Emma Kuusela

MORTALITY AND ASSOCIATED RISK FACTORS IN PATIENTS WITH SEVERE METHANOL OR ETHYLENE GLYCOL POISONING TREATED WITH DIALYSIS: A RETROSPECTIVE COHORT STUDY

Syventävien opintojen kirjallinen työ

Kevätlukukausi 2023

Emma Kuusela

MORTALITY AND ASSOCIATED RISK FACTORS IN PATIENTS WITH SEVERE METHANOL OR ETHYLENE GLYCOL POISONING TREATED WITH DIALYSIS: A RETROSPECTIVE COHORT STUDY

Kliininen laitos

Kevätlukukausi 2023

Vastuuohjaaja: Panu Uusalo

TURUN YLIOPISTO

Lääketieteellinen tiedekunta

KUUSELA, EMMA: Mortality and associated risk factors in patients with severe methanol or ethylene glycol poisoning treated with dialysis: a retrospective cohort study

Syventävien opintojen kirjallinen työ, 10s., 5 liites.

Anestesiologia ja tehohoito

Huhtikuu 2023

Methanol (MET) and ethylene glycol (EG) are toxic alcohols with a high mortality rate. Their toxic metabolites cause hypoxia, cytotoxicity, end-organ toxicity, and severe metabolic acidosis. Even with adequate treatment, patient survival rate is poor due to late presentation of symptoms. The aim of this study was to better understand the clinical course and mortality in adults with MET or EG poisoning.

In this retrospective cohort study, data were collected from 15 MET and 13 EG patients treated in the intensive care unit (ICU) at Turku University Hospital in 2010-2019. Laboratory markers, hourly urine output and Glasgow Coma Scale were measured on admission and 24 hours after initiation of renal replacement therapy (RRT) to assess the severity of acidosis, kidney function and mental status. In addition, 90-day outcome data were collected.

As a result of univariate analysis of the data, higher anion gap and lower pH, bicarbonate, base excess, and Glasgow Coma Scale score were associated with 90-day mortality. Patients with MET or EG poisoning were severely acidotic on admission with a mean pH of 7.1±0.2. Compared to MET patients, patients with EG poisoning were older and they had lower hourly urine output in the first 24 hours.

In conclusion, severe metabolic acidosis, high anion gap or altered mental status on admission were associated with mortality in both MET and EG patients. Patients with EG poisoning seem to have a lower urine output.

Keywords: metanoli, etyleeniglykoli, metabolinen asidoosi, myrkytys

Mortality and associated risk factors in patients with severe methanol or ethylene glycol poisoning treated with dialysis. A retrospective cohort study.

Emma Kuusela, BM[1,2], Mikko J. Järvisalo[1,2], MD, PhD, Tapio Hellman, MD, PhD, Panu Uusalo[1,2]*, MD, PhD

[1]Department of Anaesthesiology and Intensive Care, Turku University Hospital and University of Turku, Turku, Finland

[2]Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital and University of Turku, Turku, Finland

[3]Kidney Center, Turku University Hospital and University of Turku, Turku, Finland

Declarations of interests: none.

*Corresponding author: Panu Uusalo MD, PhD

Department of Anaesthesiology and Intensive Care, University of Turku, P.O. Box 51 (Kiinamyllynkatu 4-8), FI-20521 Turku, Finland

e-mail: pijuus@utu.fi, tel: +358 2 313 0000

Orcid-ID 0000-0001-5120-88

ABSTRACT

Objective: To compare the initial clinical course and data on 90-day mortality in adult patients with methanol (MET) or ethylene glycol (EG) poisoning treated with dialysis.

Methods: Data on patient demographics, clinical parameters at intensive care unit (ICU) admission and for the first 24 hours after dialysis initiation were collected and 90-day outcome data were collected in 28 patients with MET (n=15) or EG (n=13) poisoning treated with dialysis in this retrospective cohort study.

Results: Mean admission pH was 7.1±0.2, median bicarbonate 9.3 (7.2-14.2) mmol/l and median anion gap 22.1 (15.8-28.1). In univariate analysis, patients with EG poisoning were older (p=0.04) and had lower hourly urine output (p=0.003) during the first 24 hours after initiation of dialysis compared to patients with MET poisoning. Six (46%) patients with MET poisoning and 3 (20%) patients with EG poisoning died within 90-days of ICU admission (p=0.23). Higher anion gap (p=0.02) and lower pH (p=0.03), bicarbonate (p=0.01), base excess (p=0.01) and Glasgow Coma Scale score (p=0.04) were associated with 90-day mortality.

