Use of Out-of-Hospital Ethanol Administration to Improve Outcome in Mass Methanol Outbreaks

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Study objective: Methanol poisoning outbreaks are a global public health issue, with delayed treatment causing poor outcomes. Out-of-hospital ethanol administration may improve outcome, but the difficulty of conducting research in outbreaks has meant that its effects have never been assessed. We study the effect of out-of-hospital ethanol in patients treated during a methanol outbreak in the Czech Republic between 2012 and 2014.

Methods: This was an observational case-series study of 100 hospitalized patients with confirmed methanol poisoning. Out-of-hospital ethanol as a "first aid antidote" was administered by paramedic or medical staff before the confirmation of diagnosis to 30 patients; 70 patients did not receive out-of-hospital ethanol from the staff (12 patients self-administered ethanol shortly before presentation).

Results: The state of consciousness at first contact with paramedic or medical staff, delay to admission, and serum methanol concentration were similar among groups. The median serum ethanol level on admission in the patients with out-of-hospital administration by paramedic or medical staff was 84.3 mg/dL (interquartile range 32.7 to 129.5 mg/dL). No patients with positive serum ethanol level on admission died compared with 21 with negative serum ethanol level (0% versus 36.2%). Patients receiving out-of-hospital ethanol survived without visual and central nervous system sequelae more often than those not receiving it (90.5% versus 19.0%). A positive association was present between out-of-hospital ethanol administration by paramedic or medical staff, serum ethanol concentration on admission, and both total survival and survival without sequelae of poisoning.

Conclusion: We found a positive association between out-of-hospital ethanol administration and improved clinical outcome. During mass methanol outbreaks, conscious adults with suspected poisoning should be considered for administration of out-of-hospital ethanol to reduce morbidity and mortality. [Ann Emerg Med. 2016;68:52-61.]

Please see page 53 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Mass methanol poisonings represent a challenge for health care providers throughout the world because of the distillation and consumption of illicit alcohol.[1-5] Morbidity and mortality in methanol poisoning remain high; timely diagnosis is difficult, and the onset of treatment is often delayed.[6-8] During 2000 to 2012, more than 50 mass methanol outbreaks with approximately 5,000 poisoned subjects and more than 2,000 fatalities occurred worldwide.[9] If specific interventions are inadequate or delayed, mortality exceeding 40%, permanent visual impairment, and motor and cognitive disorders may occur.[10-12]

Although mass or cluster methanol poisonings occur regularly, especially in developing countries, reports of larger outbreaks in which complete admission clinical and laboratory data, medical treatment protocols, and outcomes are accurately documented and analyzed are scarce.[1,2] During the Czech Republic methanol poisoning outbreak in 2012 to 2014, there was a unique opportunity to study a mass exposure because sufficient medical and public health infrastructure allowed comprehensive data collection and evaluation, as well as a coordinated out-of-hospital intervention within the national health care system.

Methanol is not toxic itself, but it is metabolized to the highly toxic formic acid/formate ion, which inhibits

Editor's Capsule Summary

What is already known on this topic

Delayed treatment with an antidote is known to worsen the outcome of methanol poisoning.

What question this study addressed

Does the out-of-hospital administration of ethanol decrease mortality and morbidity of methanol poisoning?

What this study adds to our knowledge

In this case series of 100 methanol overdoses, the 30 patients who received out-of-hospital ethanol had improved survival and fewer visual and central nervous system deficits than those who did not.

How this is relevant to clinical practice

Although this study was uncontrolled, it provides support for the out-of-hospital administration of ethanol in mass-casualty methanol overdose events.

mitochondrial respiration.[13-16] The accumulation of formic acid may result in metabolic acidosis, visual impairment, and damage of the basal ganglia, especially when its concentration increases above 36 to 46 mg/dL.[17-20] Rapid administration of antidotes (such as fomepizole or ethanol) that prevent toxic metabolite formation by blocking the alcohol dehydrogenase enzyme is crucial for successful treatment.[21-23]

Importance

The role of ethanol in the treatment of acute methanol poisoning is well established.[24-26] Ethanol has approximately 10 times higher affinity for alcohol dehydrogenase than methanol, and a serum concentration of 100 to 150 mg/dL is sufficient to completely block the metabolism of methanol to formate in methanol concentrations that most poisoned patients have on admission.[27] The indications for hospital ethanol administration are a documented plasma methanol concentration of more than 20 mg/dL, a high osmolal gap with documented recent history of ingesting toxic amounts of methanol, or a metabolic acidosis with history or strong clinical suspicion of poisoning.[14]

Because of the high morbidity and mortality of methanol poisoning, ethanol should be administered as soon as possible after methanol ingestion.[14,24] Its wide availability in the community compared with fomepizole makes it attractive for an out-of-hospital "first aid" approach. Out-of-hospital administration of ethanol by paramedics or medical staff as an antidote in methanol outbreaks has previously been tried,[2] but to our knowledge the safety and effectiveness of this approach has not been assessed.

Goals of This Investigation

Close collaboration between the Ministry of Health, Czech Republic, the Toxicological Information Center, and national hospitals allowed us to address this question during a recent methanol mass poisoning in the Czech Republic.[28] We aimed to evaluate the association between out-of-hospital ethanol administration and outcome in patients with a high suspicion of methanol poisoning before laboratory confirmation could be obtained.

MATERIALS AND METHODS

Study Design

This was a prospective, observational, case-series study of patients with acute methanol poisoning treated in hospitals during the Czech Republic mass methanol poisoning outbreak from September 3, 2012, until August 31, 2014. The admission data, including out-of-hospital treatment, were collected prospectively by the treating providers, using a standardized data collection form (Appendix E1, available online at http://www.annemergmed.com) and sent to the Toxicological Information Center on the day after each admission to the hospital. The data on hospital treatment and outcome were collected and reviewed retrospectively from the hospital discharge reports. The study was approved by the General University Hospital Ethics Committee in Prague, Czech Republic.

