Extracorporeal Membrane Oxygenation in Intoxication and Overdoses: A Systematic Review

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Abstract

Background Extracorporeal membrane oxygenation (ECMO) has been increasingly applied over recent decades to treat severe cardiogenic shock and acute lung failure and cardiac arrest of various causes. Acute intoxication with therapeutic substances or other chemical substances can cause severe cardiogenic shock or even cardiac arrest. The purpose of this study was to conduct a qualitative systematic review of ECMO use in intoxication and poisoning.

Methods We searched the PubMed, Medline, and Web of Science databases from January 1971 to December 2021 and selected appropriate studies according to our inclusion and exclusion criteria to evaluate the role of ECMO in intoxication and poisoning systematically. Survival at hospital discharge was examined to describe the outcome.

Results The search resulted in 365 publications after removing duplicates. In total, 190 full-text articles were assessed for eligibility. A total of 145 articles from 1985 to 2021 were examined in our final qualitative analysis. A total of 539 (100%) patients were included (mean age: 30.9 ± 16.6 years), with a distribution of $n = 64$ (11.9%) cases with venovenous (vv) ECMO, $n = 218$ (40.4%) cases with venoarterial (va) ECMO, and $n = 257$ (47.7%) cases with cardiac arrest and extracorporeal cardiopulmonary resuscitation. Survival at hospital discharge was 61.0% for all patients, 68.8% for vaECMO, 75% for vvECMO, and 50.9% for extracorporeal cardiopulmonary resuscitation.

Conclusion When used and reported, ECMO seems to be a valid tool for adult and pediatric patients suffering intoxication from various pharmaceutical and nonpharmaceutical substances due to a high survival rate at hospital discharge.

Keywords
- extracorporeal membrane oxygenation
- intensive care
- intoxications
- shock (systemic, cardiac, or circulatory)

Introduction

In 2020, 2.1 million cases of intoxication were entered into the National Poison Data System in the United States. Intoxications with a serious outcome have risen by 4.6% per year since 2000.[1] In Germany, a total of 35,000 patients were treated in hospitals for intoxication in 2019.[2] Acute intoxication with therapeutic substances or other chemical substances, irrespective of reason either accidental ingestion or ingestion for self-harm, can cause hemodynamic

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instability or collapse, which is associated with deterioration of other organ functions, for example, respiratory depression, kidney, and liver failure as well as electrolyte and acid-base disorders. These metabolic factors and fat tissue accumulation of the toxins may further deteriorate cardiac function and potentiate toxicity. Signs of severe intoxication are metabolic acidosis, seizures, coma, cardiac arrhythmias, and refractory cardiogenic shock or cardiac arrest. Immediate management of the symptoms of intoxication and administration of specific antidotes, if they are available, to avoid acute decompensation or failure of various vital organs are usually effective but may not be sufficient if life-threatening overdose has led to cardiovascular collapse.

Extracorporeal membrane oxygenation (ECMO) has been increasingly applied to treat severe cardiogenic shock and acute lung failure during the last decade.[3] Typical indications for ECMO are severe refractory cardiac failure caused by myocardial infarction, pulmonary embolism, or decompensated heart failure or cardiomyopathy, and acute respiratory distress syndrome (ARDS) as well as pneumonia. For in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA), ECMO is increasingly applied as extracorporeal cardiopulmonary resuscitation (ECPR).[4]

However, the use of ECMO to treat refractory cardiac or pulmonary failure caused by intoxications or overdoses has primarily only been reported in numerous case reports and two registry studies.[5,6] The purpose of this systematic review is to comprehensively describe the entirety of ECMO use, including procedure and outcomes, in patients suffering intoxication and poisoning.

Methods

Search Strategy

We conducted a systematic literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA)[7] by creating a search strategy using a combination of the keywords "Extracorporeal Membrane Oxygenation" or "Extracorporeal Cardiopulmonary Resuscitation" and "intoxication" or "overdose" or "poison." We searched PubMed, Medline, and Web of Science from January 01, 1971 to December 31, 2021.

