Study Design | Vol. 6, No. 4 / Oct-Dec 2020 /p. 37-44/ PPCR Journal

Principles and Practice of Clinical Research
A Global Journal in Clinical Research

PPCR
ISSN: 2378-1890

Advanced Closed-loop Ventilation System versus Manual Mechanical Ventilation in COVID-19 induced ARDS in Intensive Care Unit patients: A Single-Center Randomized Phase II Clinical Trial Protocol

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Received December 31, 2020; accepted February 23, 2021; published March 1, 2021.

Abstract:

Introduction: *COVID-19 complications manifest with a disproportionately high rate of respiratory failure and Acute Respiratory Distress Syndrome (ARDS) overwhelming healthcare systems worldwide. In comparison with lung-protective mechanical ventilation, the mainstay treatment of ARDS ventilatory support, INTELLiVENT-ASV® (I-ASV) has shown higher efficiency with reduced weaning, ventilation times, and improved safety by eliminating human errors while providing automate and individually optimized respiratory support.*

Objective: *This study aims to determine the efficacy and safety of I-ASV compared to conventional mechanical ventilation in the context of COVID-19 ARDS (CARDS).*

Methods: *In this phase II trial protocol we describe a single-center, randomized, superiority, open-label, parallel two-arm (1:1 ratio) and active-controlled trial, comparing conventional mechanical ventilation with Volume Assist Mode (VAC) vs I-ASV, both following the lung-protective protocol in 463 adult patients diagnosed with CARDS requiring ventilation support. The primary outcome will be weaning time. Secondary outcomes will include total ventilation time, ICU time to discharge, extubation failure rate, and adverse events. We propose a competing risk analysis for improved accuracy by accounting for mortality in all time-to-event data analysis. Fisher's exact test will be used to test the difference between trial arms in terms of binary secondary outcomes.*

Discussion: *Given the limitations in conventional mechanical ventilation modes, automated closed-loop devices such as I-ASV could significantly benefit patients with CARDS while increasing resource efficiency thus extended care for the patients in need.*

Keywords: *COVID-19, Acute Respiratory Distress Syndrome, Mechanical Ventilation, INTELLiVENT, Adaptive Support Ventilation*

DOI: http://dx.doi.org/10.21801/ppcrj.2020.64.6

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a highly contagious viral infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). First isolated in 2019, it expanded to a global pandemic and rapidly overwhelmed Intensive Care Units (ICU) worldwide (WHO, 2020). The disease presentation is heterogeneous, ranging from mild flu symptoms to acute respiratory failure with rapid deterioration to

multi-organ failures which requires specialized intensive care (Phua et al., 2020).

Acute Respiratory Distress Syndrome (ARDS) is the main cause of respiratory failure and mortality associated with COVID-19 infection, occurring in 33% of hospitalized patients (Tzotzos et al., 2020). The cornerstone treatment for this acute condition is supportive care with mechanical ventilation using a lung-protective approach outlined by the ARDSnet protocol (Matthay et al., 2020). Evidence suggests that proper ventilation support improves patient outcomes, survival, and reduces ventilator-induced lung injury (VILI) (ARDS Network., 2000). Although effective, it is labor-intensive requiring trained staff, close monitoring, and multiple adjustments to ventilator settings to avoid VILI and provide optimal ventilation (Wysocki & Brunner, 2007). These limitations are further aggravated by the current healthcare emergency situation, where increased demand for ICUs requires monitoring multiple patients, overwhelming staff, and decreasing quality of care.

Innovative ventilation modalities have been developed to overcome previously mentioned shortcomings of conventional mechanical ventilation (Fernandez et al., 2013). Among them, Intellivent-ASV® (I-ASV) is a fully automated closed-loop ventilation setting that adapts to the patient's respiratory mechanics providing optimal individualized ventilatory support. Previous trials with comparable settings have shown shorter weaning times and ICU length of stay, while reducing manual adjustments compared to conventional mechanical ventilation (Bylappa et al., 2020). However, a major meta-analysis warranted the need for further research to determine the efficacy and safety associated with I-ASV given that existing studies lacked internal validity due to heterogeneous ICU populations (Rose et al., 2014). Therefore, high-level evidence is needed through randomized controlled trials to evaluate the applicability of the I-ASV in the context of COVID-19 induced ARDS (CARDS).

