Effect of non-invasive mechanical ventilation with average volume assured pressure support (AVAPS) in patients with chronic obstructive pulmonary disease with acute exacerbation: A randomized pilot trial

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Abstract

Objectives: *The primary goal of this study was to compare patient satisfaction between bi-level positive airway pressure-spontaneous/timed with average volume assured pressure support (BiPAP S/T with AVAPS) and BiPAP S/T alone in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) using self-reported intensity of dyspnea measured with the modified Borg scale (MBS) and a numeric rating scale (NRS) and comfort level measured with a dyspnea and comfort scale.*

Methods: *This pilot randomized clinical study was conducted in patients who presented with acute respiratory distress due to AECOPD to the Siriraj Hospital Emergency Department. Included patients were randomized in a 1:1 ratio to receive either BiPAP S/T with AVAPS (intervention) or BiPAP S/T (control). MBS, NRS, dyspnea and comfort scale, clinical information, and laboratory results were recorded and analyzed.*

Results: *Twenty-two patients were enrolled (11 in each group). The average decrease in the MBS, the NRS, and the dyspnea and comfort scale were higher in the group than the control group (4.09 ± 1.81 vs. 2.91 ± 1.64; 4.09 ± 1.76 vs. 2.91 ± 1.92; 3.27 ± 2.45 vs. 3.00 ± 1.90, respectively). The average increase of patient satisfaction with overall comfort was higher in the AVAPS group (1.64 ± 2.77 vs. 1.09 ± 3.02). However, none of these differences reached statistical significance.*

Conclusion: *There was no statistically significant improvement in patient comfort using AVAPS as an adjunct to standard BiPAP S/T therapy in this pilot study.*

Keyword: chronic obstructive pulmonary disease, exacerbation, NIV, AVAPS, emergency department

Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) is increasing worldwide due to tobacco usage.[1] Patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) commonly present to emergency departments (ED) and often require hospital admissions. These patients may develop acute respiratory failure and require intubation and mechanical ventilation. However, these procedures are associated with high morbidity and possible difficulty in weaning these patients from ventilators.[2–4] Furthermore, complications can result in local tissue damage, nosocomial infections, and prolonged stays in intensive care.[5,6]

The standard treatment for patients with COPD exacerbations who come to the ED include conventional oxygen therapy via nasal cannula or face-mask and pharmacologic therapy, such as inhaled

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bronchodilators and systemic corticosteroids. In addition, AECOPD patients with increased work of breathing or impaired gas exchange require consideration for non-invasive mechanical ventilation (NIV), according to the Global Initiative for Chronic Obstructive Lung Disease guidelines 2019 (GOLD 2019).[7] Non-invasive mechanical ventilation is a standard treatment for patients admitted to the hospital with respiratory failure secondary to AECOPD.[3,7] Over the last decade NIV has been increasingly used as an adjunct treatment in the management of acute exacerbations of COPD, and its use is supported by a number of case series and randomized controlled trials.[8–14] However, NIV is not successful in all cases of patients with COPD. Standard bi-level NIV with fixed-level pressure support (PS) delivery may not maintain adequate ventilation. Automatic titrating hybrid ventilatory modes that target a pre-set volume by adjustment of PS may be more effective. Average volume assured pressure support (AVAPS) is one such mode.

A previous study demonstrated that BiPAP S/T with AVAPS facilitates a more rapid recovery of consciousness when compared to traditional BiPAP S/T in patients with COPD and hypercapnic encephalopathy[15] and has long-term benefits in patients with chronic respiratory failure.[16–18] However, its role in the palliation of dyspnea and improvement in comfort in patients with AECOPD and its success rate compared to conventional BiPAP S/T have not been well established.

Our study was designed to compare patient satisfaction using BiPAP S/T with AVAPS vs. BiPAP S/T without AVAPS in patients with AECOPD. Patients were studied upon immediate arrival in the ED by measuring the intensity of dyspnea using the modified Borg scale (MBS)[19,20] and a numeric rating scale (NRS),[21,22] by measuring comfort level with a dyspnea and comfort scale,[23] and by measuring patient satisfaction based on an overall comfort scale.

Methods

Between March 2018 and September 2018, adult patients who presented to an emergency room with acute exacerbations of chronic obstructive pulmonary disease were prospectively recruited and randomized in the Siriraj hospital emergency department, Mahidol University (a large hospital center in the Bangkok metropolitan area). The study protocol was approved by the ethics committee of Siriraj Hospital, and patients or their relatives gave informed consent. We used a sample size of 11 for each group for this pilot study based on our ethics committee recommendation.

