Useful Electrocardiographic and Laboratory Findings in Shiraz Outbreak of 356 Methanol Poisoned Patients

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Abstract

Background: Binge alcohol eating especially in underdeveloped countries may be complicated by methanol toxicity, especially when blinded drunken cases come to emergency department. Unfortunately, in early months of 2020, Fars, one of the largest provinces in southern Iran, reported one of the largest methanol poisoning outbreaks with high case-fatality rate. Here we like to share our experience and introduce some simple measures which may announce more urgent dialysis to save the lives of these patients.

Method: In this study, 356 cases with methanol toxicity referred to the Tertiary Hospitals (Faghihi and Namazi) affiliated to Shiraz University of Medical Sciences during March and April, 2020. To collect the required data, clinical findings on blindness and impaired level of consciousness, laboratory data such as arterial blood gas, electrolytes, and creatinine, and the most common findings from ECGs were collected.

Results: Among the participants, 321 (90.2%) patients were male, and 162 persons (45.5%) were aged below 30 years old. Reviewing the laboratory data of the included patients revealed that PH, HCO3, and O2 saturation decreased. While PCO2, Cr, K, BS increased ($P<0.05$). In the multiple analysis, when the intervening factors of age and gender were adjusted and all ECG items were included in the model, T slope>=70, Brugada pattern, low voltage QRS, severe metabolic acidosis (PH<7.2) and lack of hyperventilation when severely acidotic showed independent relationship with mortality with the odds ratios of 3.42, 5.65, 6.70, 4.55 and 5.74 respectively.

Conclusion: Apart from usual modalities like acidosis, electrolyte imbalance, QTc prolongation and prominent U wave, we found Brugada like ECG, notch in QRS and steeply terminal T wave more than 70 degrees to be ominous signs and need urgent attention.

Introduction

Methanol, also known as wood alcohol, is a commonly-used organic solvent. Following the ingestion process, methanol is broken down by the body into formaldehyde, formic acid, and formate [1]. These highly-toxic products can cause metabolic acidosis, neurologic sequelae, and even death [2, 3]. The early symptoms of the toxicity may include a decreased level of consciousness, poor or lack of coordination, vomiting, abdominal pain, and a noticeable breath odor. Decreased vision may emerge as early as twelve hours after exposure and long-term sequelae may include blindness and kidney failure. Toxicity and death may occur even after drinking a small amount of a concerned material [2, 4].

In most cases, methanol poisoning occurs accidentally after drinking windshield washer fluid; however, in some rare cases, it can also occurs as a result of intentional ingestion in a suicide attempt [5]. In addition, outbreaks, defined as the presentation of at least three cases within 72 hours, have increasingly occurred in the recent years and were mostly due to contamination by drinking alcohols when methanol is used to adulterate moonshine (bootleg liquor) [6]. These outbreaks are more common in many parts of the developing world, especially among the members of lower socioeconomic classes [5].

Early treatment, consisting of stabilization and administration of the antidote improves the outcome of patients with methanol poisoning [7]. Although the preferred antidote is fomepizole, ethanol can be used alternatively if the former is not available [2, 8]. Hemodialysis may also be used in those cases where there is an organ damage or a high degree of acidosis. Other treatments may include sodium bicarbonate, folate, and thiamine [5].

There are severe restrictions on the production and preparation of alcohol in Iran since alcohol consumption is prohibited in Islam. Accordingly, bootleg alcohol is available on the black market through smuggling and illegal domestic production (under non-standard conditions) [9, 10]. Shortly after the Coronavirus pandemic, following the misinfodemics about the beneficial effects of alcohol in preventing and treating this viral infection, Iran experienced one of the largest methanol poisoning outbreaks [11]. According to the Iran's Health Ministry Spokesman and Iran Legal Medicine (LMO), the startling stats of more than 3,100 methanol toxicity cases and 728 deaths were reported across the country, leading to the syndemics of methanol poisoning and COVID-19 pandemic [12].

