic optic neuropathy. This involves both eyes, as was observed in this study. The optic nerve, retina, and basal ganglia are tissues most at risk from methanol poisoning [24]. Although the specific reasons for this are not yet fully understood, some research has suggested that damage to these tissues may be associated with their vulnerability to histotoxic hypoxia, possibly due to their relatively fast metabolic rates and high energy dependence. These are inhibited by formic acid [24, 38]. Eells et al. demonstrated that the accumulation of formic acid was much higher in the eyes than in the brain. This was attributed to the slower oxidation of formic acid in the eyes [39]. Furthermore, a series of clinical studies showed that patients with visual sequelae after methanol poisoning had a much lower pH than patients that had fully recovered. Results suggest a strong connection between the probability of long-term visual sequelae and the degree of acidemia, though this was not verified in the current study [6-8, 38-40]. However, early intervention is critical in correcting metabolic acidosis, eliminating toxicants via blood purification, nourishing and supporting the nerves, and promoting the circulation of blood for repair of nerve injuries.

High concentrations of methanol can directly stimulate mucosal membranes of the digestive and upper respiratory tracts, leading to gastrointestinal and respiratory problems. Gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea, were the most common in acute methanol poisoning, occurring in 65% of patients in this study. This is in agreement with previous studies that have suggested that these symptoms occur in 18-67% of cases [6, 7]. Cascallana et al. reported a case of a 67-year-old woman that committed suicide by ingesting 500 mL of absolute methanol [13]. The autopsy revealed complete detachment of the esophagus mucosa, brownish discoloration of the gastric mucosa, and approximately 200 mL of hemorrhagic liquid in the stomach. Histological findings showed diffuse hemorrhagic necrosis and intense acute inflammatory infiltration of the lamina propria [13].

In this study, some patients may have developed hemorrhages in gastrointestinal or urinary tracts, as evidenced by positive tests for

fecal and urine occult blood. Mostafazadeh et al. reported upper gastrointestinal bleeding and hematuria, after dialysis treatment, in one patient with methanol poisoning, suggesting that it could have been related to the use of anticoagulants for dialysis treatment [41]. High doses of heparin or low molecular weight heparin can facilitate bleeding in necrotic areas of the brain [42]. However, some studies have reported no remarkable connection between hemorrhagic brain lesions and the use of systemic anticoagulation during hemodialysis [22, 43, 44]. Thus, more studies are necessary to elucidate the mechanisms of methanol-mediated hemorrhages and the effects of anticoagulation on bleeding during dialysis. It should also be noted that pancreatic injury markers were significantly increased in the two patients that died during the current study, suggesting that methanol may have induced concurrent pancreatitis. A previous study reported that acute pancreatitis is a complication of methanol poisoning [42]. In addition, Hantson and Mahieu [45] reported that a 54-year-old woman developed acute necrotizing pancreatitis following acute methanol poisoning. They also retrospectively examined 11 cases of acute pancreatitis in 22 patients with methanol poisoning. They discovered an association between acute pancreatic injury and the magnitude of metabolic acidosis. However, it was not associated with alcohol abuse, suggesting that methanol likely causes pancreas injury.

As with pH and anion gap, blood parameters, such as creatinine and blood sugar, were also correlated with severity of symptoms and death in poisoned patients. Many studies have reported that hyperglycemia is a strong prognostic factor for death from methanol poisoning [8, 42, 46]. Similarly, blood sugar was higher in patients that died from methanol poisoning than survivors in the current study. Previously, Morteza et al. showed that an increased creatinine level was an independent risk factor for alcohol-related death [25]. In the current study, multivariate logistic regression did not show any independent risk factors of death among poisoned patients, possibly due to the small numbers of patients. Hence, the severity and prognosis of methanol poisoning should be evaluated comprehensively using a combination of symptoms, examinations, and blood tests. More clinical studies with larger sample sizes are necessary to assess prognostic, risk factors, and lethality of methanol poisoning.

Strengths and limitations

There were several limitations to the current study. First, this was a retrospective study that was not randomized. Hence, certain confounders were inevitable (recall bias could not be completely removed). Second, the relatively small sample size of the groups provided insufficient data confirming the relationship between the severity of methanol poisoning and certain laboratory and clinic parameters. In addition, the hospital was unable to collect all data for each patient upon admission. For instance, the two deceased patients did not receive ophthalmologic examinations. Furthermore, concentrations of other components in the alcohol-based fuels were not detected and blood levels of methanol, formic acid, and ethanol were not measured, due to a lack of available laboratory equipment. For this reason, poisoning from methanol could not be accurately distinguished from poisoning by other chemicals, such as ethanol or butanol. Despite these limitations, this study does summarize the clinic features of methanol poisoning. Consistent with previous studies, this study demonstrated associations between coma, dyspnea, pH, anion gap, blood sugar, and increased creatinine on admission with poor outcomes after methanol poisoning. In addition, the current study found that levels of calcium, potassium, amylase, and troponin I, as well as abnormal coagulation function, were related to methanol-induced death.

Conclusion

Acute oral methanol poisoning can lead to CNS damage, metabolic acidosis, visual disturbances, and gastrointestinal injuries. Association between dyspnea, coma, decreased pH, increased anion gap, and increased levels of potassium, creatinine, and blood sugar were correlated with poor patient outcomes after methanol poisoning. Most patients were discharged without sequelae after timely and effective treatment. Early and effective treatment of methanol poisoning is vitally important for patient survival.

Acknowledgements

This research received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure of conflict of interest

None.

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