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AVIPTADIL IN ACUTE RESPIRATORY DISTRESS SYNDROME ASSOCIATED WITH COVID-19 INFECTION

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ABSTRACT

Aim: This study is aimed at evaluating efficacy and safety of Intravenous Aviptadil as an add-on to the "Standard of Care" treatment in severe COVID-19 patients with respiratory failure. **Design, Setting and Participants:** A randomized, multicentric, double-blind, placebo-controlled, comparative Phase III clinical trial was conducted at 8 geographically distributed sites across India between April 2021 to October 2021. The study enrolled 150 participants who were tested and confirmed cases of severe COVID-19 with respiratory failure and acute respiratory distress syndrome. **Interventions:** 12-hour intravenous infusions of Aviptadil over 3 successive days in ascending doses given as 0.166 mcg/kg/hr on Day 1 (equivalent to one 10 mL vial of 150 mcg), 0.332 mcg/kg/hr on Day 2 (equivalent to two 10 mL vials of 150 mcg each) and 0.498 mcg/kg/hr on Day 3 (equivalent to three 10 mL vials of 150 mcg each). **Methodology:** Severe COVID-19 patients with respiratory failure were randomized in two groups in a ratio of 1:1, to receive either Aviptadil or Placebo. Both the study drugs were given as an add-on to the standard of care (SOC). The SOC was kept as close as possible to the COVID-19 treatment guidelines specified by the Government of India. The study site staff, investigator and patients were masked to the treatment allocation. The primary endpoint of the study was resolution of respiratory failure whereas the secondary endpoints were improvement in WHO 7-point ordinal scale, improvement in PaO_2:FiO_2 ratio, survival of the patients and incidences of adverse events. **Results:** After the completion of treatment in Aviptadil group, an improvement was observed in the primary outcome of resolution of respiratory failure. Proportion of patients on Aviptadil demonstrated statistically significant odds, 2.1-fold, (p=0.0410) of being free of respiratory failure (no oxygen requirement) at Day 3 and 2.6-fold (p=0.0035) at day 7 as compared to the placebo group. An earlier resolution from the respiratory failure, with a median duration of 7 days was noted in the Aviptadil-treated group as compared to 14 days in the placebo group. A higher proportion of patients on Aviptadil shifted to the milder clinical state (32.43% vs 17.80%; p=0.0410 on Day 3 and 70.27% vs 45.21%; 0.0035 on Day 7) without the requirement of oxygen than the placebo group. A reduction of severity (based on WHO 7-point ordinal scale) in clinical status were also observed on Day 14 (p = 0.0005 by Wilcoxon rank sum test) and Day 28 (p = 0.0009 by Wilcoxon rank sum test). There were 68.42% Aviptadil-treated patients who showed 2 or more points improvement on the WHO 7-point ordinal scale as compared to 44.59% in the placebo group (p=0.003; Pearson chi^2 test; odds ratio, 2.69; 95% CI, 1.38-5.24) on Day 7. On day 28, patients in the Aviptadil group had higher odds (1.38) of an improvement on WHO 7-point ordinal scale as compared to placebo with SOC. Aviptadil reduced the risk of death by 20% (relative risk 0.80; 95% CI: 0.35, 1.66) in ARDS. Patients treated with Aviptadil demonstrated significant improvement in PaO_2/FiO_2 ratio vs. placebo from day 2 to over the week ($p<0.05$) and beyond. There were 15 deaths in the Aviptadil group and 18 deaths in the placebo group. No deaths were attributed to the Investigational products. COVID-19–related mortality occurred in 22% patients of the study population, due to respiratory failure caused by underlying medical conditions. **Conclusion:** Use of Aviptadil was safe and effective in improving the resolution of respiratory failure, shortening the time to recovery, decreasing respiratory distress and preventing death in respiratory failure patients. The rapidity and magnitude of clinical effect suggests a highly specific role of Aviptadil in combating the lethal effects of Acute Respiratory Distress Syndrome associated with COVID-19.

KEYWORDS: COVID-19, Vasoactive Intestinal Peptide (VIP), Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), Alveolar Type II.

1. INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a devastating clinical syndrome of acute respiratory failure that presents with progressive arterial hypoxemia, dyspnea, and a marked increase in the work of breathing with a need for mechanical ventilation.[1] ARDS is the rapid onset of progressive malfunction of the lungs, that quickly evolves into respiratory failure. The condition is associated with extensive lung inflammation and accumulation of fluid in the alveoli (air sacs) that affects the lung's gas exchange capability.[2] ARDS is a manifestation of acute injury to the lung, associated with sepsis, pneumonia, severe pulmonary infections, aspiration of gastric contents, and major trauma.[3,4]

ARDS has been widely recognized as a major clinical problem worldwide. Globally, ARDS affects approximately 3 million patients annually, accounting for 10% of intensive care unit (ICU) admissions, and 24% of patients receiving mechanical ventilation in the ICU[5] with an estimated mortality rate of approximately 40-60% depending on disease severity.[6,7] The incidence of ARDS in patients with risk factors is 30% in India with the mortality of 41.8%.[8]

In the setting of lung injury, neutrophils accumulate in the lung microvasculature, get activated and migrate in large numbers across the vascular endothelial and alveolar epithelial surfaces, releasing several toxic mediators, including proteases, cytokines, and reactive oxygen species which result in increased vascular permeability and a sustained loss of normal endothelial barrier function.[1,9] This migration and mediator release lead to pathologic vascular permeability gaps, in the alveolar epithelial barrier and necrosis of type I and II alveolar cells. Type I alveolar cells are irreversibly damaged and the denuded space is replaced by the deposition of proteins, fibrin, and cellular debris, producing hyaline membranes, while injury to the surfactant-producing alveolar type II (ATII) cells contributes to alveolar collapse. In the proliferative phase, ATII cells proliferate with some epithelial cell regeneration, fibroblastic reaction, and remodeling. In some patients, this progresses to an irreversible fibrotic phase involving collagen deposition in alveolar, vascular, and interstitial beds with the development of microcysts.[4]

Vasoactive Intestinal Peptide (VIP) is a gut peptide hormone, containing 28-residue amino acid peptides. VIP is highly localized in the lungs (70%) and binds with ATII cells via VIP receptor type-1 (VPAC1).[10] Its action is mediated through VPAC1 and VIP receptor type-2 (VPAC2), which are activated by Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) belongs to the glucagon-secretin superfamily.[11] VIP was awarded Orphan Drug Designation in 2001 by USFDA for treatment of Acute Respiratory Distress Syndrome.[12] Aviptadil, a synthetic form of human VIP was awarded Orphan Drug Designation for treatment of Pulmonary Arterial Hypertension (in 2005 by USFDA), Acute Lung Injury (in 2006 by EMA) and Sarcoidosis (in 2007 by EMA and in 2020 by USFDA).[13-16]

Aviptadil acts as a potent anti-cytokine in the lung that provides a key defense against numerous forms of acute lung injury. Aviptadil blocks apoptosis, caspase-3 activation in the lung, inhibits inflammatory cytokines like IL6 and TNF-alpha production and reverses CD4/CD8 ratio. Aviptadil increases surfactant production by up-regulation of choline phosphate cytidylyltransferase, which increases the incorporation of methyl choline into phosphatidylcholine[17,18], the major component of pulmonary surfactant.[19] Surfactant reduces the alveolar surface tension, thereby preventing alveolar collapse and allows for breathing with minimal efforts. Furthermore, pulmonary surfactant enhances phagocytes function and maintains immune response in patients with ARDS.[20] Aviptadil prevents the activation of NMDA-induced caspases, inhibits IL-6 and TNF-α production and protects against HCl-induced pulmonary oedema.[21] In a clinical study, Aviptadil reduced the mortality rate to 12.5% during intensive care and 25% at 30 days which is lower than the expected mortality in sepsis-related ARDS.[22]

ARDS is a global threat with significant health and economic burden as it needs intensive medical and pharmaceutical care. Treatment of ARDS is mainly supportive, and it encompasses all measures such as supplemental oxygen, inflammation management (corticosteroids), fluid management, decrease oxygen consumption and increase oxygen delivery.[23] Current managements of ARDS are hampered by the failure to diagnose the condition and to prevent iatrogenic harms such as hospital-acquired infections, ICU acquired weakness, delirium, risk of bleeding and thrombosis, acute kidney injury, hypotension and renal dysfunction.[2]

Severe COVID-19 represents viral pneumonia from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to ARDS. Its manifestations can be viewed as a combination of the two events, namely viral pneumonia and ARDS.[24] The mechanism appears for lung involvement are a combination of both direct viral-mediated injury and host inflammatory response. The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infections. COVID-19 ARDS causes the typical ARDS pathological changes of diffuse alveolar damage in the lung[25,26] but the mortality is increased up to 61.5%.[24] A lethal SARS-CoV-2 infection that specifically attacks the ATII cells which perform an important role during breathing. This highly specific role of Aviptadil in the lung may be the key to combating the lethal effects of SARS-CoV-2 infection.

Considering the benefits and need of therapeutic option for the treatment of ARDS, this study was conducted in India, to evaluate the safety and efficacy of Aviptadil in severe COVID-19 patients with respiratory failure.

2. MATERIAL AND METHODS

2.1 Design and Setting

The study was a multicentric, randomized, double-blind, comparative placebo-controlled, Phase III clinical trial to evaluate the efficacy and safety of intravenous Aviptadil, as an add-on to the 'Standard of Care' (SOC) treatment in severe COVID-19 patients with respiratory failure. After an approval from the Drug Controller General of India, the study was conducted in eight geographically distributed sites across India. The protocol was approved by the institutional ethics committee at each study site.