Study Selection

We included all studies reporting the treatment of patients with intoxication or overdoses using ECMO or ECPR. We excluded animal studies, editorials, review articles, and meeting abstracts. Publications written in a language other than English or German were also excluded. In the first step, an abstract screening was performed. This was followed by full-text reading. Both processes were performed independently by two reviewers. We screened the first 10 abstracts and compared the results to avoid misinterpretations in the further screening process. In case of disagreement between the two reviewers, a third reviewer moderated the discussion to reach a consensus.

Data Collection Process

Before starting data extraction, we ran a pilot test on full-text reading with 10 publications. Data were extracted independently by two reviewers. Dissent was resolved by consensus moderated by a third reviewer. We contacted the authors if necessary information was not provided in the publication.

Data Analysis

We analyzed studies for patient demographics, the circumstance of intoxication (intentional ingestion, accidental intoxication, accidental administration of drugs), type of medication/drug and dose, therapy for intoxication (administration of antidote, intravenous lipid emulsion [ILE], dialysis, plasmapheresis, and hemoadsorption), time from intoxication to start of ECMO, indication for ECMO (ARDS, hypoxia, pneumonia, pulmonal edema, lung fibrosis, refractory cardiogenic shock, cardiac arrest, and state after cardiopulmonary resuscitation), mode of ECMO (venovenous [vv] and venoarterial [va], and ECPR), duration of ECMO therapy, location of cardiac arrest (in-hospital and out-of-hospital), duration of cardiopulmonary resuscitation, adjunctive treatments (dialysis, hemoadsorption, plasmapheresis, and Molecular Adsorbent Recirculating System [MARS]), length of hospital stay, the survival rate at hospital discharge, total number of patients per publication, digital object identifier, year of publication, and country of study. If necessary and possible, we calculated outcome parameters from the given information, for example, when intoxicated patients were presented as a subgroup of a whole cohort, including all ECMO cases. We contacted the authors of 12 publications because intoxicated patients were not described in detail in the publication or data on the ECMO procedure were described inconclusively.

Results

We conducted a literature search followed by a systematic review of the entire literature to identify ECMO's role in the treatment of intoxication and drug overdoses. The research process is shown in the PRISMA flow chart (►**Fig. 1**). The search of all databases yielded a total of 734 publications. After duplicates were removed, 365 publications remained and we reviewed 190 full-text articles after the title and abstract screening (►**Fig. 1**).

We included 145 publications, including many case reports or case series, from 1985 to 2021 in our final qualitative analysis. The number of publications per year rose over time (►**Fig. 2**). Some studies presented the treatment of patients with vvECMO and vaECMO, which led to a final number of 71 vaECMO and 27 vvECMO data records as well as 58 data records on cardiac arrest and the use of ECMO as ECPR (see ►**Supplementary Tables S1**–**S3**, available online only). Overall, $n = 539$ (100%) patients were included, with a distribution of $n = 64$ (11.9%) cases with vvECMO, $n = 218$ (40.4%) cases with vaECMO, and $n = 257$ (47.7%) cases with cardiac arrest and ECPR. Most of the included studies were done in the United States ($n = 48$) and European countries

