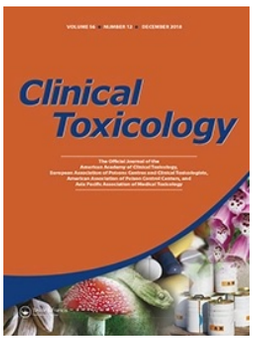

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REVIEW

Extracorporeal treatment for calcium channel blocker poisoning: systematic review and recommendations from the EXTRIP workgroup

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ABSTRACT

Background: Calcium channel blockers (CCBs) are commonly used to treat conditions such as arterial hypertension and supraventricular dysrhythmias. Poisoning from these drugs can lead to severe morbidity and mortality. We aimed to determine the utility of extracorporeal treatments (ECTRs) in the management of CCB poisoning.

Methods: We conducted systematic reviews of the literature, screened studies, extracted data, summarized findings, and formulated recommendations following published EXTRIP methods.

Results: A total of 83 publications (6 *in vitro* and 1 animal experiments, 55 case reports or case series, 19 pharmacokinetic studies, 1 cohort study and 1 systematic review) met inclusion criteria regarding the effect of ECTR. Toxicokinetic or pharmacokinetic data were available on 210 patients (including 32 for amlodipine, 20 for diltiazem, and 52 for verapamil). Regardless of the ECTR used, amlodipine, bepridil, diltiazem, felodipine, isradipine, mibefradil, nifedipine, nisoldipine, and verapamil were considered not dialyzable, with variable levels of evidence, while no dialyzability grading was possible for nicardipine and nitrendipine. Data were available for clinical analysis on 78 CCB poisoned patients (including 32 patients for amlodipine, 16 for diltiazem, and 23 for verapamil). Standard care (including high dose insulin euglycemic therapy) was not systematically administered. Clinical data did not suggest an improvement in outcomes with ECTR. Consequently, the EXTRIP workgroup recommends against using ECTR in addition to standard care for patients severely poisoned with either amlodipine, diltiazem or verapamil (strong recommendations, very low quality of the evidence (1D)). There were insufficient clinical data to draft recommendation for other CCBs, although the workgroup acknowledged the low dialyzability from, and lack of biological plausibility for, ECTR.

Conclusions: Both dialyzability and clinical data do not support a clinical benefit from ECTRs for CCB poisoning. The EXTRIP workgroup recommends against using extracorporeal methods to enhance the elimination of amlodipine, diltiazem, and verapamil in patients with severe poisoning.

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Introduction

Calcium channel blockers (CCBs) are used in the management of arterial hypertension, supraventricular dysrhythmias, angina, migraine and peripheral vasospasm. Calcium channel blocker poisoning frequently leads to morbidity and mortality despite optimal care [1]. A potential use of extracorporeal treatments (ECTRs) to enhance elimination of CCBs in poisoning has been suggested [2–5].

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Supplemental material, Table 1). Its mission is to provide recommendations on the use of ECTRs in poisoning (http://www.extrip-

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Supplemental data for this article can be accessed here.
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workgroup.org). The rationale, background, objectives, methodology, and its initial recommendations were previously published [6–22]. The objective of this article is to present EXTRIP's systematic review of the literature and recommendations for the use of ECTR in patients poisoned with CCBs.

Pharmacology and toxicokinetics

Calcium channel blockers are divided into two broad clinical pharmacological classes: dihydropyridines (e.g., amlodipine, nifedipine) and non-dihydropyridines (e.g., diltiazem and verapamil). All currently available CCBs block L-type voltage-gated calcium channels. Dihydropyridines have more affinity for L-type channels in the vascular smooth muscles whereas non-dihydropyridines target mostly those in the myocardium [23–25]. Consequently, at therapeutic doses dihydropyridines cause vasodilation whereas non-dihydropyridines, particularly verapamil, slow conduction through the atrioventricular and sinoatrial nodes [26,27]. In the setting of poisoning there can be a loss of this pharmacological selectivity [28].

Calcium channel blockers are well absorbed and undergo first pass metabolism with variable bioavailability [29,30]. They are highly protein bound and have large volumes of distribution [31–35], aside from nimodipine, nicardipine, and nifedipine. All CCBs are metabolized extensively in the liver with endogenous clearance surpassing 400 mL/min. Renal clearance of unmetabolized drug represents a negligible proportion of total clearance [26,36–40]. In overdose, protein binding and endogenous clearance appear relatively unchanged, although a prolonged apparent elimination half-life is often observed, likely because of ongoing absorption [41–50] The physicochemical and pharmacokinetic properties are presented in Table 1.

Overview of calcium channel blocker poisoning

In 2018, 13,840 single-substance CCB exposures were reported to US poison control centers. Of those, 484 were classified as having a moderate effect, 80 had a major effect, and there were 41 fatalities [1]. Mortality rates from other published cohorts vary between 0.3 and 25% [127–138]. This heterogeneity in mortality depends on factors such as the population studied (exposures reported to poison control centers, cohorts admitted to the intensive care unit [ICU]), the presence of coingestants (particularly β-adrenergic antagonists and angiotensin axis antagonists), the type and dose of CCB, the delay to medical care and differences in management [136,139]. Studies of cases of unintentional ingestions (typical in the pediatric population) report a lower incidence of morbidity and mortality, which varies between 0 and 0.3% [140,141].