Setting

The study was conducted in 30 hospitals in 11 regions of the Czech Republic, where the poisoned patients were treated. These hospitals were located in the regional city centers, had ICUs and toxicologic laboratories, and were equipped with hemodialysis and gas chromatography facilities. The patients were transferred to the regional hospitals by emergency medical services (EMS) ambulance or self-presented. EMS is a national system in the Czech Republic and is staffed with physicians and advanced life support providers.

The medical facilities situated in smaller localities were the first presentation points ("collecting points") for the patients from these localities. These hospitals were able to provide the physical examination, breath alcohol test, and osmolality measurement by freezing point depression, but could not confirm the methanol concentration and could not provide dialysis or intensive care. Patients with suspicion of acute methanol poisoning from collecting points were transferred by ambulance to the secondary regional hospitals.

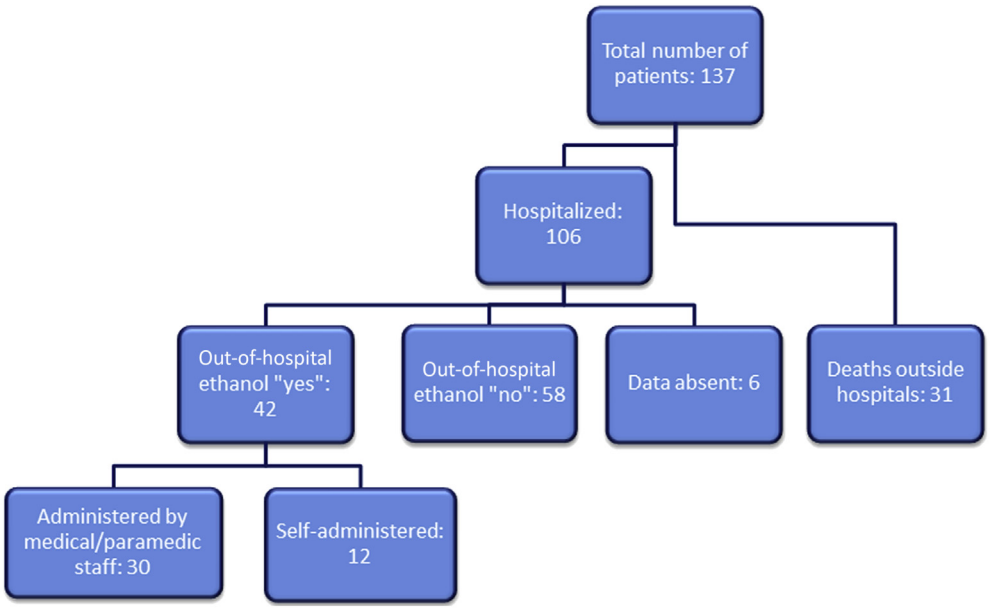

Figure. Flowchart of the study design.

Selection of Participants

All patients hospitalized with confirmed acute methanol poisoning were eligible for this study (Figure). Patients were excluded if they died out of the hospital, if their data on out-of-hospital ethanol administration could not be obtained, or if blood samples for serum ethanol measurement were not taken before hospital treatment with ethanol.

To identify the cases, mandatory reporting to the Ministry of Health and the Czech Republic Toxicological Information Center on all cases of hospital admission with laboratory-confirmed methanol poisoning and nationwide daily monitoring of the situation in all hospitals started on September 6, 2012, 3 days after admission of the first 3 patients with acute methanol poisoning.

Interventions

A recommendation to administer out-of-hospital ethanol to all patients with suspected methanol poisoning was made by the Toxicological Information Center and distributed to all medical facilities nationwide 2 weeks into the epidemic, when the ambulance and emergency department (ED) staff had become more alert to potential methanol poisoning cases. The patients treated before hospitalization received oral ethanol either directly from ambulance crews or at local collecting points before transfer to a higher-level hospital.

The protocol of out-of-hospital ethanol administration was predominantly applied in fully conscious patients with strong clinical suspicion of methanol poisoning before admission to the higher-level hospital and definite diagnosis of poisoning. The recommended oral loading dose of ethanol was 1.8 to 2.0 mL/kg body weight of 40% alcohol by volume of ethanol, with the aim of achieving serum ethanol concentrations of at least 100 mg/dL.[14] Postadmission treatment was similar in the 2 groups in regard to ethanol treatment, folate substitution, and elimination techniques. The data on postadmission treatment were reviewed from the hospital records sent to the Toxicological Information Center within the mandatory reporting system.

Methods of Measurement

A modified standardized form for collection of admission data based on a methanol outbreak in Norway in 2002 to 2004[1] was distributed to all hospitals during the second week of the outbreak and used for the prospective chart review (Appendix E1, available online at http://www.annemergmed.com). The heads of the EDs of 30 regional hospitals where poisoned patients were admitted were instructed by the research coordinators by telephone interviews and e-mails about the procedure of filling out the forms, primary data collection techniques, and training and supervising of the abstractors. The emergency physicians who admitted and examined the patients collected the primary demographic, anamnestic, clinical, biochemical, and toxicologic data and completed the standardized forms as part of their mandatory task of daily reporting of new cases of methanol poisoning. Both the abstractors and the heads of the EDs were blinded to the study hypothesis of the effectiveness and safety of out-of-hospital ethanol administration. A detailed history of the poisoning and of ocular and systemic toxicity was obtained

directly from the patient or from relatives of critically ill patients on admission to the hospital. The completed standardized admission data collection forms were sent by the ED to the Toxicological Information Center by e-mail or fax the day after admission, when the results of toxicologic assay confirmed the diagnosis of methanol poisoning. The Toxicological Information Center provided immediate feedback for the form's completeness. The data on the patients admitted before distribution of the protocol were collected retrospectively.

