BRIEF RESEARCH COMMUNICATION

Effect of Aviptadil, a Novel Therapy, on Clinical Outcomes of Patients with Viral-related Severe ARDS: A Retrospective Observational Study

Supriya Sampley[1], Deepak Bhasin[2], Kavita Sekhri[3], Harpal Singh[4], Onkar Gupta[5]

Received on: 28 June 2023; *Accepted on:* 28 October 2023; *Published on:* 31 December 2023

Abstract

Background: Dealing with life-threatening viral acute respiratory distress syndrome (ARDS) has always been challenging and with the recent COVID pandemic experience, there is still the need of newer therapies to alleviate mortality. Aviptadil, has shown significant beneficial results in COVID. We share our experience with this molecule by doing a retrospective study to evaluate the effect of this drug on clinical outcomes in viral-related ARDS patients.

Materials and methods: In this study, all patients with severe viral-related ARDS received Aviptadil along with the conventional treatment. The oxygen saturation, SpO_2/FiO_2 (ratio of pulse oximetric saturation to fractional inspired oxygen) (S/F) ratio and PaO_2/FiO_2 (ratio of arterial oxygen partial pressure to fractional inspired oxygen) (P/F) ratio, before and after completion of the drug were studied. Radiological clearance and time for complete recovery from respiratory failure was noted. All variables pre- and postadministration of the drug were compared.

Results: A total of 68 patients with viral pneumonias were admitted to intensive care unit (ICU) and only 6 patients had severe ARDS, who received Aviptadil. The mean oxygen saturation significantly improved from 87.86% before the first Aviptadil dose to 93.43% post 3 days of infusion. Similarly, improvement was seen in PaO_2 values from 54.32 to 68.4 posttherapy (p-value < 0.004). SpO_2/FiO_2 (ratio of pulse oximetric saturation to fractional inspired oxygen) ratio hiked from 149 to 336 at the end of the 3 days infusion (p-value < 0.003). RALE scoring system was used for radiological clearance and the mean change in the score was from 6.42 to 2.5 (p-value 0.00). The average length of stay in the ICU was 12.14 days. No adverse effects were noted.

Conclusion: Aviptadil has shown to improve the clinical outcomes in patients with severe viral-related ARDS without any adverse effects.

Keywords: Aviptadil, Viral acute respiratory distress syndrome, Viral pneumonia.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24594

Highlights

Respiratory failure is a lethal complication of COVID-19 that has remained resistant to the various drug therapies tried till date. Aviptadil, a synthetic form of vasoactive intestinal peptide (VIP), due to its lung protective actions, has shown encouraging results in COVID acute respiratory distress syndrome (ARDS), as evident by the interim analysis data from the previous studies. This study highlights its clinical role in other viral-related ARDS, and good clinical outcome was noted.

Introduction

Severe ARDS is a potential complication seen among patients with severe community-acquired pneumonia. Globally, ARDS affects more than 3 million people a year and accounts for 10% of intensive care unit admissions.[1]

Mortality associated with ARDS corresponds to the severity of the disease. As per the LUNG SAFE study, the mortality rate increases from 35% for mild cases to 46% for the severe ones.[2]

Respiratory viral pathogens have reigned the world and accounted for almost one third of community acquired pneumonia (CAP). Various viral pandemic or seasonal non-pandemic infections have been implicated in the pathogenesis of ARDS in adults. Since the 2009 H1N1 pandemic, influenza virus infection has emerged out as recurrent causative pathogen for ARDS.

Recently, SARS COVID-19-related ARDS had worst impact on the world by accounting for almost 12% of deaths globally.

[1]Medical Intensive Care Unit, Max Super Speciality Hospital, Mohali, Punjab, India

[2,4,5]Department of Pulmonology and Critical Care, Max Super Speciality Hospital, Mohali, Punjab, India

[3]Department of Pharmacology, Dr. Harvansh Singh Judge Institute of Dental Sciences and Hospital, Punjab University, Chandigarh, India

Corresponding Author: Supriya Sampley, Medical Intensive Care Unit, Max Super Speciality Hospital, Mohali, Punjab, India, Phone: +91 9855595407, e-mail: supriya.icm@gmail.com

How to cite this article: Sampley S, Bhasin D, Sekhri K, Singh H, Gupta O. Effect of Aviptadil, a Novel Therapy, on Clinical Outcomes of Patients with Viral-related Severe ARDS: A Retrospective Observational Study. Indian J Crit Care Med 2024;28(1):70–74.

