Received: 29 March 2019 | Revised: 15 July 2019 | Accepted: 28 July 2019

DOI: 10.1111/bcp.14087

ORIGINAL ARTICLE

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Assessment of Extracorporeal Treatments in Poisoning criteria for the decision of extracorporeal toxin removal in lithium poisoning

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Aims: To assess recommendations provided by the EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup on extracorporeal toxin removal (ECTR) in lithium poisoning.

Methods: Retrospective assessment in a 128 lithium-poisoned patient cohort previously used to identify ECTR initiation criteria that could improve outcome (*Paris* criteria). ECTR requirement using *EXTRIP* criteria was compared to the actual practice or if *Paris* criteria were used. The potential impact on outcome if these different criteria were used was investigated.

Results: Using the recommended *(Rec-EXTRIP)* or recommended + suggested *(All-EXTRIP)* EXTRIP criteria, ECTR would have been indicated in more patients than was actually done ($P < .001$), or if *Paris* criteria were used ($P < .01$). The non-actually ECTR-treated patients fulfilling *Rec-EXTRIP* or *All-EXTRIP* criteria had shorter intensive care unit stay ($P < .05$) and no significant increase in fatalities and neurological impairment on discharge in comparison to the actually ECTR-treated patients. ECTR requirements using *EXTRIP vs Paris* criteria were not concordant ($P < .001$). In the non-actually ECTR-treated patients, 31/106 and 55/106 patients fulfilled *Rec-EXTRIP* or *All-EXTRIP* but not *Paris* criteria, respectively. Those patients had longer stay ($P < .01$) but no worse neurological impairment on discharge than the patients not fulfilling any of these criteria (50/106 and 26/106, respectively). In the non-actually ECTR-treated patients, 7/106 fulfilled *Paris* but not *Rec-EXTRIP* criteria. Those patients had longer stay ($P < .05$) and worse neurological impairment on discharge ($P < .01$) than the 50/106 patients not fulfilling any of these criteria.

Conclusion: In this cohort of lithium poisonings, *EXTRIP* criteria may lead to more ECTR than actually performed or if the *Paris* criteria were used, with no demonstrated improvement in outcome.

KEYWORDS

lithium, poisoning, extracorporeal toxin removal, haemodialysis, outcome, EXTRIP

The authors confirm that the PI for this paper is Prof. Bruno Mégarbane and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Given lithium pharmacokinetics (i.e. no protein binding, limited volume of distribution, absence of metabolism, and exclusive renal elimination), extracorporeal toxin removal (ECTR) represents the method of choice for enhancing lithium elimination in poisoning, if lithium elimination is compromised despite optimal fluid management.[1] However, ECTR indications and benefits in lithium poisoning are still controversial.[2-5]

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup, an international workgroup including clinical toxicologists, nephrologists, epidemiologists and pharmacologists,[6] provided recommendations on ECTR use in lithium poisoning, based on a systematic literature review and considered to date as the most up-to-date international guideline.[1] Using the GRADE system, all recommendations were grade D (i.e. with very low level of evidence) due to the lack of well-designed prospective comparative studies.

We recently published a series of 128 severely lithium-poisoned patients admitted to the intensive care unit (ICU) over a 10-year period.[7] Using multivariate analyses and ROC curves, we identified *Paris* criteria at the bedside for initiating ECTR in lithium-poisoned patients, i.e. if serum lithium concentration exceeded 5.2 mmol/L and/or serum creatinine concentration exceeded 200 μmol/L. Interestingly, retrospective assessment of these criteria showed that among our 128 patients, 46 would have been treated with ECTR if 1 of these 2 thresholds was used while only 21 were actually treated with ECTR. Patients who would have been treated with ECTR if these criteria were used but were actually not ECTR-treated, had significantly more frequent neurological impairments (including confusion, dysarthria, hypertonia, myoclonus and ataxia) on ICU discharge than those who met the criteria and were actually treated with ECTR. This difference in neurological status was demonstrated, although patients who would have been treated with ECTR but were not actually treated were significantly less severely poisoned, supporting the relevance of our *Paris* criteria. Interestingly, no significant difference in the length of ICU stay was observed between these 2 groups of patients.

Therefore, aiming to better define the indications for ECTR in lithium poisoning, we designed this retrospective study to investigate the impact on ECTR requirement and patient outcome on ICU discharge in our cohort if *EXTRIP* or *Paris* criteria were used for the ECTR decision.

What is already known about this subject

- Indications for extracorporeal toxin removal (ECTR) in lithium poisoning are controversial.
- No strong evidence supports the proposal that ECTR can prevent central nervous system impairment and/or reduce poisoning severity.
- Recently, recommendations by the EXTRIP workgroup were published to guide clinicians initiating ECTR in lithium poisoning.

What this study adds

- We evaluated EXTRIP recommendations for ECTR in lithium poisoning using a cohort of severely lithium-poisoned patients and compared EXTRIP with *Paris* criteria.
- In our cohort, EXTRIP criteria would lead to more ECTR treatment in comparison to that carried out in practice, without observed improvement in patient outcome.

