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Patients Admitted To Our Center With Methanol Poisoning: Retrospective Analysis

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ABSTRACT

Methanol poisoning is caused by the production of toxic metabolites by the alcohol dehydrogenase enzyme;metabolic acidosis is a serious condition that can lead to life-threatening complications such as kidney failure, blindness, and death.In our study, it was aimed to examine the methanol poisoning cases admitted to the hospital terms of mortality and morbidity. Following the approval of the Ethics Committee(03/12/2019,Number: 1497),16 patients were retrospectively analyzed.The patients were divided into 2 groups as Group I(Survivor,n=11)and Group II(Nonsurvivor,n=5)and possible risk factors for mortality were examined.

No statistically significant difference was found in terms of mortality,age,gender,GCS at admission,HR,MAP,urea,creatinine, and GFR values($p>0.05$).In patients with nonsurvivor;In terms of pH values;A statistically significant increase was found at the12thhr compared to the 1sthr($p=0.046$).It was determined that the 1st hr PaCO2 were lower than Group I.($p=0.020$).No significant difference was found in terms of HCO3 values at 1.,3.,6.,12.,24. and 48.hr according to mortality($p>0.05$).In Group I;the increase in HCO3 values at the 12thhr compared to the 1st hr was found to be statistically significant($p=0.046$).The methanol level was measured in 6 patients(5-249mg/dl).Ophthalmological findings were detected in 62%of the patients.The blood sugar of Group II was 132.8mg/dl(95-210)and the Group I was 216mg/dl(70-395).Hemodialysis was performed in 56.3%of the cases from the time of diagnosis.The total mortality rate is31.2%.

On admission to the hospital due to methanol intoxication; here is no relationship between methanol blood level at admission and mortality but coma, GCS<7,seizures and metabolic acidosis(pH<6.9)are prognostic factors for fatal and permanent sequelae. Hemodialysis is considered the key element in the treatment of methanol intoxication..

Keywords: Fomepizole, hemodialysis, metabolic acidosis, Methanol poisoning

Introduction

Methanol is an organic solvent, obtained by fermentation of wood, mostly used in the industrial field. It is colorless and volatile. Methanol is not toxic, but its metabolites formaldehyde and formic acid are primarily responsible for the toxicity in methanol poisoning (1,2). Methanol poisoning (MP) is a serious condition that can lead to life-threatening complications such as metabolic acidosis, renal failure, blindness, and death due to the production of toxic metabolites after methyl alcohol intake. by the alcohol dehydrogenase enzyme (3).

Despite the improvement in treatment, the rates of morbidity and mortality are still high in MP because of difficulties in diagnosis and late admission to hospital (1). Therefore, MP is still one of the most common causes of death due to poisoning. In this study, we aimed to evaluate the clinical features, laboratory findings, treatment protocols, and prognosis in terms of mortality and morbidity of patients who admitted to the hospital because of methanol poisoning.

Material and Methods

The study was approved by the Ethics Committee of University of Health Sciences, Prof Dr Cemil Tascioglu City Hospital Hospital (03/12/2019, Number:1497).

Patients who were admitted to the emergency department of our hospital due to methanol poisoning between January 1, 2017 and December 1, 2019 and were admitted to the intensive care unit were analyzed retrospectively.

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Exclusion Criteria: Children under 18 years of age.

Patients who were taken to the intensive care unit due to intoxication other than methanol poisoning

Inclusion Criteria: Adult patients over 18 years of age

Patients admitted to the intensive care unit due to methanol poisoning

16 patients aged 22-58 were included in the study and retrospectively analyzed. The patients were divided into 2 groups as Group I (Survivor n=11) and Group II (Nonsurvivor n=5) and possible risk factors for mortality were examined.

Age, gender, Glasgow Coma Score (GCS), heart rate (HR), mean arterial pressure (MAP), urea, creatinine, glomerular filtration rate (GFR), pH, PaO_2, $PaCO_2$, SO_2, HCO_3, bicarbonate excess (Base) deficit; BE), the mean blood glucose value, lactate, K+ values were recorded at 1st hour, 3rd hour, 6th hour, 24th and 48th hours and compared with the 1st hour of arrival.