Considering the potential benefits of I-ASV, given the current healthcare crisis, we propose a clinical trial that compares conventional mechanical ventilation and I-ASV with a primary outcome of weaning time in compliance with the ARDSnet protocol.

METHODS

Trial Design

This is a phase II, superiority, randomized, open-label, controlled, parallel-group intervention, a single-center study comparing adaptive support ventilation (I-ASV) with conventional mechanical ventilation (volume assist control [VAC] mode) in ICU patients with CARDS.

Study Setting

The study will be conducted in a single-center academic hospital in the city of São Paulo, Brazil. This location provides optimal conditions for the trial due to the high incidence of COVID-19 patients as well as the large hospitalization and ICU capacities (Marcillo et al., 2020). This ensures the appropriate infrastructure and recruitment of subjects.

Eligibility Criteria

Eligible patients consist of individuals from 18 to 75 years of age, with symptomatic COVID-19 (Diagnosed with either a positive RT-PCR nasopharyngeal swab or positive IgM titers from lateral flow assay IgM or serologic ELISA) and ARDS defined according to the Berlin Guidelines (ARDS definition Task Force., 2012) which include:

(i) acute hypoxemic respiratory failure with the exclusion of cardiogenic edema and other causes;

(ii) presentation within 1 week of worsening respiratory symptoms;

(iii) bilateral airspace disease on chest x-ray, computed tomography (CT);

(iv) impairment of oxygenation must be present and classified by the arterial partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio in Mild PaO2/FiO2 ratio >200 mmHg, but ≤300; Moderate PaO2/FiO2 ratio between 100-200; Severe PaO2/FiO2 ratio <100).

In addition, patients have to be admitted to ICU with intubation criteria outlined as oxygen saturation (SpO2) < 92% or unstable work of breathing on high flow nasal cannula at 12 liters per minute or Venturi mask at FiO2 60% and an APACHE II score of 24 points or less calculated at ICU admission.

Excluded patients are those with comorbidities that might affect the ventilation parameters or confound ARDS diagnosis that include: cardiac (heart failure, valvular disease, ischemic heart disease), lung (COPD, asthma, restrictive lung disease, bronchopleural fistula), neuromuscular disorders (stroke, muscle dystrophy, amyotrophic lateral sclerosis) or any disease which can affect the capacity of triggering spontaneous breaths, and current pregnancy.

Interventions

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The ventilatory support will be provided by the HAMILTON-S1 ventilator (Hamilton Medical).

Patients assigned to the intervention group will be ventilated with I-ASV whose principles have been described elsewhere (Arnal et al., 2012). Initially, the physician will set the patient's height and gender, the ventilation and oxygenation controllers (Minute Ventilation [MV], Positive End Expiratory Pressure [PEEP], and FiO2) in automated mode and select ARDS as the lung condition. The lung condition will default target ranges of end-tidal CO2 (ETCO2) and SpO2. Throughout the ventilatory support, these parameters and the alarm limits will be reassessed by the physician twice daily during the morning and evening rounds (Arnal et al., 2013).

In the control group, patients will be ventilated with VAC mode using a low tidal volume (VT) strategy. Patients will receive a VT of 4-8 mL/kg predicted body weight (PBW), starting with 6 mL/kg and a PEEP according to the PEEP-FiO2 table from the ARDS Network (Browner et al., 2004), using a minimum of 5 cm of water. Ventilation settings will aim for a plateau pressure (PPLAT) of no more than 30 cm of water. The PBW will be calculated using the formula from the ARDS Network (ARDS Network., 2000).

