

Clevidipine and COVID 19: From Hypertension to Inflammatory Response

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Abstract: Globally, more than 4 million have died from COVID-19, World Health Organization (WHO) to declare COVID-19 a pandemic. The COVID 19 pathology, produced by SARS-COV2, a virus from the coronavirus family, emerged at the end of 2019. The majority of cases usually have a mild or moderate form, characterized by fever, cough, intense asthenia and multiple symptoms derived from the initial replicative effect and subsequent hyperimmune effect. Severe cases present with Acute Respiratory Distress Syndrome (ARDS), due to pneumonia with bilateral involvement, which lead to hospital admission of patients and the need for admission to intensive care units (ICU) of approximately 10–20%. According to the different series; the mortality of the condition once the patient is admitted to the ICU is close to 35–45%. Currently, more than 4 million people have died in the world due to this pathology. The volume of infections generated the declaration by the World Health Organization (WHO) of the pandemic situation. Factors associated with a higher risk of progression into severe disease include age and comorbidities, especially systemic arterial hypertension due to its high incidence in the general population. Clevidipine can be rapidly and effectively adjusted to the clinical status of the patient, since it can be withdrawn and its effects reversed in just a few minutes, and contains high concentrations of lipids, and it could reduce the inflammatory response induced by SARS-COV2, which is key to progression into severe disease. However, its application in pro-inflammatory settings has not yet been explored, although it must play a key role in inflammation as a scavenger molecule.

Keywords: clevidipine, COVID-19, hypertension, blood pressure, SARS-COV2

In December 2019, the world witnessed the outbreak of the pandemic of COVID-19.¹

The clinical symptoms and pattern of spread of this coronavirus has posed a challenge to medicine. Most patients develop mild/moderate disease, characterized by fever, cough, intense asthenia, and a variety of symptoms resulting from a replicative effect followed by a hyperimmune response.

A symptom of severe disease is acute respiratory distress syndrome (ARDS) secondary to unilateral pneumonia, which requires critical care in 10–20% of patients, according to the different series reported so far. Mortality after ICU admission reaches 35–45%.²⁻⁴

Globally, more than 4 million people have died from COVID-19 to date.³ The spread of the disease led the WHO to declare COVID-19 as a pandemic situation. Factors related to a higher risk of progression into severe disease include age and comorbidities, especially systemic arterial hypertension, as it is highly prevalent in the general population.^{5,6}

Some authors have proposed the use of ACE inhibitors, a first-line therapy for hypertension, for the management of COVID-19. This recommendation is based on the site of action (angiotensin-converting enzyme receptor) of this pharmaceutical group, which acts on one of the receptors that mediate COVID-19 progression into acute respiratory syndrome (ARDS).⁷

In the mechanisms of SARS/COV2 infection, the role played by serin proteasis expression (TMPRSS2) in humans' cells as main cause of the entrance and replication of SARS/COV2,⁸ and parallel the different cellular expression of ACE2 in humans, and its negative effects on clinical outcomes in humans. The population at higher risk of worse prognosis are the hypertensive patients,⁹ some questions have been trying to answer since COVID 19 started, one about this group of patients; at the first months some authors related the treatment with ACE inhibitors or angiotensin receptor

blockers (ARBs), with greater risk of contracting serious COVID-19 infection, and the diabetics; treated with a correct glycemic control in severe COVID 19 disease, decreased the risk of severe disease and death in this group of patients, and was identified as a strong predictor of outcome. Sardu et al showed not differences in mortality related to chronic antihypertensive therapy.^{10,11} In our opinion, there is no evidence that treatment with antihypertensive drugs is the cause of the worse prognosis of hypertensive patients, but probably the organic involvement of this disease could be the reason. In addition, better glycemic control is related to a better prognosis with other diseases, so it seems logical to think that its control is a factor for a better prognosis in this group of patients.¹²

Patients admitted to the ICU who develop COVID-19-related ARDS exhibit hemodynamic instability and hypertension, either because they previously had this comorbidity or developed it in the ICU as a COVID-19 complication.^{12,13}

What is new and what is known: The viral load has been related with a higher risk for endothelial dysfunction and increased coagulation in patients, this dysfunction and increased coagulation can progress in acute myocardial infarction (AMI).¹³ In patients with COVID-19 infection, AMI increases mortality.¹⁴

The mechanisms proposed are increasing coagulative state and arterial thrombus dimension in coronary circulation., the SARS-CoV-2 has high avidity for the endothelium, coronary bed and myocardium.

Outcomes from critical illness in COVID-19 are going better, decreasing the mortality of patients with COVID-19, thanks to the discovery of new therapeutic options (corticosteroids, avoid mechanical ventilation if it is possible, remdesivir, tocilizumab or the newest Paxlovid), and better evidence-based critical care.^{14,15} Mortality in patients with severe COVID-19 to be approximately 45% (89). Some of the risk factors for mortality are: older age, male sex, obesity, diabetes mellitus, cardiac disease, hypertension, pregnancy, asthma, and sickle cell disease.¹⁶

How to treat hypertension in critical patients with COVID-19 is a subject of intense debate.