There is a literature gap in literature on methanol poisoning is the rarity of such outbreaks and the small number of the reported cases. In addition, very little is known about the electrographic findings as risk factors leading to mortality in methanol poisoning patients [13–16]. Furthermore, there are even more limited published studies (Jaff et al. [17] and Sanaei-zadeh et al. [18]) about the electrocardiographic manifestations in patients with methanol poisoning; On the other hand, it has not been established yet whether or not the electrocardiographic findings can predict mortality [18]. A recent study on one of the largest outbreaks of methanol poisoning by authors of this paper described the most common ECG findings among patients with methanol toxicity and analyzed their association with the severity of intoxication [19]. Subsequently, current study aimed to re-examine the possible prognostic factors associated with the mortality risk and more precisely to investigate the ECG findings associated with mortality in methanol toxicity.

Materials And Methods

A retrospective cross-sectional study was conducted on 356 patients presenting with methanol toxicity. These patients were hospitalized in tertiary-care hospitals (Namazi and Faghihi Hospitals) affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. Demographic characteristics, history, physical examination findings, and laboratory data were collected from the existing methanol toxicity data bank of Shiraz University of Medical Sciences during March and April 2020. The data included the chronicity of alcohol consumption, the use of other substances, cardiac and non-cardiac comorbidities, blindness, altered level of consciousness, and death. The laboratory investigations were arterial blood gas measurements (PH, Bicarbonate (meq/l), Partial Pressure of Carbon Dioxide (torr) and Oxygen saturation (%)), renal function tests, electrolytes, and blood sugar. Severe acidosis is defined as PH less than 7.2 [19]. Dedicating from Winter’s formula ($PaCO2 = 1.5 \times [HCO3] + 8 \pm 2$), marked mixed metabolic and respiratory acidosis was marked as lack of hyperventilation in our patients [23]. Therefore, lack of hyperventilation group in this study was selected by with $PaCO2 > 1.5 \times [HCO3] + 10$.

The ECG data were obtained using Cardiax PC ECG application by a cardiologist. These ECGs were reviewed and reported independently by two cardiologists. The patients should have met the following inclusion criteria in this study: all the patients who used the known alcoholic beverage with proved methanol impurity and developed attributable clinical findings. Exclusion criteria were previous myocardial infarction, supra-ventricular or ventricular arrhythmias, CABG, any known genetic cardiac disease such as Brugada, long QT syndrome, and short QT syndrome. The definition of ECG parameters, renal failure, and myocardial infarction were described in our pervious study [19]. Finally, we calculated an angle, which will be named as T slope in this article, in the following way. First, we drew the symmetry line for T wave in all pericardial leads. This divides T wave in two parts, left and right side. Then, tangent line for the right side of T wave was drew. These two lines made an angle. The complementary angle of this angle was named as T slope. All methods were carried out in accordance with relevant guidelines and regulations

This study was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.059).

Data analysis

Statistical Package for the Social Sciences Version 21.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the collected data. Frequency (%) was used for categorical variable such as sex, alcohol dependency, comorbidity and ECG findings. Moreover, mean ± standard deviation was used for age and laboratory findings. Independent sample t-test was used to compare the laboratory findings and death between two samples. Chi-square test was used to assess the relationships between mortality and ECG variables, past medical history, alcohol and opium abuse, demographic features, and complications during hospitalization in methanol toxicity patients. Furthermore, odds ratio (OR) and corresponding confidence interval (95% CI) was calculated fitting a univariate logistic regression. Multiple logistic regression was performed to determine the independent relationship between death and ECG variables adjusted for sex and age. $P < 0.05$ was considered to be statistically significant.

Results

Most of patients were male (89.9%) and less than 30 years old (45.5%). More than half of the patients used alcohol infrequently or for the first time. The concurrent use of others substances was observed in 9.5% of the participants, with opium as the most common concurrently used substance. Past history of cardiac disease was observed in 23 patients (6.6%) and 18 patients reported a history of non-cardiac underlying diseases (5.2%). A total of 59 (16.6%) patients passed away. Moreover, hospital course was complicated by visual impairment in 251 (70.5%) cases and compromised renal function in 137 (38.5%) patients.