The discharge reports of all hospitalized patients with a confirmed diagnosis containing the results of neurologic and ophthalmologic examinations on admission, during hospitalization, and on discharge and the detailed report on the postadmission hospital treatment, results of biochemical and toxicologic monitoring, adverse reactions, and complications of treatment were collected retrospectively and analyzed in the Toxicological Information Center.

Laboratory analyses were performed on admission. Diagnosis was established when a history of recent ingestion of illicit spirits was available and serum methanol was higher than 20 mg/dL, or when there was a history or clinical suspicion of methanol poisoning and serum methanol was above the limit of detection, with at least 2 of the following: pH less than 7.3, serum bicarbonate level less than 20 mEq/L, or anion gap greater than or equal to 20 mEq/L.

The clinical examination protocol included complete ocular examination with standard ophthalmologic tests (visual acuity, color vision, visual fields, contrast sensitivity, and fundus examination), cerebral computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, and standard neurologic examination (including the Mini-Mental State Examination,[29] motor, sensory, cerebellar, cranial nerves, and reflexes). Patients were considered to have visual sequelae of acute methanol poisoning if the symptoms of toxic neuropathy of the optic nerve were documented on admission or during hospitalization, with pathologic findings on visual acuity, visual fields, color vision, contrast sensitivity, and persisting lesions on fundoscopy. Similarly, patients were considered to have central nervous system sequelae of poisoning if symmetric necrosis and hemorrhages of basal ganglia were present on CT or MRI.

The hospitalized patients were retrospectively assigned to 3 groups defined according to outcome: group 1, patients who survived without sequelae; group 2, patients who survived with visual or central nervous system sequelae; and group 3, patients who died. These groups were each further divided into 2 subgroups: "with out-of-hospital ethanol administration by EMS staff (ethanol EMS positive)" and "without out-of-hospital ethanol administration by EMS staff (ethanol EMS negative)." Within the latter subgroup, data from patients who self-administered ethanol shortly before presentation were analyzed separately.

Outcome Measures

The primary outcome of this study was mortality in the groups of patients with and without out-of-hospital ethanol administration. The secondary outcome was the number of survivors with visual sequelae and central nervous system sequelae of poisoning at discharge from hospitals.

Primary Data Analysis

The number of subjects with missing key data on out-of-hospital ethanol administration and serum ethanol concentration on admission before any hospital treatment was low (5.7%). We chose to exclude these subjects because no multivariate logistic regression model testing the study hypothesis with imputed values was applied as a result of the sample size.

To test the strength and the direction of association between out-of-hospital ethanol administration, positive serum ethanol on admission, and the outcome of treatment, we used both the total study population and the population of hospitalized patients after exclusion of those with a Glasgow Coma Scale (GCS) score of 10 points or fewer at presentation (contraindication for out-of-hospital ethanol administration).

As long as there was a risk of conflicting data with false-positive results (eg, on the basis of interview of ambulance staff, out-of-hospital ethanol was administered according to the recommendation) or false-negative results (eg, on the basis of interview, no ethanol was self-administered by the patient) caused by misrepresentation of history, the coding of conflicting data was suggested. However, we registered no false-positive or false-negative cases: positive serum concentration of ethanol was detected analytically in the cases of out-of-hospital ethanol administration, and no patients with negative history had a positive serum ethanol result on admission.

Descriptive statistics were assessed with medians with interquartile ranges, Spearman's rank correlation, exploratory factor analysis, and χ^2 tests. Statistical documentation was performed in Microsoft Excel 2010 (Redmond, WA), and the formal calculations were produced in QC Expert software (version 3.1; Trilobyte, Pardubice, Czech Republic) and in SPSS (version 17.0; SPSS Inc., Chicago, IL).

RESULTS

Of 137 patients, 31 (22.6%) died before contact with paramedic or medical staff and presentation to the hospital (Figure). Of the remaining 106 patients, data on out-of-hospital ethanol administration could not be obtained, or, for 6 patients, blood samples for serum ethanol measurement were not taken before hospital antidote treatment with ethanol. Of the 100 patients included, 61 were transferred to the hospital by ambulance. The remaining 39 were self-presenters, who visited the ED personally, were transported to the hospitals by their relatives, or were transported to the hospitals by police (10 cases).

Thirty patients (30%) received out-of-hospital ethanol either directly from ambulance crews (15/30) or from medical or paramedical staff at the collecting points (15/30) (ethanol EMS–positive patients). The estimated time range to secondary hospital admission from presentation to a collecting point was 1.5 to 3.5 hours.

The remaining 70 patients did not receive out-of-hospital ethanol from paramedical or medical staff (ethanol EMS–negative patients). Among them, 12 patients self-administered an unknown amount of ethanol before first contact because they believed the symptoms represented a hangover. Five of these patients were then transferred to the hospital by ambulance, 5 self-presented, and 2 were transported by the police. Fifty-eight patients did not receive ethanol before admission to the hospital. Most of them (41/58) were transferred to the hospitals by ambulance, whereas the rest self-presented.

Seventy eight patients were awake, with GCS score greater than 10, whereas 22 patients had a GCS score of 10 points or fewer on initial presentation. In patients with a GCS score greater than 10 points, out-of-hospital ethanol was administered by paramedic or medical staff to 27 of 78 patients (34.6%) and not administered to 51 of 78 (65.4%), whereas for patients with a GCS score of 10 points or fewer, it was administered in 3 of 22 (13.6%). Among the 100 patients, only 12% were admitted within 12 hours of methanol ingestion, 61% within 13 to 48 hours, and 13% after 48 hours (14% unknown).

