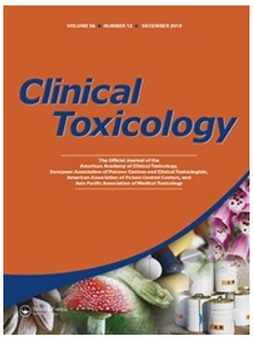

Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Joshua Trebach, Sanjay Mohan, Marlis Gnirke, Mark K. Su, Sophie Gosselin & Robert S. Hoffman (2023): Retrospective evaluation of management guidelines for extracorporeal treatment of metformin poisoning, Clinical Toxicology, DOI: 10.1080/15563650.2022.2156880

To link to this article: https://doi.org/10.1080/15563650.2022.2156880

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2022.2156880

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CLINICAL RESEARCH

Retrospective evaluation of management guidelines for extracorporeal treatment of metformin poisoning

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ABSTRACT

Introduction: The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup defined criteria for extracorporeal toxin removal in patients with metformin poisoning. The primary objective of this study was to determine the benefit of extracorporeal toxin removal in patients meeting EXTRIP criteria. The secondary objective was to determine the performance characteristics of the EXTRIP criteria.

Methods: This was a single-center retrospective analysis of metformin poisoned patients. Inclusion criteria were: suspicion of metformin poisoning with at least one of the following present: lactate concentration >5 mmol/L; pH < 7.35; or impaired kidney function. Patient data were extracted by reviewers who were unaware of the study hypothesis. Cases were analyzed based on EXTRIP criteria, whether extracorporeal toxin removal was performed, and survival. Sensitivity, specificity, negative predictive value and positive predictive value were calculated with respect to the EXTRIP criteria and survival.

Results: Of 201 patients studied, 145 patients met recommended EXTRIP criteria (EXTRIP positive) and 56 patients did not (EXTRIP negative). Among patients who met recommended EXTRIP criteria, 96 received extracorporeal toxin removal and 49 did not. There was no difference in survival between these groups: 75.0% versus 73.5%, respectively ($P > 0.05$). All 56 patients who did not meet EXTRIP criteria, survived (negative predictive value = 100%).

Discussion: The study did not demonstrate a survival benefit for extracorporeal toxin removal in those meeting EXTRIP criteria.

Conclusion: In this retrospective analysis, the recommended EXTRIP criteria had a negative predictive value for death of 100%. Further study is needed to evaluate the benefit of extracorporeal toxin removal in patients meeting EXTRIP criteria for metformin poisoning.

ARTICLE HISTORY
Received 1 June 2022
Revised 20 September 2022
Accepted 5 December 2022

KEYWORDS
Metformin; EXTRIP; hemodialysis; extracorporeal therapy

Introduction

Metformin is an essential medication for patients with diabetes mellitus, with additional indications in polycystic ovarian syndrome and obesity [1]. While metformin is generally safe and well-tolerated when appropriately dosed, a life-threatening metabolic acidosis with an elevated lactate concentration occurs in patients with impaired kidney function or following intentional overdose. This condition is variably described with the terms metformin-induced lactic acidosis and metformin-associated lactic acidosis [2]. Although there are no universally agreed upon definitions, metformin-induced lactic acidosis generally refers to events that follow an intentional overdose in otherwise healthy individuals, whereas metformin-associated lactic acidosis results from impaired metformin clearance in the setting of an acute illness [3]. The increased mortality that occurs in patients with metformin-induced lactic acidosis/metformin-associated lactic acidosis can be due to the acidosis, underlying medical conditions that predisposed to the acidosis (such as impaired kidney function), or both.

Because there is no specific antidotal therapy for patients with metformin poisoning, treatment is primarily supportive, with a focus on early gastrointestinal decontamination when appropriate, attempts to maintain, restore, or optimize kidney function, and correction of life-threatening acidemia. Extracorporeal toxin removal (ECTR) is a compelling management option for its potential to remove metformin and to correct severe acid-base, fluid, and electrolyte derangements that are often refractory to supportive treatment. Evidence for the dialyzability of metformin, however, is unclear and no

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/15563650.2022.2156880

randomized controlled studies assess the benefit of ECTR in patients with metformin poisoning [4]. Despite this, ECTR is commonly performed in metformin poisoned patients [3,5].