Source of support: Nil

Conflict of interest: None

Considering the various etiological factors, pathogenic pathways of inflammation in ARDS, efforts are being made to design pharmacotherapies, which directly block the inflammatory mediators and viral replication. Unfortunately, no drug has proven to be a definitive treatment of ARDS. Hence, there is still a need of newer drugs, which can target the cascade of ARDS pathology.

Vasoactive peptide has shown to be protective for viral-induced inflammatory damage to lung. Aviptadil, a synthetic form of VIP,

labeled an orphan drug for treatment of ARDS in USA in 2001,[3] got its approval for emergency use in treatment of ARDS in COVID-19 patients in August 2021.[4] In India, CDSO approved its use for COVID patients in April 2022.[5]

Hence, after understanding the protective role of VIP in ARDS, we conducted an observational retrospective study in patients with severe viral ARDS. The primary objective of our research was to study the clinical outcomes of aviptadil: VIP analogue, in patients with severe viral-related ARDS, in terms of recovery from respiratory failure, improvement in oxygen saturation, and radiological features. The secondary objective was to determine the recovery time from respiratory failure in patients treated with aviptadil.

Materials and Methods

This was an observational retrospective study of patients with viral-related ARDS, who required intensive care unit (ICU) admission in the Medical Intensive care Unit of Max hospital, between December 2022 and May 2023. A formal approval from the Institutional Ethics Committee and review board (ECR/691/INST/PB/2014/RR-21) was sought.

All adult patients (aged ≥18 years), who presented with cough, breathing difficulty, or fever (>38°C) and had a positive polymerase chain reaction (PCR) test for respiratory viral pathogen from a throat swab, were included. Patients, who had severe ARDS, as defined by PaO_2/FiO_2 (ratio of arterial oxygen partial pressure to fractional inspired oxygen) (P/F) ratio less than 100, on admission or within 72 hours of hospital admission, requiring high-flow nasal cannula, noninvasive ventilation or invasive mechanical ventilation, were enrolled. Eligible patients had bilateral lung involvement on chest X-ray or chest computerized tomography images.

Patients with mild to moderate disease, allergic to the drug, pregnant, lactating, and immunocompromised patients were excluded.

Methodology

All patients, who met inclusion criteria, received conventional treatment with IV antibiotics, methylprednisolone, and other supportive medications. Those patients who showed rapid clinical worsening of respiratory parameters were started on inj. aviptadil as per the recommended dosages.

The demographics, medical history, signs and symptoms, laboratory, and radiological data of all patients on admission were extracted from the records. The respiratory parameters, such as mode of respiratory support (invasive mechanical ventilation, noninvasive mechanical ventilation, oxygen mask), fraction of inspired oxygen (FiO_2), arterial partial pressure of oxygen (PaO_2), PaO_2/FiO_2 ratio, SpO_2/FiO_2 (ratio of pulse oximetric saturation to fractional inspired oxygen) (S/F) ratio, prior to administration of drug, and post 3 days of completion of drug, were noted.

Patients were observed till the complete recovery of respiratory failure as evident by getting weaned off from respiratory and oxygen support and length of ICU stay was noted. Radiological severity and clearance was noted, prior and post-administration of the drug, as per the Radiographic Assessment of Lung Edema (RALE) scoring system. Radiographic Assessment of Lung Edema score is a noninvasive measurement to quantify the degree, density and extent parenchymal abnormalities on routine chest radiographs.

Any adverse reaction or side effects of the drug were noted.

Outcomes

The primary outcome of this study was to evaluate the overall recovery of the clinical parameters, prior and post-administration of aviptadil in severe ARDS patients. The treatment effect of the drug on oxygen parameters, saturation, and S/F ratio before and after administration was analyzed. Secondary outcomes were the length of stay and radiological clearance in all patients who received aviptadil.

Statistical Analysis

Clinical data, laboratory variables, and radiology data were abstracted from electronic medical records system used in our hospital (computerized patient record system) and the patient charts during the study time period and entered into Microsoft Excel. Statistical analysis was done using Statistical Package for Social Sciences, version 21.

Mean ± standard deviation and percentages were used as to represent the demographic and continuous variables, respectively. The McNemar's Chi-square test (for categorical data) was used for pre- and postintervention comparisons to study the effectiveness of the intervention. The Wilcoxon signed-rank test was used to compare median values of continuous variables before and after administration of aviptadil. A *p*-value of less than 0.05 was considered significant.