The median serum ethanol level on admission in 30 patients with out-of-hospital administration by paramedic or medical staff (Table 1) was 84.3 mg/dL (interquartile range 32.7 to 129.5 mg/dL) and 141.0 mg/dL (interquartile range 29.5 to 377.4 mg/dL) in 12 patients who self-administered. The serum methanol concentration on admission in ethanol EMS–positive patients was similar to that of ethanol EMS-negative ones. The ethanol EMS–positive patients were less acidotic on admission, with higher arterial blood pH and lower base deficit, anion gap, and serum formate and lactate concentrations (Table 1).

Common clinical features included visual and gastrointestinal disturbances, dyspnea, chest pain, and coma (Table 2). Other less common features included fatigue, headache, dizziness, somnolence, anxiety, alcoholic delirium, tremor, seizures, and cardiac and respiratory arrest. The median ethanol concentration was higher in patients without clinical symptoms (50.2 mg/dL [range 5.1 to 137.7 mg/dL]) than in those with clinical features (0 mg/dL [range 0 to 23.0 mg/dL]).

Thirty patients (30%) received ethanol from paramedic or medical staff before presentation to a hospital able to provide definitive care. The alertness of staff for methanol poisoning increased with time, when typical symptoms were increasingly likely to have been caused by methanol poisoning. In regard to symptoms, 80% of the patients who received out-of-hospital ethanol from paramedic or medical staff had a history of suspected methanol ingestion plus at least 1 other clinical finding (including signs of inebriety); 30% had visual symptoms (blurry or cloudy vision, central visual field defects, and alterations in light, color, and depth perception, progressing to total blindness with absent direct pupillary response) or dyspnea. The other 20% had a history of drinking methanol with patients who had already been hospitalized for methanol poisoning.

The state of consciousness was a limiting factor for providing out-of-hospital ethanol. In general, ethanol was administered to patients who were less sick (awake, with GCS score >10) and was not administered to those who were unconscious. Of 78 patients with GCS score greater than 10 points at presentation, 27 (34.6%) received ethanol from paramedic or medical staff; in 12 cases (15.4%), ethanol was self-administered by the patient. In 39 patients with GCS score greater than 10 points at presentation, out-of-hospital ethanol was not administered; most of them (28 of 39) were hospitalized during the first 2 weeks of the outbreak.

Twenty two patients had a GCS score of 10 or fewer points on the arrival of the ambulance. Three of these patients received out-of-hospital ethanol. One of these 3 patients developed coma and was severely acidotic, with a serum methanol level of 348.0 mg/dL and serum ethanol level of 23.0 mg/dL. No other cases of coma or other adverse effects of the treatment protocol were recorded in the study population. Detailed information about the postadmission treatment in hospitals is presented in Table 3.

Overall, patients receiving out-of-hospital ethanol from paramedic or medical staff or by self-administration showed

Table 1. Laboratory data on admission for 100 hospitalized patients, according to the outcome groups.*

			Group 1 (n=49)		Group 2 (n=30)		Group 3 (n=21)		
Characteristic	**EtOH EMS–Positive (n=30)**	**EtOH EMS–Negative (n=70)**	**EtOH EMS–Positive (n=27)**	**EtOH EMS–Negative (n=22)**	**EtOH EMS–Positive (n=3)**	**EtOH EMS–Negative (n=27)**	**EtOH EMS–Positive (n=0)**	**EtOH EMS–Negative (n=21)**	**Total (n=100)**
Age (IQR), y	55 (47–64)	52 (37–60)	54 (47–62)	52 (35–58)	65 (56–69)	48 (37–58)	—	58 (45–63)	54 (38–61)
Serum methanol, mg/dL (IQR)	59.6 (29.2–138.1)	93.9 (41.7–180.4)	50.0 (29.5–133.0)	68.6 (39.4–101.9)	99.0 (58.0–223.7)	162.2 (80.1–263.1)	—	109.3 (69.2–189.1)	92.0 (39.4–176.0)
Serum ethanol, mg/dL (IQR)	84.3 (32.7–129.5)	0 (0–0)	88.9 (42.9–137.3)	7.4 (0–115.2)	23.0 (16.6–51.6)	0 (0–0)	—	0 (0–0)	0 (0–58.5)
Serum formate, mg/dL (IQR)	31.8 (5.5–59.8)	67.7 (53.8–76.9)	22.6 (4.6–52.0)	60.8 (36.4–70.4)	62.1 (62.1–62.1)	70.9 (62.1–85.1)	—	71.3 (58.9–73.6)	66.3 (41.0–76.4)
Serum lactate, mg/dL (IQR)	22.5 (17.1–32.4)	54.1 (17.1–83.8)	22.5 (17.1–30.6)	18.9 (15.3–36.0)	43.2 (28.8–56.8)	28.8 (12.6–66.7)	—	84.7 (60.4–116.2)	32.4 (17.1–70.3)
pH (IQR)	7.34 (7.20–7.42)	7.03 (6.79–7.26)	7.36 (7.25–7.42)	7.31 (7.25–7.41)	7.16 (7.01–7.18)	7.02 (6.83–7.17)	—	6.79 (6.65–6.93)	7.18 (6.89–7.34)
pCO_2, mm Hg (IQR)	33.8 (26.3–36.0)	30.0 (20.3–35.3)	34.5 (29.3–36.8)	32.3 (27.0–37.5)	19.5 (17.3–24.8)	21.8 (14.3–27.0)	—	33.8 (26.3–45.8)	30.8 (21.0–36.0)
HCO_3^-, mEq/L (IQR)	18.4 (11.6–22.6)	6.8 (4.1–13.5)	20.9 (12.8–22.8)	18.5 (8.8–22.7)	5.9 (4.7–8.7)	5.1 (3.6–9.3)	—	5.2 (3.9–7.7)	8.8 (4.7–19.5)
BE, mEq/L (IQR)	−6.1 (−1.5 to −14.6)	−23.2 (−11.3 to −29.0)	−3.6 (−1.2 to −12.8)	−4.5 (−1.7 to −15.6)	−22.1 (−19.6 to −27.5)	−25.4 (−19.1 to −27.5)	—	−29 (−26.9 to −31.9)	−17.8 (−3.7 to −27.7)
AG, mEq/L (IQR)	20.3 (18.3–28.6)	32.3 (22.3–39.8)	20 (18.1–26.8)	23.2 (18.2–28.5)	30.9 (29.8–31.9)	32.7 (25.3–37.7)	—	40.4 (34.8–45.1)	28.3 (19.4–36.3)
OG, mOsm/kg H_2O (IQR)	47 (21–73)	45.4 (23–77)	36 (22–73)	26 (19–44)	52 (33–86)	64 (39–100)	—	65 (45–136)	46.8 (21.7–75.9)
Serum glucose, mg/dL (IQR)	111.7 (102.7–136.9)	149.5 (111.7–234.2)	108.1 (102.7–129.7)	118.9 (109.9–147.7)	138.7 (127.9–183.8)	136.9 (108.1–203.6)	—	228.8 (185.6–290.1)	131.5 (108.1–201.8)
Time to treatment (IQR), h	25 (17–48)	48 (24–48)	26 (14–48)	24 (22–48)	24 (21–36)	48 (30–50)	—	48 (38–52)	41 (24–48)

