Seminars in Dialysis

Extracorporeal Treatment for Tricyclic Antidepressant Poisoning: Recommendations from the EXTRIP Workgroup

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ABSTRACT

The Extracorporeal Treatments In Poisoning (EXTRIP) workgroup was formed to provide recommendations on the use of extracorporeal treatments (ECTR) in poisoning. Here, the workgroup presents its results for tricyclic antidepressants (TCAs). After an extensive literature search, using a predefined methodology, the subgroup responsible for this poison reviewed the articles, extracted the data, summarized findings, and proposed structured voting statements following a predetermined format. A two-round modified Delphi method was chosen to reach a consensus on voting statements and RAND/UCLA Appropriateness Method to quantify disagreement. Blinded votes were compiled, returned, and discussed in person at a meeting. A second vote determined the final recommendations. Seventy-seven articles met inclusion criteria. Only case reports, case series, and one poor-quality observational study were identified yielding a very low quality of evidence for all recommendations. Data on 108 patients, including 12 fatalities, were abstracted. The workgroup concluded that TCAs are not dialyzable and made the following recommendation: ECTR is not recommended in severe TCA poisoning (1D). The workgroup considers that poisoned patients with TCAs are not likely to have a clinical benefit from extracorporeal removal and recommends it NOT to be used in TCA poisoning.

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[a](Correction added on 5 May 2014, after first online publication: The EXTRIP workgroup members' names were added to the Acknowledgements section of the article.)

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The Extracorporeal Treatments In Poisoning (EXTRIP) workgroup is comprised of international experts representing diverse specialties and professional societies (Table S1) and was created to provide recommendations based on evidence (or, in its absence, consensus) on the use of extracorporeal treatments (ECTR) in poisoning (www.extrip-workgroup.org). Rationale, background, objectives, complete methodology, and the first poison recommendation have been previously published (1–3). The following text reviews the results and recommendations for tricyclic antidepressants (TCAs).

Pharmacology

TCAs have been in clinical use for the treatment of depression since the 1950s. Despite having been largely replaced by newer antidepressants, TCAs continue to be prescribed for a number of conditions, including major depressive disorder, chronic and neuropathic pain, attention deficit hyperactivity disorder, cycling vomiting, nocturnal enuresis, and obsessive-compulsive disorders (4–7). TCAs share a common three-ring structure and can be classified into tertiary amines (amitryptiline, clomipramine, doxepin, imipramine, trimipramine) and secondary amines (desipramine and nortriptyline) (8). The antidepressant effects of these drugs are largely the result of presynaptic reuptake inhibition of serotonin and norepinephrine. Other pharmacologic effects include competitive muscarinic and alpha-adrenergic antagonism and histamine inhibition, as well as GABA-A antagonism. TCAs produce cardiac sodium channel blockade and can be classified as having type IA antiarrhythmic properties.

TCAs are rapidly absorbed from the gastrointestinal tract, but because of their anticholinergic effects in overdose, decreased gastrointestinal motility can prolong the time to peak drug concentrations (9). TCAs are extensively bound to plasma proteins, mainly alpha-1 acid glycoprotein and lipoproteins. Due to their lipophilicity, free drug distributes rapidly into tissues with characteristically large volumes of distribution and long half-lives of elimination (Table 1). Drug concentration in the myocardium and the brain has been reported to be 40–200 times greater than in plasma (10). TCAs undergo first-pass hepatic metabolism, and have a high endogenous clearance. Hepatic metabolism results in the generation of numerous metabolites, many with pharmacologic activity, most of which are eliminated in the urine (10,11).

Overview of Tricyclic Antidepressant Poisoning

TCAs continue to be a leading cause of mortality and morbidity in poisoned patients and are responsible for nearly half of all fatalities reported due to antidepressants (12).

The clinical features of TCA poisoning are largely an extension of their pharmacologic actions described above. Antihistaminic- and anticholinergic- mediated effects typically result in altered mental status ranging from agitation and delirium to central nervous system depression and coma. Other anticholinergic effects (dry flushed skin, tachycardia, ileus, mydriasis, urinary retention, and hyperthermia) are usually present. Seizures result from anticholinergic and GABA-A antagonism, while the cardiovascular effects are caused by muscarinic and alpha-adrenergic blockade. These effects are manifested by tachycardia, peripheral vasodilation, and hypotension. Sodium channel blockade and the resulting delayed depolarization can cause wide complex arrhythmias, AV conduction disturbances, and myocardial depression, which are the primary cause of death in TCA overdose. Most deaths occur in the prehospital environment and are reported in the first few hours after presentation (13,14).