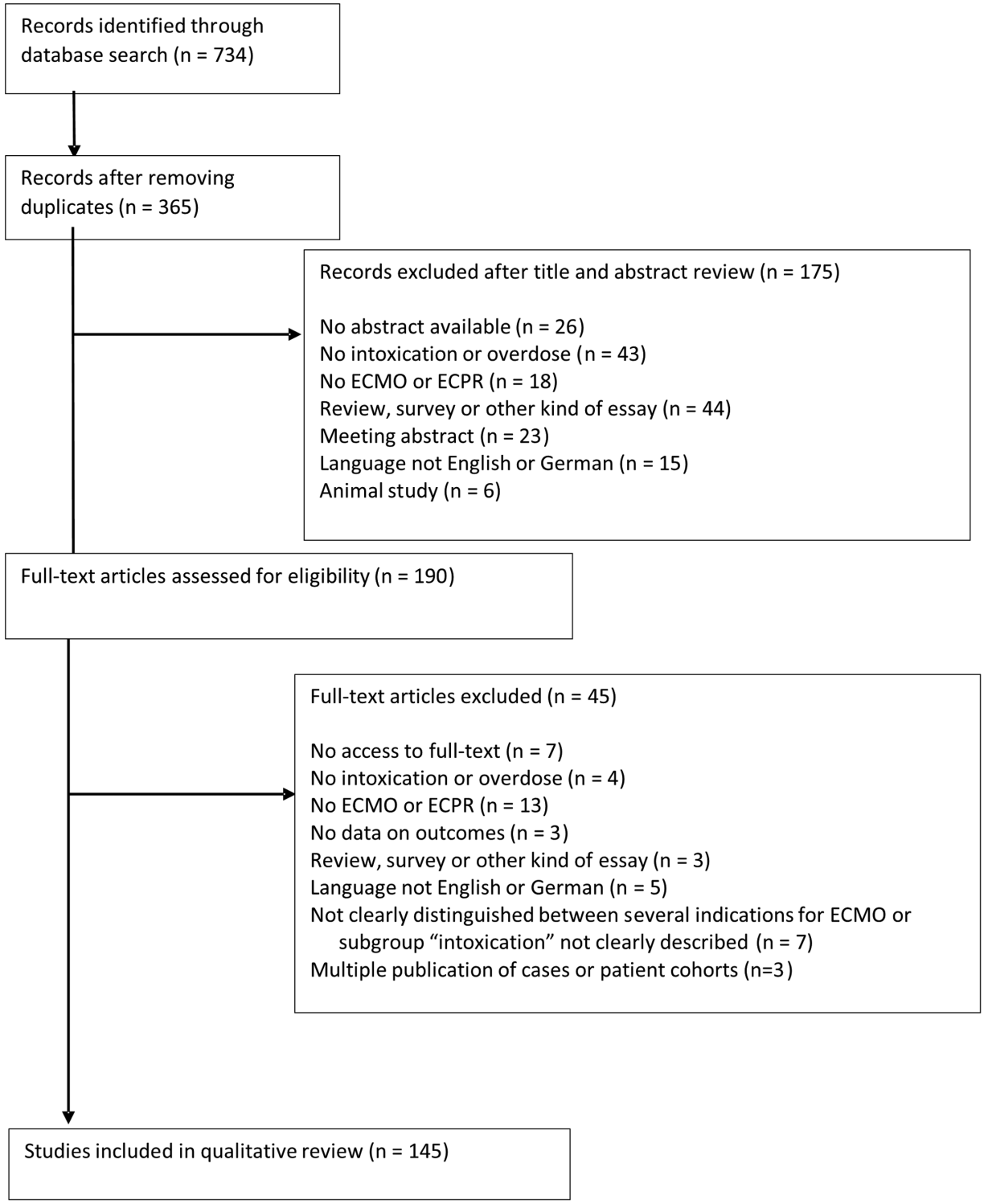

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram. Abbreviations: ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation.

($n = 49$), 35 were from Asia, 6 from Canada, 4 from Australia, and 3 from Africa.

Mean age of all patients was 30.9 ± 16.6 years. The indication for ECMO was cardiac arrest in 258 patients, post-cardiac arrest situation in 29 patients, refractory cardiogenic shock in 209 patients, metabolic/lactate acidosis in 3 patients, pneumonia in 27 patients, hypoxia in 10 patients, ARDS in 30 patients, pulmonal edema in four patients, and lung fibrosis in 3 patients, respectively. Survival at hospital discharge was 61.0% for all patients, 68.8% for vaECMO, 75% for vvECMO, and 50.9% for ECPR. The duration of the hospital stay was 26.8 ± 24.2 days. The number of patients, age, duration from exposure to the start of ECMO, duration of ECMO therapy, length of hospital stay, survival at hospital