Oral poisoning is characterized by nausea, vomiting, hypotension (due to vasodilation and/or myocardial depression), altered consciousness, and cardiac conduction disturbances such as sinus bradycardia, heart block, other bradydysrhythmias, and asystole [133]. The presence and extent of hyperglycemia is correlated to severity of non-dihydropyridine poisoning [142]: patients who required pacing, vasopressors/inotropes, and/or died as a result of their poisoning had a median serum glucose of 188 mg/dL (10.4 mmol/L) on presentation and a median peak serum glucose of 364 mg/dL (20.2 mmol/L) [142].

The onset of symptoms usually occurs within six hours of ingestion with immediate release preparations but can be delayed up to 24 h with slow-release preparations. There is no established dose that, if left untreated, will cause mortality. However, there is evidence of a dose-response effect [80,130,141,143], and studies consistently show larger ingestions in fatalities than in survivors [127,132]. Patients who are elderly and/or with underlying heart failure may develop symptoms of hypoperfusion even with ingestion of therapeutic doses, due to their sensitivity to the myocardial depressant effects of CCBs [144,145].

Blood concentrations of CCBs are rarely available to help influence clinical management, but higher concentrations are associated with worse outcomes. In one study of 65 verapamil-toxic patients admitted to an intensive care unit, the verapamil concentration was the only independent risk factor associated with mortality ($p = 0.01$), with a cut-off point determined to be 2273 μg/L [127]. In another study of 30 verapamil poisonings, the mean verapamil concentration in survivors was 1600 μg/L whereas it was 4900 μg/L in deaths [132]. A case series of diltiazem overdoses [146] reported that diltiazem concentrations over 500 μg/L were associated with first-degree heart block and sinus bradycardia, 500–1000 μg/L with hypotension alone, 1000–1500 μg/L with

Table 1. Pharmacokinetics and toxicokinetics of most commercially available calcium channel blockers.

Calcium channel blocker	Molecular mass (Da)	pKa	Protein binding (%)	VD (L/kg)	Bioavailability (%)	$T_{1/2}$ (hours)		Total body clearance (mL/min)		Therapeutic concentration (μg/L)	References
						Normal GFR	Poisoning	Normal GFR	CKD/ESKD		
Amlodipine	409	8.6	98	20–25	65	32–45	30–60	300–450	No change	3–15	[25,51–58]
Bepridil	367	9.2	99	15	N/A	25–60	N/A	600	N/A	600–2500	[57,59–61]
Diltiazem	415	7.5	80	3–6	50	4	5–16	600–800	400	30–130	[26,29,38,57,62–73]
Felodipine	384	5.1	99	5–9	12	10–22	N/A	700–1000	No change	1–12	[34,36,40,57,74–78]
Isradipine	371	5.3	97	5–7	20	6	N/A	1000	No change	0.5–2.0	[57,79–82]
Nicardipine	480	8.2	98	1–2	15	3	10.5	600–800	No change	70–100	[32,57,83–89]
Nifedipine	346	3.9	90-95	1–2	55	2–3	8–11	400–600	600–800	10–200	[49,57,90–96]
Nimodipine	418	5.4	99	1	7	1–3	N/A	800–1000	No change	10–50	[57,97–101]
Nisoldipine	388	5.3	99	4–6	55	2–7	N/A	800–1000	No change	1–3	[57,102–106]
Nitrendipine	360	5.4	98	4–10	20	8	N/A	1400–1800	1200	10–50	[57,107–112]
Verapamil	455	8.8	85-90	2.5–5	11-35	4–8	4–13	600–1000	No change	20–250	[23,30,31,33,37,57,113–127]

CCB: calcium channel blocker; Da: Daltons; VD: volume of distribution; $T_{1/2}$: elimination half-life; GFR: glomerular filtration rate; CKD: chronic kidney disease; ESKD: end-stage kidney disease; N/A: Not available.

conduction abnormalities (bifascicular block) whereas concentrations over 6100 µg/L were associated with cardiovascular collapse and deaths. The serum lactate concentration also appears to be prognostic of mortality [80,138].

Management of patients with CCB poisoning includes airway protection as indicated and treatment of bradycardia, hypotension, and myocardial depression [147]. Gastrointestinal decontamination includes activated charcoal [126] and whole bowel irrigation in those with large ingestions, especially modified release preparations [148,149]. Bradycardia may respond to atropine or isoprenaline (isoproterenol) infusion. Management of hypotension includes intravenous crystalloid infusion, calcium boluses, catecholamines, vasopressors and high dose insulin euglycemic therapy [133,135,150]. In patients with refractory bradycardia and hypotension, mechanical pacing has been performed [151,152]. In addition, extracorporeal membrane oxygenation (ECMO) has been used in patients who are refractory to the aforementioned measures e.g., if there is evidence of cardiogenic shock [153]. The Lipid Emulsion Workgroup concluded that there is insufficient evidence to recommend lipid emulsion therapy in the routine management of CCB poisoning [154].

Methods

The EXTRIP workgroup developed recommendations on the use of ECTR following the EXTRIP methodology previously published [8] with modifications, updates, and clarifications. The methods are presented in full in the online supplement.

Results

Results of the literature search (first performed on March 1, 2019 and last updated October 23, 2020) are presented in Figure 1.

