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Extracorporeal Membrane Oxygenation in the COVID-19 Pandemic

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Abstract*— Objective: This study aims to discuss the risks and benefits of ECMO in the treatment of patients with severe COVID-19. Method: This is a narrative review study of the literature with a qualitative approach, carried out in the PubMed, MEDLINE, LILACS, SciELO and Google Scholar databases in April 2021. Results: The analysis of the literature shows the importance of applying conventional treatment before opting for ECMO, and should be considered when other measures that have been

***Keywords*— Extracorporeal Membrane Oxygenation. COVID-19. Acute Respiratory Distress Syndrome.**

proven to be effective and relatively inexpensive have been performed, but without success, such as pronation, neuromuscular blockade and lung protection ventilation. Conclusion: It is concluded that further studies are needed with a larger sample and a comprehensive analysis of the evaluation of the use of ECMO in patients with COVID-19.

I. INTRODUCTION

Coronavirus 2019 disease (COVID-19) caused more than 3 million deaths worldwide until April 2021. After more than a year of pandemic, new studies are still emerging to treat and manage severe cases of the disease. One of the main complications of this pathology is the Acute Respiratory Distress Syndrome (ARDS), being responsible for deaths and hospitalizations due to COVID-19. [1]

Most patients with COVID-19 have mild symptoms and progress to cure. However, some of them progress to a severe disease state, developing dyspnea and hypoxemia about a week after onset, which can rapidly progress to ARDS and, later, to multiple organ failure or even death. [2]

Treatment of patients with ARDS by COVID-19 includes conventional therapies such as invasive mechanical ventilation with lung protection strategies, prone positioning, neuromuscular blockade, and inhaled pulmonary vasodilators. [3]

For patients who present with progressive respiratory failure despite these conventional therapies, Extracorporeal Membrane Oxygenation (ECMO) may be considered to support gas exchange and minimize ventilator-induced lung injury. ECMO has been used for decades in the treatment of severe ARDS of various etiologies [4] and constitutes one of the advanced resources in the management of patients with severe and refractory hypoxemia. The device can provide circulatory and pulmonary support. Equipped with a membrane capable of oxygenating the blood, in addition to a continuous pulse pump, it drives blood through venous and/or arterial cannulas. [5]

It is an advanced form of life support as it works directly on the heart and lungs. It may be indicated in cases of severe acute heart or lung failure that is potentially reversible and does not respond to conventional treatment. Usually in the Intensive Care Units (ICU) there are two main types of ECMO, veno-venous and veno-arterial. [6]

A multicenter study published in the Lancet in 2021 shows an analysis of data from 1,035 patients with COVID-19 who received ECMO support. Of these, 67 (6%) remained hospitalized, 311 (30%) were discharged home or to an acute rehabilitation center, 101 (10%) were discharged to a long-term intensive care center or unspecified location, 176 (17%) were discharged to another hospital and 380 (37%) died. [7]

In patients with COVID-19 who received ECMO, the estimated mortality 90 days after ECMO and the mortality in those with final disposition to death or discharge were less than 40%. These data from 213 hospitals worldwide provide a generalizable estimate of ECMO mortality in the context of COVID-19. [8]

A study carried out in the Paris-Sorbonne University Hospital Network by Schmidt et al. (2020) examined the outcome of treating 492 critically ill patients with COVID-19 with ECMO in the ICU and found positive results. The estimated 60-day survival of patients rescued by ECMO with COVID-19 was similar to studies published in the last two years on ECMO for severe ARDS. [9]

Given the above, the following question was formed: What is the published evidence about the use of ECMO for the treatment of Acute Respiratory Distress Syndrome in critically ill patients of COVID-19?

The aim of this review was to discuss the risks and benefits of ECMO in the treatment of patients with severe COVID-19.

II. METHOD

This is a study with a qualitative approach, of the narrative review type. The survey of bibliographic studies took place during the month of April 2021, in which articles published in national and international journals, available free of charge, in full, in electronic format, in the PubMed, MEDLINE, LILACS, SciELO and Google Scholar databases were selected.

The focus in the elaboration of the research was to understand the findings about the use of ECMO for severe cases of COVID-19 for presenting the ARDS, one of the main problems of COVID-19.

Therefore, the six steps indicated for the constitution of the integrative literature review were adopted: 1) selection of the research question; 2) definition of study inclusion criteria and sample selection; 3) representation of selected studies in table format, considering all common characteristics; 4) critical analysis of findings, identifying differences and conflicts; 5) interpretation of results and 6) clearly report the evidence found.

