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Use of an Automated Ventilation Mode in Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial

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Abstract

Aim: Prolonged mechanical ventilation is a clinical condition that leads to higher complication rates and a longer stay in the intensive care unit (ICU). Shortening the duration of mechanical ventilation is one of the main goals of intensive care. In this study, we aim to evaluate a fully closed-loop mode, INTELLiVENT®-ASV® (Intelligent Ventilation - Adaptive Support Ventilation), in ventilating chronic obstructive pulmonary disease (COPD) patients in terms of ventilation duration and workload of clinicians compared with a conventional mode.

Study Design: This is a randomized controlled study performed in a 23-bed medical ICU. COPD patients who were followed up on invasive mechanical ventilation (IMV) were randomized into INTELLiVENT®-ASV® or P-ACV (Pressure-Assisted Controlled Ventilation) groups. Ventilation data were recorded with dedicated software connected to the ventilator. The duration of mechanical ventilation and weaning, the number of manual and automatic settings of the ventilator, and other clinical endpoints were compared between the two groups.

Results: IMV duration was found to be lower in the INTELLiVENT®-ASV® group [1.9 (1.0-3.8) days vs. 3.0 (1.9-5.2) days, p=0.02]. The number of manual changes to ventilator settings and arterial blood gas analyses per day were significantly lower in the INTELLiVENT®-ASV® group than in the P-ACV group [1.2 (0.2-1.7) vs. 6.8 (4.6-8.2), p<0.001, and 1.38 (1.03-2.06) vs. 2.09 (1.58-7.74), p<0.05, respectively].

Conclusions: The use of closed-loop mechanical ventilation may reduce IMV duration and the workload of clinicians and respiratory therapists.

Keywords: Closed-loop ventilation; COPD; Mechanical ventilation; Prolonged mechanical ventilation; Weaning.

Introduction

Prolonged mechanical ventilation (MV) leads to higher complication rates, extended stays in the intensive care unit (ICU), and increased workloads for ICU staff. Previous studies have reported rates of prolonged mechanical ventilation ranging between 6% and 30%.[1–3] Patients in medical ICUs are more susceptible to prolonged mechanical ventilation than those in surgical ICUs, with conditions

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such as chronic obstructive pulmonary disease (COPD) being associated with this prolonged need.[4]

Prolonged mechanical ventilation is linked to increased mortality and morbidity. Additionally, it consumes significant intensive care resources and heightens the workload of ICU staff. Therefore, patients who are mechanically ventilated should be weaned from mechanical ventilation as soon as it is safe to do so. One of the most important steps in the weaning process is evaluating the patient's suitability for weaning. After this evaluation, the work of ventilation gradually shifts from the ventilator to the patient. Unfortunately, incorrect assessments of readiness-to-wean are a common cause of delayed weaning.[5]

Protocolized weaning can reduce the duration of mechanical ventilation and increase the success rate of weaning in both surgical and medical ICUs.[6,7] However, difficulties in preparing and implementing a weaning protocol and low compliance by hospital staff may also diminish the success of protocolized weaning.[8,9] Automated weaning could address these issues, benefitting from advances in ventilator technology.[10]

INTELLiVENT®-ASV® (Intelligent Ventilation - Adaptive Support Ventilation) is a fully automated closed-loop ventilation mode that has been used safely for various conditions in the intensive care unit.[6] Besides optimizing respiratory parameters, INTELLiVENT®-ASV® also provides an automated weaning protocol (Quick Wean). The Quick Wean algorithm progressively reduces pressure support, monitors suitability for weaning, and automatically initiates a spontaneous breathing trial (SBT). Fot et al.[11] reported that patients ventilated with INTELLiVENT®-ASV® using the Quick Wean protocol experienced a shorter duration of mechanical ventilation compared to those undergoing standard weaning methods after cardiac surgery. However, the efficacy of automated weaning in COPD patients, who are at risk of prolonged ventilation, is uncertain.