A total of 1563 articles were identified after removal of duplicates. In the final analysis, 83 publications were included for qualitative analysis: 55 case reports or case series [3–5,41,42,44–49,58,155–197], 1 cohort study with grouped results [198], 19 pharmacokinetic studies [23,24,33,40,61,82,106,112,199–209], 1 animal experiment [210], 6 *in vitro* studies [211–216], and 1 systematic review [147]. No randomized controlled trials or comparative observational studies were identified.

Summary of evidence

Dialyzability

Although the molecular size for all CCBs is below 500 Daltons, it is expected that CCBs would be minimally dialyzable by common diffusive and convective techniques because of their high protein binding. Furthermore, their large volumes of distribution and high endogenous clearances mean that any type of ECTR will theoretically be inconsequential at enhancing the elimination of CCBs [217].

Several *in vitro* and *ex vivo* experiments were performed. Among the most notable *in vitro* findings, molecular adsorbent recirculating system (MARS®) was better than CVVHDF at removing verapamil because of extensive adsorption to the activated charcoal column [211,214]. As expected from the extensive protein binding of amlodipine, its clearance from hemodialysis was negligible (<5 mL/min) regardless of the dialyzer used [215]; similar conclusions were reached with nifedipine using both hemodialysis and hemoperfusion [204]. Finally, the clearance of verapamil during therapeutic plasma exchange only reached 29.2 mL/min. Two closed loop recirculating bench top experiments studied the effect of hemoperfusion using CytoSorb®, a cartridge containing divinylbenzene co-polymer beads, in which blood concentrations of amlodipine and verapamil were reduced to less than 10% after 180 min [212,213].

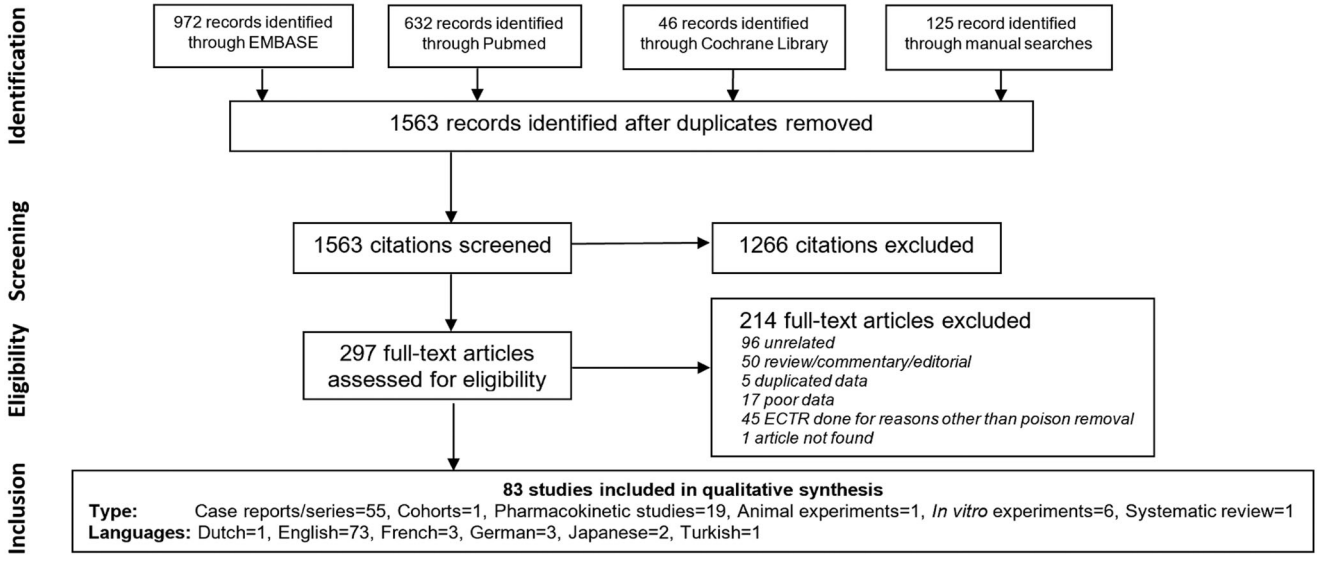

Figure 1. Flow diagram of the literature search.

Although these experiments offer insight regarding ECTR extraction ratios and clearance, they cannot be reliably extrapolated to predict dialyzability *in vivo* because of unaccountability of parameters such as volume of distribution, and endogenous metabolism/elimination, which are the limiting factors for their extracorporeal removal.

The poor dialyzability of CCBs was confirmed *in vivo*, in both pharmacokinetic experiments of patients with ESKD given a therapeutic dose of a CCB (many of which were well conducted and enrolled several patients prospectively) and in toxicokinetic analyses of poisoned patients. A total of 210 patients had pharmacokinetic or toxicokinetic data related to ECTR (amlodipine = 32, benidipine = 10, bepridil = 6, diltiazem = 20, felodipine = 5, isradipine = 8, mibefradil = 5, nicardipine = 15, nifedipine = 32, nisoldipine = 15, nitrendipine = 10, verapamil = 52). To illustrate the proportionally insignificant impact of ECTR for removal of CCBs, Table 2 presents data of ECTR clearance of various CCBs compared to their endogenous clearance; at best, extracorporeal clearance (regardless of the modality) enhances total body clearance of any CCB by 10% (and usually much less). While most publications are dated, it is not expected that results would vary much if performed again today with higher efficiency ECTRs and more performant vascular access.

