

## Chronic pain treatment with pregabalin in end stage respiratory failure patients awaiting lung transplantation on ambulatory veno-venous extra corporeal membrane oxygenator support; a series of nine cases

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### Abstract

**Background:** End-stage respiratory failure is non-treatable with mechanical ventilation and can be treated with veno-venous extracorporeal membrane oxygenators (VV-ECMO). It can also be used as a bridge to lung transplantation or recovery of lung function. This patient group can suffer from chronic pain, which is further exacerbated by painful procedures required as part of treatment. Pregabalin is licensed for chronic neuropathic pain and generalized anxiety disorder. Thus far, it has not been tried in routine analgesia protocols for pain relief of patients on VV-ECMO.

**Case Series:** We included nine patients aged 17-54 years on VV-ECMO awaiting lung transplantation. Exclusion criteria were acute kidney injury and chronic kidney disease. All patients had morphine patient-control analgesia. In addition, pregabalin 50 mg twice daily was initiated in all patients with dose escalation as required. Pain scores and quality of sleep were evaluated daily. All patients experienced significant pain relief, demonstrated by reduced pain scores after treatment commencement. The mean visual analogue scale score was reduced significantly from  $6 \pm 2$  to  $3 \pm 1$ . A significant increase in good-quality sleep duration was recorded from  $5 \pm 1.7$  hours per day before to  $8 \pm 2.1$  hours per day after pregabalin treatment. All patients except for two reported reduced anxiety levels of at least  $2 \pm 1$  scale improvement ( $p < 0.05$ ).

**Conclusions:** Pregabalin is an efficient analgesic with accompanying anxiolytic effects in this group of patients with unique characteristics such as high analgesia requirements and exacerbated psychological and emotional stress. HIPPOKRATIA 2023, 27 (1):22-24.

**Keywords:** Chronic pain, pregabalin, lung transplantation, ambulatory veno-venous extra corporeal membrane oxygenator, VV-ECMO

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### Introduction

End-stage respiratory failure, non-treatable with mechanical ventilation, can be treated now with veno-venous extracorporeal membrane oxygenators (VV-ECMO) that are used to substitute the gas exchange that takes place on the alveoli and lung membranes. It can also be used as a bridge to lung transplantation and not only as a temporary treatment until a clinical improvement of lung function occurs. End-stage lung disease patients requiring VV-ECMO as a bridge to lung transplantation may have a prolonged stay in the Intensive Care Unit (ICU) that can last from weeks up to a few months<sup>1</sup>. The management of these patients can become very challenging from many points of view. This patient group commonly suffers from pain issues, and the insertion of the VV-ECMO cannulas

complicates the matter with the development of acute or chronic pain problems. In addition, reduced mobility is a substantial burden but a necessary and unavoidable term to ensure adequate flow in ECMO lines and reduce dislodgement risk.

Moreover, polyneuropathy and neuropathic pain are not uncommon in this unique group of patients with particular clinical profiles, physical characteristics, and needs. Pregabalin is licensed for chronic neuropathic pain and generalized anxiety disorder. Thus far, it has not been tried in routine analgesia protocols for pain relief of patients on VV-ECMO. Therefore, in this preliminary study, we aimed to test the analgesic efficacy of pregabalin and patient satisfaction based on pain scales and basic anxiety scores. Lastly, we aimed to elucidate any beneficial impact and potential side effects.

### Case series

Nine patients aged 17-54 years old on VV-ECMO awaiting lung transplant were included after written consent. Ethics approval was not required as patients received standard of care and no different intervention than usual. Eight patients had a diagnosis of cystic fibrosis and one of interstitial lung disease. Median ICU stay was  $45 \pm 17$  days (one patient was admitted twice, for 2 and 8 weeks). Exclusion criteria were acute kidney injury and chronic kidney disease. All patients were awake in the ICU, and five of them were tracheostomized, requiring ventilator support. All patients had morphine patient-control analgesia (PCA). The bolus dose on demand was set at 1 mg/ml. One patient with severe polyneuropathy required a background of continuous infusion on the PCA. Pregabalin 50 mg twice daily was initiated in all patients to minimize the risk of side effects. The dose was escalated to 75-100 mg twice daily, where necessary. Pain scores were evaluated daily using the visual analog score (VAS: a scale from 0-10 measuring the intensity of pain). We used a simple four-scale anxiety-evaluating inventory and also recorded the presence of side effects (drowsiness, dizziness, and blurred vision). We evaluated sleep quality by documenting the number of undisturbed hours of sleep in the previous 24 hours and recording the total number of undisturbed sleep hours per day on patients' data.

All patients experienced significant pain relief, demonstrated by a reduction in their pain scores after the treatment commencement. The mean VAS score was reduced from  $6 \pm 2$  to  $3 \pm 1$  ( $p=0.007$ ). Duration of good quality sleep was increased from  $5 \pm 1.7$  hours per day before pregabalin to  $8 \pm 2.1$  hours per day after pregabalin initiation ( $p < 0.012$ ). All patients, except for two, reported reduced anxiety levels of at least  $2 \pm 1$  scale improvement ( $p=0.032$ ).

