Systematic Review

Review of the Literature on the Occurrence of Delirium after Veno-Venous and Veno-Arterial Extracorporeal Membrane Oxygenation: A Systematic Review

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Keywords

Extracorporeal membrane oxygenation · Delirium · Critically ill patients · Systematic review

Abstract

Introduction: Extracorporeal membrane oxygenation (ECMO) is an extracorporeal gas exchange method which, despite a number of advantages, carries the risk of many complications. ECMO is a modern intensive care method which in many cases is the last resort for the patient. Care and supervision are provided by a multidisciplinary team of specialists: physicians, perfusionists, and nurses. The aim of this review is to analyze the occurrence of delirium in ECMO patients. **Methods:** Both authors independently extracted data from all included trials and assessed the risk of bias. A systematic review was performed using the protocol of the Cochrane Collaboration Risk of Bias tool. The search was based on PubMed, Web of Science, and Mendeley. Three articles from recent years have been analyzed in this work. Literature selection was made using the PRISMA checklist. The analyzed literature proves how important the topic of delirium is in ECMO therapy. In the case of pharmacotherapy, there are many combinations of drugs that prevent the occurrence of the delirium phenomenon. **Results:** This work deals with the subject of delirium after ECMO, which is not a common subject in the popular literature. Many of the elements mentioned in the articles analyzed show how important this topic is. The authors place great emphasis on the elements which are not related to pharmacotherapy and the prevention of delirium. For the prevention of delirium after ECMO, a psychological approach to the patient is important. As far as pharmacotherapy is concerned, it is the last element to be taken into account in the prevention of delirium in ECMO patients. An overview of the literature indicates that the subject of nursing care has been omitted; however, there are tools which allow nurses to assess delirium in patients. **Conclusion:** Delirium

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in patients undergoing ECMO therapy is a topic that has not been fully described in the literature. This review of the literature shows how important it is to treat a patient with delirium during this therapy and how important it may be to have an early diagnosis of delirium to prevent complications.

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Introduction

This work deals with the subject of delirium after extracorporeal membrane oxygenation (ECMO), which is not a common subject in the popular literature. Many of the elements mentioned in the articles analyzed show how important this topic is. The authors place great emphasis on all elements which are not related to pharmacotherapy and the prevention of delirium. For the prevention of delirium in ECMO patients, a psychological approach to the patient is important. As far as pharmacotherapy is concerned, it is the last element to be taken into account in the prevention of delirium in ECMO patients. An overview of the literature indicates that the subject of nursing care has been omitted; however, there are tools which allow nurses to assess delirium in patients [1, 2].

Methods

A systematic review of the literature published in English was conducted according to the checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) using manual and electronic literature searching strategies. Inclusion and exclusion criteria were established. We systematically searched for relevant studies published prior to December 26, 2018, in Mendeley, PubMed, and Web of Science. The following terms were used for the electronic search: #ICU nurses, #extracorporeal membrane oxygenation, #delirium, #delirium in ECMO, and #delirium in extracorporeal membrane oxygenation.

No language restrictions were applied, and the reference lists from all studies included were manually checked to identify other relevant articles. Both authors independently searched and evaluated the quality of the research. The use of a combination of at least two of the accepted keywords has helped to identify 30 articles approved for further stages of analysis. At the next stage, 27 articles were disregarded. Only 3 articles met the ECMO delirium-related criteria (Tables 1, 2).

Results

Study Selection and Data Extraction

Both authors independently evaluated the titles and abstracts of all articles retrieved to identify potentially relevant studies. A full-text review was conducted when either reviewer deemed that the abstract warranted further investigation on the basis of our a priori eligibility criteria. A systematic review of the literature published in English was conducted according to the checklist of PRISMA using manual and electronic literature searching strategies. Inclusion and exclusion criteria were established. We systematically searched for relevant studies published prior to December 26, 2018, in Mendeley, PubMed, and Web of Science. The following terms were used for the electronic search: #ICU nurses, #extracorporeal membrane oxygenation, #delirium, #delirium in ECMO, and #delirium in extracorporeal membrane oxygenation.

