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REVIEW ARTICLE

Intravenous Lipid Emulsion in Beta-Blocker With or Without Calcium Channel Blocker Toxicity: A Systematic Review of Human Case Reports and Series

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ABSTRACT

Severe beta-blocker (BB) poisoning, with or without calcium channel blocker (CCB) co-ingestion, can cause refractory cardiovascular collapse and mortality. Intravenous lipid emulsion (ILE) has been used as a rescue therapy in selected severe cases, although its definitive clinical role remains uncertain. This systematic review summarizes published human case reports and case series describing ILE administration in BB with or without CCB toxicity. Databases including Medline, PubMed, EMBASE, and Google Scholar were searched from inception to December 31, 2024. Patient characteristics, poisoning details, pre-ILE clinical status, co-interventions, ILE dosing, hemodynamic and neurologic responses, and outcomes were extracted and analyzed using non-parametric methods. Twenty-two studies including 28 cases were identified, comprising 15 cases of isolated BB toxicity and 13 cases of combined BB and CCB toxicity. ILE was administered mainly as a rescue intervention for cardiovascular collapse or cardiac arrest; 17 patients (60.7%) were intubated and 10 (35.7%) required cardiopulmonary resuscitation before ILE administration. Hemodynamic improvement after ILE was reported in 21 cases (75.0%), and five patients died, corresponding to an overall mortality rate of 17.9%. Favorable discharge status was significantly associated with the absence of pre-ILE cardiopulmonary resuscitation, post-ILE clinical improvement, and blood pressure improvement after ILE. No significant association was observed between cumulative ILE dosage and clinical outcomes. Although these findings are limited by case-level evidence, publication bias, and confounding co-interventions, they support continued consideration of ILE as a last-resort rescue therapy in selected life-threatening BB/CCB poisonings rather than routine early intervention.

1 | Introduction

Severe beta-blocker (BB) and calcium channel blocker (CCB) poisoning remains a major cause of drug-induced cardiovascular collapse and mortality worldwide. These agents are widely prescribed, and overdose, intentional or accidental, can result in profound hypotension, bradycardia, shock, and cardiac arrest (Gummin et al. 2023; Tamargo et al. 2015). Cardiovascular shock due to impaired myocardial contractility, chronotropy, and vascular tone is the principal mechanism contributing to death in severe BB and CCB toxicity (Lauterbach 2019). Consistent with their clinical impact, BBs ranked seventh among the top 25 substances associated with fatal poisonings reported to the American Association of Poison Control Centers in 2018, accounting for 122 deaths (3.9% of all substances involved in fatalities) (Gummin et al. 2023).

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Although significant morbidity and mortality are generally attributed to cardiovascular shock following beta-adrenoceptor antagonist overdose, the clinical toxicity of individual BBs is heterogeneous. Several agents possess additional pharmacologic properties that contribute to increased toxicity in overdose. For example, propranolol exhibits sodium channel antagonism and central nervous system penetration, predisposing to seizures and malignant arrhythmias, whereas sotalol's potassium channel blockade may result in QT-interval prolongation and life-threatening ventricular dysrhythmias (Lauterbach 2019). These agent-specific characteristics complicate management and may influence both clinical course and response to therapy.

Current evidence-based management of BB and CCB poisoning focuses on supportive and antidotal therapies aimed at restoring hemodynamic stability. These include high-dose insulin euglycemia therapy (HIE), vasopressors, calcium salts, glucagon, and in selected cases, extracorporeal life support. Despite these interventions, a subset of patients develops refractory cardiovascular collapse, for whom treatment options remain limited and outcomes are poor (Graudins et al. 2016).

Intravenous lipid emulsion (ILE) has been proposed as a potential rescue therapy for drug-induced cardiotoxicity, largely based on mechanistic hypotheses, animal models, and human case reports (Engebretsen et al. 2011; Cave et al. 2011; Cave and Harvey 2009; Browne et al. 2010; Harvey et al. 2011; Hayes and Knight 2012; Bania et al. 2007). Nevertheless, its role in BB and CCB toxicity remains uncertain. The 2016 Lipid Emulsion Workgroup concluded that available evidence was insufficient to recommend ILE for BB or CCB poisoning, issuing a neutral position regarding its use. Current American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) guidelines assign a Class IIb recommendation, indicating that the usefulness of ILE in this setting is uncertain and that it should not be considered first-line therapy.

