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van de Laar, Inge

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Chapter 6

Extracorporeal treatment of Metformin Associated Lactic Acidosis in clinical practice: a retrospective cohort study

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Inge RF van Berlo – van de Laar
Cornelis G Vermeij
Marjo van den Elsen-Hutten
Arthur de Meijer
Katja Taxis
Frank GA Jansman

Abstract

Objectives

To assess whether extracorporeal treatment (ECTR) improves outcome of patients with metformin associated lactic acidosis (MALA) and to evaluate the clinical applicability of the Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) criteria for starting ECTR in metformin poisoning.

Methods

Patients with metformin serum concentrations above 2 mg/l who were admitted in the Deventer Teaching Hospital between January 2000 and July 2019 and complied with the definition of MALA (pH < 7.35 and lactate concentration > 5 mmol/l) were included. Mortality and clinical parameters of patients treated with ECTR or not were compared. In addition, treatment of MALA in clinical practice was verified against the criteria of EXTRIP.

Results

Forty-two patients were included. Lactate (13.8 versus 10.5 mmol/l, $p = 0.01$), creatinine (575 versus 254 umol/l, $p < 0.01$)), metformin (29.4 versus 8.6 mg/l, $p < 0.01$) concentrations and vasopressor requirement (72% versus 23%, $p<0.01$) were significantly higher in the ECTR-group. Blood pH (7.05 versus 7.19, $p = 0.03$) and bicarbonate (6 versus 11 mmol/l, $p < 0.01$) were significantly lower. Mortality, length of hospital stay and mechanical ventilation requirement were not statistically different. In 83% of patients, treatment of MALA was in accordance with the EXTRIP criteria.

Conclusion

Although there was no statistical benefit in mortality shown from ECTR, ECTR might be lifesaving in MALA, considering the ECTR-group was significantly sicker than the non-ECTR-group.

The majority of patients were treated in line with the EXTRIP criteria. Severity of lactic acidosis and renal impairment were the main indications for initiating ECTR.

Introduction

Metformin is the most commonly prescribed oral antidiabetic drug in non-insulin dependent type 2 diabetes mellitus (NIDDM). Metformin inhibits gluconeogenesis, facilitates cellular glucose uptake and decreases insulin resistance.[1] Metformin treatment is associated with a lower incidence of cardiovascular events and mortality in NIDDM.[2] Although metformin is considered to be a safe and well tolerated drug, its use may rarely be complicated by lactic acidosis.[1,3,4-6] The most widely accepted mechanism how metformin causes hyperlactatemia and metabolic acidosis is by partial inhibition of oxidative phosphorylation complex 1 of the mitochondrial electron transport chain. Another possible mechanism in which metformin may elevate plasma lactate levels is through inhibition of pyruvate carboxylase which results in both accelerated lactate production and reduced lactate metabolism.[1,3-5] There appears to be a clear relationship between metformin accumulation and lactic acidosis, although some authors have pointed out that several such patients had other confounding risk factors for lactic acidosis.[3,4,5,7]
Metformin associated lactic acidosis (MALA) is a serious adverse event with a high mortality rate of up to 50%.[1,4] The incidence of MALA varies from 0-138 per 100.000 patient years and may increase in the coming years due to the increase in the number of type 2 diabetes mellitus patients and the use of metformin.[4,6,8,9] Several studies suggest that starting timely treatment might reduce MALA-related morbidity and mortality.[8-14] Extracorporeal treatments (ECTRs) may be necessary to remove metformin, clear lactate and correct acid-base abnormalities.[1,11] Calello et al.[1] formulated specific recommendations for starting ECTR in metformin poisoning based on a systematic literature search: the Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) criteria[15] which have been included in the treatment guidelines for metformin intoxication by the Dutch Poisons Information Centre (DPIC).[16] However, the evidence levels of the EXTRIP criteria are low and their validity in clinical practice has not been assessed yet. We therefore evaluated the treatment of MALA patients in clinical practice. The aim of this study was firstly to assess whether ECTR improves outcome of MALA patients. Secondly, we aimed to evaluate whether the EXTRIP criteria for starting ECTR in MALA are applicable in clinical practice, i.e. to what extent patients who received ECTR and those who did not fulfilled the EXTRIP criteria for starting ECTR.[1]