2 | METHODS

2.1 | Patient population

The 128 severely lithium-poisoned patients admitted to the ICU were previously described.[7] The following parameters were collected: clinical parameters on admission, during ICU stay and on ICU discharge; serum lithium concentrations on admission and at peak; the Hansen and Amdisen grade[8]; the Simplified Acute Physiology Score II[9] on admission; kidney function assessment according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on acute kidney injury (AKI)[10]; poisoning severity defined by the presence of at least 1 of: (i) seizures; (ii) catecholamine infusion; (iii) mechanical ventilation lasting >48 hours; and final outcome (death in ICU, persistent neurological symptoms on ICU discharge and length of ICU stay; Table 1). Prescription for ECTR was left to the discretion of the intensivist managing the patient: 22 patients were managed with ECTR including intermittent haemodialysis (n = 12, 54%), continuous renal replacement therapy (CRRT, n = 6, 28%) and both techniques, successively performed (n = 4, 18%; Table 1). In the patients treated with intermittent ECTR, the median ECTR duration was 6.0 hours (range 6.0–6.4) and the median number of ECTR sessions was 2 (1–2). In the patients treated with CRRT, the median CRRT duration was 48.0 hours (24.0–70.0) and the median number of CRRT sessions was 2 (1–2). The median serum lithium concentration obtained immediately after the ECTR session was 0.8 (0.4–1.8) mmol/L (available in 18/22 patients). The review board of the French Society of Critical Care Medicine approved the study (CE-SRLF 13–53). Consent from the patients was not required.

2.2 | The EXTRIP criteria for ECTR initiation in lithium poisoning

EXTRIP criteria for ECTR initiation in lithium poisoning take into account the onset of complications related to lithium toxicity (decrease in consciousness, seizures and life-threatening dysrhythmia), the serum lithium concentration and kidney function.[1] There are 5 criteria including 2 supporting *recommended* ECTR and 3 other criteria for *suggested* ECTR (Table 2). Therefore, we used *All-EXTRIP* to refer to the *recommended* + *suggested* criteria, *Rec-EXTRIP* only to the *recommended* criteria and *Sug-EXTRIP* to the *suggested* criteria. Since 3 criteria were not defined exactly in the EXTRIP guideline, we chose

TABLE 1 Characteristics, treatment and outcome of the 128 lithium-poisoned patients included in the cohort and comparison of the patients who fulfilled *Rec-EXTRIP* or *Sug-EXTRIP* or *All-EXTRIP* with the patients who fulfilled *Paris* criteria

		Patients who fulfilled			
	All patients	Paris criteria	Rec-EXTRIP	Sug-EXTRIP	All-EXTRIP
***n* (%)**	**128**	**46**	**70**	**31**	**101**
Patients characteristics					
Male/female ratio	**0.7**	0.9	0.6	0.5	0.6
Age (y)	**46 [35; 56]**	48 [33;56]	44 [33;56]	52 [43;64]	48 [35;57]
Poisoning characteristics					
Type of poisoning					
▪acute, *n* (%)	**12 (10)**	5 (11)	7 (10)	1 (3)	8 (8)
▪acute on chronic, *n* (%)	**81 (64)**	28 (61)	49 (70)	17 (55)	66 (65)
▪chronic, *n* (%)	**35 (26)**	13 (28)	14 (20)	13 (42)	27 (27)
Serum lithium level					
▪on admission (mmol/L)	**2.8 [1.9; 4.1]**	3.4 [2.0; 6.1]	2.9 [1.9; 4.6]	2.9 [1.9; 4.0]	2.9 [1.9; 4.4]
▪peak (mmol/L)	**3.2 [2.3; 5.5]**	6.3 [3.2; 9.6]	4.5 [2.8; 6.8]*	3.3 [2.4; 4.6]***	4.0 [2.7; 6.1]**
Kidney function					
Serum creatinine level					
▪on admission (µmol/L)	**87 [71; 167]**	189 [86; 304]	100 [72; 202]*	88 [67; 115]**	94 [72; 171]**
▪peak (µmol/L)	**100 [75; 175]**	207 [99; 341]	120 [79; 215]*	100 [78; 121]***	106 [78; 202]***
Severity					
SAPS II	**30 [19; 45]**	42 [25; 52]	39 [27; 50]	26 [17; 35]**	35 [24; 48]
Maximal Hansen and Amdisen's score					
▪ 0–1	**24 (19)**	3 (7)	4 (6)	5 (16)***	9 (9)
▪ 2	**49 (38)**	11 (24)	13 (19)	25 (81)***	38 (38)
▪ 3	**55 (43)**	32 (70)	53 (76)	1 (3)***	54 (53)
Severe poisonings, *n (%)*	**48 (38)**	32 (70)	46 (66)	1 (3)***	47 (47)**
Treatment					
Gastrointestinal decontamination					
▪whole bowel irrigation, *n* (%)	**38 (30)**	19 (41)	28 (40)	6 (19)	34 (34)
▪gastric lavage, *n* (%)	**18 (14)**	5 (11)	11 (16)	4 (13)	15 (15)
▪activated charcoal, *n* (%)	**12 (9)**	4 (9)	7 (10)	2 (6)	9 (9)
▪sodium polystyrene sulfonate, *n* (%)	**2 (2)**	1 (2)	1 (1)	0 (0)	1 (1)
Fluids during the first 24 hours (mL)	**3000 [2500; 4000]**	4000 [3000; 4750]	4000 [3000; 4500]	3000 [2700; 3500]**	3450 [2975; 4000]
Mechanical ventilation, *n* (%)	**49 (38)**	28 (61)	48 (69)	1 (3)***	49 (49)
ECTR					
▪ECTR, *n* (%)	**22 (17)**	21 (46)	21 (30)	1 (3)***	22 (22)**
▪intermittent haemodialysis, *n* (%)	**12 (9)**	11 (24)	11 (16)	1 (3)*	12 (12)
▪continuous renal replacement therapy, *n* (%)	**6 (5)**	6 (13)	6 (9)	0 (0)	6 (6)
▪both, *n* (%)	**4 (3)**	4 (9)	4 (6)	0 (0)	4 (4)
▪none, *n* (%)	**106 (83)**	25 (54)	49 (70)	30 (97)***	79 (78)**
Outcome					
Persistent neurological impairment on ICU discharge, *n* (%)	**24 (19)**	15 (33)	16 (23)	7 (23)	23 (23)

