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TOXICOLOGY INVESTIGATION

Extracorporeal Membrane Oxygenation (ECMO) for Severe Toxicological Exposures: Review of the Toxicology Investigators Consortium (ToxIC)

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Abstract Although there have been many developments related to specific strategies for treating patients after poisoning exposures, the mainstay of therapy remains symptomatic and supportive care. One of the most aggressive supportive modalities is extracorporeal membrane oxygenation (ECMO). Our goal was to describe the use of ECMO for toxicological exposures reported to the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC). We performed a retrospective review of the ACMT ToxIC Registry from January 1, 2010 to December 31, 2013. Inclusion criteria included patients aged 0 to 89 years, evaluated between January 2010 through December 2013, and received ECMO for toxicological exposure. There were 26,271 exposures (60 % female) reported to the ToxIC Registry, 10 (0.0004 %) received ECMO: 4 pediatric (< 12 years), 2 adolescent (12–18 years), and 4 adults (>18 years). Time of initiation of ECMO ranged from 4 h to 4 days, with duration from 15 h to 12 days. Exposures included carbon monoxide/smoke inhalation (2), bitter almonds, methanol, and several medications including antihistamines (2), antipsychotic/antidepressant (2), cardiovascular drugs (2), analgesics (2), sedative/hypnotics (2), and antidiabetics (2). Four ECMO patients received cardiopulmonary resuscitation (CPR) during their hospital course, and the overall survival rate was 80 %. ECMO was rarely used for poisoning exposures in the ACMT ToxIC Registry. ECMO was utilized for a variety of ages and for pharmaceutical and non-pharmaceutical exposures. In most cases, ECMO was administered prior to cardiovascular failure, and survival rate was high. If available, ECMO may be a valid treatment modality.

Keywords ECMO · ACMT ToxIC · Exposures · Toxicology

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Introduction

In 2011, the National Poison Data System (NPDS) reported over 2.3 million human exposure calls to regional poison centers in the USA with 2765 deaths (1.1 %) [1]. Of the fatalities reported by NPDS, the majority (1689, 85 %) were due to pharmaceuticals [1]. The severity of poisonings has steadily increased over the past 30 NPDS annual reports, and the CDC reports that poisoning has recently become the leading cause of injury-related death [2, 3].

Although there have been many developments in the specific treatment of poisoning exposures, the mainstay of therapy remains symptomatic and supportive care. One of the most

aggressive supportive modalities available is extracorporeal membrane oxygenation (ECMO). ECMO is an external device that supports the cardiopulmonary system by providing oxygenation and cardiac function for a patient in cardiac and respiratory failure. ECMO has been successfully used in all ages for various medical and surgical conditions leading to cardiovascular collapse, respiratory failure, cardiogenic shock, or refractory hypotension [2–9]. ECMO has also been used in poisoning exposures when cardiac arrest or refractory hypotension develops. This has been studied in both animal models and human cases [10–35]. Our goal was to describe the use of ECMO for toxicological exposures reported to the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) since its inception in 2010.

Methods

We performed a retrospective review of cases entered into the ACMT ToxIC Registry from January 1, 2010 to December 31, 2013. The ACMT ToxIC Registry began in January of 2010 as a self-reporting database completed by medical toxicologists across the USA. In 2013, 38 consulting groups providing services to 69 specific institutions were contributing to the ACMT ToxIC Registry [36]. Standard data collection includes demographics, exposures, treatments, and survival. Included patients were between 0 and 89 years of age and received ECMO for the management of a toxic exposure between January 2010 and December 2013. After site identification, local site investigators were contacted, and if available, further detailed information was obtained using a standardized data collection form through chart review. Data collected included age, gender, ingestion/exposure, treatments, time to initiation of ECMO, duration on ECMO, and survival. An additional search of the registry between the same time periods was performed to evaluate how many patients received cardiopulmonary resuscitation (CPR). This study was approved by the ACMT Research Board as well as the local institutional review boards for participating sites.

Results

There were 26,271 toxicological exposures reported to the ACMT ToxIC Registry between January 1, 2010 and December 31, 2013 [36–39]. A total of 10 patients (0.0004 %) at 6 registry sites during the study period received ECMO for a toxicological exposure. Local investigators at all registry sites were contacted, and 4 local investigators provided more detailed information on 7 of the 10 patients. Further information on the remaining 3 patients from 2 registry sites were not available. There were 4 pediatric patients (<12 years), 2 adolescents (12-18 years), and 4 adults (>18 years). Of patients with known duration of ECMO, they received ECMO on average 35 h (range 4 h–4 days) into their hospital course and received an average 170 h (range 15 h–12 days) treatment course.