Methods

A retrospective single centre cohort study was conducted at the Deventer Teaching Hospital in the Netherlands. Laboratory data were searched for patients who had their metformin serum concentrations measured between January 2000 and July 2019. In these patients, serum metformin concentration measurement had been requested

because of a clinical suspicion of MALA, based on documented metformin use and concurrent illness leading to an Emergency Department visit. In the Deventer Teaching Hospital the metformin assay is routinely available 24 hours a day. Results are available for clinical decisions within 4 hours. Patients were included if they met the MALA definition: pH < 7.35 and lactate > 5.0 mmol/l in association with metformin exposure.[1] Only patients with serum metformin concentrations above the lower limit of quantification of our analysis method, i.e. 2 mg/l, were included. The following patient data were extracted from the medical records: age, gender, admission diagnosis, ECTR treatment (or not), reasons for initiating ECTR (or not), decreased consciousness, vasopressor requirement, mechanical ventilation requirement, length of hospital stay, mortality (defined as in-hospital mortality) and laboratory results on admission: serum concentrations of creatinine, lactate, bicarbonate and metformin and blood pH. In the Deventer Teaching Hospital ECTR is readily and unrestrictedly available for treatment of MALA patients.

Patients were divided into an ECTR and non-ECTR group and the concentrations of lactate, creatinine, bicarbonate and metformin, blood pH, decreased consciousness, vasopressor and mechanical ventilation requirement, length of hospital stay and mortality were compared. In case of normal distribution of continuous data, the independent sample t-test was used. The non-parametric Mann Whitney test was used for not normally distributed and ordinal data. The Chi square test was used to compare nominal data between groups. In all tests, a p-value < 0.05 was considered statistically significant. Data analysis was performed with SPSS version 24.0.

In the ECTR and non-ECTR group, we assessed whether patients met the EXTRIP criteria for starting ECTR depicted in table 1. Impaired kidney function is defined by the EXTRIP nephrology sub-committee as 1) Advanced stage G3b, G4 or G5 chronic kidney disease (i.e. eGFR < 45 mL/min/1.73 m2), 2) Kidney Disease: Improving Global Outcomes (KDIGO) Stage 2 or 3 acute kidney injury, 3) In the absence of a baseline serum creatinine, 176 µmol/L in adults and 132 µmol/L in elderly/low muscle mass patients, 4) the presence of oligo/anuria regardless of serum creatinine concentration. In those patients who were not treated according to the EXTRIP criteria the reasons for initiating ECTR or not were evaluated.

Table 1 EXTRIP criteria for starting ECTR in metformin poisoning[1]

Indications
ECTR is recommended if:
• Lactate concentration greater than 20 mmol/l • Blood pH less than or equal to 7.0 • Standard therapy (supportive measures, bicarbonate etc.) fails
ECTR is suggested if:
• Lactate concentration is 15-20 mmol/l • Blood pH 7.0 – 7.1
Comorbid conditions that lower the treshold for initiating ECTR:
• Impaired kidney function • Shock • Decreased level of consciousness • Liver failure

EXTRIP: Extracorporeal Treatments in Poisoning Workgroup

ECTR: Extracorporeal treatment

Results

In our hospital pharmacy laboratory database, we identified 160 patients who had serum metformin concentrations measured. Of these, 42 patients met the inclusion criteria of MALA and were included in the study. Forty patients (95%) had renal impairment on admission and 29 patients (69%) were treated with ECTR. ECTR was conducted in the intensive care unit. ECTR modalities used were continuous veno venous hemofiltration (CVVH) (19 patients), hemodialysis (HD) (7 patients) or a sequential combination of CVVH and HD (3 patients). The patient characteristics and the results of the comparison between the ECTR and non-ECTR groups are listed in table 2. The main admission diagnoses were dehydration, sepsis, shock and myocardial infarction. Detailed information of the patient characteristics per patient is given in supplementary table 1 (ECTR-group) and supplementary table 2 (non-ECTR-group).