(Continues)

TABLE 1 (Continued)

		Patients who fulfilled			
	All patients	**Paris criteria**	**Rec-EXTRIP**	**Sug-EXTRIP**	**All-EXTRIP**
***n* (%)**	**128**	**46**	**70**	**31**	**101**
Death, *n* (%)	**4 (3)**	4 (9)	4 (6)	0 (0)	4 (4)
ICU LOS (days)	**5 [3; 11]**	12 [7; 21]	8 [4; 15]	5 [3; 8]***	7 [4; 14]**

ECTR, extracorporeal toxin removal; ICU LOS, intensive care unit length of stay

Due to the lack of consensual definition in EXTRIP guidelines, decreased consciousness, significant confusion and serum lithium concentration expected to be >1 mmol/L at 36 hours with optimal management, were interpreted. Lithium poisoning was defined as severe in the presence of at least 1 of the following conditions: (1) seizures; (2) catecholamine infusion; (3) mechanical ventilation lasting >48 hours. Data are expressed as percentages or median [25th; 75th percentiles].

*P < .05, **P < .01, ***P < .001

TABLE 2 EXTRIP criteria for extracorporeal toxin removal (ECTR) in lithium poisoning

All EXTRIP criteria	
ECTR was recommended if:	- serum lithium concentration > 4 mmol/L **and** • CKD (eGFR <45 mL/min per 1.73 m^2) or • KDIGO stage 2–3 or • in the absence of baseline serum creatinine concentration, serum creatinine concentration > 176 µmol/L if age < 65 years or serum creatinine concentration > 132 µmol/L if age ≥ 65 years or • oliguria/anuria
ECTR was suggested if:	- decreased consciousness (i.e., GCS < 12) or seizures or dysrhythmia - serum lithium concentration > 5 mmol/L - significant confusion (i.e., GCS of 12–13) - serum lithium concentration expected to be >1 mmol/L at 36 hours with optimal management, i.e. serum lithium concentration > 2.5 mmol/L after 24 h admission

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

EXTRIP criteria were divided into recommended and suggested criteria. The original criteria *decreased consciousness*, *significant confusion* and *serum lithium concentration expected to be > 1 mmol/L 36 hours after admission* were interpreted in our study using the Glasgow coma scale (GCS) and elimination half-life of lithium, respectively.

to clarify *decreased consciousness* as Glasgow coma scale (GCS) < 12, *significant confusion* as GCS = 12 or 13 and the *expected time to reduce serum lithium to < 1.0 mmol/L with optimal management > 36 hours* as serum lithium >2.5 mmol/L measured 24 hours after ICU admission, taking into account the lithium half-life of ~24 hours.[1,11]

2.3 | Paris criteria for ECTR initiation in lithium poisoning

We previously identified *Paris* ECTR criteria in our 128 severely lithium-poisoned patients admitted to the ICU.[7] It was suggested that ECTR can be initiated if serum lithium concentration was ≥5.2 mmol/L and/or serum creatinine concentration was ≥200 µmol/L.