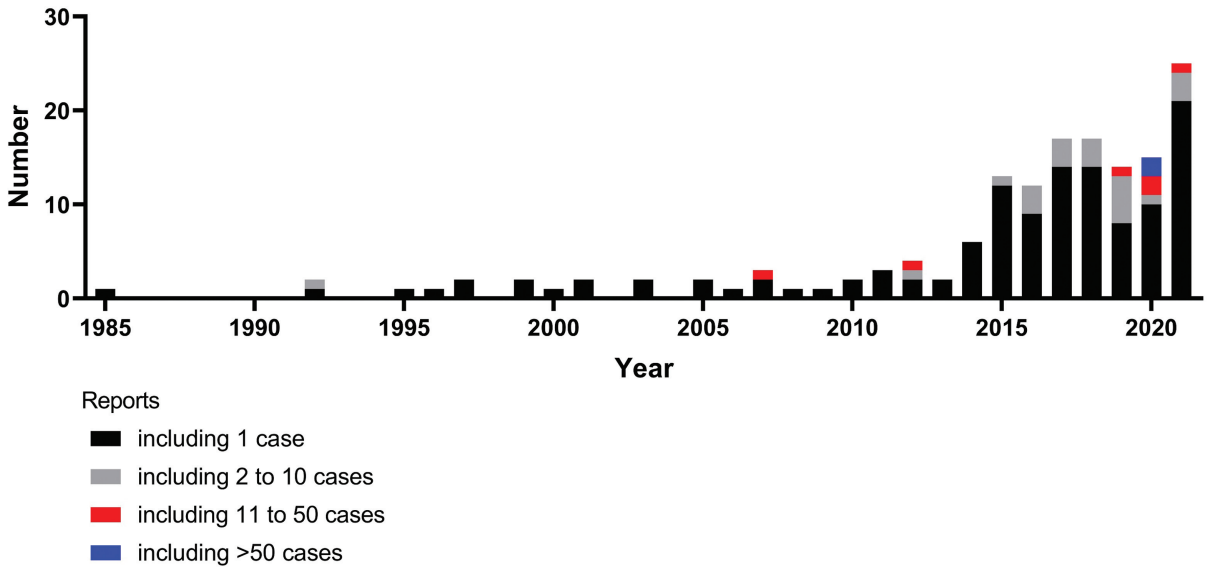

Fig. 2 Number of studies per year included in the final analysis subdivided into the number of cases per study.

discharge, and the indications for ECMO, divided into the different modes of ECMO, are shown in ►**Table 1**. Number of patients, mode of ECMO, age, duration of ECMO therapy, and length of hospital stay subdivided by patient age are listed in ►**Table 2**.

Reasons for poisoning were intentional poisoning in 323 cases, accidental poisoning in 63 cases, local anesthetic systemic toxicity in 1 case, and accidental drug administration in 5 cases. In three datasets, multiple entries were made for a total of 147 cases. In total, 273 patients had ingested only one substance, whereas 254 patients ingested several (two to seven) substances. In 12 cases, this information was not provided. ►**Table 3** shows the number of drugs involved divided into substance groups.

Table 1 Data of patients and indications, divided into the different modes of ECMO, for patients with intoxication treated with ECMO

	All patients	vaECMO	vvECMO	ECPR
Number of patients	539	218	64	257
Number of patients thereof described in case reports or case series (<10 patients)	216	91	37	88
Age (years)	30.9 ± 16.6	32.7 ± 16.4	28.5 ± 15.9	29.7 ± 16.9
Duration from exposure to start of ECMO (hours)	42.5 ± 133.6	15.4 ± 14.0	191.2 ± 301.2	17.2 ± 21.4
Duration of ECMO therapy (days)	4.8 ± 4.0	4.7 ± 2.5	7.5 ± 6.6	3.6 ± 3.2
Length of hospital stay (days)	26.8 ± 24.2	23.7 ± 19.2	32.1 ± 23.2	29.6 ± 30.8
Survival at hospital discharge	61.0%	68.8%	75.0%	50.9%
Indications for ECMO/ECPR				
Cardiac arrest	258	0	1	257
Postcardiac arrest situation	29	22	7	0
Refractory cardiogenic shock	209	208	1	0
Metabolic/lactate acidosis	3	3	0	0
Pneumonia	27	0	27	0
Hypoxia	10	4	6	0
ARDS	30	5	25	0
Pulmonal edema	4	0	4	0
Lung fibrosis	3	0	3	0

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; va, venoarterial; vv, venovenous.
Note: Continuous data are reported as mean and standard deviation; categorical variables are shown as counts.