The study was performed in accordance with International Council for Harmonization for Good Clinical Practice, Declaration of Helsinki and New Drugs and Clinical Trials, Rules, 2019, The study was registered with the Clinical Trial Registry of India (CTRI/2021/04/033118).

2.2 Participants

Patients admitted in hospital were evaluated as per the study eligibility criteria. Patients aged 18 years or older admitted to hospital with laboratory confirmation of SARS-CoV-2 infection and severe disease condition as per COVID-19 treatment guideline specified by Government of India (severe condition defined as respiratory rate >30 breaths/min or SpO2 <90% on room air or ARDS or septic shock)[27] were considered eligible.

Patients were excluded if the investigator judged that they had any serious medical conditions or irreversible condition (other than COVID-19) with projected fatal course. Patients were also excluded if they were receiving immunosuppressive therapy or having a recent history of myocardial infarction, congestive heart failure. All patients or their legally acceptable representatives provided written informed consent to participate in the study. The details of the disposition of patients in the study are given in Figure 1.

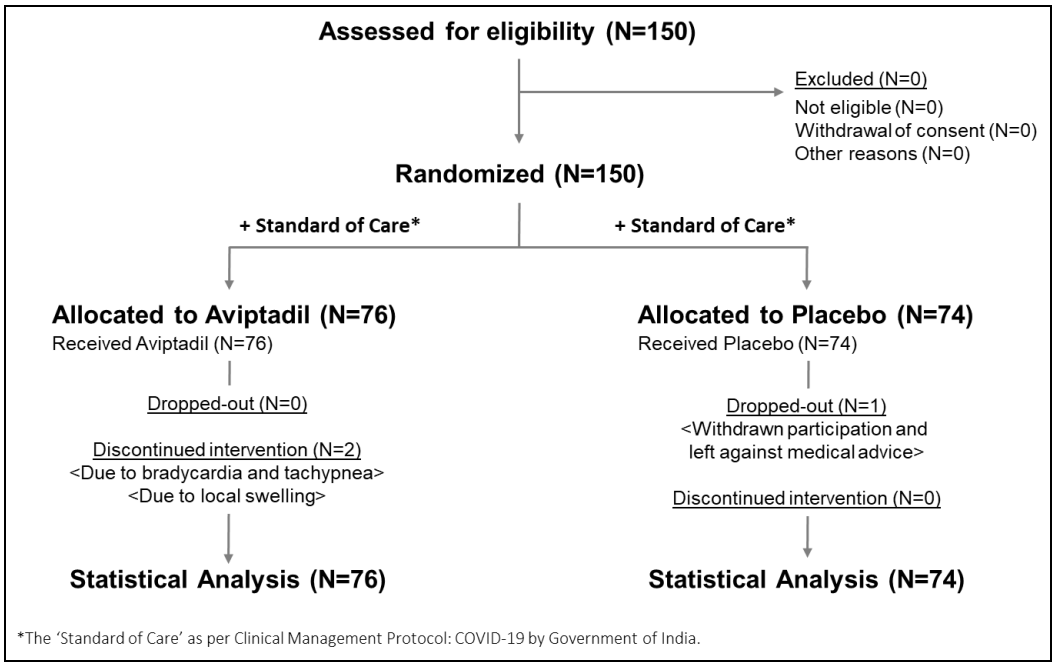


Figure 1: Disposition of patients in the study.

2.3 Randomization and Blinding

Eligible patients were randomly assigned using block randomization in a ratio 1:1 to receive Aviptadil plus SOC (Aviptadil group) or placebo plus SOC (Placebo group). Participants from Aviptadil group received 12-hour intravenous infusions of Aviptadil over 3 successive days in ascending doses given as 0.166 mcg/kg/hr on Day 1 (equivalent to one 10 mL vial of 150 mcg), 0.332 mcg/kg/hr on Day 2 (equivalent to two 10 mL vials of 150 mcg each) and 0.498 mcg/kg/hr on Day 3 (equivalent to three 10 mL vials of 150 mcg each). Since it was a double-blind study, the assigned treatment arm was not known to the site staff, investigator and the patients.

The SOC treatment was administered along with investigational products as per the COVID-19 treatment guidelines specified by the Government of India, in both the treatment groups. SOC included, symptomatic treatment, adequate hydration, oxygen support, conservative fluid management, anticoagulation, corticosteroids, anti-viral, control of co-morbid condition and regular monitoring for breathing, hemodynamic stability and oxygen requirement. The SOC was kept as

close to the Government treatment protocol as possible in all the study sites.