Fomepizole use as an antidote, vasopressor use, Continuous Renal Replacement Therapy (CRRT) time, blood ethanol level, vision-related symptoms, ICU stay were recorded, and the groups were compared in terms of mortality and morbidity.

Statistical Analysis: R version 2.15.3 program (R Core Team, 2013) was used for statistical analysis. Study data were reported as the minimum value, maximum value, median, mean, standard deviation, frequency, and percentage. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. Mann–Whitney U test was used for the comparison of non-normally distributed quantitative variables between the two groups. Wilcoxon signed- rank test was used for intragroup comparison of normally distributed quantitative variables between more than two groups and intergroup comparison of non-normally distributed variables. Fisher's exact test was used for the comparison of qualitative data. Statistical significance was set at $p<0.05$.

Results

A total number of 16 patients were included in the study. Patients were divided into two groups as Group I (survivor n=11) and Group II (nonsurvivor n=5). No statistically significant difference was found between the rate of mortality in two groups according to age, gender, Glasgow Coma Score (GCS), heart rate (HR), mean arterial pressure (MAP), urea, creatinine, glomerular filtration rate (GFR) values ($p>0.05$) (Table 1).

The changes in pH values at the third, sixth, 24th and 48th hours when compared with first hour were not statistically significant in discharged patients ($p>0.05$). However, the increase in pH value at 12th hour was found to be statistically significant when compared with the value at 1st hour ($p=0.046$). In exitus patients, the changes in values observed at the third, sixth, 12th, 24th and 48th hours compared to the first hour were not statistically significant ($p>0.05$) (Table 2).

No significant difference was found in the rate of mortality according to $PaCO_2$ values at the third, sixth, 12th, 24th and 48th hours ($p>0.05$). It was determined that the first hour values of the exitus patients were lower than the discharged patients ($p=0.020$) (Table 3). No significant difference was found for mortality according to HCO_3 values at the third, sixth, 12th, 24th and 48th hours ($p>0.05$). It was determined in discharged patients that the change (increase), which was observed at the 12th hour was statistically significant when compared with the first hour ($p=0.046$). In exitus patients, the changes in values observed at the third, sixth, 12th, 24th and 48th hours were not statistically significant when compared to the first hour ($p>0.05$) (Table 4).

No significant difference was found for the rate of mortality according to bicarbonate excess (Base deficit; BE) at third, sixth, 12th, 24th and 48th hours ($p>0.05$). It was determined in discharged patients that bicarbonate excess at the 12th hour was statistically significant compared with the first hour ($p=0.027$). In exitus patients, the changes in values observed at the third, sixth, 12th, 24th and 48th hours were not statistically significant when compared to the first hour ($p>0.05$) (Table 5.).

No significant difference was found for the rate of mortality according to the PaO_2 lactate, SO_2 lactate, K^+ values at third, sixth, 12th, 24th and 48th hours ($p>0.05$).

As an antidote, fomepizole was used in 13 patients and ethanol was used in 2 patients. Vasopressor was used in 3 patients who were severely hypotensive and bradycardic with GCS of 3 at the time of admission and these patients died. The level of ethanol was measured in 6 patients (5–249). Two of these patients were the previous two patients who had GCS of 3 and died. Ethanol value was 121 and 5 in these two patients, respectively. Vision-related symptoms were seen in 8 patients (50%) and 2 of these patients died. The mean blood glucose value was found to be

Table 1: Demographic and Laboratory Data of Patients

	Group I (n=11)	Group II (n=5)	Total (n=17)	p
	n (%)	n (%)	n (%)	
Gender				[a]0.999
Female	1 (9.1)	1 (20)	2 (12.5)	
Male	10 (90.9)	4 (80)	14 (87.5)	
CRRT				[a]0.999
(-)	5 (45.5)	2 (40)	7 (43.8)	
(+)	6 (54.5)	3 (60)	9 (56.3)	
	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	[b]p
Age	37 (22, 56)	56 (47, 58)	44 (27.5, 57)	0.112
GCS	15 (13, 15)	3 (3, 15)	14.5 (7.5, 15)	0.222
Heart Rate	80 (75, 98)	66 (60, 70)	79 (68, 97.5)	0.061
MAP	83.3 (78, 88.6)	55 (53.3, 93.3)	82.15 (65.8, 88.8)	0.610
Urea	25 (15, 27)	25 (19, 36)	25 (16.5, 29)	0.426
Creatinine	0.9 (0.74, 1.13)	1.02 (0.81, 1.39)	0.94 (0.76, 1.14)	0.496
GFR	80 (69.02, 90)	82 (57.35, 86.7)	81 (66.01, 90)	0.460
CRRT Time	12 (12, 12)	12 (12, 26)	12 (12, 12)	0.480
ICU Stay	72 (48, 120)	48 (48, 72)	72 (48, 108)	0.566