2.4 | Statistical analysis

Continuous variables are expressed as median [25th; 75th percentiles] and categorical variables as absolute values (percentages). The potential impact of *EXTRIP vs Paris* criteria on the patient outcome was analysed in the patient subgroup not actually treated with ECTR to rule out any confounding influence due to ECTR. Comparisons were performed using Mann–Whitney *U* tests for continuous variables and Fisher's exact tests for categorical variables. McNemar's tests were used to determine the marginal homogeneity between the EXTRIP and our *Paris* criteria. All analyses were performed using GraphPad Prism version 6.00 for MacOs (GraphPad Software, San Diego, CA, USA, www.graphpad.com). *P-values* ≤ .05 were considered as significant.

3 | RESULTS

3.1 | Comparison of ECTR requirement if EXTRIP was used to decide ECTR *vs* the actual practice

If *Rec-EXTRIP* or *All-EXTRIP* criteria were used to decide ECTR, significantly more patients of our cohort would have been treated with

ECTR in comparison to what was actually performed (70/128 *vs* 21/128 and 101/128 *vs* 22/128, respectively; $P < .001$). Patients who fulfilled *Rec-EXTRIP* or *All-EXTRIP* criteria but were actually not treated with ECTR, were significantly less severely poisoned ($P < .05$ and $P < .001$ respectively), had significantly shorter length of ICU stay ($P < .05$ and $P < .01$ respectively) in comparison to those who were actually treated with ECTR (Figure 1). Patients who fulfilled *Rec-EXTRIP* or *All-EXTRIP* criteria but were actually not treated with ECTR, had 2-fold more persistent neurological impairment on ICU discharge in comparison to those who were actually treated with ECTR (13/49 *vs* 3/21 and 20/79 *vs* 3/22; not significant). The use of *Rec-EXTRIP* or *All-EXTRIP* criteria would have led to initiating ECTR in the 3 patients who died in our cohort and were not actually treated with ECTR. All patients who died fulfilled the criteria *decrease in consciousness* and *serum lithium > 5 mmol/L* (See Supplemental material).

3.2 | Comparison of ECTR requirement if *EXTRIP vs Paris* criteria were used to decide ECTR

If *Rec-EXTRIP* criteria were used to decide ECTR, there would have been significantly more patients treated with ECTR in comparison to *Paris* criteria (70/128 *vs* 46/128, $P < .01$). ECTR requirements using *Rec-EXTRIP vs Paris* criteria were not concordant ($P = .0001$; Figure 2A). Concordantly, *Rec-EXTRIP* and *Paris criteria* would have indicated ECTR in 38 patients and not indicated ECTR in 50 patients. However, the use of *Rec-EXTRIP* criteria would have indicated ECTR in 32 additional patients in comparison to *Paris* criteria and the use of *Paris* criteria would have indicated ECTR in 8 additional patients in comparison to *Rec-EXTRIP* criteria.

If *All-EXTRIP* criteria were used to decide ECTR, there would have been significantly more patients treated with ECTR in comparison to *Paris* criteria (101/128 *vs* 46/128, $P < .001$). ECTR requirements using *All-EXTRIP vs Paris* criteria were not concordant ($P < .0001$; Figure 2B). Concordantly, *All-EXTRIP* and *Paris* criteria would have indicated ECTR in 45 patients and not indicated ECTR in 26 patients. However, the use of *All-EXTRIP* criteria would have indicated ECTR in 56 additional patients in comparison to *Paris* criteria and the use of *Paris* criteria would have indicated ECTR in 1 additional patient in comparison to *All-EXTRIP* criteria.

3.3 | Potential impact of EXTRIP *vs* Paris criteria on the outcome of the 106 non-actually ECTR-treated patients

- ***Rec-EXTRIP vs Paris* criteria:** The 18 patients who would have been concordantly treated with ECTR were more severely poisoned, had more frequently persistent neurological impairment on ICU discharge and longer length of ICU stay ($P < .001$) in comparison to the 50 patients who would not have been treated with ECTR by any of these criteria (Figure 3A). The 31 additional patients fulfilling *Rec-EXTRIP* but not *Paris* criteria, were more severely poisoned ($P < .001$), had 2-fold more persistent neurologic impairment on ICU discharge (not significant) and longer ICU length of stay ($P < .01$) compared to the patients not fulfilling any of these criteria. Among those 31 patients, 26 (84%) were asymptomatic on ICU discharge. The 7 additional patients fulfilling *Paris* but not *Rec-EXTRIP* criteria, did not have significantly more severe poisoning, but had 7 times more neurological impairment on ICU discharge ($P < .01$) and longer ICU length of stay ($P < .05$) in comparison to the patients not