Prone ventilation will be considered in patients with PaO2/FiO2 ≤ 150 mmHg, PEEP ≥ 5 cm of water, and FiO2 ≥ 60% unless there is a contraindication that prevents it (e.g., spinal cord injury, open chest, and unstable airway) (Guérin et al., 2013). This therapy will be performed for at least 16 hours per day in both groups following the Brigham and Women's Hospital protocol ("Brigham and Women's Hospital - COVID-19 Protocols", 2020).

Sedation protocol

A light sedation strategy will be used according to the Brigham and Women's Hospital protocol ("Brigham and Women's Hospital - COVID-19 Protocols", 2020) for COVID-19 management. Patients will receive a continuous infusion of propofol, and fentanyl titrated to a target score of 0 to -1 on the Richmond Agitation-Sedation Scale (RASS).

If patient-ventilator desynchrony persists despite ventilator adjustments, the sedation will be increased until synchrony achievement. For this purpose, the protocol will allow the use of midazolam, fentanyl, or propofol. For patients who remain desynchronous despite deep sedation (RASS score of -4 to -5), a neuromuscular blockade (atracurium or rocuronium) can be used in single doses to improve the standard of care.

Weaning protocol

Patients will be assessed daily for readiness to be weaned from the ventilator. In the intervention group, when patients have a stable respiratory disease and pass a spontaneous awakening trial (SAT), the quick wean function will be activated to screen for readiness to wean criteria. When criteria are met for 30 consecutive minutes, the system will provide an automatic spontaneous breathing trial (SBT).

In the control group, the weaning process will be performed following the European Respiratory Society Weaning Task Force recommendations (Boles et al., 2007) and the Brigham and Women's Hospital protocol for COVID-19 management ("Brigham and Women's Hospital - COVID-19 Protocols", 2020).

Patients who pass the SBT will be reassessed and extubated if the following criteria are met: spontaneous breathing, RASS 0 to -1, able to follow commands, intact cough and able to protect the airway, and requiring airway suctioning for secretion < q2h.

Discontinuation

Patients will receive the assigned study intervention until successful extubation or 30 days from randomization. The intervention will be discontinued in the following circumstances: withdrawal of consent by the patient or his/her next of kin, need for rescue therapies due to refractory hypoxemia (e.g., extracorporeal membrane oxygenation [ECMO]), technical issues related to the ventilation device, short duration of mechanical ventilation (<12 hours) or discretion of the physician due to safety concerns.

Additional specific circumstances for patient safety will be considered to deactivate the automated controllers and discontinue treatment: PPLAT reporting an increase above 35 cm of water; VT/PBW above 10 mL/kg, respiratory rate (RR) above 35 breath/min for more than 30 seconds and/or severe respiratory acidosis with a pH below 7.20 (Arnal et al., 2013).

Outcomes

The primary outcome will be the length of weaning time, defined as the time from the first SBT to successful extubation with no further need for ventilation after 48 hours of being extubated in the ICU. Secondary outcomes include: 1) total ventilation time defined as the time from intubation to successful extubation in

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days; 2) extubation failure rate defined as the need for reintubation within 48 hours after endotracheal tube removal; 3) mortality rate analyzed by arm-specific mortality and overall mortality rate based on the number of deaths events and the number of initially enrolled patients per arm and entire trial, 4); time to ICU discharge defined as the time from admission to discharge from the ICU; 5) Mechanical ventilation complications defined as the diagnosis of ventilator-associated pneumonia (pneumonia after 48 hours of mechanical ventilation) and/or barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum and/or subcutaneous emphysema); 6) Evolution to tracheostomy defined as the number of subjects requiring tracheostomy on each arm.