We aimed to compare automated weaning with INTELLiVENT®-ASV® to protocolized weaning with a conventional mode (Pressure-Assisted Controlled Ventilation, P-ACV) in terms of the duration of mechanical ventilation in COPD patients. The primary endpoint of our study was to measure the duration of mechanical ventilation using the automated weaning protocol versus the duration of the conventional weaning protocol in mechanically ventilated COPD patients. The secondary endpoint was to assess the number of manual interventions required to adjust ventilator settings during mechanical ventilation.

Materials and Methods

This was a randomized controlled study performed in a 23-bed medical ICU. Patients were recruited between August 12, 2015, and June 19, 2018. The study received approval from the Ethics Committee of a training and research hospital (Approval number: 15-2.1/52) and was registered in the Protocol Registry System of ClinicalTrials.gov (registration number: NCT02651935). Written informed consent was obtained from the patients or their next of kin. The study adhered to the principles of the 2013 Helsinki Declaration and followed Good Clinical Practice guidelines.

Patient

Patients intubated due to COPD exacerbation and expected to require mechanical ventilator for longer than 24 hours were included in the study. Exclusion criteria included septic shock, acute respiratory distress syndrome (ARDS), bronchopleural fistula, cardiac arrest with a poor neurological prognosis, short life expectancy, and tracheostomization with or without mechanical ventilation.

Sedation and medical treatment protocols were standardized for both groups. Sedation levels were maintained at a Ramsay sedation score of 2-3 with a continuous infusion of propofol (2-4 mg/kg/h).[12] All patients in both groups received the same medical treatment for COPD exacerbation, which included short-acting β-2 agonists, anticholinergics, systemic corticosteroids, and antibiotics if signs of bacterial infection were present.[13]

In our unit, the morning arterial blood gas (ABG) analysis is almost systematically prescribed by the physician for mechanically ventilated patients. The afternoon/evening ABG analysis is performed as required, that is, if there has been a change in the patient's clinical course or if ventilator settings have been adjusted during the day.

All patients were mechanically ventilated with the same type of ventilator, which was capable of providing both modes (HAMILTON-G5, Hamilton Medical, Bonaduz, Switzerland).

Randomization

Participants were randomized within the first hour after intubation. Computer-generated block randomization

and sealed envelopes were used for allocation concealment. For each patient, the randomization sequence was provided in a sealed envelope to the respiratory therapist and the physician in charge. Patients eligible for the study were randomized to either the automated ventilation group (INTELLiVENT®-ASV®) or the conventional, non-automated ventilation group (P-ACV).

Ventilation Protocols

P-ACV

Pressure control was set to 20 cmH_2O and adjusted to achieve a tidal volume (Vt) of 8 ml/kg (ideal body weight). The respiratory rate (RR) was set to 12-15 breaths per minute and titrated to achieve a pH>7.25. A positive end-expiratory pressure (PEEP) of 5 cmH_2O was applied, and the initial fractional inspired oxygen (FiO_2) was set to 100%, then gradually decreased to maintain an oxygen saturation (SpO_2) of 88-92%. The inspiratory time was set to 0.8-1.3 seconds.

Patients were assessed daily, and the mechanical ventilation mode was switched to pressure-support ventilation (PSV) if the patient was in a stable neurological state (Glasgow Coma Score [GCS]>8), under minimal or no sedation, and exhibited spontaneous breathing efforts. Pressure support (PS) was decreased by 2-4 cm H_2O each time, or at least twice a day, until a level of 15 cm H_2O was tolerated. Pressure support was titrated to achieve a Vt greater than 5 ml/kg and an RR below 35 breaths per minute. Weaning was considered if the following criteria were met for at least one hour: PEEP≤8 cmH_20, FiO_2≤50%, partial pressure of oxygen to fractional inspired oxygen ratio (PaO_2/FiO_2)>150, mean arterial pressure (MAP)≥60 mmHg, no or low-dose vasopressor support, ability to cough and clear airway secretions, minute ventilation less than 10 ml/min, Vt>5 ml/kg, PS<15 mmHg, and RR<35 breaths/min.