Many exposures to TCA will result in benign courses requiring little or no treatment at all. The incidence of severe rhythm disturbances is rare, while hypotension and coma and seizures are more frequent (11,15,16). Predicting which patients will develop severe toxicity is still debated. A range of toxic doses of approximately 5–20 mg/kg is often cited, but the reported ingested dose of TCA is neither reliable nor a good predictor of outcome (14,17). Serum testing is not generally routinely available and concentrations are less predictive than electrocardiogram (ECG) findings to identify high-risk patients (18): QRS duration is a better predictor of seizures and ventricular arrhythmia than serum concentrations (19) and an R wave in aVR of more than 3 mm had a good predictive value for seizures or arrhythmias (20).

The management of patients poisoned with TCAs includes general proactive care directed at securing the patient's airway and treating seizures with benzodiazepines. Hypotension can be a consequence of decreased vascular resistance and should be initially treated with fluid challenges, or secondary to myocardial depression and arrhythmias. An ECG

TABLE 1. Pharmacokinetic properties of TCA

Drug	Bioavailability%	Protein Binding%	Plasma half-life (hours)	Active metabolites	Volume of distribution (l/kg)
Amitryptiline	31–61	82–96	31–46	Nortiptyline	5–20
Amoxapine	46–82	NA	8.8–14		NA
Clomipramine	36–62	90–98	22–84	Desmethyl	7–20
Desipramine	60–70	73–90	14–62		22–59
Dothiepin	30	85	14–24	Dothiepin-s-oxide	11–78
Doxepin	13–45	80	8–24	Desmethyl	9–33
Imipramine	29–77	76–95	9–24	Desipramine	15–30
Maprotiline	79–87	88	27–50		16–32
Nortriptyline	32–79	93–95	18–93	10-hydroxy	21–57
Protriptyline	75–90	90–94	54–198		15–31
Trimipramine	18–63	93–97	16–40		17–48

Adapted from Dziukas 1991, DeVane CL, Cyclic Antidepressants, In: Burton ME, Shaw LM, et al. Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring 2006; Lippincott Williams & Wilkins, pp 781–797.

should be performed to identify hallmarks of TCA sodium channel blockade (ventricular arrhythmia, QRS widening, Brugada-like pattern, or terminal axis deviation of the QRS, e.g., prominent R wave in aVR). Gastrointestinal decontamination may be indicated if the patient presents early after ingestion, and is discussed more extensively elsewhere (21–23).

Although there is no specific antidote for TCA poisoning, there is a fundamental role for sodium bicarbonate in the treatment of symptomatic TCA-poisoned patients. Sodium bicarbonate may ameliorate hypotension due to volume and sodium loading, and improves myocardial conduction disturbances presumably by creating a sodium load and also by inducing alkalosis (24). Systemic alkalosis itself, achieved by hyperventilation, also improves hypotension and cardiac conduction disturbances. The beneficial effect of alkalosis is potentially due to increased protein binding thereby reducing free drug availability and altering the charge of the TCA-receptor complex (25–27). However, hypertonic sodium has also demonstrated benefit in few animal studies and isolated cases (25). Sodium bicarbonate combines the effect of sodium loading and alkalosis and remains the therapy of choice, especially for patients presenting with seizures, fluid-unresponsive hypotension, or typical ECG findings (ventricular dysrhythmia, QRS >100 ms, prominent R waves in aVR) (28). Induced hyperventilation can be considered in mechanically ventilated patients who cannot tolerate large fluid volumes. The combined effect of sodium bicarbonate and hyperventilation can result in profound alkalosis (28). Adverse effects of prolonged sodium bicarbonate therapy also include hypokalemia, hypocalcemia, impaired oxygen delivery by shifting the oxyhemoglobin dissociation curve to the left, and fluid overload. Hypotension that does not respond to adequate fluid resuscitation and bicarbonate should be treated with direct-acting vasopressors (e.g., norepinephrine).

Other experimental "rescue" treatments have been used in a limited number of critical cases unresponsive to the usual treatment. These include glucagon (29), lidocaine and magnesium sulfate (30), intra-aortic balloon pump, extracorporeal life support (31), and lipid emulsion therapy (32). Prolonged cardiac massage has also been reported to be successful after cardiac arrest in such patients (11,33).