Despite these recommendations, ILE has continued to be administered in selected cases of severe or refractory BB and CCB toxicity, particularly when conventional therapies have failed. This ongoing, off-guideline use, combined with reports of both apparent benefit and lack of response, highlights the need to better characterize the clinical contexts in which ILE has been used and the outcomes that have been observed. A survey of poison centers also documented that ILE was recommended in some cases of severe poisoning, reflecting its continued consideration in clinical toxicology practice (Christian et al. 2013).

Human data evaluating ILE in BB and CCB poisoning are limited to case reports and case series and are characterized by heterogeneity, potential publication bias, and inconsistent outcomes (Bologa et al. 2013; Chou and Lee 2021; Liang et al. 2011; Patel et al. 2013; Tale et al. 2019). Although some reports describe transient hemodynamic improvement following ILE administration, others document no benefit or fatal outcomes despite its use (Chou and Lee 2021; Cole et al. 2014). Although these limitations preclude firm conclusions regarding efficacy, the accumulation of case-level observations provides an opportunity to systematically describe patterns of use, clinical contexts, and reported outcomes.

This study therefore updates and extends the available literature by focusing specifically on BB and CCB toxicity and integrating evidence published after the larger mixed-agent review of 2020 (Paneta and Waring 2019), to clarify whether similar response patterns are observed within this subgroup.

Although these limitations preclude firm conclusions regarding efficacy, the accumulation of case-level observations provides an opportunity to systematically describe how ILE has been used in clinical practice, the contexts in which it has been administered, and the outcomes that have been reported. Such synthesis may help identify recurring patterns, generate hypotheses, and inform the design of future prospective studies aimed at defining the potential role, if any, of ILE as a rescue therapy in refractory BB and CCB toxicity.

In this context, we conducted a systematic review of published human case reports and case series describing the use of ILE in BB with or without CCB toxicity. The objective of this review is to synthesize available case-based evidence and describe observed clinical outcomes and patterns of use, with the aim of highlighting knowledge gaps and informing future research in this high-risk clinical setting.

2 | Methods

2.1 | Eligibility Criteria

2.1.1 | Study Types

Case reports and case series written in English presenting cases of BB with or without CCB toxicity were included. Case reports were defined as articles pertaining to a single case, whereas articles were classified as case series when multiple cases were presented.

2.1.2 | Participants

Studies were eligible if they involved humans poisoned with BB with or without CCB. Poisoning was defined as an "exposure causing, or capable of causing toxicity, regardless of intent." (Paneta and Waring 2019).

2.1.3 | Interventions

Studies were included if they used ILE in patients. The definition of ILE was taken to be that outlined in guidelines for use in local-anesthetic toxicity (Cave and Harvey 2009; Levine et al. 2016).

2.1.4 | Outcome Measures

Studies were required to document at least one of the primary or secondary outcomes. The primary outcome was mortality, and the secondary outcomes included improvement in hemodynamic parameters (blood pressure [BP] and heart rate [HR]) and mental status.

2.2 | Search Strategy and Data Extraction

Medline (Ovid), PubMed, and EMBASE were searched from database inception through December 31, 2024 without time restrictions. The search strategy combined controlled vocabulary and free-text terms related to BBs, CCBs, poisoning or overdose, and ILE therapy (e.g., lipid emulsion, fat emulsion, Intralipid). Individual BB and CCB drug names were also included using wildcard operators to capture spelling variations. Google Scholar was additionally searched to identify potentially relevant records. Duplicate records were removed prior to title and abstract screening. The reference lists of relevant review articles were also manually screened to identify additional eligible studies The full electronic search strategies for all databases are provided in Table S1.

The search strategy identified 160 studies. Two reviewers screened titles and abstracts prior to selecting articles for data extraction and analysis. The two independent reviewers blinded to authors and journal names selected the studies based on eligibility criteria. All disagreements were resolved by consensus or, when required, by a third reviewer. The kappa statistic was used to quantify agreement on the included articles. Twenty-two studies were included in the final review and analysis. Figure 1 describes the PRISMA flowchart for study selection.