Table 1. PRISMA for delirium in VV and VA ECMO

Identification	Records identified through database search (based on keywords and full text availability) (<i>n</i> = 30)	Records identified through manual search in journals' databases (2008–2018 or availability) (<i>n</i> = 30)
Screening	Records screened (<i>n</i> = 26)	Record after duplicates removed (<i>n</i> = 26) Records excluded (<i>n</i> = 3)
Eligibility	Full-text articles assessed for eligibility (<i>n</i> = 3)	Full-text articles excluded (<i>n</i> = 20) Grounds for exclusion: articles not exclusively devoted to delirium in ECMO, articles about children, abstracts
Included	Studies included in qualitative review (<i>n</i> = 3)	
ECMO, extracorporeal membrane oxygenation; VV, veno-venous; VA, veno-arterial.		

Table 2. Summary of the studies included in the analysis

No.	Reference	Title of the publication	Year of publication	Aim of the study	Research method, research tool
1	Acevedo-Nuevo, et al. [3]	The early diagnosis and management of mixed delirium in a patient placed on ECMO and with difficult sedation: A case report	2018	The aim of this article was to present the case of a patient placed on ECMO, who was diagnosed as having a mixed delirium and difficult sedation criteria, and outline the various assessment strategies and the employed pharmacological and non-pharmacological management	case report
2	DeGrado, et al. [4]	Evaluation of sedatives, analgesics, and neuromuscular blocking agents in adults receiving extracorporeal membrane oxygenation	2017	The objective of this study was to evaluate the use of sedative, analgesic, and neuromuscular blocking agents in patients undergoing ECMO support	research
3	deBacker et al. [5]	Sedation practice in extracorporeal membrane oxygenation-treated patients with acute respiratory distress syndrome: a retrospective study	2017	The objective was to characterize sedation management in adult patients with severe respiratory distress syndrome treated with venovenous ECMO	research
ECMO, extracorporeal membrane oxygenation.					

No language restrictions were applied, and the reference lists from all studies included were manually checked to identify other relevant articles. Both authors independently searched and evaluated the quality of the research. The use of a combination of at least two of the accepted keywords has helped to identify 30 articles approved for further stages of analysis. At the next stage, 27 articles were disregarded. Only 3 articles met the ECMO delirium-related criteria.

The process of searching and analyzing articles conducted in line with the inclusion criteria shows that there is no research regarding ICU nurses. The final analysis included 3 articles which met the inclusion criteria.

Table 3. Most important factors identified on the basis of the available literature

Reference	Most important factors
DeGrado et al. [4]	<ul style="list-style-type: none"> – Frequent pain, agitation, and delirium assessment – Pharmacological and non-pharmacological treatment – Use of neuromuscular blockade – The “pain first” approach (opioid- and benzodiazepine-based bolus prior to continuous administration) <ul style="list-style-type: none"> – Fentanyl – Opioids: hydromorphone – Propofol and midazolam applied if the patient is propofol-intolerant – All benzodiazepines have been converted to midazolam equivalents (1 mg i.v.: lorazepam = 3 mg i.v. midazolam = 5 mg i.v. diazepam) – All opioids have been converted to fentanyl equivalents (200 µg i.v. fentanyl = 1.5 mg i.v. hydromorphone = 10 mg i.v. morphine) – administration of continuous infusions – Benzodiazepines, opioids, propofol, and dexmedetomidine – The results were evaluated starting from cannulation: number of delirium days, duration of hospitalization and stay in the ICU, time until the start of ECMO, duration of ECMO, mortality, occurrence of delirium, and status at discharge <ul style="list-style-type: none"> – Patients received opioids and benzodiazepines on most ECMO days – Continuous infusions were administered on 85.1% of all ECMO days – Continuous benzodiazepine infusions were administered on fewer than half of all ECMO days – Continuous infusions of every sedative were administered on 61.7% of all ECMO days – All patients administered continuous benzodiazepine infusions also received midazolam – Continuous opioid infusions were divided equally between fentanyl and hydromorphone – Propofol, dexmedetomidine, and ketamine were not generally administered – Quetiapine, haloperidol, and clonidine were the most commonly used adjuvants – RASS at the level of 0 to –1 – The results are recorded in special checklists prepared for the patient – Daily assessments of awakening, breathing attempts, and early mobilization – The guidelines apply to ECMO patients only – Patients had their evaluation of delirium documented around halfway through the ECMO period – A total of 16 (50%) cases of delirium occurred during the analysis – VA ECMO patients were more often administered continuous opioid infusions – The total number of days on which patients received benzodiazepines was similar in both groups – As compared to VV ECMO patients, VA ECMO patients received continuous sedative infusions for more days – As compared to VA ECMO patients, VV ECMO patients had a higher median opioid dose and tended towards a lower dose of benzodiazepines – Fentanyl was the most commonly used opioid for continuous infusions in the VA group – Patients in the VV group received continuous hydromorphone infusions – The VA group underwent an opioid rotation from fentanyl to hydromorphone – Patients in the VV group received both haloperidol and quetiapine for substantially more days than patients in the VA group – Delirium was identified more frequently in the VV group
Acevedo-Nuevo et al. [3]	<ul style="list-style-type: none"> – It is recommended to avoid certain medications (opioids, benzodiazepines, etc.) – Analgosedation – Preventing sensory deprivation by allowing the use of glasses and hearing aids – Preventing sleep deprivation; assessment based on the following scales: NRS, CAM-ICU, RASS, BIS, and ESCID – Monitoring the depth of sedation/agitation with the RASS scale every 4–8 h in accordance with the unit protocol – It is recommended that approved tools be used to monitor delirium: Intensive Care Delirium Screening Checklist and Confusion Assessment Method for Intensive Care Units – Refraining from physical coercion – Early mobilization – The patient received fentanyl from the moment of admission until the moment of activation (sitting); midazolam was used for 12 days (from the day of taking up to half-time of ECMO), while remifentanyl was only given to the patient on days 2 and 3 of their stay in the ICU (before ECMO); propofol was used from day 5 to 9 and included the time when ECMO therapy was implemented; clonidine was used twice – between days 6 and 7 and from day 11 to 18 when the patient was already connected to the ECMO circuit; cisatracurium was used immediately before connecting the ECMO circuit; treatment with Dexmedetomidine was continued since the introduction of ECMO therapy for the next 4 days; haloperidol administration was required on the day after ECMO implementation for 3 days only in boluses; due to increased pain (according to the ESCID scale), ketamine administration was introduced and continued for 2 days; pentothal was included on day 4 after the start of the therapy and was maintained until the removal of ECMO cannula