The workgroup noted occasional misleading statements in some publications which concluded that an ECTR was successful because it decreased CCB concentrations during the procedure. For example, in one report, plasma verapamil concentration fell from 1060 μg/L on admission to 440 μg/L after therapeutic plasma exchange [169]. In another report, serum diltiazem concentration decreased from 1400 μg/L on day 1 to 300 μg/L on day 3. In both reports, the fall of CCB concentrations may be solely accounted for by normal endogenous metabolism [173].

All studies in which removal was quantified or could be estimated in spent dialysate, in either pharmacokinetic or toxicokinetic reports, confirmed insignificant removal of CCBs (i.e., lower than 1% of the ingested dose or total body stores in 6 h). This was confirmed for amlodipine [186,188,189,196,208], bepridil [61], diltiazem [46,160,205], nifedipine [171,200,204], nisoldipine [106], and verapamil [23,203]. The only exception was a pharmacokinetic study in which 9.3% of a felodipine dose was collected in dialysate in 4 h, which would translate into a grading of "moderately dialyzable" [40]. However, the authors claim that the hemodialysis clearance was too low to be calculated precisely. The results of this study are therefore difficult to verify and would require confirmation.

Because of the extensive volume of distribution of CCBs (Table 1), a rebound of blood/plasma concentrations is expected following ECTR [217,218], which was observed in a number of studies [4,44–48,178,196], although ongoing absorption especially from controlled release formulations may also have contributed. In four cases, the concentration of CCB increased during ECTR suggesting that absorption surpassed endogenous and ECTR elimination [41,58,162,194].

As shown in Table 3, amlodipine, diltiazem, bepridil, felodipine, isradipine, mibefradil, nifedipine, nisoldipine, and verapamil were considered not dialyzable regardless of the ECTR used, with variable levels of evidence. This was supported by several reports containing robust pharmacokinetic data. No dialyzability grading was possible for nicardipine and nitrendipine. The comparison of apparent half-lives during and off ECTR was an unreliable criterion to assess dialyzability for CCBs because of the likelihood that their large

Table 2. Endogenous versus extracorporeal clearance of various calcium channel blockers.

Calcium channel blocker	Endogenous clearance (mL/min)	References	ECTR	ECTR clearance (mL/min) Median	*N*	Range	References
Amlodipine	300–450	[25,51–54]	HD**	11.5	15		[208]
			LSD (MARS®)*	7.8	8	0.8–32.3	[186,188,198]
			CytoSorb® Hemoadsorption	17.5	1	9.6–25.6	[196]
			HCO HD	13.8	1	0–24	[196]
Bepridil	600	[59]	HD	0	6		[61]
Diltiazem	600–800 (400 in CKD)	[29,38,62–64]	HP	40.7	2	17.3–64.1	[44,46]
			CKRT	16.7	1		[173]
			TPE	48.2	1		[160]
			LSD (MARS®)*	20.3	3		[198]
			PD	1.7	6	0.1–2.7	[205]
Felodipine	700–1000	[34,40,74–77]	HD	"Low"	5		[40]
Isradipine	1000	[79]	HD	5.1	8	0–15.1	[82]
Nicardipine	600–800	[32,83–89]	LSD (MARS®)*	<0.1	2		[198]
Nifedipine	400–600	[90–94]	HD	3.0	15	0.2–8.3	[24]
			CKRT	0.9	1	0.7–1.1	[171]
Nimodipine	800–1000	[97–101]	N/A				
Nisoldipine	800–1000	[102–104]	HD	<25	7		[106]
Nitrendipine	1400–1800 (1200 in CKD)	[107–112]	N/A				
Verapamil	600–1000	[30,31,33,113–124]	HD	3.7	23	0–40.5	[23,33,157,203,206]
			IHF	1.9	7	0–13.4	[206]
			HP	73	1		[157]
			LSD (MARS®)*	6.6	7		[198]
			PD	4	5	0.3–8.1	[206]

*Includes data taken from conference proceeding.
**Assuming dialysate flow = 500 mL/min.
CKD: chronic kidney disease; HD: hemodialysis; HP: hemoperfusion; IHF: intermittent hemofiltration; CKRT: continuous kidney replacement therapy; TPE: therapeutic plasma exchange; LSD: liver support device; MARS®: molecular adsorbent recirculating system; HCO HD: high cut-off hemodialysis N/A: not available.

Table 3. Dialyzability of calcium channel blockers.