Results

As per the data retrieved, 68 adult patients with bilateral viral pneumonia and a positive throat swab for respiratory virus were admitted to ICU from December 2022 to May 2023. Among these 68 patients, 16 tested positive for influenza B, 15 patients had rhinovirus, and 14 patients had influenza A. Human metapneumovirus was detected in 7, respiratory syncytial virus in 4, SARS CoV-2 in 3, parainfluenza virus in 1, and mixed infections were seen in 8. Majority of these patients had mild disease requiring supportive care and observation in the ICU.

Only six patients had developed severe ARDS requiring respiratory support and were administered aviptadil as per the recommended dosages over a period of 3 days.

The mean age of these patients was around 51.14 ± 19.01 years. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) throat swab identified SARS-CoV-2 in one patient, influenza A in two patients, and influenza B in three patients, by PCR. The median time from symptom onset to diagnosis was 4 (2–7) days.

The mean oxygen saturation noted, at any time between admission and the first aviptadil dose was 87.86% in all patients. The mean time studied from the time of admission with respiratory failure and the first dose of aviptadil dose was ~36 hours. Aviptadil was given as infusion over 3 days as incremental dosages as per the manufacturer's product monograph. All the parameters studied showed a significant improvement post-drug administration.

In post-infusion of aviptadil, mean oxygen saturation levels improved to 93.43% from baseline 87.86%, which was statistically significant (p-value < 0.01)

PaO_2 observed in all the cases showed advancement from baseline mean 54.3 to 68.4 (p-value = 0.004)

A remarkable change in S/F ratio was also seen from 149 to 336 at the end of the 3 days infusion (p-value < 0.003)

The radiological improvement was assessed using RALE scoring system. As per the observation, the score, the mean change in

the score, was from 6.42 to 2.5, which was statistically significant (p-value = 0.00).

The improvement in the inflammatory markers was compared using C-reactive protein (CRP) values which showed decline from 204.9 to 12.1 (p-value = 0.03). All these patients were weaned off from oxygen support early and the average length of stay in the ICU was noted to be around 12.14 days. No adverse effects were noted during the therapy and no mortality was there.

Discussion

The 2019 novel coronavirus (SARS-CoV-2), severe acute respiratory syndrome coronavirus (SARS-CoV, 2003), Middle East respiratory syndrome coronavirus (MERS-CoV, 2012), and influenza viruses [influenza A virus (IAV) and influenza B virus (IBV)] are major pathogens that primarily target the human respiratory system. Seasonal IAV infection has been identified as the most common cause of pneumonia-related deaths in the developed world especially during pandemics. Influenza B virus infections are less common than influenza A, but have significantly targeted the population during inter-pandemic period. Observed mortality rates have been similar for both influenza types.

Since 1889, there have been five IAV pandemics, the severest one was in 1918 and the most recent was in 2009 H1N1, which accounted for high rate of respiratory failure involving young individuals.[6,7] Ortiz JR et al. estimated an overall incidence of influenza-associated acute respiratory failure to be around 2.7 cases per 100,000 person-years. They also recognized IAV as a contributor to around 4% of all hospitalizations for respiratory failure during the influenza season.[8]

In humans, these viral infections can have varying presentation from common flu like illness to severe acute respiratory distress syndrome and respiratory failure.

Pathophysiology of ARDS Influenza and SARS-CoV-2

Understanding the pathophysiology of ARDS related to viral pneumonia, there is a series of cascade leading to alveolar damage beginning from viral invasion, host immune response, and till other phases of ARDS.

Influenza A virus infects the upper and lower respiratory tracts but has its main target on the alveolar lining epithelium which is layered by alveolar type I (AT I) and type II (AT II) cells. Alveolar type I cells line up around 95% of the surface area of lung and facilitate gas exchange, and the rest 5% is covered by AT II cells. These type II cells play major role in production of surfactant, stabilization of airway epithelial barrier, immune defence, and airway regeneration during lung injury, by serving as a progenitor for type I pneumocytes.

The virion surface of IAV expresses two major surface glycoproteins, hemagglutinin (HA), and neuraminidase (NA). Hemagglutinin protein binds to sialic acid residues present on the plasma membrane of type II cells, triggering endocytosis of the virion and NA protein enables the virus to be released from the host cells, which promotes the release or progeny of viruses and hence spread of virus to other infected cells.[9]

Once these alveolar epithelial cells are targeted by the viruses, this leads to the loss of their integrity and impairs surfactant production leading to impaired gas exchange and atelectasis. This breach of epithelial layers exposes the endothelial layer to cytokine and viral antigen, which further amplifies inflammation with endothelial cells. This results in release of proinflammatory cytokines that drives a series of innate and adaptive immune responses.[10] Once the diffuse alveolar damage starts, the pathogenesis progresses to ARDS.