Table 3 (continued)

Reference	Most important factors
deBacker et al. [5]	<ul style="list-style-type: none"> – There was a 1:1 or 2:1 nurse-to-patient ratio in the care of these patients – Sedative and analgesic data (mode of administration, medications, and median daily dose) were recorded at 3 time points: 48 h after ECMO initiation, 24 h before ECMO discontinuation, and 48 h after ECMO discontinuation; benzodiazepine and opioid doses were presented as midazolam (1 mg midazolam = 0.5 mg clonazepam) and fentanyl (0.1 mg fentanyl = 2 mg hydromorphone = 10 mg morphine) equivalents, respectively – Incidence of delirium: Intensive Care Delirium Screening Checklist and Confusion Assessment Method for ICU – Agitation (Sedation Agitation Scale [SAS] score), on a given day, sedation depth for each patient was defined as “deep” (SAS score <3), “intermediate” (SAS score = 3), or “light” (SAS score >3) – Delirium while on ECMO was very prevalent, with a high incidence of antipsychotic and physical restraint use – Early mobilization may improve outcomes, including better functional status at discharge, reduction in delirium, and more ventilator-free days in mechanically ventilated patients – The cohort’s lower rate of agitation (24%) and device (endotracheal tube or peripheral intravenous) removal (6.6 events per 1,000 patient days) may in part be attributed to the high proportion of deeply sedated patients, the use of antipsychotics, and the high nurse-to-patient ratio – The incidence of delirium in our cohort was 58% while on ECMO – Withdrawal from large doses of benzodiazepines and opioids administered over many days may play a role in the high incidence of delirium – If sedation minimization is achieved early after the initiation of ECMO, delirium and withdrawal syndromes may be reduced, thus allowing earlier and more aggressive mobilization – Early mobilization (within 72 h) and the implementation of mobility protocols improve outcomes in mechanically ventilated patients including better functional status at discharge and reduction in delirium

VA, veno-arterial; ECMO, extracorporeal membrane oxygenation; VV, veno-venous; CAM-ICU, Confusion Assessment Method for Intensive Care Units.

Three of the original 30 articles are theoretical papers describing issues analyzed based on the literature, and 5 papers are empirical studies showing the results of research among nurses. The details of the selected methodological aspects are provided in 3 articles.

This thematic analysis resulted in the identification of the most important factors when dealing with delirium in ECMO patients (Table 3) [3–5].