Table 2 Results: patient characteristics and comparison clinical parameters ECTR versus non-ECTR group

Patient characteristics	ECTR N=29 Mean ± sd (range)	Non-ECTR N=13 Mean ± sd (range)	Statistical analysis
Gender	6M 23F	5M 8F	
Age (years)	71 ± 9 (52-87)	77 ± 11 (58-89)	
pH	7.05 ± 0.18 (6.61-7.34)	7.19 ± 0.18 (6.85-7.33)	p = 0.027
Lactate (mmol/l)	13.8 ± 4.9 (5.8-23.2)	10.5 ± 2.8 (6.7-18)	p = 0.033
Bicarbonate (mmol/l)	6 ± 3 (2-13)	11 ± 4 (2-17)	p < 0.01
Metformin concentration (mg/l)	29.4 ± 20.3 (2.3-100)	8.6 ± 11.2 (2.2-37)	p < 0.01
Creatinine (umol/l)	575 ± 268 (113-1039)	254 ± 192 (70-720)	p < 0.01
Decreased consciousness N (%)	9 (31%)	3 (23%)	p=0.699
Vassopressor requirement N (%)	21 (72%)	3 (23%)	p < 0.01
Mechanical ventilation requirement N (%)	6 (21%)	1 (8%)	p=0.296
Length of stay (days)	17.3 ± 23.6 (2-120)	7.8 ± 9.0 (1-32)	p=0.067
Mortality N (%)	11 (38%)	6 (46%)	p=0.616

ECTR: Extracorporeal treatment

Thirty-five of the 42 (83%) patients were treated in line with the EXTRIP criteria.
Of the 29 patients in the ECTR-group, 28 (97%) fulfilled the EXTRIP criteria to receive ECTR. Clinical reasons for starting ECTR in these patients were severe metabolic acidosis, renal failure, hyperkalaemia and high metformin concentrations. Ninety-seven percent of the ECTR group met the criterion of impaired renal function of Calello et al.[1] in which the threshold for initiating ECTR could be lowered. One patient (patient No. 27, supplementary table 1) did not fulfil the EXTRIP criteria. This patient was admitted because of an intentional overdose and did not meet the criterion of impaired renal function of Calello et al.[1] ECTR was started because of the combination high serum metformin concentration and lactic acidosis in order to eliminate metformin and to correct the acidosis.
Of the 13 patients in the non-ECTR group, in 7 (54%) of the patients treatment (non-ECTR) was in line with the EXTRIP criteria. One patient (patient No. 6, supplementary table 2) did not fulfil the EXTRIP criteria for starting ECTR and in 6 patients ECTR was not

necessary because they recovered after starting supportive care.
For the other 6 (46%) patients, ECTR should have been considered according to the EXTRIP criteria. Supportive care was started in these patients but they died shortly after start of the treatment. Four patients died within one day from cardiac arrest. In one patient, a conservative policy was started because of the very bad prognosis due to comorbidity and she died one day after admittance. One patient (patient No.10, supplementary table 2) did not recover with supportive care and died one month after admission probably from sepsis. There were no data available in this patients' medical record whether ECTR was considered.

Discussion

This retrospective cohort study shows a lower but not statistically different mortality in MALA patients treated with ECTR compared to those who were not. The overall mortality of 40% in our study is in line with the mortality reported in previous studies, ranging from 20-50%.[7,8,12-14,17-21] Blood pH, lactate, creatinine and serum metformin concentration in the ECTR group in this study are similar to that reported in the literature.[9,13,20-22] The significantly higher lactate and creatinine concentrations in the ECTR group compared to the non-ECTR group have also been reported in other studies.[9,12,19]
Patients in the ECTR group were sicker than patients in the non-ECTR group considering the degree of lactic acidosis, kidney function and vasopressor requirement while having a lower but not statistically different, mortality. As hyperlactatemia in general and in MALA patients is associated with increased mortality, this at least comparable outcome suggests there might be a benefit for ECTR.[8,11,23-25] This is also suggested by Peters et al.[19] Our study was probably underpowered to show a statistical difference. We also compared the length of hospital stay (17.3 versus 7.8 days, p=0.067) but in this study this parameter is less suitable as outcome measure compared to mortality because of the large range in the ECTR group (2-120 days) and the high percentage patients who died within 1-2 days in the non-ECTR group.