2.4 Outcome Measures

The clinical status of patients was assessed using the World Health Organization's (WHO) 7-point ordinal scale recommended by the WHO R&D Blueprint Group.[28] Clinical status score on WHO 7-point ordinal scale were defined as follows: '0': No clinical or virological evidence of infection; '1': No limitation of activities; '2': Limitation of activities '3': Hospitalized, no oxygen therapy; '4': Oxygen by mask or nasal prongs, '5': Non-invasive ventilation or high flow oxygen, '6': Intubation and mechanical ventilation; '7': Ventilation + additional organ support- pressors, receiving renal replacement therapy, extracorporeal membrane oxygenation; '8': Death.

The primary efficacy outcome of the study was resolution of respiratory failure up to day 28. Resolution of respiratory failure was defined as clinical status ≤3 (No Oxygen Requirement) on the WHO 7-point ordinal scale. The secondary outcomes were two or more points improvement in WHO 7-point ordinal scale, survival of the patients, improvement in PaO_2:FiO_2 ratio and incidences of adverse events (AEs). The outcomes were assessed up to Day 28 and patients were followed for survival status at Day 60. Safety was assessed by the number of patients reporting incidences of AEs.

2.5 Statistical Analysis

A sample size of 150 patients in the study was estimated to provide 80% power, with a 5% level of significance, to establish a difference between the Aviptadil group and the Placebo group. The mortality with $PaO_2/FiO_2 \leq 100$ mmHg were reported in 56% of severe COVID-19 patients with the SOC.[29] We assumed add-on treatment of Aviptadil to the 'SOC' would reduce the mortality rate by 30% in COVID-19 patients. Based on the above assumptions, the sample size required per group was found to be 62. Considering a drop-out rate of 20%, 75 patients were randomized in each group.

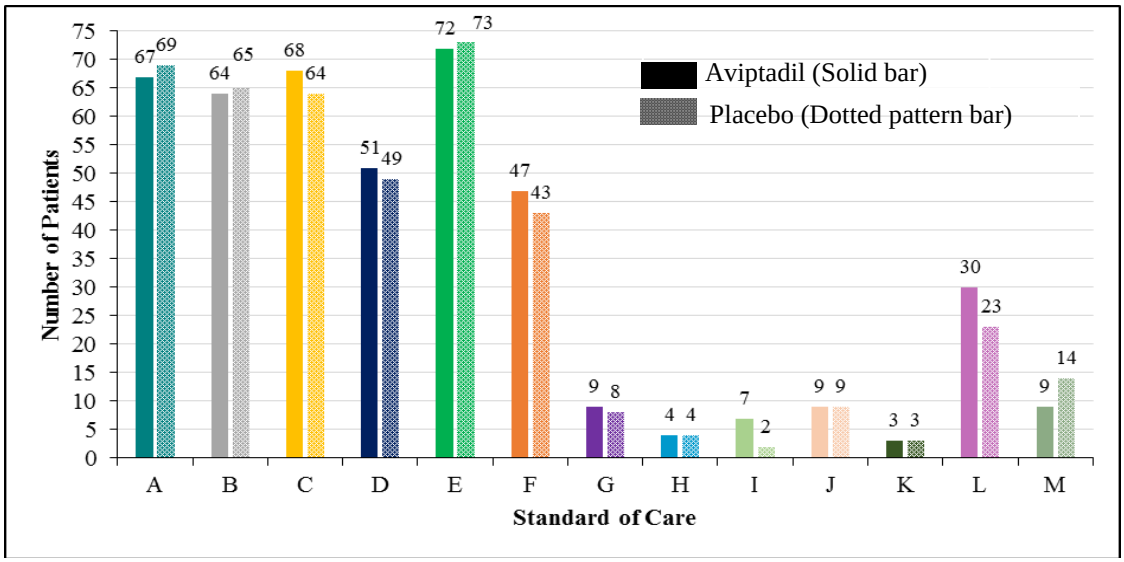
Descriptive statistics was used to summarize baseline characteristics; data was represented in terms of number of observations (n), mean ± standard deviation (SD) for continuous variables whereas frequency counts and percentages were established for categorical variables. Baseline and demographic characteristics of two treatment groups were assessed using unpaired Student's t-test or Pearson-chi^2 test.

The primary endpoint was assessed as the proportion of patients who progressed on WHO 7-point ordinal scale and significance tested using Pearson-chi^2 test. Improvement on WHO 7-point ordinal scale and PaO_2/FiO_2 ratio of two treatment groups was assessed using unpaired Student's t-test and Pearson-chi^2 test. Time to resolution from respiratory failure and survival probability were calculated on Kaplan Meier Survival method. All analysis results were presented with a significance level at 0.05 and 95% confidence intervals. Safety was summarized descriptively, and AEs and serious adverse events (SAEs) were assessed as the frequency and proportion of patients reporting the event.