Despite several anecdotal reports suggesting a benefit, current recommendations from widely consulted resources explicitly recommend against ECTR in TCA-poisoned patients (34–39). Some recent reviews and publications nevertheless advocate these therapies, including plasmapheresis, hemodialysis, and hemoperfusion for severely poisoned TCA patients (40–43). One guideline reviewing the management of tricyclic overdose does not comment on the therapeutic use of ECTR (44).

Methodology

A complete description of the methodology is provided elsewhere (2).

Articles from the literature search were obtained via the preliminary search database. Thereafter, a specific search retrieved other articles from Medline, Embase, Cochrane library (Review and Central), Conference proceedings/meeting abstracts of the EAPCCT and NACCT annual meetings, and Google Scholar. Finally, the bibliographies of all articles obtained were manually reviewed for completeness.

Search Strategy

We used the following search strategy in Medline (via PubMed), and adapted for the other databases: (tricyclic OR amitriptyline OR imipramine OR clomipramine OR doxepin OR trimipramine OR amoxapine OR desipramine OR nortriptyline OR protriptyline OR dibenzepin OR dothiepin OR maprotiline) AND (hemoperfusion OR haemoperfusion OR hemofiltration OR haemofiltration OR hemodialysis OR haemodialysis OR hemodiafiltration OR haemodiafiltration OR dialysis OR plasmapheresis OR plasma exchange OR exchange transfusion OR CRRT).

The designated subgroup completed the literature search, reviewed articles, extracted data, summarized findings, and proposed structured voting statements following a predetermined format, all of which was submitted to the workgroup. The benefit of the ECTR procedure was weighed against its cost,

TABLE 2. Criteria of dialyzability

Dialyzability[a]	Primary criteria % Removed[b]	Alternative criteria 1 CL_{EC}/CL_{TOT} (%)[c]	Alternative criteria 2 $T_{1/2\ EC}/T_{1/2}$ (%)	Alternative criteria 3 Re_{EC}/Re_{TOT} (%)[c]
D, Dialyzable	>30	>75	<25	>75
M, Moderately dialyzable	>10–30	>50–75	>25–50	>50–75
S, Slightly dialyzable	≥3–10	≥25–50	≥50–75	≥25–50
N, Not dialyzable	<3	<25	>75	<25

[a]Applicable to all modalities of ECTR, including hemodialysis, hemoperfusion, hemofiltration.
[b]Corresponds to% removal of ingested dose or total body burden in a 6-hour ECTR period.
[c]Measured during the same period of time.
These criteria should only be applied if measured or calculated (not reported) endogenous half-life is >4 hours (otherwise, ECTR is considered not clinically relevant). Furthermore, the primary criterion is preferred for poisons having a large V_d (>5 l/kg). Obtained with permission from *Clinical Toxicology*.

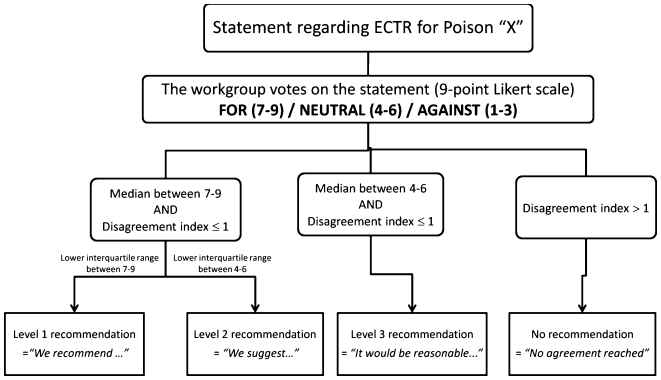

FIG. 1. Delphi method (2 rounds) for each recommendation.

availability, alternative treatments, and its related complications. Level of evidence for clinical recommendations was determined by the subgroup and the appointed epidemiologist (Table S2). Dialyzability was determined by the workgroup following criteria listed in Table 2. The strength of recommendations was evaluated by a two-round modified Delphi method for each proposed voting statement (Fig. 1) and RAND/UCLA Appropriateness Method was used to quantify disagreement between voters. Blinded votes with comments were sent to the statistician, who then compiled and returned them to each participant. The workgroup met in person in June 2012 to discuss the evidence, exchange ideas, and debate statements. A second blinded vote was later submitted and results reflect the core of EXTRIP recommendations.