Table 2 Data of patients, divided by patient age

	All patients	Neonatal (<28 d)	Pediatric (29 d–< 18 y)	Adult (≥18 y)
Number of patients	539	1	45	493
Number of patients described in case reports or case series (<10 patients)	216	1	45	170
Mode of ECMO (survival [%])				
vaECMO	218 (68.8)	0	11 (63.6)	207 (69)
vvECMO	64 (75)	0	14 (78.5)	50 (74.0)
ECPR	257 (50.9)	1 (100)	20 (80)	236 (48.3)
Age		1 d	9.9 ± 6.1 y	36.5 ± 13.6 y
Duration of ECMO therapy (days)	4.8 ± 4.0	2	5.6 ± 4.2	4.6 ± 4.0
Length of hospital stay (days)	26.8 ± 24.2	9	25.1 ± 16.4	27.5 ± 25.9

Abbreviations: ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; va, venoarterial; vv, venovenous.
Note: Continuous data are reported as mean and standard deviation; categorical variables are shown as counts.

Table 3 Involved drugs reported as counts

Group of substances	Number
Cardiovascular medication	249
Pain medication	67
Psychotropic drugs	135
Other medications	77
Illicit substances	46
Plants and animal toxins	21
Chemicals (pesticides, hydrocarbons, oils, furniture polish, ...)	100
Gaseous substances (carbon monoxide, smoke, ...)	9
Other substances	7
Unknown substances or not described	30

Note: Cases involving more than one substance groups were counted multiple times.

In addition to ECMO therapy, the use of dialysis was described in 71 data records (including 392 patients). In nine patients, plasmapheresis supplemented ECMO. In one case, the use of MARS and in seven cases hemoadsorption were described as adjunctive therapy.

In 58 data records, ECMO was used during cardiopulmonary resuscitation as ECPR including 257 patients. In 40 publications including 162 patients, the study population consisted of IHCA patients, in 13 publications OHCA was described for 34 patients, and 5 publications including 61 patients described patient cohorts without differentiating IHCA from OHCA. The time from circulatory arrest to the start of ECMO was 72 ± 48 minutes for IHCA and 98 ± 50 minutes for OHCA. Survival was 53% in IHCA and 55% in OHCA, and 43% for the patients without a specific location of cardiac arrest.

In 32 data records, the administration of ILE was described to bind drugs and thereby prevent their efficacy. A bolus of ILE was administered in most cases, followed by continuous administration. In addition to the actual ILE effect, one publication described clotting in the extracorporeal dialysis and ECMO circuits, even several hours after stopping the ILE infusion, with fatal outcomes.[8]

Discussion

ECMO has been used in a growing number of patients with widely varied indications over the past two decades.[3] Considering the total number of ECMO cases in the ELSO registry, the number of ECMO intoxication cases appears small and is mainly limited to case reports and data from registries. To the best of our knowledge, we have conducted the largest systematic review on ECMO and intoxication to date. The results from our systematic review show that ECMO is being increasingly applied to treat patients exposed to various substances at a toxic dose resulting in cardiorespiratory failure and metabolic dysfunction. Although ECMO does not neutralize or remove any substances, it provides hemodynamic assistance and oxygenation until toxins are eliminated and the organs have recovered. Consequently, considering ECMO's use in intoxication, its purpose should be extended by the terms "bridge to elimination" or "bridge to antidote." To reach those targets, other extracorporeal procedures like dialysis, plasmapheresis, or hemoadsorption are performed to remove toxins. Furthermore, almost all patients were given a substance-matched therapy for poisoning in addition to ECMO (►**Supplementary Tables S1–S3**, available online only). Nevertheless, not every poisoned patient is an ECMO candidate. Various factors such as age, comorbidities, the poison's dose, and exposure time, and no flow and low flow time during cardiopulmonary resuscitation (CPR) must be considered when deciding whether or not to apply ECMO in cases of intoxication. ECMO therapy is also known to raise a particular risk for neurologic complications,

bleeding, thrombotic events, renal failure, and vascular-access complications.[9–13]

We can summarize our systematic review findings as follows.