The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup defined a set of clinical and laboratory criteria for which they either "recommend" (1 D) or "suggest" (2 D) ECTR in patients with metformin poisoning [3]. A 1 D recommendation refers to strong consensus around weak data and translates into "most experts would perform ECTR" [6]. In contrast, a 2 D suggestion results from a lesser degree of consensus around the same weak data and generally translates into "many experts would perform ECTR, but some would not" [6]. These criteria, however, have never been subjected to external validation. This study seeks to evaluate the EXTRIP criteria through a retrospective assessment of metformin cases from a single poison center. The primary outcome was to determine if there was a survival benefit of ECTR in patients meeting EXTRIP criteria. The secondary outcome was to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the EXTRIP criteria for ECTR in patients with metformin poisoning.

Materials and methods

The New York City Poison Control Center (NYCPCC) provides toxicology consultation services to a catchment area of over 12 million people and maintains an electronic database (ToxiCall) dating back to January 1, 2000. All cases are coded for basic demographic information of the patients/callers in addition to case-specific information (route of exposure, clinical effects, treatments recommended and performed, and outcomes). There is also a free-text narrative portion that allows documentation of the clinical course and diagnostic studies that is updated until the patient's clinical course ends (patient discharge from hospital, patient death) or plateaus (no further toxicological management needed, patient medically cleared to psychiatry).

We performed a structured query language (SQL) search for all cases of suspected human metformin poisoning within the ToxiCall database from January 1, 2000 through April 30, 2021. Cases were then manually reviewed by two authors (SM, MG) who were unaware of the study hypothesis. Data were extracted and entered into a predesigned form *via* REDCap electronic data capture tools. Cases met inclusion criteria if the call originated from a healthcare facility, there was objective suspicion for metformin poisoning, and at least one of the following parameters were met: lactate concentration $\geq$5 mmol/L; pH $<$ 7.35; or impaired kidney function [7]. Cases were excluded if they were poorly or incorrectly coded, incomplete, or were home calls.

For each case, the following information was collected: patient age, patient sex, past medical history, nature of metformin overdose (acute, chronic, unknown), quantity of metformin taken (if known), co-ingestions, initial and peak metformin concentrations (if known), initial sodium, creatinine (initial, peak, baseline), pH (initial, lowest), initial PCO_2, bicarbonate (initial, lowest), lactate (initial, peak), blood urea nitrogen, creatinine, level of consciousness, presence of shock, impaired kidney function, type of ECTR performed (intermittent HD vs a continuous modality vs other vs none), and outcome including survival. Shock was defined as hypotension (systolic blood pressure $<$ 90 mmHg or mean blood pressure $<$ 65 mmHg) and impaired kidney function was defined as acute kidney injury (AKI) per the Kidney Disease Improving Global Outcomes (KDIGO) criteria or the inclusion of the words "anuria", "renal failure, or "kidney injury" in the documentation [8]. Ten percent of the extracted data were reviewed by the primary author (JT) for accuracy. Cases were then evaluated to determine if they met the recommended (1 D) indications for ECTR as established by the EXTRIP workgroup's recommendations on metformin (Box 1). Statistical analyses were performed *via* Fisher's exact test or Chi square when appropriate. A P-value$<$ 0.05 was considered statistically significant. Sensitivity, specificity, NPV, and PPV were calculated with 95% confidence intervals with respect to the EXTRIP criteria and the outcome of death.

In a post hoc analysis, stepwise modification of the EXTRIP criteria with respect to pH and lactate was performed to evaluate the criteria's sensitivity and specificity.

This study protocol was reviewed by the New York City Department of Health and Mental Hygiene Institutional Review Board institutional review board and deemed exempt from comprehensive review.

Results

The entire database contains over 1 million records for the study time frame. Figure 1 describes the case identification process. The final study population was comprised of 201 patients after inclusion and exclusion criteria were applied (Table 1). There were 145 patients who met the recommended EXTRIP criteria shown in Box 1 (EXTRIP positive) and 56 patients who did not meet those criteria (EXTRIP negative). Both groups were evaluated for whether they received ECTR or not, and their outcomes (i.e., survival or death) as shown in Figures 2 and 3. The only ECTR modalities utilized were intermittent hemodialysis ($n = 68$), continuous hemodialysis ($n = 30$), or both intermittent and continuous hemodialysis ($n = 2$).

Among the patients who met the recommended EXTRIP criteria, 96 received ECTR and 49 did not receive ECTR. In the group that received ECTR 75.0% survived ($n = 72$) and 25.0% ($n = 24$) died. Among the patients who met the

EXTRIP recommends ECTR if ANY of the following conditions are present:

- Lactate concentration >20mmol/L
- pH ≤ 7.0
- Comorbid conditions that lower the threshold for ECTR initiation
- Shock
- Impaired kidney function

Box 1. Recommended Extracorporeal Treatments in Poisoning Criteria Studied. ECTR: Extracorporeal toxin removal.