Weaning

Patients who met the readiness-to-wean criteria and were deemed ready for extubation underwent an SBT by disconnecting them from the ventilator using a T-piece. Patients who successfully completed the 30-minute SBT were extubated. If the SBT was not tolerated (manifested by impaired consciousness, RR>35/min, pH<7.35, increase in $PaCO_2$>10 mmHg, heart rate above 140/min, systolic blood pressure above 180 mmHg or below 90 mmHg), ventilation was resumed with the previous settings, and the SBT was repeated the next day.

INTELLiVENT®-ASV®

In this group, the patient's gender and height were entered, and the condition of chronic hypercapnia was selected. The target SpO_2 range was set to 88-92%. Instead of using the PEEP controller, PEEP was manually adjusted to 5 cmH20. The target end-tidal carbon dioxide ($EtCO_2$) range was set to achieve a pH>7.25. The maximum pressure (Pmax) was set to 50 cmH20.

Weaning

Patients were assessed daily, and the Quick Wean function was activated when the patient triggered the ventilator with minimal or no sedation (Sedation-Agitation Scale [SAS]=3-4), had a PaO_2/FiO_2 value above 150, was in a stable neurological condition (GCS>8), had a MAP≥60 mmHg, had no or low-dose vasopressor use, and was able to cough and clear airway secretions. An SBT was automatically activated by Quick Wean when all of the following criteria were met: FiO_2≤50%, Vt>5 ml/kg, PS<16 cmH_2O, PEEP≤8 mmHg, patient's respiratory rate ≤ 35 breaths/min, and all breaths were patient-initiated. The SBT was set to last for 30 minutes and was aborted if any of the criteria were not met for three minutes. Patients who successfully completed the SBT were extubated. Those who failed the SBT were ventilated with the previous settings, and the SBT was reactivated once the criteria were met again. The Quick Wean protocol was active during the day (08:00 AM – 06:00 PM).

Preventive non-invasive ventilation (NIV) was initiated immediately after extubation in both groups and performed for at least eight hours a day for the first 48 hours. Patients were reintubated if they exhibited one or more of the following criteria after extubation: deterioration in mental state with an inability to protect the upper airway, hemodynamic instability (tachycardia, arrhythmia, bradycardia, hypotension, or hypertension), upper airway obstruction, excessive pulmonary secretions, signs of increased respiratory work (tachypnea, use of accessory respiratory muscles, thoracoabdominal paradox), diaphoresis, severe respiratory acidosis, or hypoxemia. [14] Reintubation within the first 48 hours after extubation was considered a weaning failure.

Percutaneous dilatational tracheostomy was performed on patients in both groups if they had not been extubated within 10 days. Patients continued to be ventilated using the same modes, following an intention-to-treat principle.

Data Collection

Demographic data were recorded at the beginning of the study. Information regarding weaning and sedatives was recorded daily on each patient's case report form. Respiratory data for both groups were recorded breath-by-breath using a dedicated recording device connected to the ventilator's RS232 port.

Measurements, Definitions, and Outcomes

The primary objective of this study was to compare the total duration of invasive mechanical ventilation between the two modes. Secondary objectives included evaluating weaning success, weaning duration, the number of manual adjustments, the frequency of ABG analysis per patient per day, the number of intubation-free days, and the number of ventilator-free days at day 28.

Statistical Analyses

The normality of continuous data was assessed using the Kolmogorov-Smirnov test. Data are presented as median (interquartile range [IQR]) or number (%), and comparisons were made using the Mann-Whitney U test or Chi-Square test, respectively. Time-to-event analysis was conducted using the Kaplan-Meier method and comparisons were made using the log-rank test.