The following criteria were adopted for the selection of articles: all article categories (original, literature review, reflection, update, experience report, etc.); articles with abstracts and full texts available for analysis; those published in Portuguese and English between the years 2020 and 2021 and articles that contained in their titles and/or abstracts the following descriptors in health sciences (DeCS): Extracorporeal Membrane Oxygenation; COVID-19; Acute Respiratory Distress Syndrome. The resource used in the research was the expression “exact term”, associated with specific descriptors.

The exclusion criteria for the articles were studies that did not meet the mentioned inclusion criteria. In the databases search, 263 articles were found that address ECMO, related to ECMO with COVID-19 there were only 25. Each abstract/article was carefully read, highlighting those that responded to the objective proposed by this study, in order to organize the findings.

III. RESULTS AND DISCUSSION

In this narrative review, after successive readings of the texts, it was possible to detect the different approaches in the perspective of the theme produced. From this finding, different thematic approaches were built in order to group the results found in an understandable pattern and for a better elaboration of the synthesis of the contents focused by the researches.

SARS-CoV-2 infects host cells by targeting the angiotensin-converting enzyme 2 (ACE2) receptor, which is present in endothelial cells of the lung, heart, kidney, and gastrointestinal tissue. [10] The lungs are particularly vulnerable to SARS-CoV-2 because of their large surface area and because alveolar epithelial cells apparently act as a reservoir for virus replication, causing direct damage to lung tissue, and consequently an uncontrolled inflammatory response. [11]

Conventional high-flow oxygen therapy, non-invasive or invasive mechanical ventilation, in combination with prone positioning, have been reported to be effective in most patients. However, in severe cases, refractory hypoxemia may occur, with risk of life and secondary infections, myocardial disease involvement and a hyperclotting state, and pulmonary embolism may also occur. [12]

Given the pandemic and the high number of severe cases with refractory hypoxemia, a new possibility of therapy emerged in the scientific debate, the so-called ECMO [1]. This therapy aims to replace the pulmonary function of oxygenation, elimination of carbon dioxide and allows the use of protective or even ultra-protective ventilatory parameters, reducing the risk of lung injury induced by mechanical ventilation and providing greater pulmonary protection. [13]

The first ECMO machine was used for cardiac surgery in 1965. Modifications were made to this system to support the heart and lungs for an extended period of time. [14] ECMO is a supportive therapy where blood is pumped out of the body through a machine, indicated for patients with severe lung injury, respiratory failure and/or heart failure and has shown promise in the treatment of patients with COVID-19 serious. [15]

The main modalities of ECMO are veno-venous, which provides pulmonary support, and veno-arterial, which provides pulmonary and cardiac support, and in both, a drainage cannula removes blood from the body and directs it through a pump to a membrane in which it will be oxygenated, working as a kind of dialysis. Meanwhile, carbon dioxide is removed from the bloodstream and the device then returns oxygenated blood to the body through a return cannula. [4]

Another modality of ECMO is the venoarterial, which removes blood from a vein and returns it through an artery. It is used for both cardiac and pulmonary support. The primary objective is the restoration of tissue and end-organ perfusion to allow for stabilization or recovery of function. [16]

Regarding the atypical manifestations of COVID-19, such as predisposition to intrapulmonary thrombosis, right ventricular failure and the immunological insult aggravated by infection by COVID-19 and by the extracorporeal circuit, it has not been fully explored by recent publications. There are still few published studies that perform comparative analyzes of the effects of ECMO in patients with COVID-19, so the choice must be based on scientific evidence already available. [5]

Indications for ECMO are: acute and reversible lung disease, P/F ratio lower 50-80 with FIO2=1, patient with Murray score=lower 3.0, lower ph 7.2 due to refractory hypercapnia with little metabolic acidosis. Relative contraindications for ECMO are: prolonged period of mechanical ventilation longer than 7 days, age over 65 years, post-cardiac arrest coma, advanced cancer, incoercible bleeding and central nervous system hemorrhage. [17]

It is important to apply the conventional treatment before moving to ECMO, and it should be considered when other measures that have been proven to be effective and relatively inexpensive have been performed, but without success, such as pronation, neuromuscular blockade and lung protection ventilation [8]. In addition, the underlying diagnosis, the patient's specific risk factors, the expected duration of support, and especially whether there is a viable exit strategy, such as recovery, must be taken into account. [18]

ECMO is a therapy whose priority is preferentially given to younger patients, with a relatively low prevalence of comorbidities and with an acceptable probability of reversal of the pulmonary insufficiency typical of these patients. The ideal window for implantation is after other less invasive treatments have been considered or exhausted, but before significant target organ dysfunction begins. [7]