EtOH, Ethanol; *IQR*, interquartile range; *BE*, base excess; *AG*, anion gap; *OG*, osmolal gap; *time to treatment*, time between toxic alcohol ingestion and start of hospital treatment.

To convert from mg/dL to mmol/L, use the following conversion factors: methanol 3.205; ethanol 4.608; formate 4.603; lactate 9.009; and glucose 18.018. To convert bicarbonate and base deficit from mEq/L to mmol/L, use the conversion factor 1.0. To convert mm Hg (torr) to kPa, use the conversion factor 7.501.

*Data are presented as medians with interquartile ranges. EtOH EMS–positive: patients with out-of-hospital ethanol administration by EMS (paramedic/medical staff); EtOH EMS–negative: patients without out-of-hospital ethanol administration by EMS (paramedic/medical staff; group 1, survivors without sequelae; group 2, survivors with sequelae; group 3, died.

Table 2. Clinical symptoms on admission in 100 hospitalized patients according to the outcome groups.*

Characteristic	Group 1 (n=49)		Group 2 (n=30)		Group 3 (n=21)	Total (n=100)	
	EtOH EMS–Positive (n=27)	EtOH EMS–Negative (n=22)	EtOH EMS–Positive (n=3)	EtOH EMS–Negative (n=27)	EtOH EMS–Negative (n=21)	EtOH EMS–Positive (n=30)	EtOH EMS–Negative (n=70)
No symptoms, No. (%)	16 (59)	6 (27)	1 (33)	0	0	17 (57)	6 (9)
Visual disturbances, No. (%)	4 (15)	10 (45)	3 (100)	8 (30)	12 (57)	7 (23)	30 (43)
Gastrointestinal disturbances, No. (%)	7 (26)	18 (82)	2 (67)	8 (30)	10 (48)	9 (30)	36 (51)
Dyspnea, No. (%)	1 (4)	10 (45)	1 (33)	8 (30)	11 (53)	2 (7)	29 (41)
Chest pain, No. (%)	1 (4)	1 (5)	0	1 (4)	7 (33)	1 (3)	9 (13)
Respiratory arrest, No. (%)	0	0	0	0	3 (14)	0	3 (4)
Coma, No. (%)	0	4 (18)	1 (33)	8 (30)	15 (71)	1 (3)	27 (39)

*EtOH EMS–positive: patients with out-of-hospital ethanol administration by EMS (paramedic/medical staff); EtOH EMS–negative: patients without out-of-hospital ethanol administration by EMS (paramedic/medical staff; group 1, survivors without sequelae; group 2, survivors with sequelae; group 3, died.

increased survival without sequelae and fewer deaths than those not receiving it (Tables 4 and 5). Among the 12 patients who self-administered ethanol before hospitalization, 11 (92%) survived without sequelae. One patient presented 36 hours after methanol ingestion with a serum ethanol level of 80.2 mg/dL and serum methanol level of 99.0 mg/dL and had visual sequelae on discharge. This patient had a serum lactate level of 65.8 mg/dL, serum formate level of 96.7 mg/dL, pH 7.0, and bicarbonate level of 10.2 mEq/L on admission, suggesting that he was severely poisoned before drinking ethanol.

All 27 patients with a GCS score greater than 10 who received out-of-hospital ethanol from medical staff survived without sequelae. Only 3 patients with a GCS score of 10 or fewer points received out-of-hospital ethanol; none died and 1 developed visual and central nervous system sequelae.

In contrast, in the presumably "less sick" patients with a GCS score greater than 10 who had not received out-of-hospital ethanol from paramedics or medical staff, only 22 of 57 (38.6%) survived without sequelae. Moreover, 11 of these 22 patients self-administered ethanol shortly before presentation. Therefore, only 11 of 46 patients (23.9%) less sick without ethanol from any source survived without sequelae.

LIMITATIONS

The limitations of this study include lack of randomization and confounding, leaving the possibility of inherent bias between the groups. Direct communication by telephone and e-mails with physicians who admitted and treated poisoned patients was applied to specify the key data, if necessary. This could have created recall bias. The retrospective estimation of time of ingestion and other circumstances in mass poisonings by methanol-contaminated spirits is approximate and probably inaccurate in some patients. Interindividual differences in body weight, chronic alcoholism, and comorbidities could have played a role in the outcome as well. Differences in the availability of treatment facilities in different hospitals (mode of dialysis, type of antidote, and so on) could have had an effect on the outcome but were outside the scope of this study.