Patients enrolled in the study had known chronic obstructive pulmonary disease (on the basis of the clinical history, physical examination, and chest film) with acute exacerbations based on the current GOLD guideline. Additional criteria for enrollment included age greater than 18 years old with at least of one of the following criteria: persistent hypoxemia despite supplemental oxygen therapy (pulse oximetry less than 90%), signs of respiratory muscle fatigue or increased work of breathing, accessory muscle use, respiratory rate greater than or equal to 24 breaths/minute, or an arterial blood gas with acute respiratory acidosis ($PaCO_2$ greater than or equal to 45 mmHg and arterial pH less than or equal to 7.35). The criteria for exclusion included facial deformities, a non-cooperative patient, alterations in mental status, a co-diagnosis of following diseases (upper airway obstruction; pneumothorax; pulmonary embolism; hemoptysis), shock state, or the need for immediate intubation.

Treatment group allocation and data collection

Patients who met the trial inclusion criteria and who were not excluded on the basis of trial exclusion criteria were allocated on 1:1 basis by computer-generated allocation numbering using random sequence of 4-sized blocks and using sealed opaque envelopes to BiPAP S/T with AVAPS or BiPAP S/T without AVAPS. Both groups received the standard therapy as determined by the attending physician, including corticosteroids, nebulized bronchodilators, and antibiotic therapy. After the recruitment, consent, and randomization, patients were started on either BiPAP S/T with AVAPS or BiPAP S/T without AVAPS for a minimum period of 60 minutes. The time from

ED arrival to randomized treatment initiation was within 60 minutes.

Our data collection variables included dyspnea and comfort scales (MBS, NRS, dyspnea and comfort scale, and patient satisfaction based on an overall comfort level)[19–23] recorded at baseline and at 60 minutes after commencing treatment. Data collection variables also included physiological variables (heart rate, non-invasive blood pressure and mean arterial pressure, respiratory rate, oxygen saturation, and arterial blood gas results) recorded at baseline and at 60 minutes. Additional information, including patient demographics data, Glasgow Coma Scale (GCS), duration of mechanical ventilation, rate of NIV failure, hospital length of stay, and adverse events related to the use of NIV were also recorded.

BiPAP S/T with AVAPS

Ventilatory parameters were initially programmed in the BiPAP S/T mode with AVAPS. Initial ventilator settings were: inspiratory positive airway pressure (IPAP) maximum of 26 cmH_2O, IPAP minimum of 12 cmH_2O, and an expiratory positive airway pressure (EPAP) of 6 cmH_2O. The initial target tidal volume was 8–12 ml/kg of IBW; after the patient reached clinical stability, the target tidal volume was changed to 6–8 ml/kg/. This decision was made by the physician in charge of patient care. Other parameters included a respiratory rate 15 breaths/min, rise time set at 300–400 ms, an inspiratory time at a minimum of 0.6 s, and supplemental O_2 by an adapter circuit close to the facemask to maintain SaO_2 (oxygen saturation) above 90%. Patients were maintained on BiPAP S/T with AVAPS for 60 minutes.

Maximum IPAP delivered, exhaled tidal volume (EVT), minute ventilation (Vmin), and leaks were monitored through the ventilator software. The equipment used was BiPAP Synchrony with AVAPS (Respironics trilogy 202 ventilator, Philips).

BiPAP S/T without AVAPS

Ventilatory parameters were initially programmed in BiPAP S/T mode. IPAP was programmed at 12 cmH_2O, and EPAP was programmed at 6 cmH_2O. The respiratory rate was set at 15 breaths/min, rise time set at 300–400 ms, and inspiratory time set at a minimum of 0.6 s. IPAP was measured in increments of 2 cmH_2O according to the discretion of the attending physician. Supplemented O_2 was added through an adapter circuit close to the facemask to maintain SaO_2 above 90%. Patients were maintained on BiPAP S/T for 60 minutes.

Maximum IPAP delivered, Vmin, and leaks were monitored through the ventilator software. The equipment used was the same equipment as for the AVAPS group.