Patients may also develop cardiocirculatory instability. This complication may be caused either by COVID-19 itself, by COVID-19 complications, or by a potential co-existing overinfection favored by the immunosuppressive treatments administered for COVID-19. This instability can be exacerbated by the long-term use of anti-hypertensive vasodilators. Arterial vasodilators without effects on the venous system and a short half life emerge as a useful tool for the management of these patients.

Clevidipine is a calcium channel antagonist within the dihydropyridine group, it differs from the rest of the drugs in its group in its pharmacokinetic and pharmacodynamic characteristics. Its fundamental indication is the treatment of high blood pressure when a rapid reduction in blood pressure is needed. Its action is dose dependent, with a rapid effect on blood pressure control (2 minutes). In addition, it does not decrease the end-diastolic pressure of the right ventricle (CVP), nor of the left, and has no effect on cardiac contractility. May increase cardiac output through decreased systemic vascular resistance, which may induce increased heart rate, but less intensely than sodium nitroprusside (SNP).^{17,18}

Firstly, this anti-hypertensive treatment can be rapidly and effectively adjusted to the clinical status of the patient, since it can be withdrawn and its effects reversed in a few minutes.¹⁹

Secondly, arterial vasodilators facilitate normal right ventricular function in patients with elevated pulmonary artery pressure. In these patients, pulmonary circulation is subject to multiple aggressions such as those caused by the disease on the arterial bed and by pulmonary hypertension secondary to respiratory disease.²⁰ Third, arterial vasodilators increase oxygen supply to the heart as a result of coronary artery vasodilatation. Unlike antianginal venodilators (nitroglycerin or nitroprusside), arterial vasodilators do not reduce cardiac output, as they do not decrease venous return. However, the most important potential effects of clevidipine in this subgroup of patients are its anti-inflammatory effects. Hence, clevidipine shows promise as a treatment for COVID-19.²⁰

This disease induces a hyperimmune response that causes severe multiorgan symptoms. Hyperimmune response has been treated with blockers of the interleukins responsible for triggering the pro-inflammatory cascade (ILK 1- ILK 6) that act on other mediators of the complications of hyperimmune response.²¹

The lipids contained in the formula of clevidipine are crucial for the stability of this medication. Indeed, lipids are a key component of the molecules used in the treatment of medication-induced intoxication (local anesthetics).²² Lipids are also essential in the scavenger mechanism of other agents like propofol, a hypnotic that has been suggested to reduce systemic inflammatory response such as that induced by extracorporeal circulation.²³ This effect is enabled by the lipid emulsion that propofol contains.

The beneficial effects of clevidipine in the management of COVID-19 are two-fold. Firstly, there is strong evidence available that clevidipine controls hypertension in hemodynamically unstable patients. Secondly, clevidipine may reduce the inflammatory response induced by SARS-COV2, which causes progression into severe disease. This hypothesis is grounded on the anti-inflammatory activity of propofol, a widely-used medication in anesthesia. This hypnotic acts on the GABAergic receptors of the central nervous system. Propofol provides multiple anti-inflammatory effects in a diversity of surgical procedures, including heart surgery involving extracorporeal circulation and brain surgery. In these settings, propofol does not act directly on the surgical site, but it is its lipid component that exerts anti-inflammatory effects.

Clevidipine is formulated in a highly-concentrated lipid emulsion, as compared to propofol. However, although clevidipine undoubtedly plays a key role as a scavenger molecule and its oil base should exert beneficial effects in pro-inflammatory settings, its use in this context has not yet been explored. However, its activity warrants consideration as the treatment of choice for these conditions. It is worth noting that this agent cannot be used in patients with septic shock or generalized systemic vasodilatation. Thus, the use of clevidipine in patients with systemic arterial hypertension in the inflammatory stage of COVID-19 requires further examination.

In the light that clevidipine is used for the management of hypertension in pro-inflammatory settings, it emerges as a potential first-line treatment for COVID-19. However, further research is necessary to confirm our hypothesis. We are certain that as soon as our hypothesis is confirmed, clevidipine will become the treatment of choice for managing hypertension in COVID-19 patients.

Conclusion

In our opinion, the beneficial effects of clevidipine in the management of COVID-19 are two-fold: firstly, there is strong evidence available that clevidipine controls hypertension in hemodynamically unstable patients;^{24–26} secondly, clevidipine may reduce the inflammatory response induced by SARS-COV2, which is key to progression into severe disease.

Our group is involved in design several ongoing research projects aimed at testing this hypothesis, with encouraging results. We expect that the results of these projects will be published within the following months. Then, several clinical trials will be started to explore the potential beneficial effects of clevidipine described in this paper.

Disclosure

The authors report no conflicts of interest in this work.

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