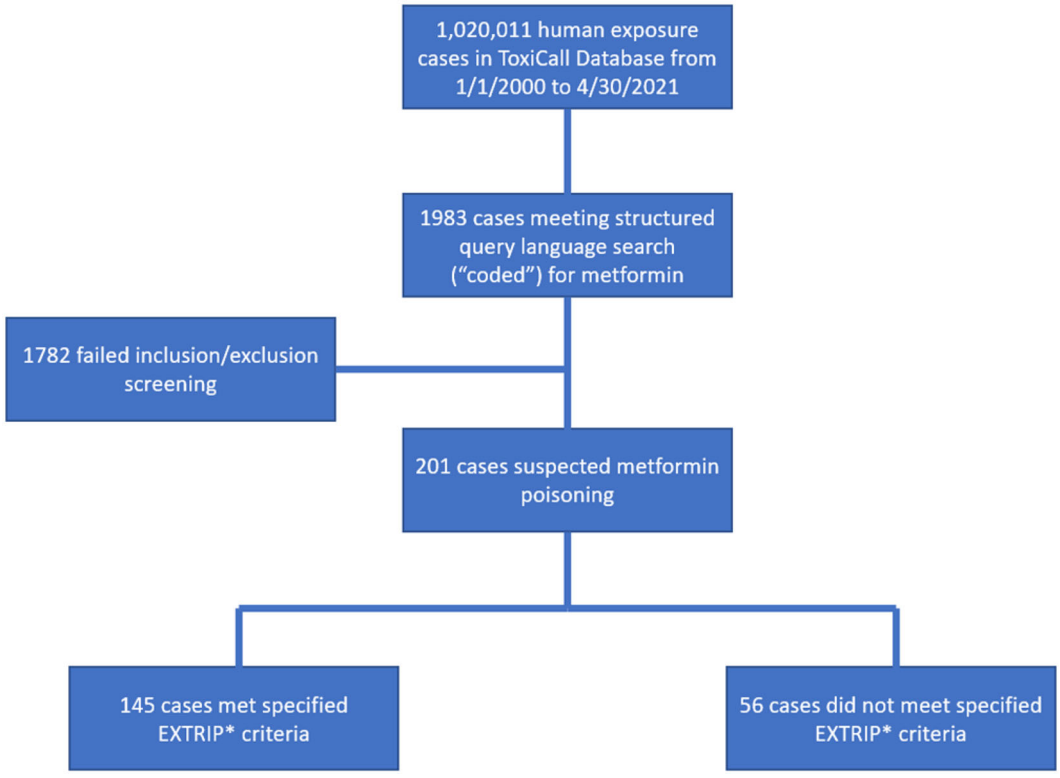

Figure 1. Flow Diagram of Study Population. *Extracorporeal Treatments in Poisoning Workgroup

Table 1. Demographics and Patient Characteristics.

	Total ($n = 201$)	EXTRIP positive[a] ($n = 145$)	EXTRIP negative[a] ($n = 56$)
Age in years (mean)	55.0 ($n = 201$)	58.0 ($n = 145$)	47.0 ($n = 56$)
Sex (% female)	51.2 ($n = 103$)	48.3 ($n = 70$)	58.9 ($n = 33$)
Initial pH (mean)	7.12 ($n = 168$)	7.05 ($n = 126$)	7.31 ($n = 42$)
Initial serum bicarbonate (mEq/L) (mean)	13.4 ($n = 145$)[b]	11.0 ($n = 105$)[d]	19.5 ($n = 40$)
Initial creatinine[c] (micromol/L) (mean)	355.4 ($n = 163$)	432.3 ($n = 127$)	84.9 ($n = 36$)
Initial lactate (mmol/L) (mean)	12.2 ($n = 181$)	14.3 ($n = 135$)	6.16 ($n = 46$)

[a]EXTRIP positive/negative means patients did/did not meet the recommended Extracorporeal Treatments in Poisoning Workgroup (1 D) criteria for metformin poisoning listed in Box 1.
[b]Four cases not included in calculation because bicarbonate was undetectable.
[c]Creatinine was converted from mg/dL to micromol/L by multiplying by 88.4.
[d]Three cases not included in calculation because bicarbonate was undetectable.