Univariate analysis

In the univariate analysis, a higher rate of mortality was observed for the patients with the age range of above 40 years old (OR = 3.61, 95% CI: 1.72–7.58, P = 0.001). Furthermore, higher mortality rates were also observed among the patients with past cardiac history (OR = 2.88; 95% CI: 1.16–7.14, P = 0.023) and complications such as decreased visual acuity (OR: 11.07; 95% CI: 2.64–46.50; P = 0.001) and renal complications (OR = 13.48, 95% CI: 6.13–29.68, P < 0.001) (Table 1).

Table 1
Association between death and demographic variables, drug abuse, past medical history and complication in hospital

		Status		P-value	Odds ratio (95% CI)	P-value
		Live	**Die**		Univariate	
Sex	**Female**	28 (80.0)	7 (20.0)	0.595	1.27 (0.53–3.06)	0.595
	Male	264 (83.5)	52 (16.5)		1	-
Age	**< 30**	146 (90.1)	16 (9.9)	0.002	1	-
	31–40	96 (80.7)	23 (19.3)		2.19 (1.10–4.35)	0.026
	> 40	48 (71.6)	19 (28.4)		3.61 (1.72–7.58)	0.001
Chronic alcohol use	**No**	126 (79.2)	33 (20.8)	0.066	1.80 (0.97–3.37)	0.064
	Yes	124 (87.3)	18 (12.7)		1	-
Opium addicted	**No**	249 (82.2)	54 (17.8)	0.251	2.02 (0.59–6.90)	0.260
	Yes	28 (90.3)	3 (9.7)		1	-
Cardiac history	**No**	275 (84.4)	51 (15.6)	0.018	1	-
	Yes	15 (65.2)	8 (34.8)		2.88 (1.16–7.14)	0.023
Non cardiac history	**No**	276 (83.4)	55 (16.6)	0.537	1	-
	Yes	14 (77.8)	4 (22.2)		1.43 (0.46–4.52)	0.539
Blindness	**No**	89 (97.8)	2 (2.2)	< 0.001	1	-
	Yes	201 (80.1)	50 (19.9)		11.07 (2.64–46.50)	0.001
Renal failure	**No**	200 (96.2)	8 (3.8)	< 0.001	1	-
	Yes	89 (65)	28 (35)		13.48 (6.13–29.68)	< 0.001

Among the deceased patients, PH (alive: 7.20 ± 0.16 vs. deceased: 6.82 ± 0.20; P < 0.001), bicarbonate levels (alive: 11.91 ± 7.44 [units]. vs. deceased: 7.45 ± 9.88; P < 0.001), and oxygen saturation levels (alive: 93.93 ± 4.98 vs, deceased: 73.25 ± 13.23; P < 0.001) have been decreased and Partial Pressure of Carbon Dioxide (alive: 25.87 ± 11.23 VS deceased 38.04 ± 20.23; P < 0.001), Creatinine (alive: 1.306 ± 10.40 VS deceased: 2.1291 ± 1.03; P < 0.001), Potassium (alive: 4.61 ± 0.90 VS deceased: 5.94 ± 1.71, P < 0.001), Blood sugar (alive: 127.86 ± 75.58 VS deceased: 226.82 ± 139.03; P < 0.001) have been increased. The

mean of Blood urea nitrogen, Sodium, Magnesium, Calcium were not statistically significant between alive and deceased patients (Table 2).

Table 2
Comparison between death and laboratory findings in methanol toxicity

	Death		P value
	No	Yes	
PH	7.20 ± 0.16	6.82 ± 0.20	< 0.001
Bicarbonate (meq/l)	11.92 ± 7.44	7.46 ± 9.88	< 0.001
Partial Pressure of Carbon Dioxide (torr)	25.87 ± 11.23	38.04 ± 20.23	< 0.001
Oxygen saturation (%)	93.93 ± 4.98	73.25 ± 13.23	< 0.001
Blood urea nitrogen (mg/dl)	13.76 ± 10.40	16.27 ± 12.96	0.117
Creatinine (mg/dl)	1.306 ± 0.40	2.1291 ± 1.03	< 0.001
Sodium (meq/l)	141.92 ± 3.71	143.38 ± 6.17	0.103
Potassium (meq/l)	4.61 ± 0.90	5.94 ± 1.71	< 0.001
Calcium (mg/dl)	9.56 ± 0.75	9.49 ± 0.88	0.600
Magnesium (mg/dl)	2.36 ± 1.65	2.72 ± 0.65	0.310
Blood sugar (mg/dl)	127.86 ± 75.58	226.82 ± 139.03	< 0.001