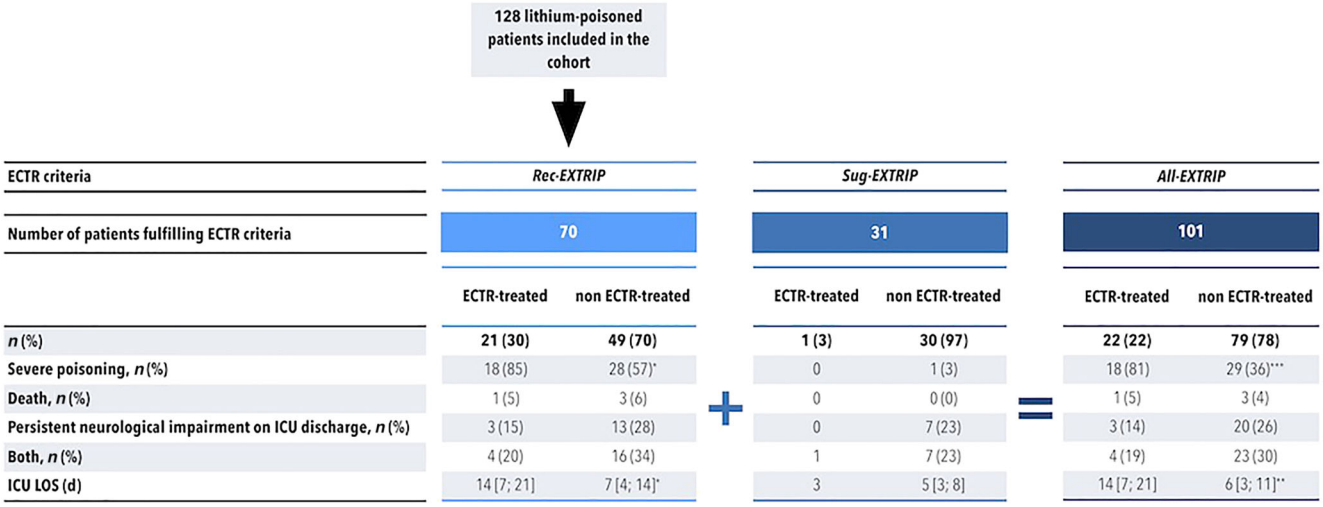


FIGURE 1 Comparison of extracorporeal toxin removal (ECTR) requirement and outcome of patients fulfilling *Paris* criteria or EXTRIP criteria for ECTR initiation according to whether they were actually treated with ECTR or not. Due to the lack of consensual definition in EXTRIP guidelines, decreased consciousness, significant confusion and serum lithium concentration expected to be >1 mmol/L at 36 hours with optimal management, were interpreted. Lithium poisoning was defined as severe in the presence of at least 1 of: (i) seizures; (ii) catecholamine infusion; (iii) mechanical ventilation lasting >48 h. data are expressed as percentages or median [25th; 75th percentiles]. *$P < .05$ and **$P < .01$. ICU LOS, intensive care unit length of stay

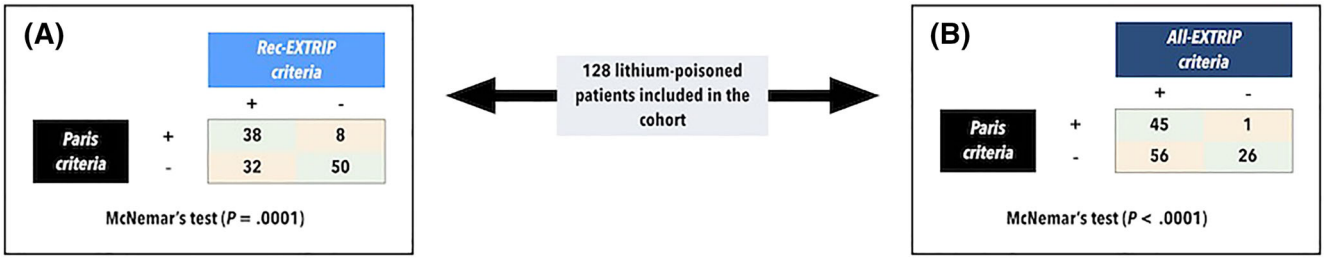
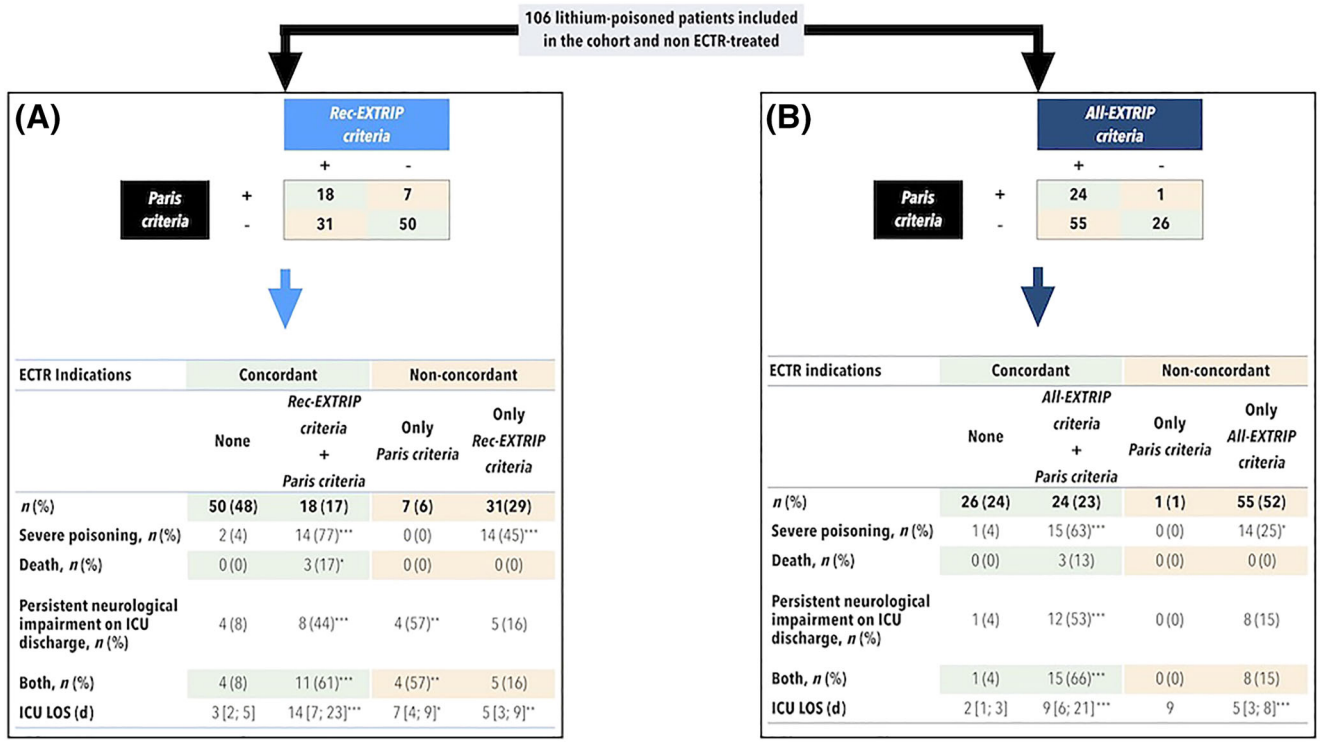