		Number of patients satisfying a criterion for dialyzability								
Drug	PK/TK grading	HD	TPE	CKRT	HP	PD	HCO-HD	CytoSorb® Hemoadsorption	LSD (MARS®)	Final grading and level of evidence
Amlodipine	Dialyzable									HD: ND, B
	Moderately dialyzable									TPE: ND, D
	Slightly dialyzable									LSD: ND, B
	Not dialyzable	15	1				1	1	6	HCO HD: ND, D
										CytoSorb® Hemoadsorption: ND, D
Bepridil	Dialyzable									
	Moderately dialyzable									HD: ND, B
	Slightly dialyzable									
	Not dialyzable	6								
Diltiazem	Dialyzable				2*				1*	HD: ND, D
	Moderately dialyzable				2*					HP: ND, D
	Slightly dialyzable									TPE: ND, D
	Not dialyzable	1	1		2	6				PD: ND, B
Felodipine	Dialyzable									HD: ND, D
	Moderately dialyzable									
	Slightly dialyzable									
	Not dialyzable	5&								
Isradipine	Dialyzable									HD: ND, B
	Moderately dialyzable									
	Slightly dialyzable									
	Not dialyzable	8								
Mibefradil	Dialyzable									HD: ND, C
	Moderately dialyzable									
	Slightly dialyzable									
	Not dialyzable	5								
Nicardipine	Dialyzable									HD: No grading
	Moderately dialyzable	8*								
	Slightly dialyzable	5*								
	Not dialyzable									
Nifedipine	Dialyzable									HD: ND, B
	Moderately dialyzable									CKRT: ND, D
	Slightly dialyzable				1*					
	Not dialyzable	10		1						
Nisoldipine	Dialyzable									HD: ND, B
	Moderately dialyzable									
	Slightly dialyzable									
	Not dialyzable	7								
Nitrendipine	Dialyzable									HD: No grading
	Moderately dialyzable	10*								
	Slightly dialyzable									
	Not dialyzable									
Verapamil	Dialyzable		1*		1*					HD: ND, B
	Moderately dialyzable									LSD: ND, D
	Slightly dialyzable	3*								
	Not dialyzable	9							1	

PK: pharmacokinetics; TK: toxicokinetics; HD: hemodialysis; HP: hemoperfusion; PD: peritoneal dialysis; CKRT: continuous kidney replacement therapy; HCO HD: high cut-off hemodialysis TPE: therapeutic plasma exchange; MARS®: molecular adsorbent recirculating system®. D: dialyzable; MD: moderately dialyzable; SD: slightly dialyzable; ND: not dialyzable.
*Grading done using T1/2 comparisons (excluded from final grading because unreliable with drugs with large VD).
& Based on clearance data stated in [40].

volumes of distribution and ongoing absorption could have other impacts on the concentration-time profile both before and after ECTR [218]. Therefore, this criterion (Alternative criterion 2, Table 2, Supplemental material) was not used in the final grading of evidence, although it was presented with an asterisk in Table 3 if this information was available. The dialyzability of metabolites appears to be higher than that of the parent drugs because of their higher water solubility [42,46,203], although this finding was inconsistent throughout the literature [23,31,61,155,162,205,219]. Norverapamil clearance during MARS® was only 3.6 mL/min [198]. Although some data were limited (e.g., dialyzability of diltiazem with hemodialysis), the panel believed it was unlikely that these modalities would have shown appreciable dialyzability had these studies been performed.

Preclinical data (animal experiments)

In one experiment [210] using rodent models, normalization of the mean arterial pressure following a verapamil ingestion occurred in 6.5 h in rats receiving liposome-supported peritoneal dialysis compared to 21 h in both those treated with peritoneal dialysis alone and in those untreated ($p < 0.05$).

Clinical data

The data for a clinical effect of ECTR in CCB poisoning is comprised exclusively of case reports and one retrospective study with aggregate results presented in abstract/conference proceeding form. Among human reports, there were 78 cases described, 32 from amlodipine, 16 from diltiazem, 23 from verapamil, 3 from nifedipine, 2 from

Table 4. Clinical summary of patients severely poisoned with calcium channel blockers receiving an ECTR.

	Amlodipine ($n = 32$)	Diltiazem ($n = 16$)	Verapamil ($n = 23$)	ALL CCBs ($n = 78$)*
Patient characteristics				
Age (years)	42 [25,57]	28 [19, 49]	25 [17, 46]	35 [22, 53]
Male (%)	44	22	31	34
Poisoning info				
Voluntary ingestions (%) and dose (mg)	100%, 575 [405,900]	100%, 7200 [4500, 8400]	87%, 5340 [4650, 5605]	96%, N/A
Modified release (%)	N/A	91	91	N/A
Coingestants (%)	50	23	56	50
Peak concentration (μg/L)	180 [120, 340]	2658 [2000, 7044]	1865 [1182, 3025]	N/A
Time between ingestion and admission (hours)	5.5 [4.0, 8.8]	3.5 [2.8, 4.3]	3.0 [2, 8]	4 [2.5, 6]
Signs/ Symptoms/ Laboratory				
Coma (%)	50	90	69	68
Altered consciousness (%)	82	90	85	87
Bradycardia (%)	38	92	94	68
Severe dysrhythmia/cardiac arrest (%)	19	46	69	40
Hypotension (%)	100	100	94	98
Acute kidney injury (%)	63	82	56	67
Serum lactate (mmol/L)	9.6 [7.5, 12]	17.1 [12.9, 20.0]	9.3 [7.0, 12.5]	9.5 [7.6, 14.0]
Serum glucose (mmol/L)	8 [6.9, 12.8]	15.3 [13.0, 17.7]	10.7 [10.7, 15.5]	10.7 [7.9, 14.9]
Other treatments				
Gastric lavage (%)	27	67	60	52
Activated charcoal (%)	47	85	43	61
Vasopressors/ inotropes (%)	100	100	94	98
Mechanical ventilation (%)	86	100	86	89
Atropine (%)	4	83	70	33
Calcium (%)	100	100	73	93
Lipid emulsion (%)	62	8	20	33
Pacemaker (%)	13	36	79	33
High dose insulin euglycemic therapy (%)	85	54	31	61
Glucagon (%)	65	91	50	67
ECLS (%)	36	23	20	30
ECTR				
Time from admission to first ECTR (hours)	12 [8, 16.3]	6 [3.5, 21]	10 [7, 16]	10 [5, 17]
Hemodialysis (*n*)	1	0	2	3
Therapeutic plasma exchange (*n*)	5	1	5	11
CKRT (*n*)	1	2	2	8
Hemoperfusion (*n*)	0	5	2	7
SLED (*n*)	1	0	0	1
HD-HP (*n*)	0	0	1	1
Liver support device (*n*)	13	7	10	30
More than 1 ECTR (*n*)	11	1	1	17
Outcome				
Survival (%)	81	88	78	82
ICU length of stay (days)	8 [6,12]	6 [5, 11]	5.5 [3, 8]	7 [4, 12]
Hospital length of stay (days)	11 [10, 18]	9.5 [5, 20]	8 [5, 12]	10 [7, 19]
Apparent improvement with ECTR (%)	63	82	83	68