In 2021, if the second wave of COVID-19 started, it is inevitable that the demand for ECMO will exceed its supply. [19] In the case of multiple candidates with suitable nominations, the ICUs will need to implement a screening to select candidates who best fit the ECMO nomination profile. This is an expensive technology that consumes a lot of resources, another important point is that it must be performed with qualified professionals and monitored by a multidisciplinary team. [8]

Regarding veno-arterial ECMO and other precautions with its maintenance, it is important to adjust the ECMO flow to maintain or restore, if possible, the function of other organs such as neurological status, renal function, liver function and pulmonary function and also provide an acid-base balance in the body. The initial flow for ECMO-VA should be 50 to 70 ml per kilogram every one minute with a mean arterial pressure > 60 mmhg. [20]

In ECMO-VA, blood ejected from the left ventricle is a mixture of venous blood supplied by the right ventricle and bronchial and pulmonary collateral blood flow. In the abnormal pulmonary gas exchange scenario, even when combined with fully oxygenated blood from the femoral arterial cannula, the blood that permeates the brain, heart and upper extremities can have a saturation below 90%, causing cyanosis in the upper body, a condition called harlequin. [6]

Patients with ECMO-VA support should be monitored with an arterial line, arterial line monitoring allows you to monitor pulse pressure as a reflection of cardiac contractility during support and weaning. Absence or low arterial pulsatility indicates that the left ventricle is not ejecting or is ejecting less than ideal volume, which can lead to an increased risk of thrombus formation. [21]

Circuit line pressures should be monitored because significant changes may indicate filter or tubing obstruction, potentially by thrombus. Therefore, the prevention of thromboembolic complications is extremely important in the management of these patients. The oxygenator should be checked frequently for evidence of clot formation directly by visual inspection of the membrane and indirectly by evaluating hemolysis measurements and gas exchange efficiency. [6]

Systemic anticoagulation is recommended, with heparin being the most used anticoagulant. The most frequent complication of ECMO is hemorrhage, whose bleeding can be increased due to systemic heparinization. However, direct thrombin inhibitors such as bivalirudin and argatroban are drugs that have been reported as safe and effective alternatives in patients with heparin-induced thrombocytopenia or heparin resistance. [19]

It is noteworthy that the role of ECMO in the treatment of disease caused by this new virus remains uncertain and, in the meantime, further research by several authors is always suggested. From this perspective, the position among researchers can be controversial, as while some authors tend to be more pessimistic when observing high mortality rates with this type of treatment, including reports of septic shock and multiple organ failure, others suggest that it may play an important role and to assist those in critical condition of ARDS due to COVID-19. [22]

IV. CONCLUSION

Advances in circuit technology have required parallel advances in the management of patients with ECMO at the bedside, including the development of multidisciplinary ECMO teams. This procedure plays an important role in the stabilization and survival of critically ill patients with COVID-19, but the usefulness of ECMO in reducing the mortality of severe ARDS caused by COVID-19 has been limited.

Therefore, the results allowed us to conclude that it is still necessary to carry out more studies with a larger sample and a comprehensive analysis of the evaluation of the use of ECMO in patients with COVID-19. Providing ECMO to a patient during a crisis also depends on the capabilities of each hospital, including the actual effectiveness of this intervention under current circumstances.

It is important to think ethically about the use of ECMO, because in the face of a pandemic it is necessary to reflect on ethical principles and screening guidelines that may or may not result in the interruption of ECMO services when demand exceeds available resources, depending on the circumstances and choices made.

It becomes evident that there is no clear or operational ethical imperative requiring the interruption of ECMO services during a public health crisis such as the COVID-19 pandemic. However, considering the high frequency of serious adverse events, ECMO should probably remain a rescue therapy and therefore only be performed in centers specialized in ECMO with adequate resources.

It was possible to observe limitations in the study, such as the lack of production of studies that made a comparison between the use of ECMO in patients with COVID-19, taking into account all the risks and benefits that this therapy involves. There is still discussion among academic and scientific circles on the subject, in which some researchers claim that ECMO is a valid support therapy to treat ARDS, and others already defend the idea that, as it is an economically expensive therapy, it needs a specialized team, which the ECMO may not compensate by taking into account all the factors that have been suppressed, including the ethical ones.

The main strength of this study is to prospectively describe the clinical course of patients with COVID-19 who required ECMO, mainly because few data are available. Our results are, however, limited by its single-center character.

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