3. RESULTS

3.1 Study Population

During the period of April 2021- October 2021, 150 patients were enrolled and randomised, 76 were assigned to "Aviptadil + SOC" and 74 to "Placebo + SOC". Assigned SOC is presented in Figure 2.



***Keywords**: A: Antibiotics; B: LMWH and Other Anticoagulants; C: Steroids; D: Antivirals; E: Multivitamins multiminerals; F: Anti-inflammatory/ Anti-allergic drugs; G: Mucolytic/Bronchodilator/Expectorant/Decongestant; H: Antifungal; I: Antihelmentics; J: Management of Hypertension, Diabetes; K: Pulmonary Fibrotic Agents; L: Others; M: Nebulization*

Figure 2: Standard of Care in both the groups.

The mean age of population was 49.9 (range 25-86) years out of which 95 (63.3%) were males and 55 (36.7%) females. Most patients (139/150 [93%]) were on high flow oxygen or on ventilation support and a few patients (11/150 [7%]) were on supplemental oxygen at baseline. The oxygen saturation (SpO_2) was below 82% at room air and respiratory rate of >34 breaths per min in both the groups at baseline. The co-morbidities included diabetes (18.66%) and hypertension (19.33%). Baseline demographics and clinical characteristics were balanced between the two study groups and are presented in Table 1 and 2 respectively. The percentage of patients receiving antiviral treatment was similar in both the groups (Aviptadil 51 [67.11%] and the placebo group 49 [66.22%]).

Table 1: Baseline demographics.

	Aviptadil Group (N = 76) n (%)	**Placebo Group (N = 74) n (%)**
Age		
18-40 years	28 (36.84)	26 (35.14)
41-60 years	28 (36.84)	29 (39.19)
≥61 years	20 (26.32)	19 (25.67)
Sex		
Male	53 (69.74)	42 (56.76)
Female	23 (30.26)	32 (43.24)
Respiratory Rate		
27-29 breaths/min	53 (69.74)	42 (56.76)
>30 breaths/min	23 (30.26)	32 (43.24)
Respiratory support		
Supplemental oxygen	7 (9.21)	4 (5.41)
NIV or high flow oxygen	51 (67.11)	55 (74.32)
Mechanical ventilation	18 (23.68)	15 (20.27)
Coexisting conditions		
Diabetes	15 (19.74)	13 (17.57)
Hypertension	11 (14.47)	18 (24.32)
Atrial Fibrillation	1 (1.32)	0
Acute Kidney Injury	1 (1.32)	0
Anemia	1 (1.32)	0
Hyperthyroidism	1 (1.32)	0
Bronchial asthma	0	1 (1.35)
COPD	1 (1.32)	0
Ischemic Heart Disease	1 (1.32)	0
Obesity (BMI ≥30.0 Kg/m^2)	10 (13.16)	14 (18.92)
Benign prostatic hyperplasia (BPH), Transurethral resection of the prostate (TURP)	1 (1.32)	0
Mucormycosis	1 (1.32)	0
At least 1 coexisting condition	25 (32.89)	23 (31.08)
>1 coexisting conditions	6 (7.89)	10 (13.51)

Table 2: Baseline clinical characteristics.

	Aviptadil Group Mean (±SD)	Placebo Group Mean (±SD)	p value*
N	76	74	-
Age, years	49.03 (± 15.28)	50.82 (± 14.62)	0.4628
Height, cm	162.07 (± 8.59)	160.55 (± 8.38)	0.2774
Weight, Kg	67.84 (± 9.00)	69.45 (± 10.24)	0.3060
Body mass index, Kg/m^2	25.95 (± 3.90)	27.06 (± 4.38)	0.1052
Pulse Rate, beats/min	87.04 (± 17.80)	84.43 (± 20.22)	0.4030
Blood Pressure			
SBP, mmHg	127.88 (± 14.24)	129.85 (± 15.14)	0.4129
DBP, mmHg	79.62 (± 12.09)	78.03 (± 14.24)	0.4614
SpO2 (%)	81.51 (± 7.97)	80.72 (± 10.31)	0.5967
Respiratory Rate, bpm	34.53 (± 5.48)	35.10 (± 6.94)	0.5689
PaO2/FiO2, mmHg	84.53 (± 29.79)	82.12 (± 22.68)	0.5796

* Unpaired t-test.

3.2 Efficacy Assessment

Primary Outcome

A higher proportion of Patients in Aviptadil group attained a WHO 7-point score of ≤3 (no need of oxygen supplementation) as compared to those in placebo group (Table 3). Aviptadil group demonstrated 2.1-fold odds (p=0.0410) of being free from respiratory failure (no oxygen requirement) at Day 3 and 2.6-fold (p=0.0035) at day 7 as compared to the placebo group.