FIGURE 2 Comparison of *Rec-EXTRIP* (a) and *All-EXTRIP* (B) criteria *vs Paris* criteria to decide ECTR initiation patients. Concordance of ECTR indication between *Paris criteria* and *Rec-EXTRIP* or *All-EXTRIP* criteria was tested using McNemar's test. Due to the lack of consensual definition in EXTRIP guidelines, decreased consciousness, significant confusion and serum lithium concentration expected to be >1 mmol/L at 36 hours with optimal management, were interpreted



ECTR Indications	Concordant		Non-concordant	
	None	*Rec-EXTRIP criteria* + *Paris criteria*	Only *Paris criteria*	Only *Rec-EXTRIP criteria*
n (%)	50 (48)	18 (17)	7 (6)	31(29)
Severe poisoning, *n* (%)	2 (4)	14 (77)***	0 (0)	14 (45)***
Death, *n* (%)	0 (0)	3 (17)*	0 (0)	0 (0)
Persistent neurological impairment on ICU discharge, *n* (%)	4 (8)	8 (44)***	4 (57)**	5 (16)
Both, *n* (%)	4 (8)	11 (61)***	4 (57)**	5 (16)
ICU LOS (d)	3 [2; 5]	14 [7; 23]***	7 [4; 9]*	5 [3; 9]**

ECTR indications	Concordant		Non-concordant	
	None	*All-EXTRIP criteria* + *Paris criteria*	Only *Paris criteria*	Only *All-EXTRIP criteria*
n (%)	26 (24)	24 (23)	1 (1)	55 (52)
Severe poisoning, *n* (%)	1 (4)	15 (63)***	0 (0)	14 (25)*
Death, *n* (%)	0 (0)	3 (13)	0 (0)	0 (0)
Persistent neurological impairment on ICU discharge, *n* (%)	1 (4)	12 (53)***	0 (0)	8 (15)
Both, *n* (%)	1 (4)	15 (66)***	0 (0)	8 (15)
ICU LOS (d)	2 [1; 3]	9 [6; 21]***	9	5 [3; 8]***

FIGURE 3 Comparison of the outcome of the non-actually-ECTR treated patients according to the ECTR requirement indicated by *Rec-EXTRIP*, *All-EXTRIP* or *Paris* criteria. Severity and outcome of the patients fulfilling none of the *Paris* criteria + *Rec-EXTRIP* criteria were compared to the patients fulfilling *Paris* criteria + *Rec-EXTRIP* criteria, only *Paris* criteria, and only *Rec-EXTRIP* criteria (a). Severity and outcome of the patients fulfilling none of the *Paris* criteria + *All-EXTRIP* criteria were compared to the patients fulfilling *Paris* criteria + *All-EXTRIP* criteria, only *Paris* criteria, and only *All-EXTRIP* criteria (B). Due to the lack of consensual definition in EXTRIP guidelines, decreased consciousness, significant confusion and serum lithium concentration expected to be >1 mmol/L at 36 hours with optimal management, were interpreted. Lithium poisoning was defined as severe in the presence of at least 1 of the following conditions: (i) seizures; (ii) catecholamine infusion; (iii) mechanical ventilation lasting >48 hours. Data are expressed as percentages or median [25th; 75th percentiles]. *P < .05,**P < .01 and ***P < .001. ICU LOS, intensive care unit length of stay

fulfilling any of these criteria (Figure 3A). Among those 7 patients, 3 (43%) were asymptomatic on ICU discharge. All 3 patients who died would have been treated with ECTR based on *Rec-EXTRIP* and *Paris* criteria.