Table 3. Treatment given in 100 hospitalized patients according to the outcome groups.*

Characteristic	Group 1 (n=49)		Group 2 (n=30)		Group 3 (n=21)	Total (n=100)	
	EtOH EMS–Positive (n=27)	EtOH EMS–Negative (n=22)	EtOH EMS–Positive (n=3)	EtOH EMS–Negative (n=27)	EtOH EMS–Negative (n=21)	EtOH EMS–Positive (n=30)	EtOH EMS–Negative (n=70)
Alkalization, No. (%)	8 (30)	12 (55)	2 (67)	25 (93)	20 (95)	10 (33)	57 (81)
Ethanol, No. (%)	21 (78)	19 (86)	2 (67)	18 (67)	16 (76)	23 (77)	53 (76)
Fomepizole, No. (%)	6 (22)	2 (9)	2 (67)	8 (30)	7 (33)	8 (27)	17 (24)
Folate substitution, No. (%)	20 (74)	19 (86)	2 (67)	22 (81)	13 (62)	22 (73)	54 (77)
CVVHD/ CVVHDF, No. (%)	10 (37)	7 (32)	1 (33)	13 (48)	15 (71)	11 (37)	35 (50)
IHD, No. (%)	8 (30)	9 (41)	1 (33)	12 (44)	5 (24)	9 (30)	26 (37)

CVVHD/CVVHDF, Continuous venovenous hemodialysis/hemodiafiltration; *IHD*, intermittent hemodialysis.
*EtOH EMS–positive: patients with out-of-hospital ethanol administration by EMS (paramedic/medical staff); EtOH EMS–negative: patients without out-of-hospital ethanol administration by EMS (paramedic/medical staff; group 1, survivors without sequelae; group 2, survivors with sequelae; group 3, died.

Table 4. Out-of-hospital administration of ethanol by paramedic or medical staff ("first aid") versus outcomes of acute methanol poisoning in 100 patients.

Characteristic	Group 1: Survived Without Sequelae (n=49)	Group 2: Survived With Sequelae (n=30)	Group 3: Died (n=21)
Out-of-hospital ethanol administered by paramedic or medical staff (n=30) (%)	27 (90.0)	3 (10.0)	0
No out-of-hospital ethanol administered by paramedic or medical staff (n=70) (%)	22 (31.4)	27 (38.6)	21 (30.0)

There was a risk of false-positive results because of inaccurate history by the patient, relatives, bystanders, or EMS providers. However, we found no evidence of false-positive cases because the history was confirmed by negative ethanol level on admission; no patients with negative history had a positive serum ethanol level on admission.

Selection bias was present because patients who died out of the hospital were not included. The consciousness of the patients on first presentation limited the study by the absence of a randomly distributed exposure: the most severely poisoned patients often did not receive out-of-hospital ethanol. There was no specific training of out-of-hospital providers and feedback to improve adherence with the protocol. An allocation bias was present in the study, caused by systematic differences other than intervention (out-of-hospital ethanol) between the groups analyzed, because the group without out-of-hospital ethanol was more severely acidotic on admission to the hospital.

DISCUSSION

Poor outcome in methanol poisoning is related to late diagnosis and delayed initiation of treatment with antidote, be it fomepizole or ethanol. In our study, both positive serum ethanol level on admission and receipt of out-of-hospital ethanol were associated with improved survival during the Czech Republic mass methanol outbreak. Our data support the use of ethanol administration to conscious patients with suspected methanol poisoning before laboratory data are available and the diagnosis is confirmed.

Table 5. Positive serum ethanol concentration on admission to the hospital versus outcomes of acute methanol poisoning in 100 patients.

Characteristic	Group 1: Survived Without Sequelae (n=49)	Group 2: Survived With Sequelae (n=30)	Group 3: Died (n=21)
Positive serum ethanol on admission (n=42)	38 (90.5)	4 (9.5)	0
Negative serum ethanol on admission (n=58)	11 (19.0)	26 (44.8)	21 (36.2)

Based on the principle "as early as possible," out-of-hospital antidote treatment during ongoing methanol outbreaks may improve patient outcomes. The decision to start the treatment cannot be based solely on the results of an assay for toxic alcohols because this is usually not readily available.[30] During the critical period before hospitalization, a poisoned patient's condition can deteriorate because of continuing accumulation of formic and lactic acids, worsening the metabolic acidosis, histotoxic hypoxia, and outcome.[31,32]

The effect of ethanol administration may be more complex than mere blocking of alcohol dehydrogenase. In animal models of cerebral, renal, liver, and cardiac ischemia, alcohol exposure is shown to reduce ischemic reperfusion injury and prevent postischemic adhesive interactions between leukocytes and endothelial cells, which can lead to organ dysfunction and death.[33-45] Ischemia caused by myelin sheath swelling and intra-axonal swelling plays a major role in compression-type injury to the optic nerve fibers, brain edema, and basal ganglia damage in methanol-poisoned patients.[14,15]

In an observational study of 11,850 patients hospitalized in an ICU,[46] positive blood alcohol concentration at hospital admission was associated with significantly decreased odds of 30-day all-cause mortality in critically ill patients. Several other studies showed a decrease of inhospital mortality in patients with positive blood alcohol concentration on hospital admission outside of the ICU, mainly in the patients with brain trauma.[47-53] An observational study of 6,733 patients hospitalized on trauma units demonstrated a decrease in inhospital mortality strongly associated with an increase in blood alcohol concentration (adjusted odds ratio=0.83 per 100 mg/dL unit change in blood alcohol concentration; 95% confidence interval 0.80 to 0.85; $P<.001$).[54]

In our study, the ethanol EMS–positive patients were less acidotic on admission to hospitals, with time to presentation and serum methanol level on admission similar to that of the ethanol EMS–negative patients. This might indicate effective blocking of the alcohol dehydrogenase enzyme in the pretreated patients. The out-of-hospital ethanol group was still able to increase ventilation adequately despite the ethanol treatment, indicating that modest administration of ethanol itself does not alter patients' ability to compensate for metabolic acidosis.