For each included study, two reviewers independently extracted study characteristics (author, publication year, country and study design), subjects' information (age, gender, co-morbidities, drug history, weight), time of ingestion, intent of ingestion, involved drug(s) (type and name of the drug, ingested dose), patient status before ILE administration, initial treatments and treatments before ILE administration, intubation and CPR before ILE administration, regimen of ILE administration, co-interventions administered with ILE, extracorporeal membrane oxygenation (ECMO) administration, hospitalization duration, mortality and the patients' discharge status, BP, HR, ECG readings, and mental status before and after ILE administration. The Institute of Health Economics Quality Appraisal Tool for Case Series Studies was used to assess the methodological quality of the included studies (Moga et al. 2012).

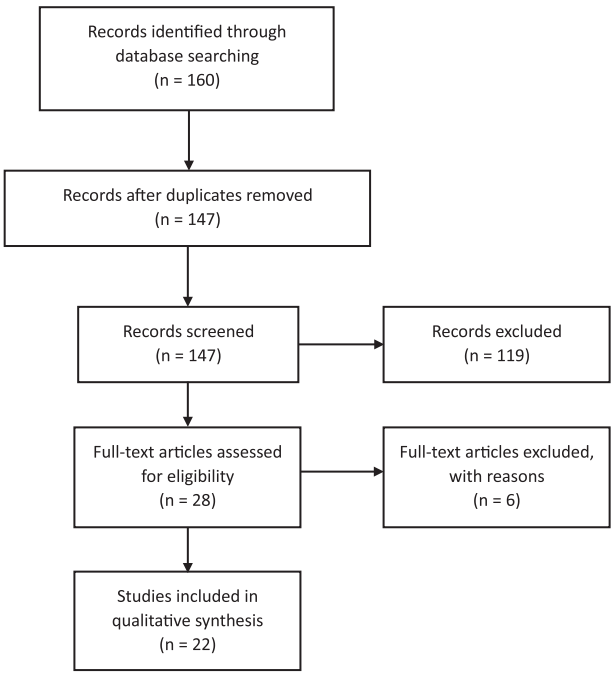

FIGURE 1 | Flowchart of study selection for systematic review.

2.3 | Statistical Analysis

Data analysis was conducted using SPSS 21.0 software. Categorical variables were assessed by chi-squared test or Fischer's exact test, and continuous variables by the Wilcoxon–Mann–Whitney or Kruskal–Wallis test. A p-value ≤ 0.05 was considered statistically significant. Due to the small sample size and the non-normal distribution of continuous variables, non-parametric statistical tests were employed for data analysis.

2.4 | Definition of Terms

The definition of terms and words used in data extraction, analysis and results of this study is as follows: Cardiovascular insufficiency: low BP, or HR, or cold extremities or arrhythmias. Altered consciousness: any consciousness level below alertness. Respiratory insufficiency: respiratory failure, need for mechanical ventilation. Cardiovascular improvement: improvement in cardiovascular functions (HR and BP). Mental improvement: improvement in mental status indicated by improvement in GCS. Fluid resuscitation: IV fluid therapy with crystalloids. Supportive care included vasopressors and gastrointestinal decontamination (gastric lavage and activated charcoal). Pharmacologic therapies included glucagon, calcium, epinephrine, and HIE. Ingestion time: time from ingestion of drug to Emergency department. BP change after ILE: change in BP before and after ILE administration. HR change after ILE: change in HR before and after ILE administration. Mental status change after ILE: change in mental status before and after ILE administration. Cardiovascular collapse: severe hypotension and/or bradycardia.

3 | Results

3.1 | Study and Patient Characteristics

Twenty-eight instances of human ILE utilization for BB with or without CCB toxicity were discovered in 22 case series and reports. Fifteen instances involved BB toxicity, and 13 involved both BB and CCB toxicity. ILE was administered primarily to enhance cardiovascular collapse/cardiac arrest in every one of the instances. The mean age of instances was 37.2 years and 13 instances were female. Among the cases with reported intent, 19 cases had ingested the drugs with suicide intention, and one 17-month-old case was poisoned accidentally by the parents. Among all the 28 cases, 12 were from United States (42.9%), 7 from Turkey (25.0%), 4 from the United Kingdom (14.3%), 2 from Serbia (7.1%), and one case each from India, the Netherlands, and Taiwan (3.6%). Twelve cases (42.9%) were found to have a history of cardiovascular disease. Clinical presentation in the cases was cardiovascular collapse (severe hypotension and/or bradycardia), central nervous system depression, and respiratory depression. Among cases with

TABLE 1 | Summary of case reports of beta-blocker poisoning with or without calcium channel blocker co-ingestion treated with intravenous lipid emulsion (ILE).