The exposure history included four intentional adolescent/adult polypharmacy ingestions, two unintentional pediatric single drug ingestions, three chemical asphyxiants (2 carbon monoxide/smoke inhalation and 1 cyanide pro-drug as “bitter almonds”) and one intentional toxic alcohol ingestion (Table 1). Pharmaceutical exposures involved antihistamines (2), antipsychotic/antidepressant (2), cardiovascular drugs (2), analgesics (2), sedative/hypnotics (2), and antidiabetic agents (2). As expected, most patients had hemodynamic compromise or multiorgan failure as evidenced by vasopressor support, cardiac dysrhythmias, metabolic acidosis, or renal insufficiency. Reasons for initiating ECMO included cardiovascular arrest, persistent hypotension, cardiac dysrhythmias, and poor ventilation (Table 1). Most patients received other aggressive supportive therapies including continuous renal replacement therapy (5), bicarbonate (4), intravenous fat emulsion (2), and hemodialysis (1). Four patients received CPR during their hospital course. Survival rate for patients receiving ECMO in this cohort was 80 %.

Discussion

Overall, ECMO is rarely reported as an intervention for patients in the ACMT ToxIC Registry. It was used in both pediatric and adult patients and for both pharmaceutical and non-pharmaceutical exposures. It can be an effective treatment modality for patients with toxicological exposures because hemodynamics and oxygenation can be supported while the xenobiotic is metabolized and/or eliminated. Most patients received ECMO in conjunction with other rescue therapies and supportive interventions, but few patients required CPR.

The two patients who received ECMO for carbon monoxide were exposed via smoke inhalation. The 4-year-old had a carboxyhemoglobin concentration of 29.6 %. A cyanide concentration was not obtained, but the patient had a peak lactate concentration of 13.8 mmol/l. The 7-month-old also had smoke inhalation injury and had a carboxyhemoglobin of 5.7 % and peak lactate of 8 mmol/l; a cyanide concentration was also not obtained. Both patients were placed on V-A ECMO for ARDS and poor ventilation by conventional and high-frequency mechanical ventilation modalities. The patient with bitter almonds toxicity reported crushed and ingested “half a bag” of bitter almonds and presented 12–16 h after ingestion. Patient had cardiac arrest 5 h after initial presentation and was admitted for over a month, and blood cyanide concentration was >500 mcg/dl.

Table 1 Clinical characteristics of patients receiving ECMO reported to the ACMT ToxIC Registry. Three patients were seen at facilities that did not participate in our study

Age (gender)	Exposure	Signs/symptoms	Other interventions	Reason for ECMO	Time to ECMO from presentation	Duration of ECMO	Survival
7 months (F)	Carbon monoxide, smoke inhalation	Coma Metabolic acidosis	Dopamine	Poor ventilation	<1 day	12 days	Y
<2 years (M)	Metformin	Ventricular dysrhythmias Coma Agitation Metabolic acidosis	CRRT	NA	NA	NA	Y
2 years (F)	Flecainide	Hypotension Bradycardia Ventricular dysrhythmias Wide QRS Seizures	Fat emulsion Sodium bicarbonate CPR	Cardiovascular arrest, cardiac dysrhythmia	4 h	4 days	Y
4 years (M)	Carbon monoxide, smoke inhalation	Coma Metabolic acidosis Rhabdomyolysis	Hydroxocobalamin	Poor ventilation	1 day	8 days	Y
17 years (F)	Methanol	Metabolic acidosis Hypotension Tachycardia Seizure	Vasopressors CRRT Bicarbonate Fomepizole	Persistent acidosis and persistent hypotension	8 h	15 h	N
18 years (M)	Diphenhydramine Quetiapine	Hypotension Bradycardia Ventricular dysrhythmias Prolonged QT interval ARDS Coma Seizures Metabolic acidosis	Fat emulsion	NA	NA	NA	N
22 years (F)	Bitter almond	Hypotension Tachycardia Ventricular dysrhythmias ARDS Coma Metabolic acidosis AKI Rhabdomyolysis	Atropine Sodium bicarbonate Vasopressors CRRT CPR	Cardiovascular arrest, ARDS	4 days	7 days	Y
42 years (F)	Verapamil Citalopram	Bradycardia ARDS Coma Metabolic acidosis AKI Rhabdomyolysis	Vasopressors CRRT CPR	Cardiovascular arrest, respiratory failure	3 days	9 days	Y
48 years (M)	Metformin Trazodone Clonazepam	Hypotension Bradycardia Ventricular dysrhythmias ARDS Coma Hypoglycemia Metabolic acidosis AKI Hemolysis	Calcium Methylene blue Sodium bicarbonate Thiamine Albuterol Antiarrhythmics Anticonvulsants Glucose CRRT CPR	Persistent acidosis, Poor ventilation	17 h	9 days	Y
19–65 years (F)	Diphenhydramine Tramadol	Hypertension Prolonged QTc Aspiration pneumonitis Hallucinations Metabolic acidosis AKI	Cyproheptadine Deferoxamine Antiarrhythmics HD	NA	NA	NA	Y

