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Evaluation of sedatives, analgesics, and neuromuscular blocking agents in adults receiving extracorporeal membrane oxygenation☆,☆☆

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ABSTRACT

Purpose: The objective of this study was to evaluate the use of sedative, analgesic, and neuromuscular blocking agents (NMBAs) in patients undergoing extracorporeal membrane oxygenation (ECMO) support.
Materials and methods: This was a 2-year, prospective, observational study of adult intensive care unit patients on ECMO support for more than 48 hours.
Results: We analyzed 32 patients, including 15 receiving VA (venoarterial) ECMO and 17 VV (venovenous) ECMO. The median daily dose of benzodiazepines (midazolam equivalents) was 24 mg, and the median daily dose of opioids (fentanyl equivalents) was 3875 μg. There was a moderate negative correlation between the day of ECMO and the median daily benzodiazepine dose ($r = -0.5515$) and a very weak negative correlation for the median daily opioid dose ($r = -0.0053$). On average, patients were sedated to Richmond Agitation Sedation Scale scores between 0 and −1. Continuous infusions of opioids, benzodiazepines, propofol, dexmedetomidine, and NMBAs were administered on 404 (85.1%), 199 (41.9%), 95 (20%), 32 (6.7%), and 60 (12.6%) ECMO days, respectively. Patients in the VA arm received a continuous infusion opioid (96.4% vs 81.6% days; $P < .001$) and benzodiazepine (58.2% vs 37.0% days; $P < .001$) more frequently.
Conclusions: Patients received relatively low doses of sedatives and analgesics while at a light level of sedation on average. Patients rarely required neuromuscular blockade.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a bridge therapy that can be used temporarily in patients with respiratory or cardiac failure who cannot be managed with conventional therapies [1-5]. Patients who require this invasive form of support often receive a variety of medications to treat their underlying diagnoses and to facilitate the initiation and maintenance of ECMO therapy. Unlike patients treated with conventional mechanical ventilation, guidelines regarding management of pain, agitation, and delirium (PAD) in patients on ECMO are extremely limited with regard to strategies or assessment [6,7]. Previous data have shown a need for significant increases in sedative and analgesic doses, as well as the need for neuromuscular blockade [8,9].

Extracorporeal membrane oxygenation is thought to cause pharmacokinetic changes affecting medications used for (PAD) management, including an increase in volume of distribution secondary to an increase in circulating volume and an alteration in medication clearance [10-14]. Lower circulating plasma levels of lipophilic medications may be due to sequestration in the ECMO oxygenator and/or the circuit tubing [12,14-19]. In addition, the degree of plasma protein binding, the drug molecule size, and the duration of oxygenator use may play a role in decreased levels and clinical effect of drugs [14]. Prolonged use of ECMO may also result in decreased renal perfusion and a subsequent decrease in renal-dependent clearance of medications [20,21].

We sought to evaluate PAD management, including sedation assessment and utilization of sedatives, analgesics, antipsychotics, and neuromuscular blocking agents (NMBAs), in patients undergoing ECMO support at our institution during a 2-year period. The objective of our study was to test the hypothesis that patients on ECMO would require increased and escalating doses of sedatives and analgesics.

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2. Materials and methods

2.1. Patient population

Brigham and Women's Hospital is a 793-bed tertiary care facility. The adult ECMO program was established in January 2013 to support the end-stage heart and lung disease programs and provide care to those with acute respiratory failure. It is a multidisciplinary collaboration incorporating members from cardiac surgery, thoracic surgery, pulmonary medicine, anesthesiology, hematology, respiratory therapy, physical therapy, pharmacy, perfusion, and nursing. Extracorporeal membrane oxygenation is utilized for a variety of indications including, but not limited to, bridge to lung transplant, management of acute respiratory distress syndrome (ARDS), and cardiogenic shock.

2.2. Study design

We performed a single-center, prospective, observational cohort analysis of adult patients who were supported on ECMO at our institution between January 2013 and December 2014. Patients were identified using an institution-specific database to track and monitor patients managed with ECMO. Patients were included in the analysis if they required ECMO support for more than 48 hours. Patients cannulated at an outside hospital more than 24 hours before transfer to our institution were excluded. Brigham and Women's Hospital institutional review board approval was obtained before the beginning of this study. Informed consent from patients was waived because of the observational nature of the study.

Baseline patient demographics, including the indication for ECMO, type of cannulation, and laboratory data were collected upon inclusion in the analysis. Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated for each patient. In this analysis, patients were placed on heparin and albumin-bonded polyvinyl chloride tubing (Bioline coating, Maquet, Orleans, France) and polymethylpentene membrane oxygenators (Quadrox, Maquet).