Patients at the highest risk of death (those on mechanical ventilators) at the time of enrollment, demonstrated 4-fold increased odds of being free of respiratory failure in the Aviptadil group. An earlier resolution from the respiratory failure with a median duration of 7-days was seen in the Aviptadil-treated patients as compared to 14 days in the placebo group.

Table 3: Number of patients with resolution of respiratory failure.

	Aviptadil Group (N = 74) n (%)	Placebo Group (N = 73) n (%)	p value*
Day 1	0	0	-
Day 2	10 (13.51)	6 (8.22)	0.303
Day 3	24 (32.43)	13 (17.80)	0.0410
Day 7	52 (70.27)	33 (45.21)	0.0035
Day 14	59 (79.73)	46 (63.01)	0.0406
Day 28	59 (79.72)	53 (72.60)	0.310

* Pearson chi^2 test

Almost twice the percentage of patients shifted from severe state to mild state after 3-days of Aviptadil infusion, 33% (no oxygen requirement) as compared to 18% of the placebo group.

Secondary Outcomes

Improvement on a WHO 7-point ordinal scale was assessed in terms of patients' clinical status improvement (defined as reduction of 2 or more points), representing a clinically meaningful improvement. On Day 7, Aviptadil group had 1.5 times more patients showing 2 or more points improvement as compared to the placebo group viz. 68.42% versus 44.59% (p=0.003). (see Table 4)

Table 4: Number of patients with ≥2-point improvement on WHO 7-point Ordinal Scale.

Study Day	Aviptadil Group (N = 74) n (%)	Placebo Group (N = 73) n (%)	p value*	Odds Ratio (95% CI)
Day 3	19 (25.00)	14 (18.92)	0.369	1.43 (0.66-3.12)
Day 7	52 (68.42)	33 (44.59)	0.003	2.69 (1.38-5.24)
Day 14	59 (77.63)	46 (62.16)	0.039	2.11 (1.03-4.32)
Day 28	59 (77.63)	53 (71.62)	0.397	1.38 (0.66-2.88)

* Pearson chi^2 test

On day 3, the higher and statistically significant (p=0.0410) proportion of patients on Aviptadil (32.43% vs 17.80%) shifted to the milder clinical state without the requirement of oxygen than the placebo group. A major clinical shift is seen between severe and mild disease condition on day 7 where 70.27% vs 45.21% (p=0.0035) patients attained milder clinical state in the Aviptadil group vs placebo group (p = 0.0072 by Wilcoxon rank sum test). The difference between the groups was also observed on Day 14 (p = 0.0005 by Wilcoxon rank sum test) and Day 28 (p = 0.0009 by Wilcoxon rank sum test).

The improvement in clinical status score on WHO 7-point ordinal scale was significantly (p<0.05) better in the Aviptadil group than the placebo group. The mean value for clinical status on WHO 7-point ordinal scale at day 28 was 2.18 in the Aviptadil group and 3.23 in the placebo group (between-group difference, 1.01; 95% CI, 0.0686 to 1.9592; p = 0.0357). The results are presented in Table 5.

Table 5: Mean difference of WHO 7-point ordinal score.

Study Day	Aviptadil Group Mean (±SD)	Placebo Group Mean (±SD)	Mean Difference (95% CI)	p value
Day 1	5.17 (± 0.6194)	5.20 (± 0.6188)	-0.0433 (-0.2459 to 0.1593)	0.6732
Day 3	4.28 (±1.6262)	4.62 (± 1.5867)	0.2893 -0.2067 to 0.7853	0.2508
Day 7	3.46 (± 2.1783)	4.26 (± 1.9932)	0.7575 (0.1092 to 1.4058)	0.0223
Day 14	2.65 (± 2.5719)	3.66 (± 2.5068)	0.9656 (0.1685 to 1.7626)	0.0179
Day 28	2.18 (± 2.9948)	3.23 (± 2.9464)	1.0139 (0.0686 to 1.9592)	0.0357

*Unpaired t-test

The death rate was 19.74% in the Aviptadil group versus 24.32% in the placebo group, a relative risk reduction of 20% (relative risk 0.80; 95% CI: 0.35, 1.66). Aviptadil-treated patients survived 1.1-fold more at day 60 as compared to placebo.