- The use of ECMO in cases of poisoning is associated with good survival at hospital discharge.
- vaECMO is used in the majority of cases to treat refractory cardiogenic shock or cardiac arrest
- ECMO can be used in intoxication as a "bridge to elimination" or "bridge to antidote."
- When ECMO is applied due to intoxication, the interaction of the extracorporeal circuit and toxin-removal measures must be kept in mind.

Brunet et al reported their single-center ECMO results in cardiac arrest and refractory cardiogenic shock due to various causes.[14] In a multivariate analysis, two factors were independently associated with survival: severe poisoning caused by drug intoxication as a reason for refractory cardiac arrest and arterial pH. Masson et al demonstrated the outcome of 62 intoxicated patients treated with and without ECMO therapy.[15] Survival after cardiac arrest due to the intoxication of patients who underwent ECMO therapy was 100%, whereas all patients with cardiac arrest who did not receive ECMO therapy died. Eleven intoxicated patients underwent vaECMO due to refractory cardiogenic shock with a survival of 81%. Out of 41 patients with refractory cardiogenic shock who did not receive ECMO, only 56% survived.

There are several potential reasons for the good survival at hospital discharge of intoxicated patients who underwent ECMO.

- Compared with registry data or current studies on ECPR, these patients are significantly younger.[3,4,16]
- The reason for the cardiopulmonary collapse is not a pathology of cardiac or cardiopulmonary origin and intoxication is a reversible cause of respiratory or cardiac failure.
- These patients are unlikely to have preexisting internal disease or structural heart disease.

Nevertheless, the study situation must be considered when interpreting the results from our systematic review. Due to the high number of case reports and case series published and reporting on mostly positive patient outcomes, a study bias may exist and must be considered when interpreting our results.

Compared with vaECMO and ECPR applied in acute situations in patients suffering refractory cardiogenic shock or cardiac arrest (duration from exposure to ECMO start: 15.4 hours and 17.2 hours), vvECMO was employed much later after exposure (191.2 ± 301.2 hours). vvECMO is applied in intoxicated patients for two main reasons: primary lung damage from the toxins and eventual bridge to lung transplantation, or "secondary" problems during prolonged ICU treatment such as pneumonia or ARDS. The latter may occur during the course of intensive care treatment rather than being directly linked to the intoxication. That would result in ECMO's comparatively late start after the actual event.

Although hemoadsorption devices can be used to adsorb certain drugs like amitriptyline, diazepam, digoxin, quetiapine, rivaroxaban and venlafaxine, and most cases described in our review involved poisoning with severe symptoms, its use was described in connection with only seven cases in our systematic review.[17–21] A reason for this could be ECMO's stabilization of the circulatory situation and the resulting improved metabolism of the toxins by the liver and/or kidneys or the elimination of the toxins via the dialysis often used, whereby using a hemoadsorption device has no advantage, such as eliminating toxins faster.

A Word of Caution

We identified one case where the patient died after intravenous administration of lipid emulsion and subsequent clotting in the ECMO and dialysis circuits.[8] We also identified other publications describing the occurrence of clotted ECMO circuits, sometimes without visible thrombi, since the lipid emulsion is deposited on the membrane oxygenator's fibers.[22,23] Badulak et al performed a review of the literature regarding ECMO failure due to hypertriglyceridemia and lipid emulsion and found several cases describing lipid-induced membrane oxygenator failure.[22] Lee et al conducted in-vitro experiments with ILE and ECMO in 2014 and observed "layering" and "agglutination" in all circuits after 30 minutes.[24] Therefore, caution should be taken when administering ILE to bind drugs during ECMO or dialysis therapy. However, we observed repeatedly ILE administration of after 2014 in our systematic review (see ►**Supplementary Tables S1–S3**, available online only). It should be considered whether eliminating drugs by administering ILE during ECMO is beneficial in a stable patient or whether ILE administration can be omitted.