The same pathogenesis applies for SARS COVID infection. The SARS-CoV-2 virus also attacks AT II cells, where it gains entry into these cells by binding its spike or S glycoprotein with angiotensin-converting enzyme 2 (ACE 2) receptor presents on pneumocytes.[11] This attachment accelerates the entry of viral RNA, which induces RNA replication leading to mass production of viruses and finally cell lysis takes place.[12] This attachment of SARS-CoV-2 to ACE 2 receptor also results in damage to the cells of immune system leading to release of specific inflammatory mediators and cytokines. The whole process of invasion, replication, lysis, and release of cytokines result in vasodilation and increased capillary permeability, eventually leading to pulmonary edema and surfactant deficiency and dysfunction. The cascade events ultimately lead to alveolar collapse and impaired gaseous exchange.[8]

The current understanding of the central role that AT II cells and surfactant in pathogenesis of SARS-COV-2 infection as well as influenza, has led to the development of new therapeutic agents: VIP analog: aviptadil.

Understanding VIP and Role in ARDS

Vasoactive intestinal peptide is a proteinaceous peptide hormone, which consists of 28 amino acids and was first isolated by Said and Mutt.[13] This neuropeptide is synthesized and discharged by both immune cells and nerve endings. Hence, it is widely distributed in central and peripheral nervous systems, cardiovascular, respiratory, gastrointestinal, and reproductive systems.

Considering its high expression in lung tissues, VIP has an important respiratory physiological role. It exerts its action in lung via two receptors vasoactive intestinal peptide receptor (VPAC) 1 and VPAC 2. VPAC 1 receptors are primarily located in lung and t cells, while VPAC 2 receptors are found in the smooth muscles, mast cells, and basal part of lung mucosa.[14]

Vasoactive intestinal peptide binds to AT II cells via VPAC 1 receptor,[15] which plays an important role in surfactant production and maintenance of type I cells. By upregulating enzyme choline phosphate cytidylyltransferase, VIP augments surfactant production. Secondly, it inhibits apoptosis by blocking various enzymes and inhibits T-cell proliferation and reduces the production of proinflammatory cytokines by downregulation of receptors.[16] Various other physiological effects of VIP are bronchodilation, positive chronotropic effect, ionotropic, and coronary vasodilatory properties, and increased gut motility.

Considering these properties of VIP, aviptadil was launched, and this molecule received the US Food and Drug Administration (FDA) Fast Track Designation in June 2020 for dealing critical COVID-19 with respiratory failure. Aviptadil, a synthetic form of VIP, also named as RLF-100, is at present under phase II/III clinical trials. This drug has been designated as an orphan drug by FDA and has been used in past to treat respiratory airway diseases, such as asthma, chronic obstructive pulmonary disease (COPD), ARDS, and sarcoidosis.[17] The first reported use of intravenous aviptadil was by Youssef et al., who used this drug to treat double-lung transplant COVID patient with respiratory failure. A dramatic recovery was seen and the patient was discharged in satisfactory condition.[18]

Currently, nine clinical trials are on the list where aviptadil is being tried both intravenously and inhalational in COVID patients, but none in influenza. Hence, after understanding the role of aviptadil in severe ARDS along with the common target at AT II cells,

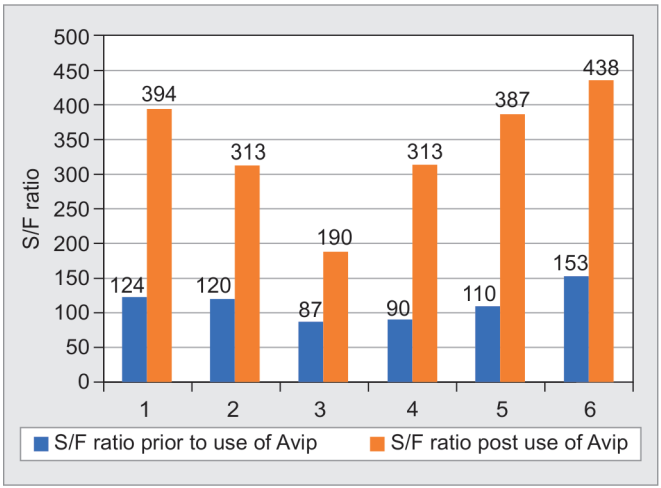

Fig. 1: Comparative values of S/F ratio pre- and post-administration of aviptadil

we used this drug as rescue therapy in six patients who had severe ARDS, not responding to conventional treatment.