Conclusions: Metabolic acidosis, high anion gap and altered mental status on admission appear to be associated with mortality in MET or EG poisoning. Patients with EG poisoning may have lower urine output compared to patients with MET poisoning.

INTRODUCTION

Methanol (MET) and ethylene glycol (EG) are considered extremely toxic substances. MET is a clear liquid that has a taste similar to ethanol and is commonly used in industrial products such as windshield washer fluids (1). EG is an odorless and colorless liquid found in antifreeze and other chemical compounds (2). Ingested MET and EG are metabolized by alcohol dehydrogenase (ADH) and then aldehyde dehydrogenase (ALDH). MET is metabolized into formaldehyde and then formic acid, which inhibits mitochondrial respiration leading to cellular hypoxia and cytotoxicity. EG is oxidized into glycolic acid and finally oxalic acid. Oxalic acid causes end-organ toxicity through deposition of precipitated calcium oxalate crystals into various tissues. Furthermore, oxalic acid and glycolic acid induce tissue toxicity and the metabolic acidosis (3, 4, 5)

Patients with voluntary or inadvertent MET or EG poisoning often present with analogous symptoms, that may resemble other common acute illnesses such as diabetic ketoacidosis or sepsis. Furthermore, laboratory tests needed for the diagnosis of MET or EG poisoning may not be immediately available leading to potential delays in care (6). Apart from high serum MET or EG concentrations, the indications for renal replacement therapy (RRT) in patients with MET or EG poisoning include acute kidney injury (AKI), severe metabolic acidosis and high anion gap (7, 8). MET poisoning typically results in visual impairment and central nervous system damage (8), whereas AKI is more typical in EG poisoning (9). Without sufficient care MET and EG poisoning result in significant morbidity and mortality (8-10).

The primary aim of RRT in patients with MET or EG poisoning is to promptly remove the toxin and its injurious metabolites. The preferred RRT modality is intermittent hemodialysis (IHD). IHD is considered superior to continuous renal replacement therapy (CRRT) due to more rapid toxin clearance (8), whereas CRRT is usually preferred in hemodynamically unstable patients (11). Even with sufficient treatment, MET and EG poisoning are associated with poor survival often due to late presentation (9, 12).

In this observational retrospective cohort study, our aim was to compare the characteristics and outcomes of patients with MET or EG poisoning treated with RRT in the ICU of a tertiary academic medical center during a ten-year period.

METHODS

This retrospective single-center cohort study included consecutive patients admitted to the ICU of Turku University Hospital between January 1st, 2010 and September 31st, 2019 due to MET or EG poisoning requiring RRT. MET or EG poisoning were confirmed with a corresponding serum MET or EG concentration of 3 mmol/l or more on ICU admission. Patients under the age of 18 were excluded as well as patients with a history of chronic severe liver disease (Child-Pugh A or worse) or chronic kidney disease (eGFR <20 ml/min or need for maintenance dialysis).

Blood pH, glucose, lactate, bicarbonate, electrolytes as well as hemodynamics and vasoactive medication were recorded on ICU admission and at 6-hour intervals for the first 24 hours after RRT initiation. Patient demographics, disease history, medications and biochemical data were also extracted from the hospital medical records. Creatinine and eGFR, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, were assessed on admission and at hospital discharge.

Laboratory assays

All blood pH, lactate, bicarbonate, glucose and electrolyte samples were collected with a lithium heparin syringe from an arterial line within 5 min of venous blood sample collection and analyses were conducted with the ABL90 point-of-care cartridge-based blood gas analyzes (Radiometer Medical ApS, Brønshøj, Denmark). The analysis of lactate was performed using an amperometric method based on lactate oxidase. Venous blood samples were analyzed in the central laboratory of Turku University Hospital (TYKSLAB).

CRRT and IHD

The choice of RRT modality between CRRT and IHD was under the discretion of the attending ICU physician according to clinical care standards and patient hemodynamics. CRRT was chosen for hemodynamically compromised patients.