[a]Fisher's exact test [b]Mann-Whitney U test CRRT: Continuous Renal Replacement Therapy, MAP: Mean Arterial Pressure, GCS: Glasgow Coma Score, GFR: Glomerular Filtration Rate

Table 2: Comparison of pH Values According To Mortality

pH	Group I (n=11)		Group II (n=5)		[b]p
	Median (Q1, Q3)		Median (Q1, Q3)		
1st hr	7.26 (6.73, 7.35)		7.17 (7.12, 7.25)		0.668
3rd hr	7.22 (6.76, 7.26)		7.14 (7.14, 7.14)		0.614
6th hr	7.01 (6.73, 7.28)		7.37 (7.33, 7.41)		0.064
12th hr	7.3 (6.9, 7.38)		7.22 (7.11, 7.41)		0.897
24th hr	-		7.39 (7.39, 7.39)		-
48th hr	7.4 (7.2, 7.49)		7.34 (7.24, 7.44)		0.999
	Median (Q1, Q3)	[c]p	Median (Q1, Q3)	[c]p	
3rd -1st hr	0.03 (-0.02, 0.04)	0.492	-0.11 (-0.11, -0.11)	-	0.137
6th -1st hr	0.07 (0.04, 0.08)	0.102	0.06 (-0.05, 0.16)	0.655	0.999
12th -1st hr	0.11 (0.09, 0.16)	0.046*	-0.01 (-0.16, 0.24)	0.999	0.439
24th -1st hr	-	-	0.22 (0.22, 0.22)	-	-
48th -1st hr	0.44 (0.3, 0.57)	0.180	0.03 (-0.14, 0.19)	0.655	0.121

[b]Mann-Whitney U test, [c]Wilcoxon signed-ranks test, *p<0.05

216mg/dl (70–395) in Group I patients and 132.8mg/dl (95–210) in Group II patients.

Discussion

Methanol poisoning often occurs in epidemics and affects low-income populations (4). Information on this subject is limited and mainly provided through retrospective clinical studies (5). It can be seen in the form of many cases and even epidemics. Most are undiagnosed and result in unnecessary deaths of patients (4). The most comprehensive data on epidemiology, treatment and outcomes are reported as a retrospective study of three major MP outbreaks from Libya and Kenya. While more than 1,000 patients have been poisoned in Libya, with a reported mortality rate of 10%, two outbreaks resulted approximately 341 and 126 patients with mortality rates of 29% and 21% respectively in Kenya. There was no significant effect on the outcome due to late admission of cases to the hospital, but trainings

Table 3: Comparison of $PaCO_2$ Values According To Mortality

PaCO2	Group I (n=11)		Group II (n=5)		bp
	Median (Q1, Q3)		Median (Q1, Q3)		
1st hr	42.5 (41, 51)		21 (12, 25.4)		0.020*
3rd hr	42.5 (34, 51)		25 (25, 25)		0.206
6th hr	36 (26.4, 44)		44.5 (34, 55)		0.439
12th hr	36 (28.2, 47)		23 (15.7, 40.7)		0.300
24th hr	36 (22, 51)		41.9 (41.9, 41.9)		0.655
48th hr	40 (36, 51)		37 (28, 46)		0.564
	Median (Q1, Q3)	cp	Median (Q1, Q3)	cp	
3rd -1st hr	0 (0, 1)	0.109	4 (4, 4)	-	0.238
6th -1st hr	-3 (-6, 2)	0.279	13.2 (-7.6, 34)	0.655	0.699
12th -1st hr	0.5 (-6, 7)	0.917	3.7 (-18.6, 15.3)	0.999	0.796
24th -1st hr	8 (-6, 8)	0.276	16.5 (16.5, 16.5)	-	0.157
48th -1st hr	10 (-2, 22)	0.655	5.7 (-13.6, 25)	0.655	0.999