In the univariate analysis, the patients with QTc > 500 mm had higher mortality rates (OR = 4.16, 95% CI: 2.24–7.72; P < 0.001). This higher mortality rate was observed in patients with QTD > 40 (OR = 1.96, 95% CI: 1.1–3.50; P = 0.023), atrioventricular block (OR = 10.21, 95% CI: 2.88–36.20; P < 0.001), Brugada pattern (OR = 4.76, 95% CI: 1.87–12.09; P = 0.001), J elevation (OR = 2.98, 95% CI: 1.36–6.55; P = 0.007), ST elevation myocardial Infarction (OR = 5.25, 95% CI: 2.03–13.59; P = 0.001), and bundle branch block (OR = 2.45, 95% CI: 1.01–5.94; P = 0.048), Osborn wave (OR = 3.89; 95% CI: 1.12–12.72, P = 0.001), severe metabolic acidosis (PH < 7.2) (OR = 12.12; 95% CI: 4.70-31.23, P < 0.001) and lack of hyperventilation when severely acidotic (OR = 9.5; 95% CI:4.48–18.29, P < 0.001). Furthermore, there was no relationship between severe acidosis with T slope, poor R wave progression, notch QRS and low voltage QRS (P > 0.05) (Table 3).

Table 3
Association between death, ECG variables and acidosis evaluation in methanol toxicity with univariate and multiple logistic regression.

		Status		P-value	Odds ratio (95% CI) Univariate	P value	Odds ratio (95% CI) Multiple**	P value
		Live	**Dead**					
QTC	**< 500**	246 (88.2)	33 (11.8)	< 0.001	1	-	1	-
	>=500	43 (64.2)	24 (35.8)		4.16 (2.24–7.72)	< 0.001	1.81 (0.78–4.21)	0.165
QT dispersion	**< 40**	160 (87.9)	22 (12.1)	0.022	1	-	1	-
	>=40	130 (78.8)	35 (21.2)		1.96 (1.10–3.50)	0.023	1.85 (0.811-4.20)	0.144
T slope	**< 69**	197 (86.0)	32 (14.0)	0.072	1	-	1	-
	>=70	95 (78.5)	26 (21.5)		1.69 (0.95–2.99)	0.074	3.42 (1.36–8.61)	0.009
AVB	**No**	286 (85.4)	49 (14.6)	< 0.001	1	-	1	-
	Yes	4 (36.4)	7 (63.6)		10.21 (2.88–36.20)	< 0.001	4.55 (1.47–14.07)	0.120
Heart rate	**60–100**	214 (86.3)	34 (13.7)	0.058	1	-	1	-
	< 59	8 (66.7)	4 (33.3)		3.15 (0.90-11.02)	0.073	2.20 (0.16–29.46)	0.553
	> 100	68 (78.2)	19 (21.8)		1.76 (0.94–3.28)	0.076	1.76 (0.76–4.09)	0.188
Brugada	**No**	279 (85.3)	48 (14.7)	< 0.001	1	-	1	-

*BBB = bundle branch block, STEMI = ST segment elevation myocardial infarction, AVB = atrioventricular conduction block, P value less than 0.05 considered significant

