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Analgosedation in extracorporeal membrane oxygenation: a retrospective UK cohort study

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Editor - Patients often require high doses of analgosedation (opioids, benzodiazepines and propofol) when receiving extracorporeal membrane oxygenation (ECMO). [1] Reasons for higher drug doses are not clearly understood but may include patient factors, drug pharmacokinetics (PK), and the effects of ECMO circuit on drug PK. [2] Patient factors including age, gender, critical illness induced organ dysfunction, augmented renal clearance (ARC) and extremes of body weight may affect plasma concentrations of drugs such as fentanyl, midazolam and propofol. [3,4] Drugs used for analgosedation are lipophilic and sequester to the ECMO circuit increasing their apparent volume of distribution, [5] with the effect of reduced drug plasma concentration. This may explain why patients on ECMO require higher drug doses to achieve equivalent analgosedation. [6]

Our primary objective was to report peak continuous infusion doses per hour, and median daily doses per kg of analgosedation used for ECMO patients for the duration of ECMO treatment. Our secondary objective was to explore associations between analgosedation doses with patient and ECMO factors.

We describe a retrospective observational cohort study of patients receiving ECMO at a tertiary academic hospital in London, UK. We included patients aged 16 years and over receiving continuous intravenous opioids or sedatives, and invasively ventilated while receiving ECMO. We included patients admitted between January 2016 and July 2021. We documented all intravenous (excluding boluses) and enteral opioid and sedative (e.g., benzodiazepine) doses. Opioids were converted into fentanyl dose equivalents; benzodiazepines into midazolam dose equivalents. To calculate the median drug dose kg^{-1} day^{-1} we divided the total fentanyl equivalents, midazolam equivalents and propofol doses by the number of days the patient received ECMO and adjusted using actual body weight recorded on ECMO unit admission. We collected the length of stay in our hospital and 90-day survival.

Data are presented as counts and proportions; continuous data as medians and interquartile range (IQR). We generated separate multi-variable linear regression models for median daily dose per kg of

fentanyl equivalents, midazolam equivalents, and propofol (dependent variables) with patient and ECMO factors selected a priori based on expert opinion and existing evidence.

Institutional assessment and approval deemed this study a service evaluation (defined by the UK NHS Health Research Authority from the local quality improvement and safety committee (reference number: 12578, approval date: 19th July 2021).

We included 546 patients. Most patients were male (60.6%), with severe respiratory failure (74.7%) with a median (IQR) age of 46 (35-53) years, and few co-morbidities. Veno-venous (VV)-ECMO was the most common modality (90.7%). Median pain and Richmond Agitation and Sedation (RASS) scores during ECMO were 0 (IQR: 0, 0) and -2 (IQR: -1, -4) respectively, indicating no pain presence and light sedation. Peak continuous infusions doses per hour (median (IQR)) of fentanyl, midazolam and propofol were 400 (300-500) micrograms, 13 (8-20) milligrams (mg) and 250 (200-280) mg, respectively. Median (IQR) daily doses per kg of actual admission body weight of fentanyl, midazolam and propofol were 58.6 (36.1-83.0) mcg, 1.6 (0.6-2.8) mg and 35 (26-48) mg, respectively. Lower drug doses were required to achieve desired levels of analgosedation in patients treated with veno-arterial (VA)-ECMO compared to other ECMO modalities. Lower fentanyl and propofol doses were associated with higher Acute Physiology and Chronic Health Evaluation (APACHE II) scores and use of VA-ECMO; higher midazolam dose was associated with COVID-19 disease; lower propofol dose was also associated with older age. Median (IQR) length of stay in tertiary hospital was 19 (11, 30) days and 90-day survival was 73.9%.