Author/year	Drug	Patient age/sex	Regimen of ILE	Initial treatment	Pre-ILE status	Post-ILE status	CPR before ILE	Intubation before ILE	BP change after ILE	HR change after ILE	Mental status change after ILE	Outcome
Barton/2015 (Barton et al. 2015)	BB	59/M	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	Yes	Yes	Improvement	Improvement	Improvement	Fully recovered
Eren Cevik/2014 (Eren Cevik et al. 2014)	BB	32/F	> 20 mL/kg	NR	Cardiovascular collapse	Cardiovascular improvement	No	No	Improvement	Improvement	No change/ worsening	Fully recovered
Chou/2021 (Chou and Lee 2021)	BB and CCB	72/M	< 10 mL/kg	FR, SC	Cardiovascular collapse	Cardiovascular improvement	No	No	Improvement	Improvement	No change/ worsening	Fully recovered
Cole/2014 (Cole et al. 2014)	BB	50/F	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	No improvement/ worsening	Yes	Yes	No data	No change/ worsening	No data	Expired
Cole/2014 (Cole et al. 2014)	BB and CCB	53/M	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, respiratory failure	No improvement/ worsening	Yes	Yes	No change/ worsening	No change/ worsening	No data	Expired
Cumpston/2017 (Cumpston et al. 2017)	BB and CCB	55/M	> 20 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	No	Yes	No change/ worsening	Improvement	Improvement	Fully recovered
Dean/2010 (Dean et al. 2010)	BB	27/F	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	Yes	Yes	Improvement	Improvement	Improvement	Fully recovered
Doepker/2014 (Doepker et al. 2014)	BB and CCB	35/M	10–20 mL/ kg	FR, SC, AT	Cardiovascular collapse	Cardiovascular and mental improvement	No	Yes	Improvement	Improvement	Improvement	Fully recovered
Escajeda/2015 (Escajeda et al. 2015)	BB	47/M	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	Yes	Yes	Improvement	Improvement	Improvement	Fully recovered
Jovic-Stosic/2011 (Jovic-Stosic et al. 2011)	BB	31/F	> 20 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	No	Yes	Improvement	No data	Improvement	Fully recovered

(Continues)

TABLE 1 | (Continued)

Author/year	Drug	Patient age/sex	Regimen of ILE	Initial treatment	Pre-ILE status	Post-ILE status	CPR before ILE	Intubation before ILE	BP change after ILE	HR change after ILE	Mental status change after ILE	Outcome
Jović-Stosić/2016 (Jović-Stosić et al. 2016)	BB and CCB	41/M	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	No improvement/ worsening	Yes	Yes	No change/ worsening	No data	Improvement	Expired
Lashari/2018 (Lashari et al. 2018)	BB and CCB	44/M	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse	Cardiovascular and mental improvement	No	Yes	Improvement	Improvement	Improvement	Fully recovered
Le Fevre/2017 (Le Fevre et al. 2017)	BB	25/F	10–20 mL/ kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	Yes	Yes	Improvement	Improvement	Improvement	Fully recovered
Rodríguez/2014 (Rodríguez et al. 2014)	BB and CCB	26/M	> 20 mL/kg	FR, SC, AT	Cardiovascular collapse	No improvement/ worsening	No	No	No change/ worsening	Improvement	No data	Expired
Stellpflug/2011 (Stellpflug et al. 2011)	BB and CCB	30/F	> 20 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	No	No	Improvement	No data	Improvement	Fully recovered
Stellpflug/2010 (Stellpflug et al. 2010)	BB and CCB	48/M	10–20 mL/ kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	Yes	Yes	Improvement	Improvement	Improvement	Fully recovered
Tale/2019 (Tale et al. 2019)	BB and CCB	66/M	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	Yes	Yes	Improvement	Improvement	Improvement	Fully recovered
Thompson/2016 (Thompson et al. 2016)	BB	17 months/F	< 10 mL/kg	FR	Cardiovascular collapse, altered consciousness	Cardiovascular and mental improvement	No	No	No change/ worsening	Improvement	Improvement	Fully recovered
Van den Berg/2016 (van den Berg and Bosch 2016)	BB	22/M	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse	Cardiovascular and mental improvement	No	Yes	Improvement	No data	Improvement	Fully recovered
Walter/2018 (Walter et al. 2018)	BB and CCB	51/F	> 20 mL/kg	FR, SC, AT	Cardiovascular collapse	Cardiovascular improvement	No	No	Improvement	No change/ worsening	No change/ worsening	Fully recovered