IHD was performed using Fresenius Cordiax 5008 dialysis monitors with 5–10 h treatment duration, blood flow rates 250-300 ml/min, dialysate flow rate of 500 ml/min, and low-molecular-weight heparin (LMWH) anticoagulation, as appropriate, depending on the clinical condition of the patient.

CRRT was performed according to a standard protocol employed in our centre using Fresenius Multifiltrate CRRT monitors and 1.80 m2 polysulfone hemofilter Ultraflux AV1000 or Ultraflux EMiC2 membranes with the CiCa® dialysate K2 and 4 % trisodium citrate to achieve regional citrate anticoagulation (Fresenius Medical Care, Bad Hamburg, Germany). Blood and dialysate flow rates were prescribed according to the weight of the patient and by the caring ICU physician to target a dialysis dose of 30 ml/kg/h.

Compliance with ethical standards

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This retrospective register-based study involved data from the hospital medical records to produce an anonymized dataset for analyses. Informed consent was not required due to the retrospective

nature of the study. The study was approved by the Ethics committee of South-West Finland Hospital District (ref T143/2016). All patient details were de-identified before conduction of the analyses and reporting. The reporting of this study conforms to STROBE guidelines. (13)

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request after permission of the Ethics Review Board.

Statistics

Results on continuous covariates were expressed as mean values with standard deviations (SD) for normally distributed variables, and as medians with inter-quartile ranges (IQR) when the normality assumption was not met. Categorical covariates were reported with absolute and relative (percentage) frequencies. The Shapiro-Wilks test ($P > 0.05$) was used to assess normality assumptions in continuous covariates.

Repeated measures analysis of variance (ANOVA) was used to compare pH, bicarbonate, anion gap, lactate, norepinephrine dose and hourly urine output during the first 24 h after RRT initiation between the study subgroups (MET vs. EG poisoning; 90d survivors vs. non-survivors). The correlation/clustering between repeated measurements within a subject was taken into account by using autoregressive or unstructured correlation structures, respectively, based on Akaike's and Bayesian information criterion examination. Student's t-test was used to compare continuous normally distributed covariates and Chi-square test or Fisher's exact test for categorical covariates in the study subgroups. For skewed variables, groupwise comparisons were performed using a non-parametric Kruskall-Wallis test. Due to the limited number of deceased patients in the dataset, multivariable logistic regression models for 90 d mortality could not be constructed due to the increased risk for overfitting.

$P < 0.05$ (two-tailed) was considered statistically significant. The analyses were performed with JMP Pro 13.0 for Mac (SAS Institute Inc., Cary, NC, USA).

RESULTS

Altogether, twenty-eight patients with EG (15/54%) or MET (13/46%) poisoning treated with RRT in the ICU between years 2010 and 2019 were included in the study. Mean age of the study population was 52±13 years, mean BMI 25.7±5.9 kg/m2 and 5 (17.9%) patients were female.

Twenty-three patients received IHD and 5 patients received CRRT due to instable hemodynamics. Median time from ICU admission to RRT initiation was 2.0 (0.5-10) hours (Table 1). Furthermore, 10 (36%) patients received ethanol infusion and 12 (43%) patients received fomepizole medication. One patient received both ethanol infusion and fomepizole, whereas 6 patients received no antidote. Furthermore, 5 (33%) and 5 (38%) patients received ethanol infusion while 6 (40%) and 7 (54%) patients received fomepizole medication for EG or MET poisoning, respectively. There was no difference in the use of antidotes between EG and MET groups (p=0.33).

Median duration of ICU stay was 43 (22-60) hours, 18 (62%) patients required mechanical ventilation and 8 (29%) patients requirer vasopressor support. Median duration of RRT was 15 h (10-26). ICU-, hospital, 90 day and 365-day mortality were 18% (5 patients), 25% (6 patients), 32% (9 patients) and 36% (10 patients), respectively (Table 2).

Patients with EG poisoning were older (57.0±13.2 vs. 44.9±11.6 years; p=0.03) and had higher blood lactate (21.0 (5.4-28.0) vs. 4.5 (2.1-8.5); p=0.003) on admission (Table 3) and higher lactate (p=0.01) and lower hourly urine output (p=0.003) during the first 24 h after RRT initiation compared to patients with MET poisoning (Fig. 1 and Fig. 2).