*All included cases of calcium channel blocker poisoning treated with ECTR (not only verapamil, diltiazem, and amlodipine).
Expressed as medians with quartiles when applicable.
N/A: not available; ECTR: extracorporeal treatment; ECLS: extracorporeal life support (e.g., ECMO); HD: hemodialysis; HP: hemoperfusion; SLED: sustained low efficiency dialysis; CKRT: continuous kidney replacement therapy; ICU: intensive care unit; CCB: calcium channel blockers.

nicardipine, 1 from felodipine, and 1 from mixed diltiazem and nifedipine. The majority of cases were of low methodological quality and lacked reporting of critical information [11]. Additionally, these data are inherently anecdotal, limited by a lack of controls, and susceptibility to publication bias. Their interpretation is further limited by the elevated incidence (50%) of coingestants (including β-adrenergic antagonists) which are known to worsen prognosis from CCB poisoning [136]. The treatments administered were very heterogeneous and may not be considered current care by today's standards (less than two thirds of patients received high dose insulin euglycemic therapy). Therefore, the quality of the evidence for all reported patient-important outcomes assessing the potential benefits of ECTR in addition to standard care was graded as very low. The demographics, clinical findings, management, and outcomes of included patients are listed in Table 4. In 35 out of 78 cases (45%), liver support devices were used, either alone or in combination with other ECTRs. Several reports suggested an improvement of hemodynamics during ECTR as supported by reduction in vasopressor requirement, reducing lactate concentration, and increasing mean arterial blood pressure [41,42,44,45,48,164,168,178,181,183,184, 186, 187,192,195] although this was not confirmed in others [46,47,49,58,157,159,166,189,191,193]. Overall, median ICU length of stay was 7 days (IQR 4,12) and hospital length of stay was 10 days (IQR 7, 19). There were 14 fatalities (overall mortality 18.2%).

Complications of ECTR included deep venous thrombosis from a catheter [179], fungal septicemia related to therapeutic plasma exchange [160], hypotension during hemoperfusion [47], thrombocytopenia associated with hemoperfusion [46], and hypoglycemia during liver support devices [48]. A 15–30% decrease was noted in both serum albumin and total protein during MARS® [192].

Table 5. ECTR and standard care compared to standard care in patients severely poisoned with calcium channel blockers (Evidence profile table).

Quality assessment							Summary of findings				
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care	Standard care (controls)	Effect	Quality	Importance
Mortality											
ALL CCBs[a] $n = 6$	Observational studies	Very serious[b]	Not serious	Serious[c]	Serious[d]	Publication bias strongly suspected[e]	**17.9**% (14/78)	**9.6**% (17/177) in patients admitted to 1 ICU 2007–19 (138) **8.7**% (4/46) in patients treated with HIET from a PCC [137] **30.5**% (104/341) in patients from US PCCs presenting with at least major effect of CCB poisoning 2017–18 [1,236]	Groups not comparable	⊕◯◯◯ VERY LOW	CRITICAL
All non-DHP $n = 4$	Observational studies	Very serious[b]	Not serious	Serious[c]	Serious[d]	Publication bias strongly suspected[e]	**17.9**% (7/39)	**6.8**% (7/103) in patients admitted to 1 ICU 2007–19 (138) **8.3**% (1/12) in a subgroup of hospitalized patients with composite endpoint for severity [142] **23.3**% (7/30) in patients presenting with at least major effect of CCB poisoning and treated with HIET [128]	Groups not comparable	⊕◯◯◯ VERY LOW	CRITICAL
Verapamil $n = 2$	Observational studies	Very serious[b]	Not serious	Serious[c]	Serious[d]	Publication bias strongly suspected[e]	**21.7**% (5/23)	**8.0**% (5/65) in patients admitted to ICU [127]	Groups not comparable	⊕◯◯◯ VERY LOW	CRITICAL
Diltiazem $n = 1$							**12.5**% (2/16)	No data	No comparison possible due to lack of data in control group		CRITICAL
Amlodipine $n = 2$	Observational studies	Very serious[b]	Not serious	Serious [c]	Serious[d]	Publication bias strongly suspected[e]	**18.8**% (6/32)	**23.5**% (4/17) in patients presenting with at least major effect of DHP poisoning and treated with HIET [128]	Groups not comparable	⊕◯◯◯ VERY LOW	CRITICAL
Length of hospital stay											
All CCBs[f] $n = 2$	Observational studies	Very serious[b]	Not serious	Serious[c]	Serious[d]	Publication bias strongly suspected[e]	Median = **10.0 days** Mean = **13.7 days**	Cohort of 9 hospitalized patients receiving ILE: Median = **6 days** Mean = **6 days** [224]	Groups not comparable	⊕◯◯◯ VERY LOW	IMPORTANT
Length of ICU stay											
All CCBs[g] $n = 1$							Median = **7.0 days** Mean = **8.6 days**	No data	No comparison possible due to lack of data in control group		IMPORTANT
Serious complications of catheter insertion[h]											
$n = 5$[i]		Not serious	Not serious[j]	Not serious[k]	Not serious[l]	Strong association[m]		≈ **0%**			CRITICAL