Recruitment

The recruitment process will be facilitated by the distinctive qualities of the site selected, such as high incidence of COVID-19 patients and infrastructure. Additionally, we will use targeted strategies that include: physician referrals, consultant mailouts, and trial awareness events. This approach will create awareness within the hospital, thus increasing the chances of enrolling subjects with appropriate characteristics. Once subjects are identified or transferred to the ICU, staff will evaluate eligibility and receive informed consent. Recruitment will be carried until completion of the sample size or a maximum period of 12 months.

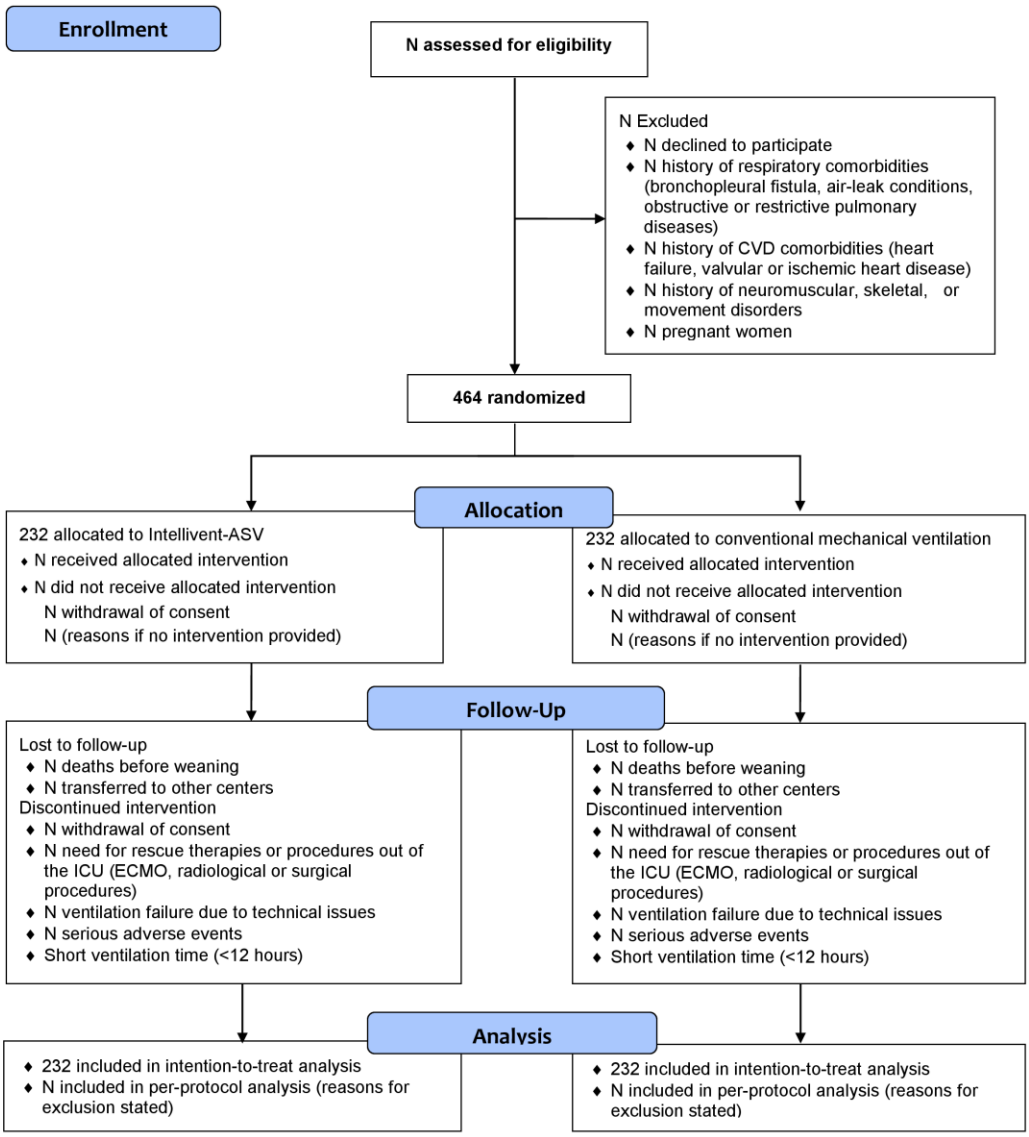

Figure 1. Study flow diagram

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Adherence

Patient adherence strategies will not be established. Subjects enrolled in the study will be in an altered level of consciousness, therefore not affecting the outcomes. On the other hand, adherence strategies will focus on ICU medical professionals involved in the trial as they have to follow complex protocols for accurate results. These protocols will be enforced by previous training, conferences, and poster reminders in the ICU.