- ***All-EXTRIP vs Paris* criteria:** The 24 patients who would have been concordantly treated with ECTR were more severely poisoned, had more frequently persistent neurological impairment on ICU discharge and longer length of ICU stay (P < .001) in comparison to the 26 patients who would have not been treated with ECTR by any of these criteria (Figure 3B). The 55 additional patients fulfilling *All-EXTRIP* but not *Paris* criteria, were more severely poisoned (P < .05), had 4-fold more persistent neurologic impairment on ICU discharge (not significant) and longer ICU length of stay (P < .001) compared to the patients not fulfilling any of these criteria. Among those 55 patients, 47 (85%) were asymptomatic on ICU discharge. One additional patient fulfilled *Paris* but not *All-EXTRIP* criteria.

He was asymptomatic on ICU discharge (Figure 3B). All 3 patients who died would have been treated with ECTR based on *All-EXTRIP* and *Paris* criteria.

4 | DISCUSSION

The use of *EXTRIP* criteria to decide ECTR in our cohort of severely lithium-poisoned patients admitted to the ICU, would have indicated more ECTR in comparison to what was actually performed or if *Paris* criteria were used. All patients who died fulfilled *Rec-EXTRIP*, *All-EXTRIP* and *Paris* criteria. However, only decisions based on *Paris* criteria showed significantly different outcome, if considering neurological status on ICU discharge, between actually ECTR- and non-ECTR-treated patients.[7] Additionally, EXTRIP criteria would lead to treating a large proportion of asymptomatic patients (>80%) while they would not indicate ECTR in patients with poor neurological outcome as identified by *Paris* criteria.

The use of serum lithium threshold regardless of the patient symptoms for initiating ECTR in lithium poisoning is controversial.[12] EXTRIP consensus suggested ECTR requirement in lithium poisoning for a threshold of >5 mmol/L.[1] In our series,[7] serum lithium ≥5.2 mmol/L on admission was independently associated with severe lithium poisoning as defined by the presence of at least 1 of the following conditions during ICU hospitalization: seizures, catecholamine infusion, mechanical ventilation lasting >48 hours and fatality onset in the ICU. Moreover, all patients who died presented serum lithium >5 mmol/L during their ICU stay. As the thresholds were similar, the serum lithium >5 mmol/L criterion, currently suggested for initiating ECTR by the EXTRIP workgroup, should be considered as valid. However, it is clear that such a criterion would rarely be reached in cases of chronic poisoning and thus probably only used in acute and acute-on-chronic lithium poisoning.[13]

Neurological impairment is usually considered a criterion for ECTR initiation in lithium poisoning.[1] EXTRIP consensus recommended ECTR in cases of decrease in consciousness and/or seizure onset and suggested ECTR in cases of significant confusion. In our series, GCS ≤ 10 was independently associated with severe lithium poisoning.[7] However, ECTR could not be associated with any significant clinical improvement whether the neurologic impairment criteria were used individually or not. The exact mechanisms involved in lithium-induced neurotoxicity remain unknown. Recent rat studies mimicking acute and acute-on-chronic lithium poisoning have shown that lithium-induced neurotoxicity was associated with lithium accumulation in the brain followed by slower and delayed elimination in comparison to the blood.[14-16] If pharmacokinetic studies have demonstrated the effectiveness of ECTR in removing lithium from the blood,[17,18] there is no evidence that ECTR could enhance lithium elimination from the brain.[1,3] In accordance, no difference in outcome was reported between lithium-poisoned patients for whom haemodialysis was carried out and those for whom it was recommended by the poison control centre but not done, suggesting that indications for haemodialysis in lithium poisoning should be reconsidered to include only the more severe cases.[19] The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT), a neurological complication of lithium toxicity with unknown prevalence and risk factors, seems limited to a small number of case reports and aggressive extracorporeal lithium removal, even after nontoxic concentrations, encouraged by some authors, remains controversial.[1,20] Moreover, neurological impairment specifically attributable to lithium may be difficult to assess since co-ingestion of other psychotropic drugs is frequent in poisoned patients and can be responsible by itself for the observed neurological impairment.[21] We have not limited the retrospective assessment of EXTRIP criteria to lithium-poisoned patients with no co-ingestions because EXTRIP guidelines did not mention this parameter for assessing the lithium contribution to the neurological impairment and it would have not mirrored real life. Finally, the use of ECTR in significantly confused patients is questionable. ECTR requires patient cooperation and its use in such patients may induce severe adverse events responsible for complications and even fatalities, as previously reported.[19]