(Continues)

TABLE 1 | (Continued)

Author/year	Drug	Patient age/sex	Regimen of ILE	Initial treatment	Pre-ILE status	Post-ILE status	CPR before ILE	Intubation before ILE	BP change after ILE	HR change after ILE	Mental status change after ILE	Outcome
Hopkins/2017 (Hopkins et al. 2017)	BB and CCB	21/F	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness, respiratory failure	No improvement/ worsening	No	Yes	No change/ worsening	No change/ worsening	No change/ worsening	Fully recovered
Chenoweth/2017 (Chenoweth et al. 2017)	BB and CCB	26/F	< 10 mL/kg	FR, SC, AT	Cardiovascular collapse, altered consciousness, respiratory failure	No improvement/ worsening	No	Yes	No change/ worsening	No change/ worsening	No change/ worsening	Fully recovered
Sebe/2015 (Sebe et al. 2015)	BB	51/M	< 10 mL/kg	FR, AT	Cardiovascular collapse	No improvement/ worsening	Yes	Yes	No data	No data	No data	Expired
Sebe/2015 (Sebe et al. 2015)	BB	23/F	< 10 mL/kg	FR, AT	Cardiovascular collapse	Cardiovascular improvement	No	No	No data	No data	No data	Fully recovered
Sebe/2015 (Sebe et al. 2015)	BB	21/F	< 10 mL/kg	FR, AT	Cardiovascular collapse	Cardiovascular improvement	No	No	No data	No data	No data	Fully recovered
Sebe/2015 (Sebe et al. 2015)	BB	26/F	< 10 mL/kg	FR, AT	Cardiovascular collapse	Cardiovascular improvement	No	No	No data	No data	No data	Fully recovered
Sebe/2015 (Sebe et al. 2015)	BB	24/M	< 10 mL/kg	FR, AT	Cardiovascular collapse	Cardiovascular improvement	No	No	No data	No data	No data	Fully recovered
Sebe/2015 (Sebe et al. 2015)	BB	33/M	< 10 mL/kg	FR, AT	Cardiovascular collapse	Cardiovascular improvement	No	No	No data	No data	No data	Fully recovered

Abbreviations: AT: antidote therapy; BB: beta-blocker; BP: blood pressure; CCB: calcium channel blocker; CPR: cardiopulmonary resuscitation; FR: fluid resuscitation; HR: heart rate; ILE: intravenous lipid emulsion; NR: not reported; SC: supportive care.

TABLE 2 | Comparison between intravenous lipid emulsion (ILE) regimen and demographic, clinical and outcome variables.