2.3. Management of pain, agitation, and delirium

Our institution has a guideline for the management of PAD in mechanically ventilated patients in the intensive care unit (ICU). This guideline focuses on frequent assessment of PAD, suggestions for both pharmacologic and nonpharmacologic options in the management of PAD, a "pain first" treatment approach, administration of boluses of both opioids and benzodiazepines before initiating and titrating continuous infusions, analgosedation to minimize benzodiazepines, and use of neuromuscular blockade. Patients are assessed daily for spontaneous awakening and breathing trials, as well as for early mobilization. Although this guideline is not consistently used specifically for patients on ECMO, these general strategies are used. Fentanyl and hydromorphone are the preferred opioids, whereas propofol and midazolam are the preferred sedatives. Continuous infusions of benzodiazepines are typically reserved for patients who cannot tolerate propofol and who have received several boluses already. Our target sedation level in most of the patients is a Richmond Agitation Sedation Scale (RASS) score of 0 to −1, whenever possible. Data regarding PAD management and assessment were recorded daily using the electronic medication administration record and patient-specific flow sheets. Administration of benzodiazepines, opioids, propofol, dexmedetomidine, clonidine, ketamine, and antipsychotics was assessed, and the total median daily dose for each was recorded. All benzodiazepines were converted to midazolam equivalents (1 mg intravenous [IV] lorazepam = 3 mg IV midazolam = 5 mg IV diazepam), and all opioids were converted to fentanyl equivalents (200 μg IV fentanyl = 1.5 mg IV hydromorphone = 10 mg IV morphine) [22]. The use of continuous infusions of benzodiazepines, opioids, propofol, and dexmedetomidine was documented. The utilization of NMBAs, inhaled epoprostenol, vasopressors, and continuous renal replacement therapy was also recorded. The RASS and Bispectral Index (BIS) were used to assess sedation depth. The Confusion Assessment Method for the ICU (CAM-ICU) was used to determine the presence of delirium.

2.4. Outcomes

The main outcome of our study was the median total daily dose of benzodiazepines and opioids administered. Other outcomes included the percentage of days where a continuous infusion of sedative (benzodiazepine, propofol, and/or dexmedetomidine) was administered, the percentage of days where a continuous infusion of sedative or opioid was administered (benzodiazepine, propofol, dexmedetomidine, or opioid), and the percentage of days where an NMBA was administered. The use of adjunctive agents, such as antipsychotics, was also analyzed. Outcomes were assessed starting at the time of ECMO cannulation.

Clinical outcomes assessed included number of days spent delirious, hospital and ICU length of stay (LOS), time to initiation of ECMO, duration of ECMO support, mortality, incidence of delirium, and discharge disposition. The time to initiation of ECMO was defined as the duration of invasive ventilatory support before ECMO cannulation. The duration of ECMO support was calculated in hours. Mortality status was assessed upon ICU discharge and hospital discharge. Discharge location and ventilator status were assessed upon hospital discharge.

We performed subgroup analyses comparing patients requiring VA ECMO support and those requiring VV ECMO support, as well as patients requiring ECMO as a bridge to transplant compared with other indications. Outcomes assessed between patients in the VA and VV groups were performed using the χ^2 test for categorical data, Student t test for parametric continuous data, and Mann-Whitney U test for nonparametric continuous data. Assuming a β value of .80, an α value of .05 was considered to be statistically significant.

2.5. Statistics

Descriptive statistics including baseline characteristics, variables related to PAD management, and those pertaining to clinical outcomes were stratified as continuous or binary. Continuous variables were presented as means with standard deviations or medians with interquartile ranges (IQRs). Binary variables were presented as numbers and proportions. The Pearson correlation test was performed to determine the relationship between the day of therapy on ECMO and the median doses of benzodiazepines and opioids that patients received. Pearson correlation coefficients were considered as follows: greater than 0.8, very strong; 0.6 to 0.8, strong; 0.4 to 0.6, moderate; 0.2 to 0.4, weak; and less than 0.2, very weak [23].

3. Results

Of the 45 patients screened, 32 patients were analyzed, including 17 patients who received VV ECMO and 15 patients who received VA ECMO. Nine patients were excluded for an ECMO duration of less than 24 hours, and 4 patients were excluded for receiving ECMO for longer than 24 hours before transfer to our institution. The primary indication for VA ECMO was cardiogenic shock, whereas VV ECMO was mainly used as a bridge to lung transplant or in patients with severe ARDS (Table 1). We evaluated a total of 475 ECMO days including 110 VA ECMO and 365 VV ECMO days.

The median daily dose of benzodiazepines was 24 mg, and the median daily dose of opioids was 3875 μg (Table 2). Fig. 1 shows the variations in benzodiazepine and opioid requirements by ECMO day. There was a moderate negative correlation between the day of ECMO and the median daily benzodiazepine dose ($r = -0.5515$) and a very weak negative correlation for the median daily opioid dose ($r = -0.0053$).