### Discussion

#### *End-stage respiratory failure and ECMO*

Ambulatory VV-ECMO for bridging to urgent lung transplantation is a safe treatment and prevents mechanical ventilation in patients with end-stage lung disease and hypercapnia-related acute respiratory failure. This agrees with other studies that demonstrated the benefits of early VV-ECMO application<sup>2</sup>. Other studies have shown that the early initiation of the above treatment can prevent the development of muscle atrophy and weakness alongside accompanying mobilization in patients with acute respiratory distress syndrome, and the same may apply to our small cohort<sup>3</sup>. VV-ECMO uses peripheral vascular access either from the neck or the femoral vessels. The tip of the drainage cannula is ideally positioned on the junction between the vena cava and the right atrium. It can be positioned with percutaneous techniques and not necessarily surgically. Suturing is necessary, and occasionally, purse string sutures are used to stabilize the cannulas<sup>4</sup>. All the above remain a source of pain and discomfort while being necessary steps of the treatment. Mobilization is

challenging, and our cohort experience also highlighted this. To the authors' knowledge, this is the first case series of patients on VV-ECMO awaiting lung transplantation that were treated with pregabalin for analgesia.

#### *Pregabalin for acute and chronic pain*

Pregabalin is a gabapentinoid initially introduced for the treatment of chronic and neuropathic pain. However, increasingly, acute pain management protocols use pregabalin for moderate to severe pain control, especially where there is resistance to gabapentin. It has a better opioid-sparing profile, and randomized controlled trials showed significant differences in VAS pain scores and prolonged timing for first rescue dose analgesia<sup>5</sup>. The drug has well found its place in multimodal non-opioid analgesia protocols for acute pain management<sup>6</sup>. Most of these protocols involve enhanced recovery projects after trauma, orthopedic surgery, and even in non-critical burn population<sup>7</sup>. There is very little evidence in the literature of its use in critical care areas and hardly any for patients on VV-ECMO support. In Harefield Hospital, pregabalin is preferred over gabapentin as it is considered more effective and easier to titrate. Also, it lacks severe side effects such as drowsiness and renal impairment when introduced in low doses with gradual escalation. It is also used safely in patients with chronic pain issues post thoracotomies, especially after bilateral sequential lung transplantation, with satisfactory outcomes.

#### *Opioids and sedation*

Conventional treatment with opioids and mild sedatives remains the cornerstone in almost all analgesia protocols. A study by Dzierba et al showed that fentanyl and hydromorphone are the most commonly used opioids in North America<sup>8</sup>; however, morphine can also be used in cases of preserved renal function. Even though deep sedation should generally be avoided, drugs such as dexmedetomidine or low-dose propofol can be used in order to avoid delirium and cognitive dysfunction. In cases where deep sedation is required, propofol and benzodiazepines are the drugs of choice. Nevertheless, it is important to maintain patients awake and at full capacity in order to recognize complications. Early neurological compromise and complications such as strokes and intracranial hemorrhage, unfortunately, are not uncommon<sup>9</sup>. A randomized, double-blind, crossover study with combinations of pregabalin with remifentanyl and placebo showed that the pregabalin and remifentanyl combination had an additive analgesic effect and adversely affected cognition. At the same time, pregabalin potentiated the remifentanyl-induced ventilatory depression<sup>10</sup>. This perhaps suggests that we should rationalize the use of pregabalin in combination with other opioids and use strict dosing limits to avoid respiratory depression and over-sedation in this unique group of patients. There are several comparative studies between different opioids (sulfentanyl, fentanyl) and midazolam, which perhaps is the most common benzodiazepine in use for this purpose. These studies use

morphine and midazolam equivalents in order to quantify the analgesedation requirements. It becomes evident that the use of VV-ECMO rapidly increases the demands for analgesia and sedation, regardless of the agents used, and the optimal multimodal treatment is difficult to determine<sup>11</sup>. Dexmedetomidine and clonidine infusions have also been used for sedation with satisfactory outcomes. A comparative study of the analgesedation requirements between SARS-CoV-2 and non-SARS-CoV-2 patients with respiratory distress syndrome on VV-ECMO showed that the first group had significantly higher dexmedetomidine requirements. In comparison, the second group had higher propofol requirements, and adjunct therapy was needed in both groups<sup>12</sup>.

#### *Other rescue treatments*

Non-steroidal anti-inflammatories are not indicated as they affect platelet function and aggregation and precipitate bleeding even in normal individuals. VV-ECMO use is associated with hemolysis, platelet destruction, and heparin-induced thrombocytopenia. Ketamine, an NMDA receptor agonist, has demonstrated sedative and opioid-sparing effects in critically ill patients when used as a continuous infusion. Its other beneficial effects include the lack of respiratory depression and hemodynamic stability, which perhaps make it promising for VV ECMO patients<sup>13</sup>. Local anesthetic infiltration at the cannula's insertion point could perhaps be considered, but with limited value only during the immediate post-insertion period. A-2 adrenergic receptor agonists are proven to be beneficial in pain management; however, hypotension and tachycardia are common issues associated with their use. The role of gabapentinoids and duloxetine needs to be further established with additional studies<sup>14</sup>. Regional anesthesia techniques such as continuous ilioinguinal nerve block have been described as an alternative treatment in combination with other multimodal analgesia techniques for pain treatment on the femoral ECMO insertion site<sup>15</sup>.

#### **Conclusions**

Pregabalin is an effective analgesic with accompanying anxiolytic effects in this group of patients with unique characteristics such as high analgesia requirements and exacerbated psychological and emotional stress. No significant side effects were noted, and there was no further respiratory compromise secondary to increased drowsiness in this preliminary report of nine cases.

#### **Conflicts of Interest**

The authors declare no conflict of interest relevant to this article.

#### **Acknowledgment**

Informed consent was obtained from all subjects involved in the study. This study was presented as poster at the 33rd Annual ESRA Congress, Seville, 3-6 September 2014, and its abstract was included in the Congress abstract book.

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