The study was originally planned as a non-inferiority study with an aim to recruit 122 patients for each group. However, an interim analysis in 2018 led to the decision to terminate the study early due to slow patient recruitment. In our previous study, the average total duration of MV for a conventional ventilation mode was six days, with a standard deviation (SD) of five days.[2] According to this data, a sample size of at least 44 patients in each group was chosen to provide a power of 0.80 to detect a 50% reduction in the mean total duration of ventilation, assuming an SD of five days with a two-sided test at the 0.05 level. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 90 patients were enrolled in the study. A flowchart of the patient distribution is shown in Figure 1. Baseline characteristics and disease severity were comparable between the groups (Table 1).

The duration of invasive mechanical ventilation (IMV) was found to be shorter in the INTELLiVENT®-ASV® group (1.9 days vs. 3.0 days, p=0.02). The total duration of MV and NIV duration were comparable between the groups. The numbers of intubation-free days and ventilator-free days at day 28 did not differ between the two groups. The passive duration was significantly shorter in the INTELLiVENT®-ASV® group. Other comparisons are presented in Table 2.

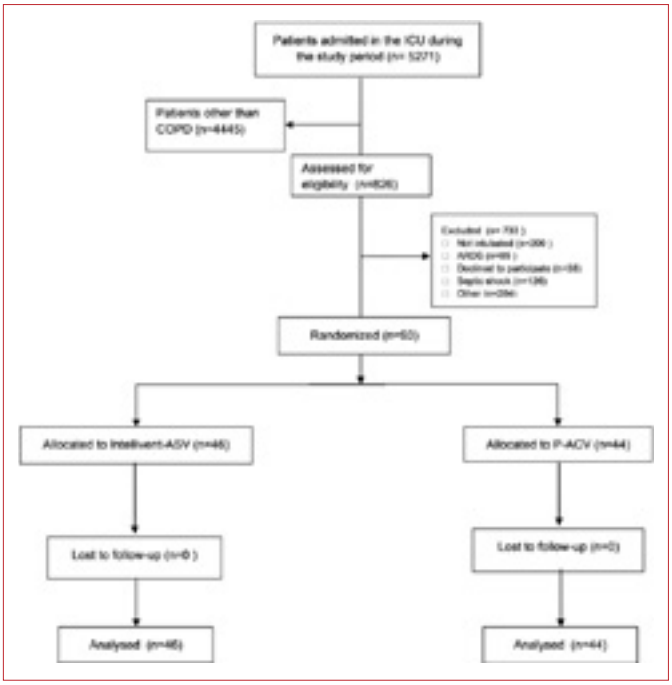

Figure 1. Flowchart of patients throughout the study.
Definition of abbreviations: ICU: intensive care unit, COPD: chronic obstructive pulmonary disease, ARDS: acute respiratory distress syndrome, P-ACV: pressure assist-control ventilation.

Table 1. Demographic and baseline characteristics of the patients at the time of randomization

Variable	INTELLiVENT®-ASV® (n=46)	P-ACV (n=44)
Age, years	70 (62-76)	65 (59-73)
Male gender, n (%)	39 (84.8)	37 (84.1)
SAPS II	40 (33-44)	41 (34-44)
Cause of MV, n (%)		
Hypercapnia + Acidosis	28 (61)	31 (70)
Hypoxemia + Hypercapnia	17 (39)	13 (30)
pH	7.20 (7.17-7.27)	7.20 (7.14-7.24)
$PaCO_2$, mmHg	99 (82-117)	101 (88-115)
PaO_2/FiO_2	150 (112-195)	194 (155-244)
HCO_3, mmHg	29 (27-36)	29 (24-34)

ASV: adaptive support ventilation; P-ACV: pressure assist-control ventilation; SAPS II: simplified acute physiology score; MV: mechanical ventilation. Data are presented as a number (%) or median (IQR).