[b]Mann-Whitney U test, [c]Wilcoxon signed-ranks test, *p<0.05

Table 4: Comparison of HCO_3 Values According To Mortality

HCO_3	Group I (n=11)		Group II (n=5)		[b]p
	Median (Q1, Q3)		Median (Q1, Q3)		
1st hr	7.75 (4.7, 22)		8.9 (6.9, 9)		0.903
3rd hr	8.7 (5.4, 15)		10 (10, 10)		0.999
6th hr	5.5 (3.75, 14.5)		25 (24, 26)		0.064
12th hr	15.95 (7.9, 25)		15.2 (4.8, 25.6)		0.999
24th hr	13 (7.5, 24)		25.5 (25.5, 25.5)		0.180
48th hr	23 (15, 30)		22.1 (13, 31.2)		0.999
	Median (Q1, Q3)	[c]p	Median (Q1, Q3)	[c]p	
3rd -1st hr	0.4 (0.4, 0.9)	0.498	1 (1, 1)	-	0.228
6th -1st hr	-0.05 (-0.3, 1)	0.999	8.5 (0, 17)	0.317	0.240
12th -1st hr	4.45 (3.8, 5)	0.046*	8.9 (1.1, 16.7)	0.180	0.737
24th -1st hr	2.5 (1, 8.9)	0.109	16.6 (16.6, 16.6)	-	0.180
48th -1st hr	14.45 (10.9, 18)	0.180	5.6 (-11, 22.2)	0.655	0.999

[b]Mann-Whitney U test, [c]Wilcoxon signed-ranks test, *p<0.05

were conducted to increase the awareness and knowledge of MP. Basic treatment protocols, diagnostic tools, and early support were determined as the most important components that will affect the consequences of MP outbreaks (4).

The most comprehensive data on treatment and outcomes were given from 121 cases with methanol poisoning from the Czech Republic in 2012. In this study, 20 patients died outside the hospital and 101 were hospitalized. Among the hospitalized patients, 20 patients died (the total and hospital mortality rates were 34% and 21%, respectively). Among these patients, 59% were survived with visual sequelae and 20% were survived with visual/CNS sequelae (6). Hemodialysis is considered as the key factor in the treatment of MP. However, no difference in the rate of mortality was found in the treatment of these patients with continuous hemodialysis and intermittent hemodialysis, and with folate, fomepizole and ethanol. Although treatment consists of correction of acidemia, use of antidotes, and hemodialysis, the severity of metabolic acidosis, state of consciousness, and serum ethanol level at admission were accepted as mortality-related parameters (3,6). Hemodialysis was performed in 54.5% of surviving patients in our study and it was found that the increase in pH value at the 12th hour compared with the basal value was not observed in patients who died. However, hemodialysis was performed in 60% of

Table 5: Comparison of Bicarbonate Excess (BE) Values According To Mortality

BE	Group I (n=11)		Group II (n=5)		[b]p
	Median (Q1, Q3)		Median (Q1, Q3)		
1st hr	-15 (-28.2, -1)		-24.4 (-29.2, -17.89)		0.405
3rd hr	-16 (-27.6, -4)		-20 (-20, -20)		0.999
6th hr	-23.4 (-29.4, -10.5)		2.7 (2.7, 2.7)		0.157
12th hr	-9 (-24, 2)		-18 (-23.2, 1.5)		0.796
24th hr	-14 (-19, 1.3)		1 (1, 1)		0.655
48th hr	-1 (-12, 6.8)		-4.45 (-16, 7.1)		0.999
	Median (Q1, Q3)	[c]p	Median (Q1, Q3)	[c]p	
3rd -1st hr	1 (0.6, 2)	0.176	-	-	-
6th -1st hr	0.7 (-0.3, 2.5)	0.357	-	-	-
12th -1st hr	6 (4.4, 8)	0.027*	10.3 (1.2, 19.39)	0.180	0.737
24th -1st hr	4 (2.3, 18)	0.109	18.89 (18.89, 18.89)	-	0.180
48th -1st hr	21 (20, 22)	0.180	-	-	-

[b]Mann-Whitney U test, [c]Wilcoxon signed-ranks test, *p<0.05

Group II patients. Among this group of patients, 2 patients (40%) were those who presented with a GCS of 3 at the time of admission. The severity of metabolic acidosis and GCS are the main factors that determine the responsiveness to the treatment and mortality.