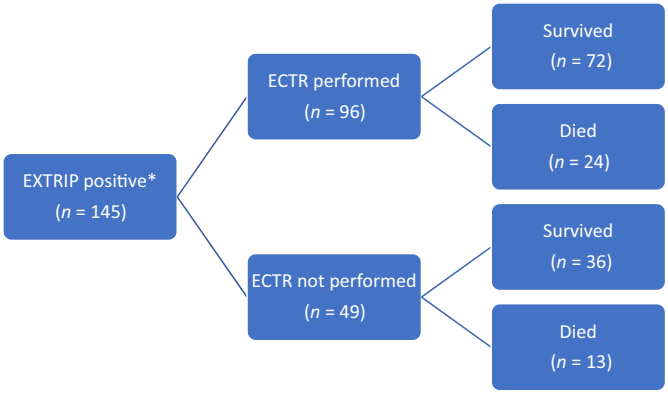

Figure 2. EXTRIP positive, ECTR, and Mortality. *EXTRIP positive means patients met the Extracorporeal Treatments in Poisoning Workgroup (1D) criteria for metformin poisoning listed in Box 1. ECTR: Extracorporeal toxin removal.

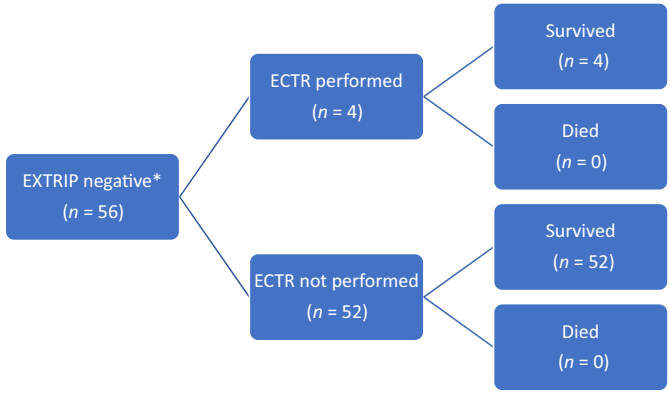

Figure 3. EXTRIP negative, ECTR, and Mortality. *EXTRIP negative means patients did not meet the recommended Extracorporeal Treatments in Poisoning Workgroup (1D) criteria for metformin poisoning listed in Box 1. ECTR: Extracorporeal toxin removal.

Table 2. Test Characteristics of the Entire Patient Population.

	Died	Survived	Totals
EXTRIP positive[a]	37	108	145
EXTRIP negative[a]	0	56	56
	37	164	201

Sensitivity: 37/37 = 100% (95% CI: 90.5–100.0%).
Specificity: 56/164 = 34.1% (95% CI: 26.9–42.0%).
PPV: 37/145 = 25.5% (95% CI: 23.5–27.7%).
NPV: 56/56 = 100% (95% CI: n/a).
[a]EXTRIP positive/negative means patients did/did not meet the recommended Extracorporeal Treatments in Poisoning Workgroup (1 D) criteria for metformin poisoning listed in Box 1.

Table 3. Test Characteristics of the EXTRIP Positive Patient Population.

	Died	Survived	Totals
EXTRIP Positive[a] ECTR performed	24	72	96
EXTRIP Positive[a] ECTR not performed	13	36	49
	37	108	145

Sensitivity: 24/37 = 64.9% (95% CI: 47.5–79.8%).
Specificity: 36/108 = 33.3% (95% CI: 24.6–43.1%).
PPV: 24/96 = 25.0% (95% CI: 20.3–30.4%).
NPV: 36/49 = 73.5% (95% CI: 62.4–82.2%).
[a]EXTRIP positive means patients met the recommended Extracorporeal Treatments in Poisoning Workgroup criteria (1 D) for metformin poisoning listed in Box 1.

recommended EXTRIP criteria and did not receive ECTR, 73.5% ($n = 36$) survived and 26.5% ($n = 13$) died ($P > 0.05$). Among the 56 patients who did not meet EXTRIP criteria, 100% survived.

The test characteristics of the recommended EXTRIP criteria for predicting death were determined for the entire study population. The sensitivity and specificity of the recommended EXTRIP criteria for predicting death are shown in Tables 2 and 3. Of note, the negative predictive value of the recommended EXTRIP criteria for predicting death was 100%. In a post hoc analysis, we evaluated the effects of modifying the recommended EXTRIP criteria with respect to lactate and pH to see if they were appropriately sensitive and specific. Changes made were as follows: lactate concentration >15 mmol/L, pH ≤7.1, or pH ≤6.9. The performance characteristics of the recommended EXTRIP criteria, when applied to these patients did not change after these modifications (supplemental data). Lastly, the analysis was repeated with EXTRIP criteria modified from the recommended criteria to the suggested criteria (lactate concentration > 15 mmol/L, pH ≤ 7.1, decreased level of consciousness) and were found to be nonsignificant (P-value > 0.05) with respect to the primary objective (supplemental data).