Six (46%) patients with MET poisoning and 3 (20%) patients with EG poisoning died within 90 days of ICU admission and there was no difference in mortality risk between the study groups (p=0.23). Patients deceased within 90 days required more often mechanical ventilation (89% vs. 47%; p=0.04), had higher anion gap (30±9 vs. 21±8; p=0.02) and lower pH (6.9±0.2 vs. 7.1±0.2; p=0.03), bicarbonate (7.5 (5.6-9.0) vs. 13.2 (7.6-19.3); p=0.01) and base excess (-15 (-26-(-5)) vs. -27 (-31-(-23)); p=0.01) at baseline compared to survivors (Table 3).

Lactate and urine output during the first 24 h after RRT initiation were not different in the patients deceased within 90 days compared to survivors (Fig. 1 and Fig. 2). Moreover, there was no statistically significant difference in pH (Fig. 3), norepinephrine requirement, anion gap (Fig. 4) or bicarbonate level during the first 24 hours after RRT initiation between the study groups or between survivors and non-survivors. Toxin concentrations on admission were not associated with 90 day mortality in patients with EG (16 (7-49) mmol/l; p=0.26) or MET (94 (50-148) mmol/l; p=0.13) poisoning (Table 1).

Reduced LMWH anticoagulation was used in 6 (46%) patients with MET poisoning due to clinical reasons. However, in the majority of MET patients managed with IHD circuit anticoagulation was not applied as per current treatment guidelines due to case reports of intracranial hemorrhage.

DISCUSSION

The present study shows that patients with EG poisoning requiring RRT may lower hourly urine output on ICU admission and within 24 hours after RRT initiation compared to patients with MET poisoning. Mortality was high and similar in patients with either type of poisoning. Patients deceased within 90 days had higher anion gap and lower pH, bicarbonate, base excess and GCS scores at baseline compared to survivors. To our knowledge this is the first study comparing the outcomes in patients with EG or MET poisoning managed with RRT in the ICU using extensive repeated measures clinical and biochemical data during the first 24 hours after RRT initiation.

Fomepizole and ethanol can be used as antidotes in the treatment of EG or MET poisoning as both inhibit the function of ADH and, thereby, decrease the production of toxic metabolites (7). However, IHD has been found to be the most effective RRT modality in the management of MET or EG poisoning and CRRT is recommended in only hemodynamically unstable patients (11, 14). Nevertheless, hemodialysis efficiently reduces the half-life of circulating MET, EG and their metabolites in spite of the chosen modality (8). In our study 23 patients received IHD and 5 patients CRRT due to instable hemodynamics. Though used in a subset of patients in our cohort, in general, current guidelines recommend against the use of circuit anticoagulation when treating methanol poisoning with hemodialysis due to case reports of intracranial hemorrhage. (8)

It is still under debate, whether to administer or refrain form an antidote, fomepizole or ethanol infusion, in patients with EG or MET poisoning receiving RRT. Out of the two possible antidotes, fomepizole has been considered the first-line choice due to its higher potency in ADH inhibition and easier administration and monitoring protocol (15). However, the efficacy of the antidotes in managing patients with EG or MET poisoning is limited by the formation of deleterious metabolites prior to antidote administration as fomepizole and ethanol can only inhibit ADH but not remove or cancel the effects of already formed metabolites. It has been reported that high anion gap and severe acidosis in patients with EG or MET poisoning is associated with the delay between toxin ingestion and hospital admission. (9, 12) Accordingly, the patients in the present study had a high anion gap and severe metabolic acidosis on admission suggesting a prolonged delay between ingestion and presentation. Thus, hemodialysis was required to remove both the toxin and formed metabolites and correct the metabolic acidosis.