During outbreaks of mass methanol poisonings, we recommend that conscious adults with a strong suspicion of methanol poisoning receive out-of-hospital ethanol before confirmation of the diagnosis is available, with a serum ethanol goal of at least 100 mg/dL. This approach is even more important if the distance to the hospital is long or other factors may delay the definite diagnosis. Given a standard regimen, a worst-case scenario would mean that a certain number of patients will be given a limited amount of ethanol unnecessarily, which can be considered acceptable from a risk-benefit point of view.

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Author contributions: SZ and DP conceived of the study and wrote the first draft of the article. SZ, DP, and KEH collected the data. PU, ON, KK, and PD examined the patients and estimated the prevalence of visual and central nervous system damage in the population of methanol-poisoned patients. PU, ON, KK, PD, IK, ME, and KEH interpreted the data. IK provided the toxicologic measurements of methanol, ethanol, and formic acid. TN, JB, and MK conducted the statistical analysis. ME initiated the process of extracting the out-of-hospital ethanol administration from the original epidemiologic data. KEH participated in the planning of the study protocol and supervised the primary data procession. KEH and ME participated in data analysis, conceived the final format of its presentation, and critically reviewed the drafts of the article. All authors approved the final version of the article. SZ had full access to all the data in the study and had final responsibility for the decision to submit for publication. SZ takes responsibility for the paper as a whole.

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REFERENCES

1. Hovda KE, Hunderi OH, Tafjord AB, et al. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. *J Intern Med*. 2005;258:181-190.
2. Paasma R, Hovda KE, Tikkerberi A, et al. Methanol mass poisoning in Estonia: outbreak in 154 patients. *Clin Toxicol*. 2007;45:152-157.
3. Bennett IL, Cary FH, Mitchell GL, et al. Acute methyl alcohol poisoning: a review based on experiences in an outbreak of 323 cases. *Medicine*. 1953;32:431-463.
4. Kumar SS, Seerala Boopathy K, Bhaskar ME. Methanol poisoning—a Chennai experience. *J Assoc Physicians India*. 2003;51:425-426.
5. Ahmad K. Methanol-laced moonshine kills 140 in Kenya. *Lancet*. 2000;356:1911.
6. Hovda KE, Hunderi OH, Rudberg N, et al. Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. *Intensive Care Med*. 2004;30:1842-1846.
7. Zakharov S, Navratil T, Pelclova D. Analysis of serum anion gap and osmolal gap in diagnostics and prognosis of acute methanol poisoning: clinical study in 86 patients. *Monatsh Chem*. 2015;146:787-794.
8. Megarbane B, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. *Intensive Care Med*. 2005;31:189-195.
9. Zhang G, Grews K, Wiseman H, et al. Application to include fomepizole on the WHO model list of essential medicines (2012). Available at: http://www.who.int/selection_medicines/committees/expert/19/applications/Fomepizole_4_2_AC_Ad.pdf. Accessed May 17, 2015.
10. Roberts DM, Yates C, Megarbane B, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. *Crit Care Med*. 2015;43:461-472.
11. Zakharov S, Pelclova D, Diblik P, et al. Long-term visual damage after acute methanol poisonings: longitudinal cross-sectional study in 50 patients. *Clin Toxicol*. 2015;53:884-892.
12. Bezdicek O, Klempir J, Liskova I, et al. Sequelae of methanol poisoning for cognition. *Cesk Slov Neurol N*. 2014;77/110:320-325.
13. Liesivuori J, Savolainen H. Methanol and formic acid toxicity: biochemical mechanisms. *Pharmacol Toxicol*. 1991;69:157-163.
14. Barceloux DG, Bond GR, Krenzelok EP, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol*. 2002;40:415-446.
15. Nurieva O, Kotikova K, Urban P, et al. Prevalence, dynamics, and biochemical predictors of optic nerve remyelination after methanol-induced acute optic neuropathy: a two-year prospective study in 54 patients. *Monatsh Chem*. 2016;147:239-249.
16. Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol*. 1986;1:309-334.
17. Sejersted OM, Jacobsen D, Ovrebo S, et al. Formate concentrations in plasma from patients poisoned with methanol. *Acta Med Scand*. 1983;213:105-110.
18. Zakharov S, Kurcova I, Navratil T, et al. Is the measurement of serum formate concentration useful in the diagnostics of acute methanol