Discussion

This single-center retrospective analysis of metformin poisoned patients demonstrated that when patients did not meet the recommended EXTRIP criteria, they had a favorable outcome. The 100% negative predictive value suggests that the recommended EXTRIP criteria likely identies patients who, at the time of application of the criteria, do not need ECTR.

The study did not demonstrate a survival benefit for ECTR in those meeting EXTRIP criteria. Several reasons may account for this. First, patients who met the recommended EXTRIP criteria were clinically more sick than those who did not. Moreover, among the patients who met the recommended EXTRIP criteria, those who received ECTR had higher lactate concentrations, lower bicarbonate concentrations, and lower pH values than those who did not. This likely skewed the data as survival would be expected to be worse in the sickest patients given that ECTR is not a panacea. Second, we were not able to quantify the effects of delay to the initiation on ECTR (clinical decision making, overnights and other off hours, transfers, staffing issues, etc.) after it was indicated. Additionally, the fact that many patients suffered severe complications before ECTR was initiated further skewed the data against a benefit of ECTR. Lastly, unless data are derived from a randomized controlled trial that omits ECTR in a very sick cohort of patients, any suggestion of an effect of ECTR is limited. In our opinion, such a study would be unethical.

There are several additional limitations to this study. First, this is a retrospective study that utilized data from a single poison center data. Poison center data varies in its accuracy and coding [9]. Poison center reporting is also voluntary, and cases may have been missed that simply were not reported. Because this is a retrospective data set, we were unable to control for patients to be similarly distributed between receiving continuous vs intermittent HD. Data points (such as lowest pH) were often unavailable. Another limitation is that we are not able to comment on the outcome of these patients other than short-term survival due to the nature of poison center data as routine follow up of cases is uncommon after they are transferred out of the intensive care unit or discharged from the hospital. Furthermore, metformin concentrations were not obtained on most of these patients and thus we cannot exclude the possibility that other etiologies are responsible for the clinical findings in these patients. However, there are very few etiologies for the acidemia and hyperlactatemia, and the history and progression of these cases are consistent with others reported metformin case series [3,10]. Nevertheless, this limitation represents a real-world analysis as we are unaware of many institutions that can report quantitative metformin concentrations in a clinically meaningful time frame or, even if that were possible, that there is a concentration threshold at which ECTR would be indicated.

We were also unable to evaluate all of the EXTRIP criteria due to the limitations of poison center data. Specifically, we were not able assess if failure of standard therapy or liver failure were present in our patients due to this data not being universally available. It is also possible there is a component of selection bias in our study population, both from the voluntary reporting of cases and the identification of cases to be included in the study.

Our statistical analyses focused only on the ability of the EXTRIP criteria to predict mortality. We did not examine other factors (such as cost or hospital length of stay) that could potentially influence the overall recommendations. Furthermore, our findings are limited to our data set—although the NPV of 100% is notable, further studies with different populations are needed to determine if these findings persist.

Another limitation in our study is that the person entering the data into ToxiCall was not directly at the patient's bedside for every action that occurred. Thus, our data set represents a combination of actions that were recommended by the poison control center team, recommended by other consultants, or performed by the primary team. Because of these complexities, the exact delay between meeting EXTRIP criteria and the initiation of ECTR was unavailable. A randomized control study with attention to timing of ECTR would be a more reliable way of studying this topic and the cause-and-effect relationship between EXTRIP and mortality in the future.

Nonetheless, this study comprises a large cohort of patients with clinical metformin poisoning including many with severe metabolic acidemia and hyperlactatemia. In the entire study population, 68.7% ($n = 138$) had either a lactate concentration >10 mmol/L or a pH less than 7.2. Even in those patients who did not meet EXTRIP criteria the mean initial lactate was 6.2 mmol/L (median initial lactate concentration 9.8 mmol/L) and the mean initial pH was 7.31. Despite that, survival was excellent without ECTR if the recommended EXTRIP criteria were not met.

Conclusions

In this retrospective study, application of the recommended EXTRIP (1 D) criteria had a negative predictive value for death of 100%. The primary objective was unmet and we were unable to demonstrate a survival benefit for extracorporeal therapy for patients meeting the recommended EXTRIP criteria. Further study either utilizing data from multiple poison centers or prospective data is needed to determine the benefit of ECTR in patients meeting EXTRIP criteria for metformin poisoning. Case identification can be improved by confirmation with metformin concentrations if testing becomes widely available to clinicians.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This was a trainee research grant through the American Academy of Clinical Toxicology [https://www.clintox.org/grants/toxicology-trainee-research-grant].

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