Clinical recovery was seen in all the patients after 3 days of infusion of the drug, who showed symptomatic improvement. As per the observation, a significant improvement was seen in the oxygen parameters, SpO_2 and S/F ratio showed a remarkable improvement from 87 to 93% and 149 to 336, respectively, which was statistically significant (Fig. 1).

As per the literature reviewed, till date, aviptadil has shown positive results in COVID-related ARDS, since its fast-track approval. The first documented use of aviptadil was reported by Youssef et al. In Houstan Methodist hospital, in a double-lung transplants COVID-positive patient who showed dramatic improvement in saturation and radiology after third dose of aviptadil.[18]

In another case series of 21 consecutive lab-confirmed patients with SARS-CoV-2, Youssef et al. showed a significant improvement both from the radiological as well as a clinical point of view as compared with standard treatment care.[19]

In a multicenter, placebo-controlled, phase 2b/3 trial, 196 patients with COVID-19 were enrolled and randomized 2:1 to receive 3 days of intravenous aviptadil or placebo. Although the primary end point (alive and free from respiratory failure at day 60) did show any statistical, but still improvement in respiratory distress ratio, reduction in interleukin (IL-6) release, and improvement in survival rate at 60 days were seen by aviptadil.[20]

Only one recent single study by Brown SM et al. has shown negative trial for VIP in COVID-associated acute hypoxemic respiratory failure.[21] They studied long-term survival and found no significant improvement in clinical outcomes up to day 90. But we wish to enforce on the immediate clinical recovery seen in previous clinical trials, which showed noteworthy recovery in respiratory parameters as well as oxygenation with no immediate short-term effect. Similarly, we highlight our results, where patients showed prompt restoration of oxygen parameters and were weaned off from high-flow nasal oxygen (HFNO) support in a short time with an average length of stay was shortened to 12 days and were discharged in stable condition.

Conclusion

After a comprehensive understanding of the pathophysiology of influenza and role of VIP in ARDS, we used aviptadil with standard care, in patients with influenza, with severe ARDS, who showed rapid clinical recovery without any side effects. As per the literature reviewed, till date, aviptadil has not been used in influenza and this research molecule is still under clinical trials; we wish to emphasize more open trials on this drug which can prove a fruitful pharmacological care in treating not only COVID but also in influenza-related ARDS.

Orcid

Supriya Sampley https://orcid.org/0000-0001-6938-1188
Deepak Bhasin https://orcid.org/0000-0003-1526-7018
Kavita Sekhri https://orcid.org/0000-0002-0062-6340
Harpal Singh https://orcid.org/0000-0002-8541-4514
Onkar Gupta https://orcid.org/0009-0003-8864-9380