The rate of mortality is quite high in MP. Although fomepizole is the recommended first-line antidote for MP, ethanol has traditionally been used for this purpose. Fomepizole has 500-1,000 times greater affinity for alcohol dehydrogenase than ethanol and it has been shown to reduce and reverse visual impairment despite of its potential effect of inhibiting retinol dehydrogenase, which is an essential enzyme for vision after MP (7). As an antidote, fomepizole was used in 13 patients and ethanol was used in 2 patients in our study.

Serious sequelae can be observed in recovered patients; however, their diagnosis is difficult, and they are one of the most common conditions for late admission to the hospital. In an outbreak of MP in Norway, 51 patients applied to the hospital and 9 patients died because of late admission and severe symptoms. Among these patients, 24% were comatose on admission. Despite applying fomepizole treatment (71%) and hemodialysis (%73), 67% of patients died. A trend to lower pCO_2 by respiratory compensation for falling pH among surviving patients was associated with survival. However, the opposite trend is valid for death, and the difference was statistically significant with linear regression analyzes (P<0.001) (5).

In a retrospective case series study of Gulen et al. (8), involving 67 patients over 3 years, the rate of mortality was 26.9% and only 20.9% of these patients were recovered without sequela. Patients (12/25), who applied to the poison center of Iran Loghman-Hakim hospital between 1999 and 2000 with the complaint of methanol poisoning, died. (The rate of mortality 48%). While 23% of survivors developed blindness, only 10 patients fully recovered without any complications. The mean pH value in arterial blood gas of exitus patients and living patients was 6.82± 0.03 and 7.15 ± 0.06, respectively ($P < 0.001$). The mean duration between poisoning and admission to the emergency department was 46 ± 15.7 hours in dead patients, 16.7 ± 6.7 hours in survivors with sequelae and 10.3 ± 7.2 hours in survivors without sequelae ($P < 0.002$) (9). In our study, mean blood pH value at admission was 7.26 (6.73, 7.35) for discharged patients and 7.17 (7.12, 7.25) for dead patients. It was also observed in our study that the mean PaCo2 values at admission were 42.5 (41,51) and 21 (12, 25.4) for living and dead patients, respectively. This shows that the dead patients try to reduce pCO2 by respiratory compensation for severe metabolic acidosis a result of delay in admission to the hospital. Metabolic acidosis (pH < 7.07, AG > 26.7), low Glasgow Coma Score and increased lactate (lactate > 2.55 mmol/L) levels are related to poor outcomes. It was found that the folate administration is effective on mortality but not on vision. Metabolic acidosis, confusion, and visual disturbances should alert the clinician about MP (8). In our patients, the results were

very similar; The mean GCS of Group I patients was 15 (13, 15), and 3 (3, 15) in Group II.

Similar results were found with all countries of the world in a methanol toxicity study in Pakistan (n=35). Initial findings of patients include male gender, young age, low GCS, severe metabolic acidosis (arterial pH 6.8±0.5), visual field defect, complete blindness (28%). Although 15 (42.8%) patients received dialysis, only 5 (33.3%) of them survived (10). In our study, 3 of 5 dead patients received hemodialysis, 2 patients applied with GCS 3 and there was no time left for hemodialysis. Hemodialysis should be planned as soon as possible, but more importantly, the patient's response to treatment at the time of admission should be evaluated.

In conclusion; there is no relation between blood level of methanol and mortality in patients who were admitted to the hospital because of MP. However, coma, GCS<7, seizures, and metabolic acidosis (pH<6.9) are prognostic factors for fatal and permanent sequelae. Hemodialysis is considered as a key factor in the treatment of methanol poisoning.

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