In this study, we report peak continuous infusion doses per hour, median daily doses per kg of analgosedation, and associations between analgosedation doses with patient and ECMO factors in a large ECMO patient cohort. The main findings were 1) doses of continuously administered analgosedation were high compared to data previously reported on non-ECMO patients; [6] 2) lower fentanyl and propofol doses were associated with higher severity of illness and in patients receiving VA-ECMO treatment; 3) higher midazolam dose was associated with COVID-19 disease; 4) lower propofol dose was also associated with older age. High doses of analgosedation in our cohort may be explained by factors related to patient characteristics, critical illness, and potentially by the effect of ECMO sequestration on plasma drug concentrations. Patients in our study were relatively young, overweight, with mostly single organ respiratory failure and few co-morbidities compared to patients in non-ECMO studies. [6] These factors are likely to play a significant role in higher analgosedation dose requirements. [6] Critical illness due to severe respiratory failure requiring ECMO may result in higher doses of sedatives to suppress injurious spontaneous respiratory effort. [7] A moderate proportion of patients (50.4%) in our study received a neuromuscular blocking drug during the early phases of ECMO treatment, which may be a further contributing factor to high doses of analgosedation. Additionally, higher doses of midazolam in patients with COVID-19 disease may be associated with augmented renal clearance (ARC) leading to a higher clearance of drug. [8] One study investigating patients with COVID-19 disease reported a frequent occurrence of ARC (15.6 days per 100 ICU days), which was more common in younger patients. [8] Furthermore, the effects of a lower staff-to-patient ratio during the COVID-19 pandemic on the higher doses of midazolam cannot be excluded. [9] Patients requiring VA-ECMO in our study also received lower fentanyl and propofol doses compared to VV-ECMO. This is likely due to a higher severity of illness of patients treated with VA-ECMO compared to VV-ECMO. [10]

Our study has several limitations; this was a single-centre respective analysis with no control group which is susceptible to confounders and may limit its generalisability.

We conclude that doses of analgosedation in our ECMO study were high compared to previous non-ECMO studies most likely due to patient factors, changes in drug PK that occur during critical illness, and ECMO treatment. Analgosedation dose was associated with age, APACHE II score, COVID-19 disease and ECMO modality, with less analgosedation used in sicker patients.

Details of author's contributions

CR, C.A.M, LC, FH, BS, LR: study design and analysis; CR: data collection and writing the first manuscript draft. All other authors were involved in data interpretation, writing of the manuscript and approval of the final version of the manuscript.

Declaration of interests

The authors declare they have no conflicts of interest.

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Table 1: Multivariable linear regression models describing associations of analgosedation dose with demographic and clinical factors

Fentanyl			
Independent variable	**Effect size**	**95% CI**	**p value**
Intercept	99.04	80.24, 117.84	<0.001
Age, years	-0.13	-0.50, 0.24	0.502
APACHE II score	-1.26	-2.12, -0.39	0.005
Charlson Comorbidity	-3.98	-8.37, 0.42	0.076
Substance use disorder	11.04	-3.19, 25.3	0.128
V-A ECMO	-23.70	-37.88, -9.52	0.001
V-VA ECMO	-21.63	-51.01, 7.75	0.899
COVID-19 disease	-4.66	-15.30, 5.98	0.390
Model summary: Adjusted R-squared: 0.06. F statistic: 6.342;			
Midazolam			
Independent variable	**Effect size**	**95% CI**	**p value**
Intercept	2.27	1.50, 3.03	<0.001
Age, years	-0.01	-0.03, 0.00	0.085
APACHE II score	-0.001	-0.04, 0.03	0.936
Charlson Comorbidity	-0.09	-0.27, 0.10	0.370
Substance use disorder	-0.03	-0.55, 0.49	0.904
V-A ECMO	-0.30	-0.99, 0.38	0.385
V-VA ECMO	1.59	-0.01, 3.18	0.051
COVID-19 disease	0.86	0.49, 1.24	<0.001
Model summary: Adjusted R-squared: 0.09. F statistic: 5.628;			
Propofol			
Independent variable	**Effect size**	**95% CI**	**p value**
Intercept	62.50	54.76, 70.24	<0.001
Age, years	-0.32	-0.47, -0.16	<0.001
APACHE II score	-0.59	-0.95, -0.23	0.002
Charlson Comorbidity	0.87	-0.96, 2.69	0.351
Substance use disorder	4.84	-0.83, 10.51	0.094
V-A ECMO	-11.01	-17.29, -4.72	<0.001
V-VA ECMO	-8.37	-20.56, 3.83	0.179
COVID-19 disease	-2.40	-6.70, 1.90	0.273
Model summary: Adjusted R-squared: 0.10. F statistic: 9.488;			