To evaluate whether the EXTRIP criteria for initiating ECTR in patients with MALA are applicable in clinical practice we compared the indications for starting ECTR in this study with the recommendations of Calello et al.[1] Overall, 83% of our patients were treated in line with the EXTRIP criteria. In the ECTR group, 97% and in the non-ECTR group 54% of the patients fulfilled the EXTRIP criteria. Severity of lactic acidosis and kidney function were the main indications for initiating ECTR in this study. This is also shown in the EXTRIP criteria and the study of Corcia et al.[1,9,15] Moreover, in accordance with Corchia et al.[9], we identified hyperkalaemia as a reason for starting ECTR. In contrast, hemodynamic instability and shock, as proposed by Corcia et al.[9] and EXTRIP[1,15] for initiating

ECTR, were not recorded in the patients' medical records in this study. Calello et al.[1] have not formulated a threshold for metformin serum concentration because at the time of formulation of these recommendations, there was much uncertainty regarding the value of metformin concentrations in relation to the prognosis and the limited availability of the metformin assays. Some studies have shown a correlation between metformin concentration and mortality[8,9,20] while others have not.[17,21,25,26] Despite the uncertainty concerning its prognostic value, measuring metformin serum concentrations could be of diagnostic value in MALA and may assist in its management.[9,22,26] However, establishing a specific threshold for metformin serum concentrations is not possible based on the results of this study.

The EXTRIP criteria include lowering thresholds of pH and lactate for initiating ECTR in impaired kidney function, shock, decreased level of consciousness and liver failure but this is not quantified. The majority of the ECTR group in this study had impaired renal function and the mean pH and lactate concentration were 7.05 and 13.8 mmol/l respectively. In clinical practice, comorbidity is common and it is not always clear whether there is metformin accumulation, showing the heterogeneity regarding the EXTRIP criteria and real-life scenarios. Because of this heterogeneity, formulating more concise criteria for initiating ECTR in MALA patients is very difficult. The main reasons for not initiating ECTR in this study were recovery after starting supportive care or death shortly after admission. Six patients who met the EXTRIP criteria were not treated with ECTR and died. At the time of admission of these patients, the EXTRIP criteria were not implemented in our hospital. Four out of these six patients died within 1 day from cardiac arrest and there was no renal indication for starting ECTR. Additionally, in the non-ECTR group, 54% of patients had serum metformin concentrations lower than 5 mg/l which is in line with the 'normal' value of serum metformin concentrations in therapeutic use.[4,27] Therefore, it is debatable whether metformin was the cause of MALA in these patients. Lalau et al.[4] suggested adding serum metformin concentration higher than 5 mg/l as criterion to MALA to distinguish it from metformin unrelated lactic acidosis (MULA). However, we used the definition of MALA pH < 7.35 and lactate > 5 mmol/l in association with metformin exposure as formulated by Calello et al.[1] because we wanted to evaluate Calello's recommendations in clinical practice. In addition, we validated metformin exposure by only including patients with verifiable serum metformin concentrations to avoid discussion about metformin exposure.

The present study is one of the largest cohort studies regarding the management of MALA. The strength of our study is that metformin concentrations, lactate, blood pH and kidney function were measured simultaneously on admission and during subsequent treatment. Furthermore, only patients with verified metformin serum concentrations

were included. Lalau et al.[4] presented the lack of these combined data as major methodological flaw in most studies on MALA. However, we did not measure metformin concentrations in erythrocytes, which probably better reflects metformin tissue effects, and we have no information on last intake so we cannot refer to peak versus trough concentrations.[4] A limitation of our study is that other causes of lactic acidosis were not ruled out which could have influenced the mortality in this study. Other limitations include the retrospective and monocentric design and selection bias. We selected patients based on serum metformin concentration measurement. MALA patients without serum metformin concentration measurement could have been missed. Finally, as presented in the EXTRIP guidelines, metformin and lactate clearance are lower with continuous renal replacement therapy (CRRT) than with intermittent HD. As such, the predominant use of CVVH in our study might have weakened the results in favor for ECTR.