The time-course of plasma lithium concentration determined by repeated measurements is probably the best criterion for ECTR decision in the absence of clinical studies assessing ECTR-related improvement or prevention of neurological complications. Renal impairment in lithium poisoning is frequent. In our series, 77% of the patients developed AKI including 44% at KDIGO stages 2 or 3.[7] As lithium is almost exclusively eliminated by the kidneys, onset of AKI during poisoning may result in its delayed elimination with increased brain exposure and the consequent enhancement in toxicity. In our series, kidney function impairment on admission was not a risk factor for severe poisoning.[7] This may be related to the adequate hydration and supportive care provided in the ICU, which may have restored kidney function and allowed the rapid clearance of lithium. Consistently, blood lithium pharmacokinetics should always be interpreted dynamically, as follows: increase in serum lithium would suggest persisting lithium absorption requiring whole bowel irrigation, whereas stagnation of serum lithium or onset of AKI would suggest delayed elimination requiring ECTR.[2,18] Such a dynamic approach should be complementary to ECTR recommendations based on serum lithium or kidney function criteria.

Seven patients developed dysrhythmia in our cohort[7]: 1 patient was haemodialysed and 2 died with serum lithium concentrations >10 mmol/L. All these patients would have been dialysed according to the different criteria studied here, independently of dysrhythmia onset. The other 4 patients received supportive management and did not develop further recurrent dysrhythmia. These observations suggest that severe lithium-induced recurrent dysrhythmia may only occur in patients with elevated serum lithium concentrations who would thus probably have been treated with ECTR whatever criteria were used to decide ECTR initiation.

Our retrospective study has several methodological limitations: (i) We acknowledge that our work assessed a modified version of EXTRIP criteria rather than the exact criteria approved by the EXTRIP workgroup itself. Therefore, we cannot rule out that our interpretation

of some EXTRIP criteria may have overestimated the need for ECTR. However, to be able to perform any assessment of EXTRIP criteria as in our study, the exact definition of all criteria was necessary. (ii) We performed a validation study on the same cohort from which the data were derived (circular study). As such, it is predictable that the criteria derived from these patients outperformed any other criteria. (iii) Our analysis was performed on a relatively small number of patients and is thus possibly underpowered for both death and neurological outcomes. (iv) While the EXTRIP workgroup suggests clearly defined aims to report ECTR indications and patient outcome, we were not able to provide some exact endpoints like blood dialysate flows and hospital length of stay, due to the 20-year study period. (v) No patient follow-up was available after ICU discharge and thus we cannot rule out that patients symptomatic on ICU discharge did not develop long-term neurologic sequelae. Accordingly, ICU length of stay, used as a study endpoint, may have been confounded by more than just poisoning outcome. However, our ICU, dedicated to the management of acute poisonings, uses effective protocols for poisoned patient discharge, developed over years of experience. Psychiatrists and internists systematically evaluate patients' conditions, 24/24 7/7 before ICU discharge to assess neurological recovery. We therefore are confident that length of ICU stay could be considered as an accurate surrogate marker to estimate the date of neurological recovery. (vi) Patients were more severely poisoned than those previously reported by poison control centres. Therefore, optimal management in the ICU may not mirror the usual management of lithium-poisoned patients in other medical or psychiatric settings. Additionally, we cannot rule out that we provided a level of care that might not be obtained in many places elsewhere, in which case an intervention might be preferred over a level of inferior supportive care.

5 | CONCLUSION

To date, indications for, as well as optimal time to ECTR initiation in lithium poisoning are still controversial. Based on our cohort analysis, EXTRIP criteria, if used, would have led to the performance of more ECTR than in actual practice or if *Paris* criteria were used. In the patients for whom ECTR was indicated based on EXTRIP criteria, no significant difference in neurological outcome was observed between those who were actually treated with ECTR and those who were not. Further prospective investigations are required to identify and validate more specific criteria such as those suggested by our study. However, physicians in charge of lithium-poisoned patients should be aware that the impact of ECTR on reversal of lithium-induced complications has still to be demonstrated.

ACKNOWLEDGEMENTS

The authors would like to thank Mrs Alison Good (UK) for her helpful review of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests except that B.M. is member of EXTRIP.

CONTRIBUTORS

D.V. and B.M. designed and planned the study. D.V., S.B., J.L., L.L. and B.M. collected and analyzed the data. E.V. performed the statistical analyses. D.V. and B.M. drafted the paper and all authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Vodovar D, Beaune S, Langrand J, Vicaut E, Labat L, Mégarbane B. Assessment of Extracorporeal Treatments in Poisoning criteria for the decision of extracorporeal toxin removal in lithium poisoning. *Br J Clin Pharmacol*. 2019;1–9. https://doi.org/10.1111/bcp.14087