Randomization

Patients will be randomized to either a control or experimental group using random blocks of two, four, and six with a 1:1 allocation ratio. A randomization sequence will be created using an internet-based randomization generator software. This sequence will be printed, placed in opaque envelopes, and locked in a cabinet until the inclusion of a patient. To avoid selection bias, randomization and allocation procedures will be performed by trial staff that will not be part of the treatment or assessment of subjects.

Blinding

An open-label approach was selected for this clinical trial, due to the nature of the intervention (mechanical ventilation) and primary outcome. Blinding of ventilators would be difficult to achieve, especially for ICU staff. Therefore, masking will not be feasible due to safety and the handling of ventilator parameters. In the case of adverse events, a rapid response is needed, and blinding might delay this reaction. For these reasons most randomized controlled trials (RCTs) on the field are open-label. Furthermore, the primary outcome evaluated is an objective measurement (a hard endpoint), less prone to be affected by the awareness of staff involved in data collection. However, we will blind statisticians to group allocation.

Data Management & Monitoring

Participant information will be initially collected in paper and electronic forms. Codes will be assigned to each participant file for identification to preserve privacy and confidentiality. Information will be uploaded to an electronic data capture system with a password-protected database. All trial and patient-related documents will be kept in a secure closet with restricted access only by the principal investigator and authorized study staff.

An independent data monitoring committee (DMC) will be established for periodic inspections to ensure the safety of the trial participants by evaluating on a weekly basis and keeping the accuracy of the data. Also, the DMC will be in charge of unmasking treatment allocation to the patient when the circumstance arises for the patient's health benefit. All the collected information will be forwarded to the independent statistician, blinded for the treatment allocation, for data analysis. The trial data will be stored for 10 years after finishing the study.

Statistical Analysis Plan

Primary Analysis will be conducted according to intention-to-treat and per-protocol principles. Baseline demographics and clinical characteristics will be summarized using descriptive statistics for both intervention and control groups for key variables: sex, age, days from COVID-19 symptoms onset, body mass index, and the number of comorbidities.

To estimate a marginal probability of an event (weaning time in this study) more accurately in the presence of competing events (death before weaning) we will use competing risk analysis for the time-to-event outcomes: time to weaning, total ventilation time, and time to ICU discharge. Cumulative incidence functions for each competing event will be calculated using competing risks methodology.

Secondary outcomes of mortality, extubation failure, and mechanical ventilation complications will be dichotomized. A statistical significance of the difference between groups by these variables will be determined by Fisher's exact test. All statistical tests will be 2-sided with an α of 0.05 to be considered for statistical significance. Statistical analyses will be conducted using STATA 13 (StataCorp LLC, College Station, TX, USA) and R software's 3.6.2 version (R Project for statistical computing, Vienna, Austria).

Sample Size

The sample size was calculated using the software R based on formulas for competing for risk analysis (Latouche et al., 2004). A median weaning time of 7 days in the control group and a reduction of 2 days in the intervention group, as well as a standard deviation of 5 days, were assumed with reference to similar studies (Lellouche et al., 2013). A hazard ratio of 1.4 was deduced based on the median survival times ratio (Cortés et al., 2014). We estimated that 60% of subjects will experience the event (weaning) taking into account the mortality rate of 40% according to APACHE II scores (Rowan, Kerr et al., 1993). Administrative censoring has been assumed to be negligible given that the follow-up

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time in this study will be 30 days, thus, a minimal loss in follow-up would be anticipated (Z+5 of the distribution). Given these assumptions stated, a total sample size of 464 will yield a power of 80% to enable us to detect the differences in hazard ratios between the groups considering a type one error rate of no more than 5%. Sample size calculation was conducted using R-function: ssizeEpi.default for the Sample Size Calculation for Cox Proportional Hazards as part of the R-package: powerSurvEpi for the Power and Sample Size Calculation for Survival Analysis of Epidemiological Studies (Qiu et al.,2018).