PaO2/FiO2 ratio is the ratio of arterial oxygen partial pressure to fractional inspired oxygen and low value is associated with increase in hospital stay in patients admitted to the intensive care unit and mortality. PaO2/FiO2 ratio measures oxygenation status of critically ill patients and severity of lung injury. PaO_2/FiO_2 of less than 100 is considered as very serious and between 100-150 is considered as serious.[30] Both treatment groups had a baseline PaO_2/FiO_2 ratio of 80 and with the treatment of Aviptadil the ratio improved to above 100 within 3 days and remained above 150 after the 6th day, whereas the ratio was below 100 in the placebo treated patients. Patients treated with Aviptadil significantly improved the PaO_2/FiO_2 ratio at day 2 and over the week as compared to placebo group (p<0.05). After end of the study treatment (3 days' infusion), 41% patients in the Aviptadil-treated group increased PaO_2/FiO_2 by more than 50 mmHg as compared to placebo group (15%). The point to be noted here that, 18% patients showed increase in PaO_2/FiO_2 ratio by 100 mmHg in Aviptadil-treated group. Patients in the Aviptadil group had a mark improvement in PaO2/FiO2 ratio, as compared to placebo group. The net increase in PaO_2/FiO_2 ratio were considered to substantial increase for beneficial effect of Aviptadil treatment compared with placebo. (Figure 3)

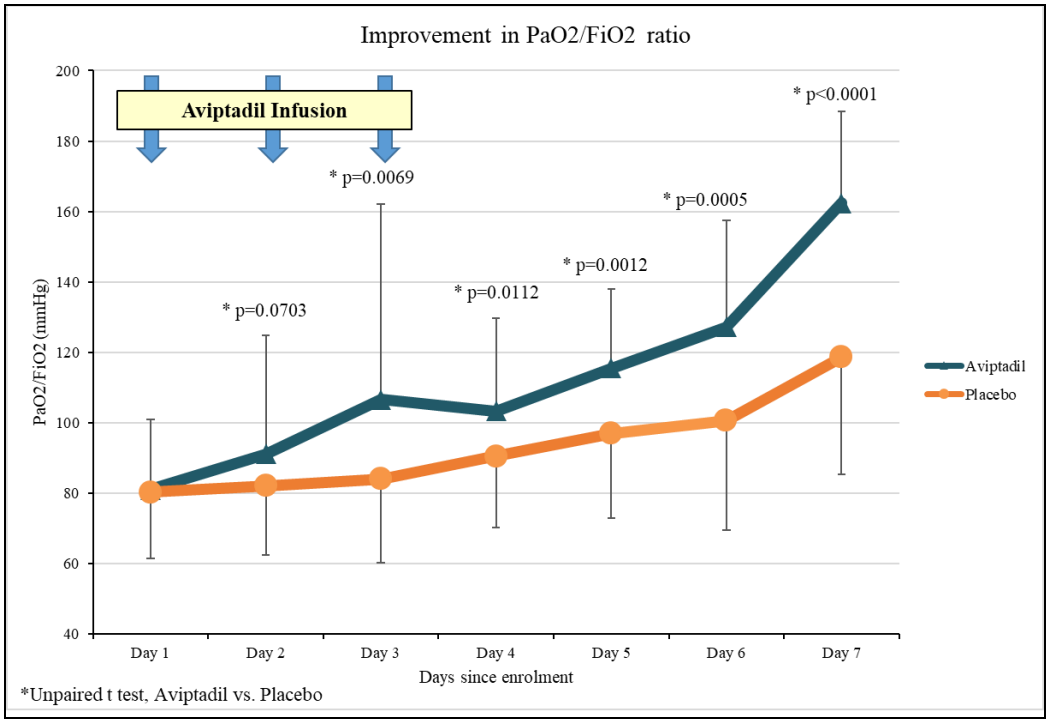


Figure 3: Improvement in PaO_2/FiO_2 ratio.

3.2 Safety Assessment

Safety was evaluated based on the incidences of AEs and SAEs reported during the study. There were 11 AEs and 33 SAEs reported during the study. In the Aviptadil group, 7 AEs (severe bronchospasm, tachypnea, tachycardia, swelling and redness, dizziness, irregular heart rate, chills and headache) were reported in 6 patients, whereas 4 AEs were reported in 4 patients in the placebo group (nausea, headache, rashes and excessive sweating). The causality assessment revealed that the AEs may or may not be associated with the investigational drugs as all the patients were receiving SOC along with. All adverse events were of mild to moderate in severity and resolved without any sequelae. Aviptadil treatment was well tolerated and the safety was found to be comparable to the Placebo.

A total of 33 Serious Adverse Events (SAEs) were reported in the study including 15 (deaths) in the Aviptadil group and 18 (deaths) in the Placebo group. Respiratory failure was the primary cause of death in COVID-19. The reported SAEs (death due to COVID pneumonitis, acute respiratory distress syndrome, respiratory failure, septic shock, cardiac arrest, presence of comorbidities) were not related to the investigational products.