	<10 mL/kg	10–20 mL/kg	>20 mL/kg	*p*
Sex				0.51
Female	8 (42.1)	1 (33.3)	4 (66.7)	
Male	11 (57.9)	2 (66.7)	2 (33.3)	
Pre-ILE status				0.90
Cardiovascular insufficiency	9 (47.4)	1 (33.3)	3 (50.0)	
Cardiovascular insufficiency and altered consciousness	7 (36.8)	2 (66.7)	3 (50.0)	
Cardiovascular and respiratory insufficiency	1 (5.3)	0	0	
Cardiovascular insufficiency, altered consciousness, and respiratory insufficiency	2 (10.5)	0	0	
Initial treatment				0.57
Fluid resuscitation, supportive care and antidote therapy	11 (57.9)	3 (100)	5 (83.3)	
Fluid resuscitation and supportive care	1 (5.3)	0	0	
Fluid resuscitation	1 (5.3)	0	0	
Fluid resuscitation and antidote therapy	6 (31.6)	0	0	
Not reported	0	0	1 (16.7)	
Intubation before ILE				0.14
Yes	12 (63.2)	3 (100)	2 (33.3)	
No	7 (36.8)	0	4 (66.7)	
CPR before ILE				0.09
Yes	8 (42.1)	2 (66.7)	0	
No	11 (57.9)	1 (33.3)	6 (100)	
Post-ILE status				0.35
Cardiovascular improvement	6 (31.6)	0	2 (33.3)	
Cardiovascular and mental improvement	7 (36.8)	3 (100)	3 (50.0)	
No improvement or worsening	6 (31.6)	0	1 (16.7)	
ECMO administration				0.60
Yes	2 (10.5)	0	0	
No	17 (89.5)	3 (100)	6 (100)	
Discharge status				0.67
Recovered	15 (78.9)	3 (100)	5 (83.3)	
Expired	4 (21.1)	0	1 (16.7)	
Blood pressure change after ILE				0.39
Improvement	7 (36.8)	3 (100)	4 (66.7)	
No change/worsening	5 (26.3)	0	2 (33.3)	
No data	7 (36.8)	0	0	
Heart rate change after ILE				0.46
Improvement	7 (36.8)	3 (100)	3 (50.0)	
No change/worsening	4 (21.1)	0	1 (16.7)	

(Continues)

TABLE 2 | (Continued)

	<10 mL/kg	10–20 mL/kg	>20 mL/kg	*p*
No data	8 (42.1)	0	2 (33.3)	
Mental status change after ILE				0.46
Improvement	8 (42.1)	3 (100)	3 (50.0)	
No change/worsening	3 (15.8)	0	2 (33.3)	
No data	8 (42.1)	0	1 (16.7)	
Age (years)	37.2 (18.4)	36.0 (11.5)	37.5 (12.2)	0.89
Ingestion time (hours)	4.4 (7.0)	2.0 (1.4)	4.5 (3.6)	0.56
Duration of hospitalization (hours)	161.8 (176.5)	192.0 (101.8)	56.0 (55.4)	0.20

Note: Values are presented as *n* (%) or mean (standard deviation). Percentages were calculated within each ILE-regimen group. "No data" indicates that the relevant variable was not reported in the original case report. *p*-values for blood pressure, heart rate, mental-status change, and initial treatment were calculated after excluding "No data" or "Not reported" observations.
Abbreviations: ECMO: extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion.

available data, the patients were brought to the ER in a mean of 4.1 h after ingestion. Fluid resuscitation was provided for 27 cases (96.4%), and traditional antidotes for BB with or without CCB toxicity (glucagon, epinephrine, calcium, and hyperinsulinemia euglycemia) were administered for 25 cases (89.3%). Seventeen cases (60.7%) were intubated before the administration of ILE, and 10 cases (35.7%) needed CPR before the administration of ILE. ECMO was administered for two cases (7.1%). Hemodynamic improvement was seen in 21 (75.0%) cases following the administration of ILE. A brief overview of all the cases is presented in Table 1.

3.2 | ILE Regimen

In order to check the potential influence of ILE dose, cases were classified into three groups based on the cumulative dose of 20% Intralipid solution administered: Group 1, less than 10 mL/kg; Group 2, 10–20 mL/kg; Group 3, greater than 20 mL/kg. Most cases were in Group 1 (19, 67.9%), followed by Group 3 (6, 21.4%), and Group 2 (3, 10.7%). Statistical analysis revealed no significant correlation of the ILE regimen with the following parameters: pre-ILE status (pre-administration status of the patient), initial treatment (type of initial treatments given), intubation before ILE (whether intubation was performed before ILE administration), CPR before ILE (whether CPR was required before ILE administration), post-ILE status (post-administration status of the patient), ECMO administration, discharge status (status at discharge of the patient), hemodynamic and neurologic changes (changes in BP, HR, and mental status observed before and after ILE administration). These results are tabulated in Table 2.