For clinical practice, we recommend that clinicians be alert to MALA in the Emergency Department when patients are admitted with lactic acidosis in combination with metformin use. ECTR might be lifesaving in the treatment of MALA and should therefore be considered at an early stage. The EXTRIP-criteria are a good starting point for the decision to start ECTR but each individual patient needs to be evaluated separately. Severity of lactic acidosis and renal impairment are the main indications for initiating ECTR. Knowledge of the metformin concentrations may be a valuable additional parameter for the diagnosis and management of MALA. Therefore, we recommend implementing metformin assays as routine investigation with 24-hour availability in hospitals treating MALA patients.

Conclusion

Although there was no statistical difference in mortality between the treatment with or without ECTR, ECTR might be lifesaving in treating MALA. Patients in the ECTR group were sicker compared to the non-ECTR group considering the degree of lactic acidosis, kidney function and vasopressor requirement and had at least a comparable mortality. In 83% of the patients, treatment was in line with the EXTRIP criteria. Severity of lactic acidosis and renal impairment were the main indications for initiating ECTR. Measuring serum metformin concentrations may assist in the diagnosis and management of MALA.

Ethics approval

This study was assessed by the Medical Ethical Committee of Isala Hospital (Zwolle, the Netherlands) and approved as a non-interventional study.

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Supplementary table 1 Patient characteristics ECTR group

Nr	Sex	Age (years)	pH	Lactate (mmol/l)	Bic (mmol/l)	Metformin (mg/l)	Creatinine (umol/l)	Diagnosis	DC	VR	MVR	LoS (days)	Out-come	Reason ECTR
1	F	67	7.05	19.0	8	2.9	478	Hemorrhagic shock	Y	N	N	34	D	Renal failure
2	F	66	7.12	13.5	7	19.4	640	Dehydration	Y	Y	N	120	S	Severe metabolic acidosis and renal failure with metformin use
3	F	75	7.03	16.5	7	5.0	266	Myocardial infarction	Y	Y	N	2	D	Severe metabolic acidosis and renal failure with metformin use
4	F	75	7.22	5.8	12	32	813	Myocardial infarction	N	N	N	18	S	Renal failure
5	M	58	6.77	23	2	38	1039	Dehydration	N	Y	Y	19	S	Severe metabolic acidosis and renal failure with metformin use
6	F	72	7.15	14.5	8	20	814	Renal failure	N	N	N	38	S	Severe metabolic acidosis and renal failure with metformin use
7	F	77	7.18	11.1	7	25.4	960	Dehydration	N	N	N	22	S	Renal failure, hyperkalaemia, MALA
8	F	68	7.07	9.9	10	22	706	Dehydration	N	N	N	2	S	Renal failure, hyperkalaemia
9	F	78	6.94	20.3	4	44	612	Dehydration	N	Y	N	2	S	Severe metabolic acidosis and renal failure with metformin use
10	F	62	6.9	13.8	2	34	590	Dehydration	Y	Y	N	14	S	Severe metabolic acidosis and renal failure with metformin use
11	F	82	6.82	23.2	2	47	691	Dehydration	N	Y	N	15	S	Severe metabolic acidosis and high metformin serum concen-tration
12	F	56	7.12	8.8	7	31	882	Dehydration	Y	Y	N	7	S	Severe metabolic acidosis and renal failure with metformin use, hyperkalaemia
13	F	67	7.25	6.6	12	22.8	519	Pneumonia	N	Y	N	18	D	Lactic acidosis and high met-formin serum concentration
14	F	62	6.61	15.6	4	45	808	Septic shock	Y	Y	Y	2	D	Failure supportive care, severe metabolic acidosis and high metformin serum concentration
15	F	76	7.12	8.0	3	27.5	669	Urosepsis	N	Y	N	14	S	Failure supportive care, high metformin serum concentration
16	F	72	6.82	11.2	4	45	1004	Dehydration	N	Y	N	2	D	Severe metabolic acidosis and renal failure with metformin use
17	M	82	7.12	8.8	8	4.1	414	Urosepsis	N	N	N	25	S	Renal failure, hyperkalaemia
18	M	87	7.34	11.7	9	8.2	263	Urosepsis	N	Y	N	2	D	MALA
19	F	79	6.94	13.5	2	46	642	Dehydration	N	Y	N	8	S	Failure supportive care, se-vere metabolic acidosis