poisoning? a prospective study of 38 patients. *Basic Clin Pharmacol Toxicol*. 2015;116:445-451.
19. Osterloh JD, Pond SM, Grady S, et al. Serum formate concentrations in methanol intoxication as a criterion for hemodialysis. *Ann Intern Med*. 1986;104:200-203.
20. Zakharov S, Pelclova D, Navratil T, et al. Intermittent hemodialysis is superior to continuous veno-venous hemodialysis/hemodiafiltration to eliminate methanol and formate during treatment for methanol poisoning. *Kidney Int*. 2014;86:199-207.
21. Zakharov S, Navratil T, Pelclova D. Fomepizole in the treatment of acute methanol poisonings: experience from the Czech mass methanol outbreak 2012-2013. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2014;158:641-649.
22. Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of methanol poisoning. *N Engl J Med*. 2001;344:424-429.
23. Zakharov S, Pelclova D, Navratil T, et al. Fomepizole versus ethanol in the treatment of acute methanol poisoning: comparison of clinical effectiveness in a mass poisoning outbreak. *Clin Toxicol*. 2015;53: 797-806.
24. Bergeron R, Cardinal J, Geadah D. Prevention of methanol toxicity by ethanol therapy. *N Engl J Med*. 1982;307:1528.
25. Hantson P, Wittebole X, Haufroid V. Ethanol therapy for methanol poisoning: duration and problems. *Eur J Emerg Med*. 2002;9: 278-279.
26. Zakharov S, Navratil T, Salek T, et al. Fluctuations in serum ethanol concentration in the treatment of acute methanol poisoning: a prospective study of 21 patients. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2015;159:666-676.
27. Jacobsen D, Jansen H, Wiik-Larsen E, et al. Studies on methanol poisoning. *Acta Med Scand*. 1982;212:5-10.
28. Zakharov S, Pelclova D, Urban P, et al. Czech mass methanol outbreak 2012: epidemiology, challenges and clinical features. *Clin Toxicol*. 2014;52:1013-1024.
29. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
30. Megarbane B. Treatment of patients with ethylene glycol or methanol poisoning: focus on fomepizole. *Open Access Emerg Med*. 2010;2:67-75.
31. Zakharov S, Nurieva O, Navratil T, et al. Acute methanol poisonings: folates administration and visual sequelae. *J Appl Biomed*. 2014;12: 309-316.
32. Zakharov S, Nurieva O, Kotikova K, et al. Factors predicting optic nerve axonal degeneration after methanol-induced acute optic neuropathy: a two-year prospective study in 54 patients. *Monatsh Chem*. 2016;147:251-261.
33. Miyamae M, Camacho SA, Zhou HZ, et al. Alcohol consumption reduces ischemia-reperfusion injury by species-specific signaling in guinea pigs and rats. *Am J Physiol*. 1998;275:H50-56.
34. Miyamae M, Diamond I, Weiner MW, et al. Regular alcohol consumption mimics cardiac preconditioning by protecting against ischemia-reperfusion injury. *Proc Natl Acad Sci U S A*. 1997;94:3235-3239.
35. Wang Q, Kalogeris TJ, Wang M, et al. Antecedent ethanol attenuates cerebral ischemia/reperfusion-induced leukocyte-endothelial adhesive interactions and delayed neuronal death: role of large conductance, Ca^{2+}-activated K^{+} channels. *Microcirculation*. 2010;17:427-438.
36. Collins MA, Neafsey EJ, Mukamal KJ, et al. Alcohol in moderation, cardioprotection, and neuroprotection: epidemiological considerations and mechanistic studies. *Alcohol Clin Exp Res*. 2009;33:206-219.
37. Pagel PS, Krolikowski JG, Kehl F, et al. The role of mitochondrial and sarcolemmal K(ATP) channels in canine ethanol-induced preconditioning in vivo. *Anesth Analg*. 2002;94:841-848.
38. Louboutin JP, Marusich E, Gao E, et al. Ethanol protects from injury due to ischemia and reperfusion by increasing vascularity via vascular endothelial growth factor. *Alcohol*. 2012;46:441-454.
39. Chen CH, Budas GR, Churchill EN, et al. Activation of aldehyde dehydrogenase-2 reduces ischemic damage to the heart. *Science*. 2008;321:1493-1495.
40. Churchill EN, Disatnik MH, Mochly-Rosen D. Time-dependent and ethanol-induced cardiac protection from ischemia mediated by mitochondrial translocation of varepsilon PKC and activation of aldehyde dehydrogenase 2. *J Mol Cell Cardiol*. 2009;46:278-284.
41. Wang Q, Sun AY, Simonyi A, et al. Ethanol preconditioning protects against ischemia/reperfusion-induced brain damage: role of NADPH oxidase-derived ROS. *Free Radic Biol Med*. 2007;43:1048-1060.
42. Yuan Q, Hong S, Han S, et al. Preconditioning with physiological levels of ethanol protect kidney against ischemia/reperfusion injury by modulating oxidative stress. *PLoS One*. 2011;6:e25811.
43. Yamaguchi T, Dayton CB, Ross CR, et al. Late preconditioning by ethanol is initiated via an oxidant-dependent signaling pathway. *Free Radic Biol Med*. 2003;34:365-376.
44. Yamaguchi T, Dayton C, Shigematsu T, et al. Preconditioning with ethanol prevents postischemic leukocyte-endothelial cell adhesive interactions. *Am J Physiol Heart Circ Physiol*. 2002;283:H1019-1030.
45. Eltzschig HK, Collard CD. Vascular ischaemia and reperfusion injury. *Br Med Bull*. 2004;70:71-86.
46. Stehman CR, Moromizato T, McKane CK, et al. Association between blood alcohol concentration and mortality in critical illness. *J Crit Car*. 2015;30:1382-1389.
47. O'Phelan K, McArthur DL, Chang CW, et al. The impact of substance abuse on mortality in patients with severe traumatic brain injury. *J Trauma*. 2008;65:674-677.
48. Blondell RD, Looney SW, Krieg CL, et al. A comparison of alcohol-positive and alcohol-negative trauma patients. *J Stud Alcohol*. 2002;63:380-383.
49. Kraus JF, Morgenstern H, Fife D, et al. Blood alcohol tests, prevalence of involvement, and outcomes following brain injury. *Am J Public Health*. 1989;79:294-299.
50. Salim A, Ley EJ, Cryer HG, et al. Positive serum ethanol level and mortality in moderate to severe traumatic brain injury. *Arch Surg*. 2009;144:865-871.
51. Tien HC, Tremblay LN, Rizoli SB, et al. Association between alcohol and mortality in patients with severe traumatic head injury. *Arch Surg*. 2006;141:1185-1191.
52. Ward RE, Flynn TC, Miller PW, et al. Effects of ethanol ingestion on the severity and outcome of trauma. *Am J Surg*. 1982;144:153-157.
53. Yaghoubian A, Kaji A, Putnam B, et al. Elevated blood alcohol level may be protective of trauma patient mortality. *Am Surg*. 2009;75:950-953.
54. Friedman LS. Dose-response relationship between in-hospital mortality and alcohol following acute injury. *Alcohol*. 2012;46:769-775.