Prompt initiation of care is essential in the management of EG or MET poisoning. However, delays in initiating care can be substantial for several reasons. First, ascertaining the toxic agent in patients presenting with a poisoning can often be difficult, especially so in patients with altered level of consciousness. Conversely, conscious patients may be hesitant to admit the ingestion of MET or EG and seek help due to embarrassment or self-destructive motivations (2). Second, the availability of blood gas chromatography–mass spectrometry instruments required for diagnosis varies between centers (15, 16). Third, the time interval between ingestion and presentation at the hospital has been found to average at 24-48 hours (16-18). Fourth, many clinicians rely upon the osmolar gap to screen for toxic alcohol poisoning, but the osmolar gap, though often helpful, is neither 100% sensitive nor 100% specific for detection of toxic alcohol poisoning. (16) For these reasons it is often mandatory to initiate treatment based on patient history and clinical condition before the detrimental toxin is identified. Moreover, the observed clinical condition, laboratory findings and disease characteristics in patients with EG or MET poisoning have been similar in prior studies (19).

When surrogate alcohol poisoning is suspected, rapid initiation of RRT, while not a toxin-specific treatment, is the most effective way to remove both the toxin and the produced toxic metabolites and prevent end-organ damage. Furthermore, both EG and MET can cause permanent neurologic damage and, therefore, prompt toxin removal is necessary to minimize adverse CNS sequelae. (8, 20).

The association between higher baseline anion gap and lower pH, bicarbonate, base excess and GCS score observed in the present cohort is in line with previous observational studies on patients with severe MET or EG poisoning (9, 19, 21). Furthermore, high serum creatinine (6, 22), blood glucose (17, 23) or hypothermia (22) at baseline have been shown to be associated with mortality in patients with MET or EG poisoning in prior studies. Notably, baseline lactate appeared to be higher in EG group. However, we measured blood lactate with an oxidase-based system, which has been shown to produce a falsely elevated lactate level in the presence of glycolic acid that is structurally similar to lactate. Although true lactate levels could not be reported for patients with EG poisoning in our study, we believe that it is important to inform the healthcare community about this diagnostic issue with EG poisoning since point-of-care assays using oxidase based methods for blood lactate measurement are widely in use in western countries. (24)

Limitations of this study include its retrospective design and relatively limited number of patients with EG or MET poisoning treated in our unit. The lactate dehydrogenase method, which is more specific to lactic acid and is not affected by the presence of glycolic acid would have been more precise method to analyze lactate. Regrettably, this method was not available in our study. Thus, no direct conclusions can be drawn about the lactate levels in patients with EG poisoning as we used the oxidase based analysis in the measurement of blood lactate. However, the study included all critically ill patients with EG or MET poisoning requiring RRT during a ten-year period at our ICU. Furthermore, patients treated in the ICU of the research hospital are monitored continuously and all vital parameters are recorded to the electronic patient database. Moreover, the study included comprehensive serial measurements of a vast array of hemodynamic and biochemical variables recorded on admission and every 6 hours during the first 24 hours after RRT initiation enabling the use of repeated measures analyses to examine differences between patients with MET or EG poisoning and 90d survivors and non-survivors, respectively.

To conclude, patient survival was poor and comparable in this retrospective cohort study comparing patients with severe MET or EG poisoning treated with RRT in the ICU and severe metabolic acidosis, high anion gap or altered mental status on admission were associated with mortality. Patients with EG may lower urine output over the first 24 hours of RRT compared to patients with MET poisoning.

Acknowledgements: The authors are grateful to Mrs. Eveliina Loikas, RN for help with the data collection.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interests: None.

REFERENCES

1. Ashurst JV, Nappe TM. Methanol Toxicity. 2021 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. https://www.ncbi.nlm.nih.gov/books/NBK482121/. Accessed Sept 12, 2021.

2. Iqbal A, Glagola JJ, Nappe TM. Ethylene Glycol Toxicity. 2021 Aug 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. https://www.ncbi.nlm.nih.gov/books/NBK537009/. Accessed Sept 12, 2021

3. King JD, Kern MH, Jaar BG. Extracorporeal Removal of Poisons and Toxins. Clin J Am Soc Nephrol. 2019 Sep 6;14(9):1408-1415. doi: 10.2215/CJN.02560319. Epub 2019 Aug 22.

4. Bove KE. Ethylene glycol toxicity. Am J Clin Pathol. 1966 Jan;45(1):46-50. doi: 10.1093/ajcp/45.1.46.

5. Jacobsen D, Hewlett TP, Webb R, Brown ST, Ordinario AT, McMartin KE. Ethylene glycol intoxication: evaluation of kinetics and crystalluria. Am J Med. 1988 Jan;84(1):145-52. doi: 10.1016/0002-9343(88)90024-1

6. Lung DD, Kearney TE, Brasiel JA, Olson KR. Predictors of Death and Prolonged Renal Insufficiency in Ethylene Glycol Poisoning. J Intensive Care Med. 2015 Jul;30(5):270-7. doi: 10.1177/0885066613516594. Epub 2013 Dec 26. PMID: 24371252.

7. Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol. 2008 Jan;3(1):208-25. doi: 10.2215/CJN.03220807

8. 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 Feb;43(2):461-72. doi: 10.1097/CCM.0000000000000708.

9. Grigorasi GR, Nistor I, Corlade-Andrei M, et al. Outcomes of death and prolonged renal insufficiency in ethylene glycol poisoned patients. Int Urol Nephrol. 2021 Mar 18. doi: 10.1007/s11255-021-02837-3.

10. Gallagher N, Edwards FJ. The Diagnosis and Management of Toxic Alcohol Poisoning in the Emergency Department: A Review Article. Adv J Emerg Med. 2019 May 22;3(3):e28. doi: 10.22114/ajem.v0i0.153.

11. Zakharov S, Rulisek J, Nurieva O, et al. Intermittent versus continuous renal replacement therapy in acute methanol poisoning: comparison of clinical effectiveness in mass poisoning outbreaks. Ann Intensive Care. 2017 Dec;7(1):77. doi: 10.1186/s13613-017-0300-7.

12. Hovda KE, Hunderi OH, Tafjord AB, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. J Intern Med. 2005 Aug;258(2):181-90. doi: 10.1111/j.1365-2796.2005.01521.x.

13. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007; 147: 573-577.

14. Kim Z, Goldfarb DS. Continuous renal replacement therapy does not have a clear role in the treatment of poisoning. Nephron Clin Pract. 2010;115(1):c1-6. doi: 10.1159/000286343.

15. Rietjens SJ, de Lange DW, Meulenbelt J. Ethylene glycol or methanol intoxication: which antidote should be used, fomepizole or ethanol? Neth J Med. 2014 Feb;72(2):73-9. PMID: 24659589.

16. Krasowski MD, Wilcoxon RM, Miron J. A retrospective analysis of glycol and toxic alcohol ingestion: utility of anion and osmolal gaps. BMC Clin Pathol. 2012 Jan 12;12:1. doi: 10.1186/1472-6890-12-1.

17. Yousefinejad V, Moradi B, Mohammadi Baneh A, Sheikhesmaeili F, Babahajian A. Prognostic Factors of Outcome in MET Poisoning; an 8-year Retrospective Cross-sectional Study. Arch Acad Emerg Med. 2020 Sep 5;8(1):e69. PMID: 33134965

18. Zakharov S, Pelclova D, Navratil T, et al. Intermittent hemodialysis is superior to continuous veno-venous hemodialysis/hemodiafiltration to eliminate MET and formate during treatment for MET poisoning. Kidney Int. 2014 Jul;86(1):199-207. doi: 10.1038/ki.2014.60.

19. Coulter CV, Farquhar SE, McSherry CM, Isbister GK, Duffull SB. Methanol and ethylene glycol acute poisonings - predictors of mortality. Clin Toxicol (Phila). 2011 Dec;49(10):900-6. doi: 10.3109/15563650.2011.630320.

20. Ethylene glycol. National Institute for Occupational Safety and Health. Emergency Response Database. August 22, 2008. https://www.cdc.gov/niosh/ershdb/EmergencyResponseCard_29750031.html. Accessed Sept 12, 2021.

21. Thanacoody RH, Gilfillan C, Bradberry SM, et al. Management of poisoning with ethylene glycol and methanol in the UK: a prospective study conducted by the National Poisons Information Service (NPIS). Clin Toxicol (Phila). 2016;54(2):134-40. doi: 10.3109/15563650.2015.1116044.

22. Lee CY, Chang EK, Lin JL, et al. Risk factors for mortality in Asian Taiwanese patients with methanol poisoning. Ther Clin Risk Manag. 2014;10:61-67. doi:10.2147/TCRM.S51985

23. Sanaei-Zadeh H, Esfeh SK, Zamani N, Jamshidi F, Shadnia S. Hyperglycemia is a strong prognostic factor of lethality in MET poisoning. J Med Toxicol. 2011 Sep;7(3):189-94. doi: 10.1007/s13181-011-0142-x.