Furthermore, despite the encouraging results that ECMO enables in intoxicated patients, it must be noted that certain substances, such as nitrates, sulfonamides, and other aniline derivates as well as benzocaine and lidocaine and some illicit substances like amyl nitrate (poppers), and the adulterants used in cocaine, can, depending on the dose, cause severe methemoglobinemia.[25] In these cases, oxygen delivery to the tissue can be impaired and ECMO can provide no benefit without parallel substance-matched therapy for intoxication.

In our view, there should be made some special considerations when putting patients with intoxication on ECMO support:

- In the acute phase of intoxication: find out possible elimination routes of the toxins (via kidney, via plasmapheresis, and via hemoadsorption) and ensure or establish them.
- Evaluate possible permanent damage to organs by the toxins (e.g., intoxication with paraquat and resulting pulmonary fibrosis; see Supplement ►**Table 2**, vvECMO).
- Consider the possible interaction of already administered lipid emulsion with the ECMO circuit.

- Avoid administration of intravenous lipid emulsion to bind toxins when ECMO is already in progress.

Registries on Extracorporeal Membrane Oxygenation or Poisoning

Unfortunately, depending on the registries' focus (ECMO or intoxication), detailed information about ECMO or intoxication is missing. Cole et al. published a report on 407 ECMO patients from a poisoning registry. Nevertheless, this report does not include detailed information on ECMO like mode of ECMO (vv, va, ECPR) or runtime, location of cardiac arrest, CPR duration, thus exemplifying the missing-data problem in studies on the use of ECMO for intoxication.[5] Weiner et al evaluated the ELSO registry regarding poisoned patients and were not able to describe either the time from exposure to ECMO, the reason for intoxication, or therapy for intoxication.[6]

Limitations

The present systematic review has several limitations, that is, the lack of information in registry studies, heterogeneous etiologies of poisoning as well as reporting bias. The exclusion of publications not written in English or German may reduce the methodological and reporting quality of this review. Morrison et al stated that language bias due to language restrictions seems interesting not to affect summarized treatment effects, but the precision of pooled estimates improved with the inclusion of trials with languages other than English.[26] The high number of case reports is also a limitation because case reports are notorious for often describing only successful cases. In contrast to many case reports, two registry studies reporting on 111 and 70 cases can affect our systematic review results, too. Due to the variety of pharmaceutical and nonpharmaceutical substances and the completely different mixture of substances and their doses in patients who ingested more than one substance, no subgroup analysis was possible.

Conclusion

In conclusion, this is the most comprehensive systematic review on the use of ECMO in patients suffering intoxication. When it is used and reported on, ECMO seems to be a valid tool for adult and pediatric patients suffering intoxication from various pharmaceutical and nonpharmaceutical substances. We noted that ECMO was usually used to treat patients in cardiogenic shock or cardiac arrest, with a good survival at hospital discharge. The use of intravenous lipid emulsion to bind drugs while ECMO is running or during dialysis can trigger dangerous complications.

Authors' Contributions

S.M., L.R., and L.S. were responsible for the conception and design of the work; S.M., L.S., L.R., and J.S. were responsible for literature search; S.M., L.S., L.R., and J.S. were responsible for data collection; M.C., F.B., and C.B. were reposnible for data analysis and interpretation; M. C., F.B., and C. B. were responsible for statistical analysis; S.M., M.C., and C.B. were responsible for drafting the manuscript; M.C., F. B., and C.B. were responsible for critical revision the work.

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None declared.

Conflicts of Interest

Friedhelm Beyersdorf, Christoph Benk and Georg Trummer are shareholders of ResuSciTec GmbH, Freiburg, Germany. Christoph Benk and Georg Trummer are part-time employees of ResuSciTec GmbH, Freiburg, Germany. The other authors report no conflicts of interest regarding this work.

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