3.3 | Discharge Status

Of the 28 patients, five (17.9%) succumbed to cardiovascular collapse. The remaining patients recovered completely with no sequelae reported. Discharge status was found significantly associated with the following: pre-ILE CPR ($p = 0.041$), post-ILE status ($p < 0.001$), and BP change after ILE ($p = 0.026$), whereas HR change after ILE was not significantly associated with discharge status ($p = 0.172$). The specific correlations of discharge status with different parameters in the current study are shown in Table 3.

4 | Discussion

In this systematic review of published human case reports and case series, we evaluated the use of ILE in BB and CCB toxicity. The primary contribution of this review is not to establish efficacy, but to describe patterns of use and reported clinical responses in real-world, high-severity poisoning scenarios where ILE was administered.

Across the included reports, ILE was most commonly used in patients with severe, refractory toxicity, frequently characterized by profound hypotension, shock, or cardiac arrest. In this context, hemodynamic improvement following ILE administration was reported in a notable proportion of cases, including improvements in BP, HR, or return of spontaneous circulation. These observations represent clinically relevant findings of this review. Although causal inference is not possible based on case-based evidence, the recurrence of such responses across heterogeneous reports suggests that ILE administration was temporally associated with meaningful physiological changes in some critically ill patients. These findings are consistent with those of a previous large-scale narrative review (Paneta and Waring 2019), which described similar response patterns across diverse cardiotoxic agents, reinforcing the observation that ILE use has been largely confined to severe, refractory cases.

At the same time, outcomes were variable. Not all patients improved following ILE, and fatal outcomes were also reported. This heterogeneity likely reflects differences in poisoning severity, agent characteristics, timing of administration, and concurrent therapies. Importantly, ILE was frequently administered alongside other advanced interventions, such as HIE, vasopressors, calcium salts, glucagon, and extracorporeal life support, making it difficult to isolate the independent contribution of

TABLE 3 | Comparison between discharge status and demographic, clinical and outcome variables.

	Recovered	Expired	*p*
Sex			0.33
Female	12 (52.2)	1 (20.0)	
Male	11 (47.8)	4 (80.0)	
Pre-ILE status			0.24
Cardiovascular insufficiency	11 (47.8)	2 (40.0)	
Cardiovascular insufficiency and altered consciousness	10 (43.5)	2 (40.0)	
Cardiovascular and respiratory insufficiency	0	1 (20.0)	
Cardiovascular insufficiency, altered consciousness, and respiratory insufficiency	2 (8.7)	0	
Initial treatment			1.00
Fluid resuscitation, supportive care and antidote therapy	15 (65.2)	4 (80.0)	
Fluid resuscitation and supportive care	1 (4.3)	0	
Fluid resuscitation	1 (4.3)	0	
Fluid resuscitation and antidote therapy	5 (21.7)	1 (20.0)	
Not reported	1 (4.3)	0	
Intubation before ILE			0.62
Yes	13 (56.5)	4 (80.0)	
No	10 (43.5)	1 (20.0)	
CPR before ILE			0.041
Yes	6 (26.1)	4 (80.0)	
No	17 (73.9)	1 (20.0)	
Post-ILE status			< 0.001
Cardiovascular improvement	8 (34.8)	0	
Cardiovascular and mental improvement	13 (56.5)	0	
No improvement or worsening	2 (8.7)	5 (100)	
ECMO administration			1.00
Yes	2 (8.7)	0	
No	21 (91.3)	5 (100)	
Blood pressure change after ILE			0.026
Improvement	14 (60.9)	0	
No change/worsening	4 (17.4)	3 (60.0)	
No data	5 (21.7)	2 (40.0)	
Heart rate change after ILE			0.172
Improvement	12 (52.2)	1 (20.0)	
No change/worsening	3 (13.0)	2 (40.0)	
No data	8 (34.8)	2 (40.0)	
Mental status change after ILE			1.00
Improvement	13 (56.5)	1 (20.0)	
No change/worsening	5 (21.7)	0	

(Continues)

TABLE 3 | (Continued)

	Recovered	Expired	*p*
No data	5 (21.7)	4 (80.0)	
Age (years)	35.6 (16.9)	44.2 (11.2)	0.22
Ingestion time (hours)	4.0 (6.0)	5.4 (6.5)	0.94
Duration of hospitalization (hours)	111.8 (70.5)	264.8 (357.9)	0.78

Note: Values are presented as *n* (%) or mean (standard deviation). Percentages were calculated within each discharge-status group. "No data" indicates that the relevant variable was not reported in the original case report. *p*-values for blood pressure, heart rate, mental-status change, and initial treatment were calculated after excluding "No data" or "Not reported" observations.
Abbreviations: ECMO: extracorporeal membrane oxygenation; ILE: intravenous lipid emulsion.