24. Sagar AS, Jimenez CA, Mckelvy BJ. Lactate gap as a tool in identifying ethylene glycol poisoning. BMJ Case Rep. 2018 Mar 9;2018:bcr2018224243. doi: 10.1136/bcr-2018-224243.

FIGURE LEGENDS

Figure 1. Hourly urine output (ml/h) measured every 6 hours during the first 24 hours after initiation of renal replacement therapy in patients with EG vs MET poisoning (panel A) and survivors vs non-survivors (panel B).

Figure 2. Blood pH (U) measured every 6 hours during the first 24 hours after initiation of renal replacement therapy in patients with EG vs MET poisoning (panel A) and survivors vs non-survivors (panel B).

Figure 3. Anion gap (mmol/l) measured every 6 hours during the first 24 hours after initiation of renal replacement therapy in patients with EG vs MET poisoning (panel A) and survivors vs non-survivors (panel B).

Figure 4. Blood lactate (mmol/l) measured every 6 hours during the first 24 hours after initiation of renal replacement therapy in patients with EG vs MET poisoning (panel A) and survivors vs non-survivors (panel B).

Table 1. Baseline measurements on intensive care unit admission

		Normal laboratory range
pH (U)	7.08±0.24	7.35-7.43
Base excess (mmol/l)	-23 (-27 - -13)	-2.5-2.5
Bicarbonate (mmol/l)	9.3 (7.2-14.2)	22-26
Anion gap (mEq/l)	22.1 (15.8-28.1)	8-16
Blood lactate (mmol/l)	8 (2-21)	< 2.0
Plasma creatinine (µmol/l)	116 (79-146)	60-100[3] / 50-90[4]
Serum methanol concentration (mmol/l)[1]	94 (50-138)	> 2.0
Serum ethylene glycol concentration (mmol/l)[2]	16 (7-49)	> 1.0
Plasma sodium (mmol/l)	143±5	137-144
Plasma potassium (mmol/l)	4.8±1.1	3.5-4.8
Plasma chloride (mmol/l)	109±6	99-111
Blood hemoglobin (g/l)	145 (129-154)	134-167[3] / 117-155[4]
Plasma glucose (mmol/l)	9 (7-14)	5-10
Plasma bilirubin (µmol/l)	4 (0-9)	< 21
Plasma alanine aminotransferase (U/l)	26 (21-51)	< 35
Plasma international normalized ratio	1.1 (0.9-1.0)	0.9-1.2
Mean arterial pressure (mmHg)	86±14	65-90
PaO2/FiO2-ratio (kPa)	63 (48-76)	> 40
SOFA	7±4	
SAPS-II	38 (25-63)	
APACHE-II	20 (15-32)	
Glasgow coma scale score	13 (3-15)	

Continuous variables are expressed as mean ± SD or median (IQR)

[1]Only patients with methanol poisoning included, [2]Only patients with ethylene glycol poisoning included,

[3]For male patients, [4]For female patients

APACHE-II = Acute Physiology And Chronic Health Evaluation score; SAPS-II = simplified acute physiology score II; SOFA = sequential organ failure assessment; PaO2/FiO2 = ratio of arterial oxygen partial pressure/fraction of inspired oxygen

Table 2. Treatment specifics and patient outcomes in the study

Highest recorded SOFA	8.0±3.8
Highest requirement of norepinephrine (µg/kg/min)	0.11±0.13
Time to dialysis from ICU admission (h)	2.0 (0.5-10)
Duration of renal replacement therapy (h)	15 (10-26)
PaO2/FiO2-ratio at admission (kPa)	63 (48-76)
Mechanical ventilation (n/%)	18/62.1
Duration of ICU stay (h)	43 (22-60)
Mortality ICU (n/%)	5/17.9
Mortality 90 d (n/%)	9/32.1
Mortality 365 d (n/%)	10/35.7

Continuous variables are expressed as mean ± SD or median (IQR)

SOFA = sequential organ failure assessment; PaO2/FiO2 = ratio of arterial oxygen partial pressure/fraction of inspired oxygen

Table 3. Univariate comparisons between the study subgroups.