(*continued*)

Table 5. Continued.

Quality assessment							Summary of findings				
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECTR + standard care	Standard care (controls)	Effect	Quality	Importance
	Observational studies						Rate of serious complications of catheter insertion varies from **0.1 to 2.1**%		Absolute effect is estimated to be varying from 1 to 21 more serious complications per 1000 patients in the ECTR group	⊕⊕⊕◯ MODERATE	
Serious complications of ECTR[n] $n = 6$[o]	Observational studies	Not serious	Not serious	Not serious	Not serious	Strong association[p]	Rate of serious complications of ECTR varies according to the type of ECTR performed from **0.005**% (HD and CKRT), to **0.6**% (TPE) and up to **1.9**% (HP)	≈**0%**	Absolute effect is estimated to be varying from > 0 to 19 more serious complications per 1000 patients in the ECTR group depending of the type of ECTR performed	⊕⊕⊕◯ MODERATE	CRITICAL

CCB: calcium channel blocker; DHP: dihydropyridines; ECTR: extracorporeal treatment; HD: intermittent hemodialysis; TPE: therapeutic plasma exchange; CKRT: Continuous kidney replacement therapy; HP: Hemoperfusion; ILE: Intravenous lipid emulsion; HIET: High-dose insulin euglycemic therapy; PCCs: Poison Control Centers.

Note: "Requirement for ECMO/ECLS" and "Length of requirement of vasopressors" were outcomes ranked important or critical although no data were reported in the control group.

Explanations

[a] Includes our systematic review of the literature on ECTR (72 patients from 51 case reports and 1 cohort) and 8 case series/cohort studies on standard care alone. Case series were included in the "standard care alone" group if reporting on mortality in adult patients presenting with severe CCB poisoning (of note, stratification per drug or class of drug was presented when reported by authors). Severity of poisoning was defined as: admitted to ICU, requiring vasopressors or temporary pacemaker, and/or being classified as "major effect" or "death" according to National Poison Data System outcomes. No exclusion was based on the presence of co-ingestion or the use or not of co-interventions such as HIET.

[b] Case reports published on effect of ECTR. Uncontrolled and unadjusted for confounders such as severity of poisoning, co-ingestions, supportive and standard care, and co-interventions. Confounding-by-indication is inevitable since ECTR was usually attempted when other therapies have failed.

[c] ECTR and standard care performed may not be generalizable to current practice.

[d] Few events in small sample size, optimal information size criteria not met.

[e] Publication bias is strongly suspected due to the study design (case reports published in toxicology either report very severe poisoning with/without impressive recovery with treatments attempted).

[f] Includes our systematic review of the literature on ECTR (21 case reports) and 1 case series on standard care alone.

[g] Includes our systematic review of the literature on ECTR (30 case reports) and none was identified for standard care alone.

[h] For venous catheter insertion: serious complications include hemothorax, pneumothorax, hemomediastinum, hydromediastinum, hydrothorax, subcutaneous emphysema retroperitoneal hemorrhage, embolism, nerve injury, arteriovenous fistula, tamponade, and death. Hematoma and arterial puncture were judged not serious and thus excluded from this composite outcome. DVT and infection complications were not included considering the short duration of catheter use.

[i] Five single-arm observational studies: two meta-analyses comparing serious mechanical complications associated with catheterization using or not an ultrasound, which included six RCTs in subclavian veins [225] and 11 in internal jugular veins [226]; two RCTs comparing major mechanical complications of different sites of catheterization [227,228]; one large multicenter cohort study reporting all mechanical complications associated with catheterization [229]. Rare events were reported from patient series and patient reports.

[j] Not rated down for inconsistency since heterogeneity was mainly explained by variation in site of insertion, use of ultrasound, experience of the operator, populations (adults and pediatric), urgency of catheter insertion, practice patterns and methodological quality of studies.

[k] Not rated down for indirectness since cannulation and catheter insertion was judged similar to the procedure for other indications.

[l] Not rated down for imprecision since wide range reported explained by inconsistency.

[m] The events in the control group are assumed to be zero (since no catheter is installed for ECTR), therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95%CI which included the null value and all observed complications occurred in a very short timeframe (i.e. few hours).