** Also adjusted for sex and age

	Yes	11 (55.0)	9 (45.0)		4.76 (1.87–12.09)	0.001	5.65 (1.55–20.56)	0.009
J elevation	**No**	95 (92.2)	8 (7.9)	0.002	1	-	1	-
	Yes	192 (79.2)	49 (20.3)		2.98 (1.36–6.55)	0.007	2.14 (0.70–6.56)	0.185
STEMI*	**No**	280 (85.4)	48 (14.6)	< 0.001	1	-	1	-
	Yes	10 (52.6)	9 (47.4)		5.25 (2.03–13.59)	0.001	3.66 (0.77–17.41)	0.103
BBB*	**No**	270 (84.6)	49 (15.4)	0.042	1	-	1	-
	Yes	18 (69.3)	8 (30.7)		2.45 (1.01–5.94)	0.048	2.31 (0.66–8.05)	0.189
Osborn wave	**No**	283 (84.5)	52 (15.5)	0.016	1	-	1	-
	Yes	7 (58.3)	5 (41.7)		3.89 (1.12–12.72)	0.025	4.38 (0.71–27.07)	0.112
Notch QRS	**No**	189 (84.0)	36 (16.0)	0.746	1	-	1	-
	Yes	97 (82.2)	21 (17.8)		1.10 (0.61–1.99)	0.746	0.92 (0.40–2.12)	0.843
Poor progression	**No**	270 (84.4)	50 (15.4)	0.109	1	-	1	-
	Yes	18 (72.0)	7 (28.0)		2.10 (0.83–5.29)	0.115	1.65 (0.44–6.14)	0.459
Low voltage	**No**	279 (84.3)	52 (15.7)	0.063	1	-	1	-
	Yes	9 (64.3)	5 (35.7)		2.98 (0.96–9.25)	0.059	6.70 (1.17–38.29)	0.032

*BBB = bundle branch block, STEMI = ST segment elevation myocardial infarction, AVB = atrioventricular conduction block, P value less than 0.05 considered significant

** Also adjusted for sex and age

Metabolic acidosis (PH)	**< 7.2**	133 (71.9)	52 (28.1)	< 0.001	1	-	1	-
	>=7.2	155 (96.9)	5 (3.1)		12.12 (4.70-31.23)	< 0.001	4.55 (1.47–14.07)	0.009
Lack of hyperventilation when severely acidotic	**No**	197 (94.7)	11 (5.3)	< 0.001	1	-	1	-
	Yes	91 (66.4)	46 (33.6)		9.50 (4.48–18.29)	< 0.001	5.74 (2.29–14.38)	< 0.001
*BBB = bundle branch block, STEMI = ST segment elevation myocardial infarction, AVB = atrioventricular conduction block, P value less than 0.05 considered significant								
** Also adjusted for sex and age								

Multiple analysis

In multiple logistic regression after adjustment for age and sex, there was an independent relationship between mortality rate with T slope (OR = 3.42, CI = 95%: 1.36–8.61; P = 0.009), Brugada pattern (OR = 5.65, CI = 95%: 1.55–20.56; P = 0.009), low voltage QRS (OR = 6.70, CI = 95%: 1.17–38.29; P = 0.032), severe metabolic acidosis (PH < 7.2) (OR = 4.55; 95% CI: 1.47–14.07, P < 0.001) and lack of hyperventilation when severely acidotic (OR = 5.74; 95% CI:2.29–14.38, P < 0.001). (Table 3).

Discussion

To the best of our knowledge, this is the first study on the association between comprehensive analysis of electrocardiographic findings and mortality in methanol toxicity with a considerable sample size. The mortality rate in this study was 16.6% which is comparable with various published data [4, 13, 14]. Furthermore, the mortality rate was higher among female patients and patients aged above 40 years. However, it should be noted that this study only observed the mortality rate of the hospitalized patients and the mortality rates of the outpatients with methanol toxicity or long-term mortality rates was not included. As expected, patients with a past history of cardiac diseases showed a higher mortality rate. Moreover, the results further highlighted the correlation between the development of complications such as blindness and renal problems and increased morbidity and mortality, which is in line with previous evidences [13, 14].

Our study provided further insight into the correlation between some laboratory findings and mortality in methanol toxicity patients. It has been demonstrated in multiple reports that PH is the most prominent factor for predicting poor outcome and mortality in methanol poisoning [13, 20]. Based on our findings, higher levels of acidosis and subsequent hyperkalemia (from shifting of potassium out of cells), lower levels of bicarbonate, higher partial pressures of carbon dioxide and lower oxygen saturation are

associated with an increased mortality in these patients. These values correlate favorably with a multicenter study of Paasma et.al [21] and further support the idea that these patients have difficulty in compensating the metabolic acidosis by inducing hyperventilation.