	By poisoning			By 90 day mortality
Variable	EG (n=15)	MET (n=13)	p-value	Survivors (n=19)
Women	2 (13%)	4 (31%)	0.37	5 (26%)
Age (years)	57.0±13.2	44.9±11.6	0.03	52.9±16.0
Weight (kg)	75 (73-85)	75 (65-80)	0.22	75 (65-85)
BMI (kg/m^2)	25.4 (24.2-26.8)	23.9 (21.1-26.7)	0.16	24.9 (22.4-26.8)
Maximum SOFA score	9±4	7±3	0.50	7±4
SAPS-II score	46±19	33 (23-62)	0.31	37 (25-58)
APACHE-II score	23±8	18 (14-34)	0.63	19 (15-31)
PaO2/FiO2 (kPa)	68 (50-77)	59 (32-68)	0.16	68 (52-76)
MAP (mmHg)	99±25	92 (79-97)	0.09	96±23
NE requirement (mcg/kg/min)	0.00 (0.00-0.00)	0.00 (0.00-0.11)	0.18	0.00 (0.00-0.00)
MV requirement (n/%)	8 (53%)	9 (69%)	0.39	9 (47%)
pH (U)	7.1±0.2	7.1±0.3	0.53	7.1±0.2
Blood lactate (mmol/l)	21.0 (5.4-28.0)	4.5 (2.1-8.5)		11.1 (2.3-25.0)
Blood bicarbonate (mmol/l)	11.8 (7.6-13.9)	7.5 (6.1-17.1)	0.17	13.2 (7.6-19.3)
Plasma chloride (mmol/l)	109±7	109±5	0.71	110±6
Blood base excess (mmol/l)	-18 (-14-(-26)	-26 (-29-(-9))	0.24	-15 (-26-(-5))
Anion gap (mmol/l)	25±10	23±10	0.80	21±8
Plasma glucose (mmol/l)	8.5 (7.0-9.7)	10.2 (7.2-16.0)	0.29	8.5 (7.1-9.7)
Blood hemoglobin (mg/l)	141±15	144±15	0.66	145±17
Plasma creatinine (µmol/l)	119 (77-147)	96 (81-139)	0.71	95 (77-124)
Plasma sodium (mmol/l)	144±6	144±5	0.99	145±4
Plasma potassium (mmol/l)	4.9±1.0	4.7±1.3	0.56	4.5±0.9
INR	1.0 (0.9-1.0)	0.9 (0.9-1.0)	0.49	1.0 (0.9-1.0)
Plasma bilirubin (µmol/l)	4 (3-11)	3 (0-8)	0.36	5 (0-10)
ALAT (U/l)	26 (23-41)	25 (20-54)	0.72	26 (21-52)
Urine output (ml/kg/h)	1.2 (0.5-1.9)	1.8 (1.1-2.3)	0.15	1.3 (0.6-1.9)
ICU fluid balance (ml)	381 (48-2422)	191 (27-710)	0.47	104 (27-1012)
GCS	13 (3-15)	12 (5-15)	0.74	14 (5-15)
Body temperature (°C)	34.5 (0.5)	34.4 (0.4)	0.40	34.7 (0.4)
Duration of RRT (h)	19 (9-26)	14 (11-28)	0.95	15 (9-26)
Length of ICU stay (h)	1.81 (0.94-2.48)	1.72 (0.96-2.49)	0.60	1.72 (0.88-2.29)
ICU mortality (n/%)	1 (7%)	4 (31%)	0.15	0 (0%)
Hospital mortality (n/%)	1 (7%)	5 (38%)	0.07	0 (0%)
90 day mortality (n/%)	3 (20%)	6 (46%)	0.23	0 (0%)
365 day mortality (n/%)	4 (27%)	6 (46%)	0.28	1 (5%)

Values are mean±SD or median (IQR).

ALAT = plasma alanine amino transferase; APACHE-II = Acute Physiology And Chronic Health Evaluation score; BMI = body mass index; ICU = intensive care unit; INR = international normalized ratio; MV = mechanical ventilation; NE = norepinephrine; SOFA = sequential organ failure assessment; SAPS-II = simplified acute physiology score II; PaO2/FiO2 = ratio of arterial oxygen partial pressure/fraction of inspired oxygen