References

1. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Med 2004;30(1):51–61. DOI: 10.1007/s00134-003-2022-6.
2. Gordon D, Rubenfeld MD, Ellen Caldwell MS, Eve Peabody BA, Jim Weaver RRT, Diane P, et al. Incidence and outcomes of acute lung injury. Engl J Med 2005;353:1685–1693. DOI: 10.1056/NEJMoa050333.
3. Orphan Drug Designations and Approvals: Vasoactive Intestinal Peptide: Acute Respiratory Distress Syndrome, USFDA 2001. Available at: https://www.accessdata.fda.gov/scrpits/opdliting/oopd/listResult.cfm.
4. CEO Update: Nation of Georgia Emergency Use Authorization. Oct 25, 2021. Available on https://www.nrxpharma.com/ceo-update-nation-of-georgia-emergency-use-authoristaion.
5. Recommendations of the SEC meeting to examine COVID -19 related proposal under accelerated approval process made in its 218th meeting held on 05/04/2022 at CDSCO, HQ Ne Delhi. Available at: https://cdsco.gov.in/opencmd/opencms/system/modules/CDSCO.WEB/common_download .jsp?num_id_pk+MTY3NA==.
6. Webster RG, Govorkova E A. Continuing challenges in influenza. Ann N Y Acad Sci 2014;1323:115–139. DOI: 10.1111/nyas.12462.
7. Saunders-Hastings PR, Krewski D. Reviewing the history of pandemic influenza: Understanding patterns of emergence and transmission. Pathogens 2016;5:66. DOI: 10.3390/pathogens5040066.
8. Ortiz JR, Neuzil KM, Rue TC, Zhou H, Shay DK, Cheng PY, et al. Population-based incidence estimates of influenza-associated respiratory failure hospitalizations, 2003 to 2009. Am J Respir Crit Care Med 2013;188(6):710–715. DOI: 10.1164/rccm.201212-2341OC. PMID: 23855650.
9. Chen X, Liu S, Goraya MU, Maarouf M, Huang S, Chen JL. Host immune response to influenza A virus infection. Front Immunol 2018;9:320. DOI: 10.3389/fimmu.2018.00320.
10. Teijaro JR, Walsh KB, Cahalan S, Fremgen DM, Roberts E, Scott F, et al. Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. Cell 2011;146(6):980–991. DOI: 10.1016/j.cell.2011.08.015.
11. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell 2020;181(4):894–904. DOI: 10.1016/j.cell.2020.03.045. e9.
12. Tsatsakis A, Calina D, Falzone L, Petrakis D, Mitrut R, Siokas V, et al. SARS-CoV-2 pathophysiology and its clinical implications: An integrative overview of the pharmacotherapeutic management of COVID-19. Food Chem Toxicol 2020;146:111769. DOI: 10.1016/j.fct.2020.111769.
13. Said SI, Mutt V. Potent peripheral and splanchnic vasodilator peptide from normal gut. Nature 1970;225: 863–864. DOI: 10.1038/225863a0.
14. Voice JK, Grinninger C, Kong Y, Bangale Y, Paul S, Goetzl EJ. Roles of vasoactive intestinal peptide (VIP) in the expression of different immune phenotypes by wild-type mice and T cell targeted type

II VIP receptor transgenic mice. J Immunol 2003;170:308–314. DOI: 10.4049/jimmunol.170.1.308.
15. Gonzalez-Rey E, Delgado M. Vasoactive intestinal peptide and regulatory T-cell induction: A new mechanism and therapeutic potential for immune homeostasis. Trends Mol Med 2007;13:241–251. DOI: 10.1016/j.molmed.2007.04.003.
16. Berisha H, Foda H, Sakakibara H, Trotz M, Pakbaz H, Said SI. Vasoactive intestinal peptide prevents lung injury due to xanthine/xanthine oxidase. Am J Physiol 1990;259:L1515. DOI: 10.1152/ajplung.1990.259.2.L151.
17. Sharma V, Delgado M, Ganea D. Granzyme B, a new player in activation-induced cell death, is downregulated by vasoactive intestinal peptide in Th2 but not Th1 effectors. J Immunol 2006;176:97110. DOI: 10.4049/jimmunol.176.1.97.
18. Youssef JG, Zahiruddin F, Al-Saadi M, Yau S, Goodarzi A, Huang HJ, et al. Brief report: Rapid clinical recovery from critical COVID-19 with respiratory failure in a lung transplant patient treated with intravenous vasoactive intestinal peptide. Crit Care Explor 2022;4(1):e0607. DOI: 10.1097/CCE.0000000000000607.
19. Youssef J, Al-Saadi M, Zahiruddin, Faisal, Beshay, Sarah et al. Rapid recovery from COVID-19 respiratory failure with comorbidity in 21 patients treated with vasoactive intestinal peptide. SSRN Electron J 2020. DOI: 10.2139/ssrn.3679909.
20. Youssef JG, Lavin P, Schoenfeld DA, Lee RA, Lenhardt R, Park DJ, Fernandez JP, et al. The use of IV vasoactive intestinal peptide (aviptadil) in patients with critical COVID-19 respiratory failure: Results of a 60-day randomized controlled trial. Crit Care Med 2022;50(11):1545–1554. DOI: 10.1097/CCM.0000000000005660.
21. Brown SM, Barkauskas CE, Grund B, Sharma S, Phillips AN, Leither L, et al. ACTIV-3b/Therapeutics for severely Ill inpatients with COVID-19 (TESICO) study group. Intravenous aviptadil and remdesivir for treatment of COVID-19-associated hypoxaemic respiratory failure in the USA (TESICO): A randomised, placebo-controlled trial. Lancet Respir Med 2023;11(9):791–803. DOI: 10.1016/S2213-2600(23)00147-9.