This study also suggests hyperglycemia as a strong prognostic factor in methanol poisoning. Although the exact underlying pathophysiology is not clear, this may be due to a stress-induced hyperglycemia in these critically ill patients. Furthermore, higher serum levels of creatinine were also evident among the patients who died. This substantiates previous findings in the literature, probably explained by a compromised circulation [13].

Sinus tachycardia, longer QTc and T wave changes are the most commonly reported ECG changes in methanol poisoning patients. In addition, presence of Brugada pattern, QRS complex widening, AF induction are the other ECG findings reported in several cases [17,19,22.23]. Besides, our recent publication on this topic revealed noteworthy results. J point elevation, presence of U wave, fragmented QRS and STEMI are the prominent ECG changes among methanol poisoning patients [19]. However, none of these evidences reported an ECG finding as an independent predictor of mortality.

Based on previous studies, the most remarkable finding was positive associations between various ECG findings such as QTc > 500, QTD > = 40, AVB, sinus tachycardia, Brugada pattern, J point elevation, STEMI, BBB and Osborn wave and increased mortality rate in methanol toxicity [19, 22, 23]. However, multivariate analysis, after adjustment for sex and age revealed the significance T slope, Brugada pattern and low voltage remained significantly associated with mortality.

A few case reports on myocardial infarction with ST segment elevation in methanol toxicity are present in the literature [24, 25]. However, they were not able to determine the infarction rate and mortality hazard ratio in methanol poisoning because of sparsity of cases. This ratio was calculated in our previous article and further explained in this one [19].

Although there are numerous previous reports about ECG finding in methanol toxicity, this study demonstrated some newly introduced ECG findings in the methanol toxicity and suggesting a similarity between the finding among deceased patients in this sample and mortality in interesting cardiac electrical conduction disorders named Brugada phenocopy. The latter was reported recently by a study in Spain [26]. This similarity can de based on the ionic channel blockage by formaldehyde or other metabolites and they can be of utmost practical importance because of their potential ability to predict mortality.

Our study showed a prominent correlation with death when T wave slope is equal or more than 70 degree. Although literature review shows a few researches about repolarization abnormalities measured by T slope such as the work of Strebel et al. [27] in myocardial infarction and Heijman et al. [28] in drug-induced ventricular arrhythmias, the significance of it remained to be determined in future surveys.

Another remarkable ECG finding for death was low voltage QRS. This finding was reported for tamponade and severe heart failure and showed a hazardous situation in those patients [29]. However, to best of our knowledge there is no report for significance in methanol toxicity. It can be hypothesized that jeopardized myocytes are this toxicity cannot produce enough electrical voltage gradient to be presented with prominent electrical waves.

Conclusion

This article indicates that ECG can be a valuable para-clinic tool in the management of patients with methanol toxicity with the potential to predict certain critical outcomes such as mortality. This writing has tried to introduce some relatively recent ECG findings to the toxicology of methanol toxicity like Brugada pattern, terminal T slope and low voltage QRS.

Abbreviations

ECG: Electrocardiogram, PH: potential of hydrogen, PCO2: Partial Pressure of Carbon Dioxide, BS: Blood sugar, OR: Odds Ratio, CI: Confidence Interval, QTD: QT Dispersion, AVB: AV block, STEMI: ST elevation MI, BBB: Bundle Branch Blockbbreviations

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.059). There were some problems with literacy, visual acuity and understanding of participation in data gathering, accordingly we talk to everyone in best simple way and then they sign the written informed consent. If the patient was under legal age, has visual impairment or unlettered, the parents or guardians included in explanation session and they sign instead. However, any participant is included only if the consent is existed and the ethical committee are aware of the situation. Informed consent was obtained from legal guardian.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MHN, and STH contributed in designed the study, analyzed the data, interpreted the results, and wrote the manuscript drafting. ARE, MP, and FA contributed in analysis of data, interpretation the results, and wrote the manuscript drafting. All authors have read and approved the manuscript.

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