NA information not available, local sites did not participate in data extraction, *CRRT* continuous renal replacement therapy, *CPR* cardiopulmonary resuscitation, *HD* hemodialysis, *AKI* acute kidney injury, *ARDS* acute respiratory distress syndrome

Many of the exposures reported in our cohort have specific antidotes including sodium bicarbonate for drugs with sodium channel blockade, hydroxocobalamin for cyanide, fomepizole for methanol, high-dose insulin for verapamil, and oxygen for

carbon monoxide. This demonstrates that although specific antidotal therapy may be helpful, it may not be sufficient in all cases, and aggressive supportive care was still needed. ECMO may be helpful in the setting of many significant toxicological exposures that result in cardiorespiratory failure or metabolic dysfunction. ECMO alone does not remove or neutralize any toxins but provides hemodynamic support and oxygenation until elimination of the toxin or eventual end-organ recovery.

Initial research involving ECMO and poisoning exposures began in animal models. These early studies showed improved mortality in models of lidocaine and amitriptyline poisoning [11, 12]. Numerous human case reports and case series have since shown favorable outcomes although ECMO has been primarily used in poisonings involving pharmaceuticals such as antidysrhythmics and other cardiovascular medications, as well as tricyclic antidepressants [13–25]. Many of the pharmaceutical exposures in our cohort were similar to cases reported in the literature with most leading to cardiotoxicity or hemodynamic collapse (flecainide, diphenhydramine, and verapamil). Metformin toxicity treated with ECMO has not been previously described. Non-pharmaceutical exposures involving ECMO as a treatment modality have been reported sparingly and include carbon monoxide, zinc chloride, arsenic, hydrocarbon pneumonitis, and taxus poisoning [28–35]. Several of the patients in our cohort were due to non-pharmaceutical exposures (bitter almonds/cyanide, carbon monoxide/smoke inhalation, and methanol).

As expected, our cohort displayed signs of severe toxicity prior to receiving ECMO including metabolic acidosis, seizures, coma, cardiac dysrhythmias, and hypotension. In spite of this, few patients were reported to have periods of cardiovascular collapse as only four patients received CPR. Over the same time period, 125 patients reported to the ToxIC registry received CPR, though only four of them (included in this search) received ECMO. It is unclear whether ECMO would have improved survival in these other cases. The timing of when to initiate ECMO has also yet to be determined. Attempting to initiate ECMO during cardiac arrest is difficult as it requires pauses in CPR in order to cannulate and initiate the procedure. Prolonged CPR with periods without effective chest compressions may lead to increased morbidity and mortality [40, 41]. The use of ECMO prior to cardiovascular collapse in the majority of our patients may have led to improved overall survival. A case series of 62 patients in France showed similar survival rates of 76 % in patients receiving ECMO due to severe acute drug intoxication with a lower overall mortality rate when compared to patients who received supportive care alone [26, 27]. In this study, 10 of 62 patients were in persistent cardiac arrest when ECMO was initiated. Further studies are needed to determine criteria for considering ECMO in poisoned patients.

Not every poisoned patient is a candidate for ECMO, and ECMO does not come without risks. Potential complications include limb ischemia, compartment syndrome, stroke, acute kidney injury, bleeding, emboli, and infection [42, 43]. Several factors must be considered in an individual basis such as age, co-morbidities, risk for complications, survivability, specific drug or chemical involved in the exposure, and time of hypoperfusion or cardiac arrest. A large amount of resources are required to perform and manage ECMO, and few facilities have the capability or the ability to activate it in a timely fashion. The decision should be made in conjunction with a multidisciplinary team including toxicologists, intensivists, and surgeons.

There were several limitations to this study. This was a retrospective chart review and limited to the information provided by documentation. The ACMT ToxIC Registry reflects cases only cared for at the bedside by medical toxicologists, and thus, cases reported may have been more severe; thus, it may not be an accurate representation of the number or severity of most poisoning exposures. Many of the institutions reported were large academic medical centers with significant resources at the disposal of medical providers and may not be reproducible in all hospitals. Not all facilities and physicians who registered patients to the database have ECMO capabilities at their institution. The registry is a self-reported database, so there may be inaccuracies in data entry and collection, and there may be missed cases if ECMO was not coded as a mode of therapy. As in most toxicology patients, dose and concentrations were not readily available.

Conclusion

ECMO was rarely used for toxicological exposures in the ACMT ToxIC Registry. When utilized, it was for a variety of pharmaceutical and non-pharmaceutical exposures in both adults and pediatric patients. In most cases, ECMO was administered prior to cardiac arrest, and the survival rate was high. If available, ECMO may be a valid treatment modality for severe poisoning exposures prior to cardiovascular collapse.

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Conflicts of Interest The authors declare that they have no competing interests.

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