Ethical

To be included in the trial an informed consent has to be completed. This requires subjects to be evaluated (prior entry to ICU) by staff to determine: decision-making capacity, with a previously approved instrument by the institutional review board; mental status, assessed by Glasgow scale; and eligibility. In case a patient is deemed not decision capable then a surrogate decision-maker will be approached. Once enrolled, withdrawal from the trial can be done at any stage by the surrogate decision-maker as the patient's conscious state will be compromised.

DISCUSSION

We propose a pioneering phase II RCT to evaluate the efficacy of I-ASV in the management of CARDS. Severe cases of COVID-19 are associated with the development of ARDS and a high risk of mortality, which exerts an unprecedented burden on healthcare systems worldwide. Conventional mechanical ventilation, which remains the mainstay treatment, has several limitations owing to its human-involved monitoring and the significant risk of VILI(Wysocki & Brunner, 2020). In this context, it is important to determine whether advanced ventilation modes such as I-ASV would help overcome these limitations and improve health care efficiency.

To date, no study has directly assessed the efficacy and safety of the use of I-ASV in patients with CARDS. Although previous studies have shown that I-ASV is safe in patients with different underlying causes of ARDS (Arnal et al., 2012; Arnal et al., 2013), existing data is limited to heterogeneous populations, and the majority of studies have not been able to assess clinical outcomes with adequate statistical power (Bialais et al., 2016; Arnal et al., 2018). Therefore, it remains unknown whether these automated ventilation modes are more efficacious than conventional mechanical counterparts, and if they should be considered as the first-choice ventilatory support for patients with CARDS.

The expected impact of this RCT includes the reduction of weaning time and expert's involvement in management. Meaning shorter ventilator exposure and risk of complications while improving ICU resource efficiency, to be extended to those in need. In addition, the study design is intended to create a fair comparison by the optimal balance in weaning strategies across study arms. For this purpose, we have established a clear protocol for mechanical ventilation and weaning in both groups. Furthermore, we propose competing risk analysis to improve methodological accuracy in identifying the difference in weaning time and the other time-to-event study outcomes between groups by accounting for mortality among patients before being weaned.

Possible limitations related to restricted generalizability based on our eligibility criteria and single-center design should be noted. Given the open-label design, there is potential performance and observer bias. However, statisticians will be blinded to prevent the introduction of bias in data analysis. In the presence of potentially increased performance bias, we will recruit and train ICU personnel with comparable expertise in the operation of both I-ASV and mechanical ventilation to serve as a blinded assessor on the weaning decision.

CONCLUSION

This protocol provides a framework for the conduct of a phase II RCT that will compare the efficacy and safety of I-ASV with conventional mechanical ventilation. As the COVID-19 pandemic persists, the number of patients in need of timely ICU care increases. Results from this study would provide important insights into CARDS management by improving patient outcomes and optimizing ICUs given the current pandemic situation.

Acknowledgments

We thank Prof. Felipe Fregni, Dr. Alma Sanchez, and all Principles and Practice of Clinical Research Program staff at Harvard T.H. Chan School of Public Health, ECPE for the overall directions and support.

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Conflict of Interest

All listed authors have completed the International Committee or Journal of Medical Journals Editors (ICMJE) form for conflict of interests. There are no personal or financial conflicts of interest disclosed by the authors in relation to this study. Additionally, the authors have read and approved the contents of this manuscript.

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