Results

Results of the literature search, last updated on November 1st 2013, are presented in Fig. 2.

From the initial 1312 studies obtained, 77 studies met the inclusion criteria, including 1 observational study (45), 5 animal studies (46–50), 4 in vitro studies (51–54), 4 pharmacokinetic (PK) studies (55–58), and 63 case reports (40–42,59–118), 39 of which had sufficient toxicokinetic (TK) data. In total, 108 patients were included for analysis. No randomized trials were identified.

Dialyzability

Tricyclics are small molecules (between 200 and 400 Da) and can therefore cross any hemofilter or hemodialyzer, despite their extensive protein binding; this is confirmed by the many publications describing either a high extraction ratio, a significant reduction in TCA plasma concentrations, or a high plasma clearance during ECTR (55,78,91,95,107,119). However, based on their large V_D, TCAs would be expected to be distributed extensively out of the vascular space; any reduction in plasma concentrations will therefore have an inconsequential effect on total body stores. Furthermore, significant redistribution from deeper compartments into plasma, commonly referred to as "rebound", would be expected after any extracorporeal session.

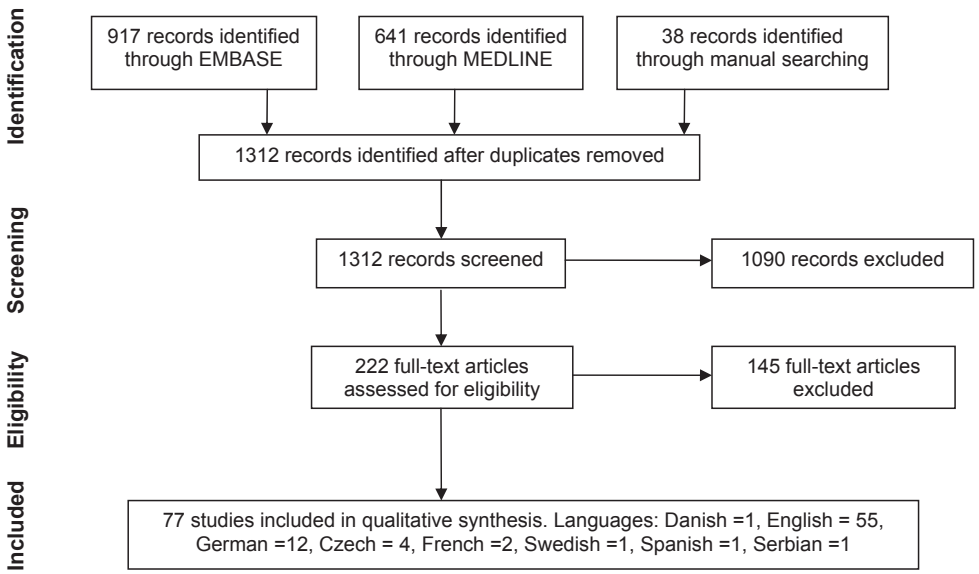

FIG. 2. Results of search, selection, and inclusion of studies.

For these reasons, according to EXTRIP criteria, the dialyzability of TCAs would be assumed to be poor, whatever extracorporeal modality is used and whatever the specific tricyclic studied. As described in Table 2, the EXTRIP workgroup only reviewed publications in which the recovered amount of TCAs could be quantified; these are summarized in Table S3.

As expected, all of the articles that qualified for TK grading showed negligible TCA removal, despite high plasma clearance. This was true for all ECTR modalities: exchange transfusion (108,110), intermittent hemodialysis (IHD) (69,81,105), hemodialysis–hemoperfusion (HD–HP) (66), charcoal hemoperfusion (HP) (73,75,103,104), resin HP (83), liver dialysis (59), peritoneal dialysis (94,97,99,120), and continuous hemoperfusion (84).