Table 2. Outcomes of the two groups

Outcome	INTELLiVENT®-ASV® (n=46)	P-ACV (n=44)	p
IMV duration, days	1.9 (1.0-3.8)	3.0 (1.9-5.2)	0.02
NIV duration, hours	30 (14-63)	31 (12-48)	0.64
Total MV duration, days	3.6 (2.5-6.3)	5.1 (3.2-6.7)	0.19
Intubation-free days at day 28	25 (18-27)	24 (21-26)	0.31
Ventilator-free days at day 28	24 (7-26)	23 (18-25)	0.37
Pinsp, cmH_2O	19 (15-21)	19 (17-21)	0.73
Passive duration, hours	1.8 (0.1-17.7)	17.2 (8.7-31.3)	0.02
Passive/total (%)	6 (0-28)	36 (12-41)	
Manual adjustments/day	1.2 (0.2-1.7)	6.8 (4.6-8.2)	<0.001
VT, ml/kg	8.6 (8.1-9.7)	8.1 (6.4-8.4)	0.06
ABG per day	1.38 (1.03-2.06)	2.09 (1.58-7.74)	0.01
ICU LOS, days	6 (4-15)	7 (5-10)	0.37
ICU mortality, (%)	10 (21)	5 (11)	0.26

ABG: arterial blood gas; ASV: adaptive support ventilation; ICU: intensive care unit; IMV: invasive mechanical ventilation; LOS: length of stay; MV: mechanical ventilation; NIV: non-invasive ventilation; P-ACV: pressure assist-control ventilation; Pinsp: inspiratory pressure; TV: total ventilation; VT: tidal volume, Data are presented as a number (%) or median (IQR).

Table 3. Weaning status and weaning duration in the two groups

Weaning parameters	INTELLiVENT®-ASV® (n=46)	P-ACV (n=44)	p
Weaning success, n (%)	40 (86)	37 (84)	0.67
Weaning failure, n (%)	3 (7)	2 (5)	
Non-weaned, n (%)	3 (7)	5 (11)	
Self-extubation	8 (17)	13 (30)	0.22
Re-intubation	9 (20)	5 (11)	0.38
Tracheostomy	8 (17)	6 (14)	0.77
Weaning group			
Simple	35 (88)	20 (54)	0.004
Difficult	4 (10)	16 (43)	
Prolonged	1 (2)	1 (3)	

ASV: adaptive support ventilation; P-ACV: pressure assist-control ventilation. Data are presented as a number (%) or median (IQR).

The number of manual adjustments to ventilator settings and the number of ABG analyses conducted per day were significantly lower in the INTELLiVENT®-ASV® group than in the P-ACV group. There were no differences between the two groups in terms of sedation requirements or inspiratory pressure. However, patients in the INTELLiVENT®-ASV® group had more spontaneous breaths (Table 2).

The number of patients successfully extubated on the first attempt was significantly higher in the INTELLiVENT®-ASV® group (35 vs. 20, p=0.004). Weaning success, self-extubation, re-intubation, tracheostomy rates, and 28-day mortality were comparable between the two groups (Table 3).

Discussion

We discovered that, compared to protocolized weaning using a conventional mode (P-ACV), INTELLiVENT®-ASV® equipped with the Quick Wean protocol enabled a shorter duration of weaning from mechanical ventilation and required fewer manual interventions. INTELLiVENT®-ASV® appears to encourage patients to be more actively engaged in triggering the ventilator, resulting in a higher number of spontaneous breaths in the study group. We did not observe an increased re-intubation rate in the study group.

Fully automated modes are able to manage a majority of patients in both surgical and medical ICUs.[6,15,16] Katayama et al.[7] found that 135 of 189 ICU patients were successfully ventilated with INTELLiVENT®-ASV®, demonstrating a 94% success rate in post-elective surgery patients. However, this rate decreased to 55% in patients admitted to the ICU for medical reasons other than surgery. Fot et al.[11] reported that the weaning duration for INTELLiVENT®-ASV® using the Quick Wean protocol was comparable to that of protocolized weaning in post-cardiac surgery patients, but it was shorter when compared to standard weaning. Managing mechanical ventilation is difficult in patients predisposed to chronic respiratory failure, such as COPD, who are more likely to experience prolonged mechanical ventilation.[4] In our study, INTELLiVENT®-ASV® with the Quick Wean protocol facilitated a quicker weaning from IMV compared to protocolized weaning with a conventional mode in COPD patients. INTELLiVENT®-ASV® aims to maintain patients within optimal respiratory parameters while promoting spontaneous breathing. Arnal et al.[17] observed that INTELLiVENT®-ASV® may lead to a longer duration of spontaneous ventilation compared to conventional modes. In a study involving 265 patients, those in the INTELLiVENT®-ASV® group exhibited more spontaneous breaths than those in the conventional ventilation group (volume control, PSV, and biphasic positive airway pressure).[18] The progressive decrease in pressure support by INTELLiVENT®-ASV®, tailored to the patient's needs, may be the reason patients engage