Intercept of each model is predicted drug dose kg^{-1} day^{-1} for a VV ECMO patient. 95% CI = 95% Confidence Interval. Veno-venous (V-V), veno-arterial (V-A), veno-venous-arterial (V-V-A) extracorporeal membrane oxygenation (ECMO). Acute Physiology and Chronic Health Evaluation (APACHE II) score. Coronavirus-19 (COVID-19) disease. Substance use disorder = history of recurrent use of illicit drugs.

Tables

Table 1: Baseline characteristics for included patients

Characteristic	
Age, years	46 (35, 53)
Sex: female	215 (39.4)
male	331 (60.4)
Admission weight, kg	83 (71, 100)
APACHE II score	17 (14, 21)
Charlson Comorbidity Index	0 (0, 1)
Current smoker	140 (25.6)
*Alcohol use	117 (21.4)
Substance use disorder	45 (8.2)
Numeric pain score	0 (0, 0)
RASS score	-2 (-1, -4)
ECMO modality	
VV-ECMO	495 (90.7)
VA-ECMO	42 (7.7)
V-VA-ECMO	9 (1.6)
Admission diagnosis	
Respiratory failure (including ARDS)	408 (74.7)
Cardiovascular failure	74 (13.6)
Sepsis	36 (6.6)
Trauma	15 (2.7)
Haematological failure	9 (1.6)
Gastro-intestinal failure	2 (0.4)
Other organ failure	2 (0.4)
Admission category	
Medical	503 (92.1)
Surgical	28 (5.1)
Trauma	15 (2.7)
Admission infection	
Bacterial	198 (36.3)
Viral (non-COVID-19 disease)	147 (26.9)
Viral COVID-19 disease	95 (17.4)
Outcomes	
ECMO duration, days	9 (5, 16)
Length of stay in study hospital, days	19 (11, 30)
90-day survival	404 (73.9)
Discharge from hospital after 90 days	403 (73.8)

Continuous data are presented as median (IQR); categorical data as n (%). Pain and RASS scores recorded whilst on ECMO treatment. Veno-venous (V-V), veno-arterial (V-A), veno-venous-arterial (V-V-A) extracorporeal membrane oxygenation (ECMO). Acute Physiology and Chronic Health Evaluation (APACHE II) score. Coronavirus-19 (COVID-19). RASS = Richmond Agitation and Sedation Scale. *Alcohol use = reported consumption of more than 14 units of alcohol/week. Substance use disorder = history of recurrent use of illicit drugs

Table 2: Analgosedation doses administered during ECMO treatment

Dose parameter	Fentanyl equivalents	Midazolam equivalents	Propofol
Average daily dose	5049 (3291, 6865)	142 (42, 241)	3057 (2233, 4166)
Average daily dose kg $^{-1}$	58.6 (36.1, 83.0)	1.6 (0.6, 2.8)	35 (26, 48)
Dose per hour on ECMO initiation	200 (150, 250)	6 (4, 10)	140 (80, 200)
Minimum dose per hour on ECMO	100 (50, 150)	2 (1, 4)	40 (20, 60)
Maximum dose per hour on ECMO	400 (300, 500)	13 (8, 20)	250 (200, 280)

Continuous data are presented as median (IQR). Fentanyl dose equivalents reported in micrograms, midazolam and propofol dose equivalents reported in milligrams. ECMO = extracorporeal membrane oxygenation.