ILE (Bologa et al. 2013; Chou and Lee 2021; Liang et al. 2011; Patel et al. 2013; Tale et al. 2019). Rather than diminishing the observed responses, this finding highlights the complex clinical environments in which ILE has been considered and the challenges inherent in evaluating rescue therapies for life-threatening poisoning.

Current evidence-based recommendations do not support the routine use of ILE in BB or CCB toxicity, largely reflecting the absence of controlled human studies and inconsistent findings from experimental models (Levine et al. 2016; Gosselin et al. 2016; Cao et al. 2025). Within this context, the present review demonstrates that, in reported clinical practice, ILE has not been used routinely or early, but rather predominantly in critically ill patients as a late or rescue intervention. This pattern of use is broadly consistent with the cautious stance of existing recommendations, while also illustrating why clinicians continue to consider ILE in selected high-risk situations.

Beyond outcomes, this review identifies several important knowledge gaps. No included reports provided systematic pharmacokinetic measurements or standardized dosing strategies, and no consistent association between ILE dose and clinical outcome was identified (Engebretsen et al. 2011; Cave et al. 2011). These limitations do not negate the reported clinical responses but emphasize the need for more structured investigation. The variability in patient outcomes observed across cases suggests that specific subgroups, such as those with profound cardiovascular compromise or exposure to highly lipophilic agents, may warrant focused evaluation, an issue that cannot be adequately addressed through isolated case reports alone.

5 | Clinical Implications

The findings of this review indicate that ILE has primarily been used as a rescue therapy in cases of severe BB and CCB toxicity, rather than as part of routine management. In a subset of critically ill patients, its administration was followed by apparent hemodynamic improvement, whereas in others no benefit was observed (Chou and Lee 2021; Cole et al. 2014). These mixed outcomes reinforce that ILE should not be considered a standard intervention; however, they also suggest that its use in carefully selected, life-threatening cases remains an area of ongoing clinical interest. This interpretation aligns with observations from earlier broad analyses (Paneta and Waring 2019), which similarly emphasized rescue-use patterns and called for prospective registry-based data to determine predictors of response and safety.

From a practical perspective, this review supports continued reliance on established therapies as the cornerstone of management while recognizing that ILE has been employed in refractory cases where conventional treatments have failed. The reported clinical responses in some patients highlight the need for further evaluation rather than dismissal of ILE's potential role as a last-resort therapy.

6 | Limitations

This review is limited by the exclusive inclusion of case reports and case series, which are subject to publication bias, incomplete reporting, and confounding by co-interventions. Substantial heterogeneity in patient characteristics, toxic agents, treatment timing, and outcome reporting limits comparability across cases. Nonetheless, these limitations are inherent to the available human literature and underscore the need for more systematic observational studies to better characterize the role of ILE in severe cardiotoxic poisoning.

7 | Conclusion

This systematic review describes the use of ILE in reported cases of BB and CCB toxicity, where it was most often administered in the setting of severe, refractory cardiovascular compromise. Although outcomes were variable, hemodynamic improvement was reported in a subset of cases, suggesting that ILE may exert clinically relevant effects under certain conditions.

Although current evidence is insufficient to support routine use, the patterns and responses identified in this review indicate that ILE continues to be considered as a rescue therapy in extreme scenarios. These findings highlight the need for further structured evaluation, such as prospective registries or standardized reporting, to better define which patient populations may derive benefit and to clarify the risk–benefit profile of ILE in severe BB and CCB poisoning.

Conflicts of Interest

The authors declare no conflicts of interest.

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 can be found online in the Supporting Information section. **Table S1:** Complete search strategies used in PubMed, MEDLINE (Ovid), and EMBASE.