4. DISCUSSION

In this randomized trial, hospitalized severe COVID-19 patients were given infusion of Aviptadil and placebo for 12-hour duration for 3 consecutive days. After completion of Aviptadil treatment, improvement was observed in the resolution of respiratory failure. A nearly two-time resolution of respiratory failure was observed in Aviptadil treated patients as compared to the placebo group. Thereby the study achieved its primary end point. An earlier resolution from the respiratory failure, with a median duration of 7 days was noted in the Aviptadil-treated group as compared to the placebo group (median duration of 14 days). Patients on Aviptadil group demonstrated a statistically significant proportion with 2.1-fold odds of being free of respiratory failure (no oxygen requirement) at Day 3 and increase to 2.6-fold at day 7 as compared to the placebo group.

A substantially higher proportion (Approx 78%) of patients from Aviptadil group achieved clinically meaningful improvement on the WHO 7-point ordinal scale at Day 28. A notable difference was observed on completion of consecutive 3-days Aviptadil infusion wherein 33% of the patients from Aviptadil group shifted from severe state to mild state (no oxygen requirement) as compared to 18% of the placebo group. In this clinical study of patients with severe COVID-19 pneumonia, those who were randomized to 3-day Aviptadil treatment had significantly higher odds of having a better clinical status distribution on day 7 than those receiving placebo with SOC. The difference in the distribution of clinical status on day 14 and 28 between the Aviptadil and placebo group was significant. A major shift from severe to mild condition was observed in Aviptadil group, and patients didn't require any oxygen. This observation is in line with the observations seen in recently published study where major shift from higher to lower severity of the disease condition was observed.[31]

Adult ARDS patient usually exhibit the surfactant change of amount and function. In the early stage of ARDS, surfactant deficiency and dysfunction leads to loss in alveolar epithelium which results in poor gas

exchanges and leads to lung injury.[32] Aviptadil binds to VPAC1 receptors present in ATII cells in the lungs. ATII cells are responsible for oxygen transfer, surfactant production and the formation of alveolar type-1 cell.[33] The worst PaO2/FiO2 ratio within the first 3 days is associated with ICU mortality. In the current study, patients treated with Aviptadil demonstrated significant improvement in oxygenation and reduced the respiratory distress. The 3-day treatment Aviptadil significantly improved PaO2/FiO2 ratio which was sustained over the weeks and beyond.

The high mortality of COVID-19 is not only because of uncontrolled viral replication but is also due to the respiratory failure caused by the accompanying cytokine storm. The severe cytokine storm leads to lung injury and finally causes fatal symptoms such as ARDS in hospitalized COVID-19 patients [34,35] In the Aviptadil group, the incidence of death was lower than that in the placebo group. This study data revealed improvement in survival status upto 60 days (survived 1.1-fold) and reduction in the risk of death by 20% with Aviptadil treatment. Additionally, the mortality rate of 27.77% patients who required mechanical ventilation in this study is also markedly lower than earlier published literatures with critically ill patients with COVID-19.[36,37,38]

The increased resistance to airflow across the lungs increases in patients with ARDS and remains unaltered which contributes to the workload of breathing.[39] VIP is a widely distributed neuropeptide, acting as a neurotransmitter that influences many aspects of pulmonary biology. VIP potently relaxes pulmonary vessels.[40] Intravenous VIP at the rate of 6 pmol/kg/min for 15 min causes bronchodilation significantly and it protects against histamine-induced bronchoconstriction in asthmatic patients.[41,42]

The short-and long-term efficacy of VIP inhalation (daily 200mcg) was evaluated[43,44] indicating a beneficial effect in primary pulmonary hypertension, sarcoidosis and chronic lung inflammation. VIP acts as a potent systemic vasodilator and increases oxygen saturation and decreases pulmonary artery pressure, pulmonary vascular resistance, dyspnoea, TNF-α production. In the current study an ascending dose of Aviptadil as an intravenous infusion of 150 mcg to 450 mcg per day over a period of three days, has been found to be efficacious in treating respiratory failure and the treatment was well tolerated.

The study was conducted in a limited number of patients and an approval for marketing was obtained from the regulatory agency of India. We recommend a larger post-marketing study to evaluate safety and efficacy study in a diverse population and other non COVID-19 conditions.

5. CONCLUSION

The results of this clinical study shows that Aviptadil treatment results in a faster and higher rate of ARDS resolution, better improvement in PaO_2/FiO_2 ratio and patient survival. Aviptadil treatment was well tolerated and the safety was found to be comparable to the Placebo. The current study reinforced the point that Aviptadil is an effective drug in treating acute respiratory distress syndrome.

The study has some limitations since it was conducted in patients who were receiving maximum SOC (standard of care treatment) along with the investigational drugs, therefore the effect of drug given alone needs to be studied in a larger set of population. Further studies are needed to evaluate the efficacy and safety of Aviptadil in diverse etiology of ARDS along with minimal use of conventional drugs in a larger population.

ETHICAL APPROVAL

The authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Study protocol and related documents were approved by the Institutional Ethics Committee at each hospital study center.

CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

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