in spontaneous breathing for longer periods compared to those on conventional modes. INTELLiVENT®-ASV® enables patients to remain active for longer periods, which is believed to be the primary reason for faster weaning.

We also observed a higher number of patients undergoing simple weaning in the INTELLiVENT®-ASV® group compared to the conventional group. T-piece and pressure support SBTs have a similar success rate in terms of successful weaning.[19] Pressure support SBT was associated with decreased work of breathing compared to T-piece.[20] Although the two SBT methods achieved similar weaning success, weaning with a T-piece may have resulted in fewer instances of simple weaning among patients in the conventional group.

The most important innovation that INTELLiVENT®-ASV® introduces to intensive care practice is the reduction of dependency on the clinician for managing mechanical ventilation. Studies have shown that INTELLiVENT®-ASV® requires fewer manual adjustments to ventilator settings compared to conventional modes in both surgical and medical ICU patients. Lellouche et al.[15] reported that only five manual interventions were needed with INTELLiVENT®-ASV® to maintain patients within the safe ventilation zone, whereas 148 manual interventions were necessary in a conventional mode to achieve the same safety level in post-cardiac surgery patients. Arnal et al.[17] found that INTELLiVENT®-ASV® required 50% fewer manual interventions compared to a conventional mode in medical ICU patients. In our study, the frequency of manual adjustments to the settings per day was lower in the INTELLiVENT®-ASV® group, aligning with the findings of these studies. Thus, utilizing a closed-loop ventilation mode may reduce the workload on medical staff, especially considering that parameters such as FiO_2, PEEP, and pressure-support require careful attention and frequent reassessment throughout the day. As the number of skilled clinicians or respiratory therapists capable of managing ventilator settings is still below the desired level in most countries, the use of automated, fully closed-loop ventilation systems represents a potential solution that may reduce the workload of the ICU team.

This study has several potential limitations. Firstly, the primary endpoint was changed because not enough patients could be recruited to test the original primary end-point. Secondly, the study was conducted on a homogeneous patient population, necessitating further clarification of this mode's effects on other patient groups. Thirdly, the use of a T-piece for SBTs in the conventional group may have caused the more favorable outcomes observed with INTELLiVENT®-ASV®. Lastly, this study was conducted at a single center with considerable experience in closed-loop ventilation, so these results cannot be generalized to other centers.

Conclusion

In this randomized controlled study, INTELLiVENT®-ASV® demonstrated some advantages over conventional ventilation modes in the treatment of intubated COPD patients. The implementation of closed-loop mechanical ventilation may serve as a strategy to alleviate the workload on clinicians and respiratory therapists without increasing the duration of mechanical ventilation.

Ethics Committee Approval: This study was approved by Ege University Faculty of Medicine Clinical Research Ethics Committee (Date: 02/03/2015, Number: 15-2.1/52).

Informed Consent: Written consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contribution: Concept: C.K., I.N.G.; Design: C.K., I.N.G., B.A.C., S.Y.; Supervision: C.K.; Materials: C.K., T.Y., H.O.; Data Collection and/or Processing: T.Y., H.O., B.A.Ç., I.N.G.; Analysis and/or Interpretation: C.K.; Literature Search: B.C.C., H.O., T.Y.; Writing: B.A.C., C.K., S.Y.; Critical Review: C.K.

Conflict of Interest: The authors declare they have no conflict of interest relevant to this article.

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