Implications for Clinical Practice

Conscious sedation and strict monitoring protocols for pain, sedation/agitation, and delirium using validated tools allow an early diagnosis and management of patients. In the case of delirious critically ill patients undergoing ECMO, daily care is challenging and risky due to the highly critical condition of these patients and the risk associated with life-threatening devices. Nursing interventions, such as cognitive stimulation, refraining from the use of physical restraints, reality orientation, or improvement of sleep patterns can prove effective strategies for the management and recovery of critically ill patients with delirium. Early implementation of pharmacological and non-pharmacological measures entails better results at the patient’s discharge from the critical care unit.

Conclusions

The management of mixed delirium in a patient on ECMO and with difficult sedation criteria is challenging for the entire ICU staff. This factor, coupled with other elements, could contribute to a difficult sedation management and mixed delirium, which are handled through a multimodal approach and avoidance of the use of physical restraints. Finally, we can conclude that the multimodal and multidisciplinary approach to the patient using a combi-

nation of nursing interventions, strict pain, agitation, and delirium monitoring, and pharmacological measures can result in good patient results reaching significant milestones in a relatively short period of time. Failure to diagnose and treat delirium is a serious problem which affects the physical and cognitive judgement of the patient [6, 7].

Currently, all articles published on this topic offer a general outline of delirium in ECMO, but they do not address the topic of nursing care provided to delirium patients. These works present many essential conditions that must be met in order to avoid delirium. It is highly important that the patient is mobilized and activated. Long immobilization can cause a full-blown delirium and extend the patient's stay at the ICU. The available literature does not address the topic of nurse participation while caring for a patient with delirium during an ECMO therapy. While the subject of pain and the analysis of risk factors are approached in a very precise manner, the role of the nurse in this respect is not clearly indicated. The authors emphasize the importance of all elements which are not related to pharmacotherapy. For the case of prevention, psychological aspects should be employed: conversation, keeping the patient informed about the activities performed, refraining from raising one's voice, allowing the use of glasses or hearing aids, allowing contact with the family, etc. Furthermore, direct coercion, according to the authors' knowledge, should only be used in very specific cases. Pharmacotherapy should only be used as a last resort, if the patient is dangerous for themselves and people around them [8, 9].

Statement of Ethics

The consent of the bioethical commission was not needed to conduct a literature review due to the type of article. The authors state that the literature review does not affect the privacy of patients in any way, as it only concerns the analysis of research results of other researchers.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Both authors made the same contribution to writing the paper and collaborated on an equal level.

References

- 1 Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al.; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013 Jan;41(1):263–306.
- 2 Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med*. 2014 Jan;370(5):444–54.
- 3 Acevedo-Nuevo M, González-Gil MT, Romera-Ortega MÁ, Latorre-Marco I, Rodríguez-Huerta MD. The early diagnosis and management of mixed delirium in a patient placed on ECMO and with difficult sedation: A case report. *Intensive Crit Care Nurs*. 2018 Feb;44:110–4.
- 4 DeGrado JR, Hohlfelder B, Ritchie BM, Anger KE, Reardon DP, Weinhouse GL. Evaluation of sedatives, analgesics, and neuromuscular blocking agents in adults receiving extracorporeal membrane oxygenation. *J Crit Care*. 2017 Feb;37:1–6.

- 5 deBacker J, Tamberg E, Munshi L, Burry L, Fan E, Mehta S. Sedation Practice in Extracorporeal Membrane Oxygenation-Treated Patients with Acute Respiratory Distress Syndrome: A Retrospective Study. [ASAIO J](#). 2018 Jul/Aug;64(4):544–51.
- 6 van den Boogaard M, Schoonhoven L, Evers AWN, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact in long-term health-related quality of life and cognitive functioning. [Crit Care Med](#). 2012 Jan;40(1):112–8.
- 7 Palencia-Herrejón E, Romera MA, Silva JA; Grupo de Trabajo de Analgesia y Sedación de la Semicyuc. Delirio en el paciente crítico. [Med Intensiva](#). 2008;32(Suppl. 1):77–91.
- 8 Christensen M. An exploratory study of staff nurses' knowledge of delirium in the medical ICU: an Asian perspective. [Intensive Crit Care Nurs](#). 2014 Feb;30(1):54–60.
- 9 Barnes-Daly MA, Phillips G, Ely W. Improving hospital survival and reducing brain dysfunction at seven California Community Hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. [Crit Care Med](#). 2017 Feb;45(2):171–8.