For example, HD treatment for severe TCA poisoning in two reports failed to show any parent poison recovered in the dialysate (69,105). In another report of an imipramine overdose patient, HD recovered only 0.6% of the ingested dose (81). Even HP, which is in principle the ideal modality for protein-bound poisons, removed, in the best-case scenario, 7% of ingested dose during 6 hours of charcoal HP (103) and 2.7–6.2% in a series of eight cases treated with resin HP (83), despite extraction ratios nearing 100% and plasma clearance reaching 200 ml/minute (73,83). In another example, HD–HP was only able to remove 4 mg of amitriptyline in 4 hours despite a clearance of 72 ml/minute (66). Similarly, in a patient who overdosed with meprobate and amitriptyline treated with HP-HD for anuria, the author concluded that the removal of amitriptyline was inconsequential (76). Treatment with other less popular ECTR modalities confirmed the expected results based on TCA properties: in 2 cases of imipramine poisoning, exchange transfusion failed to recover more than 1% of the ingested dose (108,110). Four patients treated with peritoneal dialysis for amitriptyline, opipramol, and desipramine overdoses also had less than 1% of the estimated ingested dose removed (94,97,99,120). A hemodiabsorption technique also reported negligible removal of different TCAs (59).

Pharmacokinetic studies of TCA removal in non-poisoned end-stage renal disease (ESRD) patients reveal similar results: in two studies, HD did not alter TCA kinetics (56,121). In another prospective study of five ESRD patients, a single HD session removed on average 37 μg in 4 hours, which was <1% of the administered oral dose of doxepin (57).

Although several of these papers are dated, results would not be expected to be significantly improved had more efficient technology been used (higher blood flows, higher efficiency filters), as extraction from earlier reports sometimes approach 100%. Again, the limiting factor appears to be the massive volume of distribution of TCAs and not extraction by the filter or adsorbent column. This can be illustrated by the following example: if a 60 kg patient ingests 2400 mg of amitryptiline (V_D = 20 l/kg), assuming complete absorption and distribution, the plasma amitriptyline concentration will be 2,000 ng/ml. If charcoal HP is performed for 4 hours, with a blood flow equal to 350 ml/minute (or plasma flow = 200 ml/minute for a hematocrit of 40%), assuming in the best-case scenario an extraction ratio of 100%, the HP clearance will be 200 ml/minute. Therefore, 400 μg will be removed per minute, for a total removal of 96 mg over 4 hours. Thus, despite a high plasma clearance, HP will decrease the total body drug burden of the drug by less than 5%.

In those articles that satisfied criteria for dialyzability evaluation, most confirm very small amounts of TCA removed and are therefore categorized as "*slightly dialyzable*" or "*not dialyzable*" according to criterion 1 of the dialyzability grading. The EXTRIP workgroup concluded: TCAs are not dialyzable (Evidence = B)

Recommendations

Executive Summary

- General: We recommend NOT to perform ECTR in patients with TCA poisoning.

Rationale

There are no randomized controlled trials or large observational series to analyze clinical outcome data of patients undergoing ECTR for TCA poisoning. One small retrospective observational study was identified in which five patients were treated with HP, and four were not (45): the fall in TCA serum concentrations was faster and the length of stay shorter in the HP group, although one patient in the HP group was not accounted for due to an extremely long and complicated stay. Unfortunately, the study was underpowered and statistical analysis impossible to perform.

In an animal model, a group treated with both HP and cardiopulmonary bypass was compared with another group only treated with cardiopulmonary bypass. When compared to the control group, HP did not improve hemodynamic instability and also did not remove more than 1–2% of administered dose (49).

The remaining evidence of a clinical effect of ECTR consists of case reports and case series that are often dated, that lacked control groups, had multiple confounders, heterogeneous treatments, and suffered from definite publication bias. The quality of evidence for all recommendation statements would therefore be graded as "very poor" (122).

It is interesting to note that 12 deaths were reported among the case reports included and that clinical improvement that occurred during or shortly after ECTR was reported in 68 of the 108 cases treated with any ECTR modality. Among the cases where improvement was reported, confounding therapies such as intubation, gastrointestinal

decontamination, vasoactive drugs, and bicarbonate were consistently present. What effect, if any, was achieved by extracorporeal measures is therefore impossible to elucidate. Often the improvement reported some reversal of coma, while other more severe cardiovascular end-organ effects were not shown to dramatically improve during ECTR in a convincing time-related manner, such as the prompt ECG changes typically reported with sodium bicarbonate therapy. In fact, ECGs were rarely provided in the cases where improvement was reported, and sometimes ECG normalization only occurred days after ECTR had been completed (60).

Despite overwhelming TK evidence suggesting little to no significant enhancement of TCA elimination with ECTR, several authors still suggest a beneficial clinical effect of ECTR and have postulated several reasons for this: 1) TCA removal prior to distribution, 2) Protein binding alteration during ECTR, 3) Critical removal from the toxic compartments, and 4) Metabolic manipulation. These are presented here.