[n] For IHD and CKRT: serious complications (air emboli, shock and death) are exceedingly rare; minor bleeding from heparin, transient hypotension, and electrolytes imbalance were judged not serious. For HP: serious complications include severe thrombocytopenia, major bleeding, and hemolysis; transient hypotension, hypoglycemia, hypocalcemia, and thrombocytopenia were judged not serious. For TPE: serious complications include citrate toxicity, severe allergic reaction, arrhythmia, and vasovagal reaction; hypotension, hypocalcemia, and urticaria were judged as not serious. All non-serious complications were excluded from this composite outcome.

[o] For IHD and CKRT: two single-arm studies describing severe adverse events per 1000 treatments in large cohorts of patients [230,231]. For TPE: two most recent one-arm studies reporting potential life-threatening adverse events [232,233]. For HP: two small single-arm studies in poisoned patients [234,235]. Rare events were reported in case series and case reports.

[p] Assuming that patients in the control group would not receive any form of ECTR, the events in the control group would be zero; therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95%CI which included the null value and all observed complications occurred in a very short timeframe (i.e., few hours).

When comparing patients receiving ECTR to historical cohorts receiving standard care alone (Table 5), there was no direct or indirect evidence of added benefit from ECTR with regards to patient-important outcomes. Mortality from all CCBs and from verapamil were higher in our cohort compared to other contemporary cohorts admitted to an intensive care unit [127,138], although our cohort had greater indices of severity. For example, the median verapamil dose and peak verapamil concentration in our cohort was 5340 mg and 1865 μg/L, respectively, compared to 3000 mg and 823 μg/L in another [127]. No benefit could be inferred from ECTR but there was a non-null evidence of added harms and costs related to the insertion of a double lumen catheter and the procedure itself, the magnitude of which vary according to local practices, methods of catheterization and type of ECTR used [220].

Recommendations

General statement regarding use of ECTR

We proposed formal recommendations only for amlodipine, diltiazem and verapamil. Despite the low dialyzability and lack of biological plausibility for a clinical ECTR effect for other CCBs, there were insufficient clinical cases for drafting recommendations, as per agreed methods.

Final recommendation

In patients severely poisoned with amlodipine, diltiazem or verapamil, we *recommend against* using ECTR in addition to standard care rather than standard care alone (strong recommendation, very low quality of the evidence)

Rationale

The workgroup agreed almost unanimously that the risks and costs associated with ECTR surpass any potential benefit in amlodipine, diltiazem, and verapamil poisoning (results of votes: median = 1, upper quartile = 1, disagreement index = 0); further, these members could not postulate a single clinical scenario in which ECTR would be employed for removal of amlodipine, diltiazem, and verapamil.

Despite reports of high morbidity and mortality following massive CCB poisoning, the panel did not support the use of ECTRs to enhance elimination of CCBs because they were all classified as non-dialyzable (Table 3). Regardless of the ECTR, pharmacokinetic and toxicokinetic data noted that ECTR could, at best, increase overall clearance by 5–10%. This was unlikely to have a clinical benefit, whereas the cost and non-null complication rate were significant. Furthermore, it was considered that ECTR may be impractical to perform in when severe cardiogenic and distributive shock are present. The panel could not exclude a potential indirect toxicodynamic effect from ECTR, as some studies suggested an improvement in hemodynamics during ECTR (especially liver support devices). Postulates for this effect include extracorporeal removal of nitric oxide and pro-inflammatory vasoactive cytokines, as well as support of liver function [221–223]. However, because of the high endogenous clearance of CCBs, this apparent improvement may be attributed to metabolism of these drugs rather than an ECTR effect. Although there are circumstances ECTR may be used as adjunct therapy for CCB poisoning, for example to correct fluid overload or acidemia, the panel did not identify scenarios in which ECTR would be beneficial in enhancing elimination of CCBs. The clinical data consisting of a very low quality of evidence, did not directly or indirectly suggest an improvement in outcomes with ECTR.

Research gaps

Because of the lower volume of distribution of nifedipine compared to other CCBs, several panel members expressed the opinion that there are toxicokinetic arguments in support of trialing ECTRs that can remove protein-bound poisons, such as hemoperfusion, high cut-off hemodialysis or liver support devices. However, the workgroup acknowledges that the contribution of these ECTRs in increasing total body clearance will likely be minor (endogenous clearance = 400–600 mL/min). The panel also notes that *in vitro* hemoperfusion clearance of nifedipine (14.4 mL/min with a blood flow of 235 mL/min) does not support it being beneficial [204]. If these techniques are trialed, serial sampling in blood/effluent should be obtained, mass removal quantified, and adequate calculations performed [11].

Conclusion

This article presents a systematic review of the effect of ECTRs in calcium channel blocker poisoning. Current dialyzability and clinical data both support a lack of biological efficacy from ECTRs. Thus, the EXTRIP workgroup recommends against performing ECTR for amlodipine, diltiazem, or verapamil poisoning.

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Author contributions

Marc Ghannoum, Sophie Gosselin, Robert S. Hoffman, Valery Lavergne, Thomas D. Nolin, and Darren M. Roberts designed the study; Marc Ghannoum, Steven J Walsh, and Anselm Wong carried out extractions. Anselm Wong, Marc Ghannoum, Robert S. Hoffman, and Darren M. Roberts drafted the manuscript. Anselm Wong, Marc Ghannoum, and Valery Lavergne made the tables and figures; all authors drafted and revised the paper; and all authors approved the final version of the manuscript.

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