20	F	78	7.22	14.3	8	12.6	147	Heart failure	N	N	N	11	D	MALA
21	F	70	6.98	12.8	8	42.4	419	Septic shock	Y	Y	Y	5	D	Severe metabolic acidosis, high metformin serum concentration
22	F	69	7.22	19	7	23.4	523	Dehydration	N	Y	N	9	S	Failure supportive care, lactic acidosis, renal failure, high metformin serum concentration
23	F	82	6.66	10.6	2	44.5	574	Septic shock	Y	Y	Y	60	S	Renal failure, severe metabolic acidosis
24	F	72	7.14	6.5	8	30.4	841	Sepsis	N	Y	Y	17	D	Failure supportive care
25	F	72	7.16	14	4	2.3	140	Heart failure	Y	N	N	11	D	MALA
26	M	58	7.00	21.6	6	100	208	Intentional overdose	N	Y	Y	10	S	Severe metformin intoxication, lactic acidosis
27	M	52	7.26	11.4	13	50	113	Intentional overdose	N	Y	N	5	S	Severe metformin intoxication, lactic acidosis
28	M	69	7.17	16	5	4.6	255	Hemorrhagic shock	N	Y	N	3	D	Renal failure, MALA
29	F	65	6.97	18	4	23.3	645	Dehydration	N	Y	N	8	S	Renal failure, hyperkalaemia, MALA

DC = decreased conciousness: Y= yes, N = no, U = unknown

VR = Vassopressor requirement: Y= yes, N = no

MVR = mechanical ventilation requirement: Y= yes, N = no

LoS = Length of Stay

Outcome: D = died, S = survived

MALA = metformin associated lactic acidosis

Supplementary table 2 Patient characteristics non-ECTR group

Nr	Sex	Age (years)	pH	Lactate (mmol/l)	Bic (mmol/l)	Metformin (mg/l)	Creatinine (umol/l)	Diagnosis	DC	VR	MVR	LoS (days)	Outcome	Reason ECTR
1	F	78	6.85	10.2	2	4	547	Dehydration	N	N	N	1	D	Supportive care but cardiac arrest and passed away the same night
2	F	87	7.24	9.4	10	2.5	146	Cardiogenic shock, myocardial infarction	N	N	N	2	D	Supportive care but passed away within 1 day after admittance
3	F	85	7.33	8.8	13	6.8	257	Hypovolemic shock by bleeding	N	N	N	10	S	Recovery with supportive care
4	F	58	7.04	12.6	7	37	720	Sepsis	N	N	N	6	S	Recovery with supportive care
5	M	89	7.3	9.4	12	6.1	136	Hypovolemic shock by bleeding	N	N	N	12	S	Recovery with supportive care
6	M	63	7.31	9	14	3	73	MALA	N	N	N	3	S	Recovery with supportive care
7	F	80	7.14	13.3	12	3	366	Pneumosepsis	Y	N	N	2	D	No recovery with supportive care, conservative policy because of bad prognosis, passed away within 1 day after admittance
8	M	58	7.08	8.8	11	7.9	207	Myocardial infarction	N	Y	Y	1	D	No recovery with supportive care, passed away within 1 day after admittance from cardiac arrest
9	F	77	7.32	10.4	11	29.3	70	MALA	Y	N	N	3	S	Recovery with supportive care
10	F	88	7.3	11	14	2.3	126	Pneumonia, 3rd grade AV-block	N	Y	N	32	D	No recovery with supportive care, passed away probably from sepsis
11	M	83	7.33	9.3	7	2.4	158	Cardiogenic shock	U	N	N	17	S	Recovery with supportive care
12	F	78	7.33	6.7	17	2.2	200	Dehydration	N	N	N	12	S	Recovery with supportive care
13	M	77	6.86	18	6	5.5	301	Myocardial infarction	Y	Y	N	1	D	Passed away after cardiopulmonary resuscitation (CPR)

DC = decreased conciousness; Y= yes, N = no, U = unknown
VR = Vassopressor requirement: Y= yes, N = no
MVR = mechanical ventilation requirement: Y= yes, N = no
LoS = Length of Stay
Outcome: D = died, S = survived
MALA = metformin associated lactic acidosis

Part 3

Binding interactions