Early intervention with ECTR may clear TCA from plasma before it distributes to tissues and before it produces its toxic end-organ effects (60,78,79,83,117). However, it is also plausible that the rapid fall in TCA concentrations reported by these authors during early ECTR is more likely a result of TCA distribution than true drug removal. Furthermore, many of TCAs' end-organ toxic effects occur early after exposure, as has been shown in prospective series designed to evaluate the utility of ECG parameters (19,20). Due to the lack of availability and utility of serum drug concentrations to predict outcome as well as the difficulty in initiating ECTR during the supposed predistribution phase in a realistic time frame (which includes transfer to a specialized unit, organizing ECTR, and installation of a central catheter), such an attempt to either correct or prevent the appearance of life-threatening symptoms would not be realistic in most clinical contexts.

Other arguments made by authors who advocate the use of ECTR for patients with serious TCA poisoning involve the toxicokinetics of tricyclics in overdose. One hypothesis is that in a severely poisoned patient, hypotension contributes to decreased hepatic blood flow and tissue perfusion as well as acidosis, which in turn would favor a larger amount of free ionized drug by decreasing both protein binding and volume of distribution and prolonging half-life of elimination, making more drug available for extracorporeal elimination (60,61,83).

Another hypothesis attempting to justify why ECTR might be effective despite removing only a negligible amount of drug suggests that increasing intercompartmental clearance with hemoperfusion facilitates redistribution of just enough drug away from the toxic compartments (i.e., cardiac receptors) to improve the cardiovascular status (83,123). The same authors admit that even if this were true, intercompartmental clearance would be reduced by the same hemodynamic conditions in severely poisoned patients.

The possibility that metabolic manipulation may have contributed to the effect of treatments with hemodialysis exists. Frank et al. described a very dramatic case of a patient treated after cardiac arrest due to doxepin with persistent cardiovascular instability, acidosis, and hypokalemia. They describe improvement during treatment with HP/HD and rapidly falling drug concentrations. The decision to use HP/HD in extremis in this case was partially motivated by the patient's hypokalemia and fear of fluid overload with prolonged bicarbonate infusion. Drug removal or clearance was not measured or calculated, and the improvement in this case may be largely due to the metabolic acidosis correction (61). Hemodialysis and hemofiltration would both expect to correct acidosis much quicker than bicarbonate infusion and could therefore contribute to clinical improvement despite a lack of meaningful TCA removal. Metabolic correction was not the intent of the authors in the remainder of cases reviewed, most of which used hemoperfusion. It is also possible that the outcome in this case was the natural course of the disease and other measures simultaneously administered; this type of dramatic improvement has in fact been reported in other patients not receiving ECTR (11,33).

For those cases with cardiovascular disturbances, several other measures are available. Considering the lack of significant TCA removal and unconfirmed clinical benefit, the use of ECTR is questionable. Furthermore, the application of ECTRs, even if they are usually considered generally safe, is not without cost and risks. In the present literature review, adverse effects of ECTRs, other than death, were reported: in subjects undergoing hemoperfusion, thrombocytopenia was reported in 25 patients, anemia in 12, bleeding or coagulation problems in 2, a clotting cartridge in 1, hypotension in 2, hypocalcemia in 5, and pulmonary edema in 1 (67,71,75,78–80,83,87,91,96,98,104,107,109). Peritoneal dialysis-related peritonitis was reported in one patient, hyperglycemia in three cases, and hypothermia in one (99,100). Worsening acidosis was reported in one case treated with exchange transfusion (65).

Although some anecdotal reports have documented patient improvement, considering the lack of toxicokinetic benefit from most studies, the questionable clinical benefit, the absence of quality observational studies or trials, and the existence of efficacious alternative treatments, the EXTRIP workgroup strongly and unanimously recommended NOT proposing ECTR in TCA poisoning.

Conclusion

The EXTRIP workgroup presents here its recommendations for extracorporeal treatments in TCA

poisoning. The workgroup recommends NOT performing ECTR for TCA poisoning.

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See online appendix Data S1 for additional acknowledgments.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1 Acknowledgements, financial disclosure, and competing interests.

Table S1 Supporting societies.

Table S2 Strength of recommendation and level of evidence scaling.

Table S3 TK analysis of individual patients in which TCA removal was quantified.