Discontinuation of NIV and intubation

Treatment with NIV was continued based on patient tolerance. The weaning process was initiated when clinical stability was achieved, defined by a respiratory rate less than or equal to 24 breaths/minute, a heart rate of less than or equal to 90 beats/minute, improved awareness, a “normalized” pH values, and an adequate SaO_2 on a low percentage of inspired O_2 (3 liters per minute). After the patient remained stable, NIV was discontinued.

To make the decision whether to perform endotracheal intubation, we used criteria based on the clinical experience of the participating physicians and on reported data.[24] The major criteria for intubation included cardiopulmonary arrest, respiratory pauses with loss of consciousness, worsening psychomotor agitation, worsening mental status, and hemodynamic instability.

Statistical analysis

All outcomes were assessed by intention-to-treat analysis. Demographics and baseline characteristics of all randomized patients were summarized by treatment arms.

The primary outcome variable was the change in the patient’s dyspnea level determined by the modified Borg scale (MBS),[19,20] numeric rating scale (NRS),[21,22] and a comfort level measured by a dyspnea and comfort scale.[23] Patient satisfaction was

based on an overall comfort level. Secondary end points were the change in physiologic parameters, the length of the hospital stay, and complications from NIV.

The effect of the NIV support intervention in individuals was analyzed by using a paired T test for each parameter. The outcomes in the two groups were compared using 2-sample t-tests. Differences in group means are reported with associated p-value and 95% confidence intervals. For categorical data, chi-square tests were used to analyze the data. All statistical tests were two-sided at a 5% significance level. For interim analysis, O'Brien-Fleming method was used to analyze the data. The IBM SPSS statistics 21 statistical software package was used.

Results

Between March to September 2019, 22 patients were randomly assigned to the study; 11 in the control group (BiPAP S/T) and 11 in the study group (BiPAP S/T with AVAPS) (see Figure 1 for enrollment process). All the patients enrolled to the study were diagnosed with COPD with acute exacerbations without pneumonia and used a Respironics full facemask (Comfort gel) during the study period.

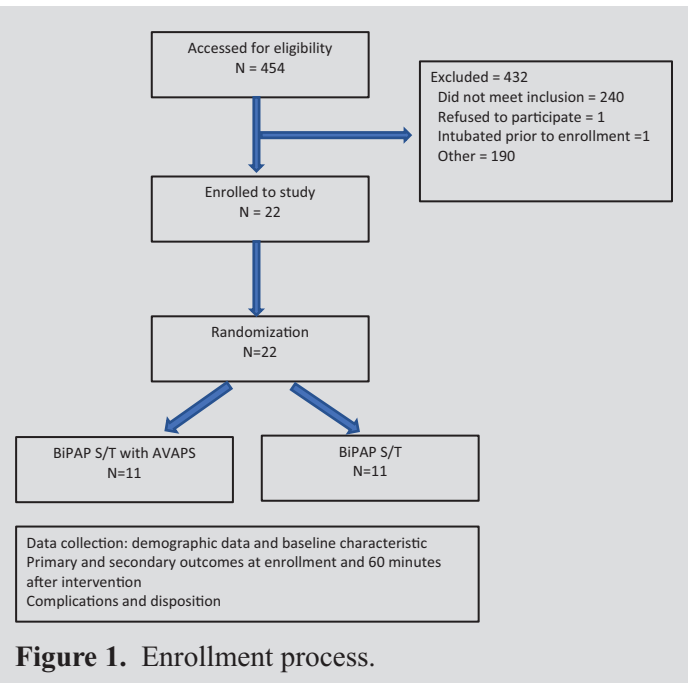

Figure 1. Enrollment process.

The majority of the patients were male (10 [90.9%] in each group). The median (interquartile range [IQR]) age of the patients was 77 (64, 84) years in BiPAP S/T group and 69 (49, 77) years in BiPAP S/T with AVAPS group. The two groups had similar characteristics, including underlying medical problems, initial vital signs, and arterial blood gas parameters, on presentation at emergency department (ED) (Table 1). There were no differences in medications administered to the two groups, including antibiotics, corticosteroids, and bronchodilators.

Clinical outcomes

Dyspnea scores improved with both modes of respiratory support in both study groups based on paired t tests (Table 2). The average decreases in MBS, NRS, and dyspnea and comfort were greater in the BiPAP S/T with AVAPS group than the BiPAP S/T group (4.09±1.81 vs. 2.91±1.64, *p*-value=0.125; 4.09±1.76 vs. 2.91±1.92, *p*-value=0.148; 3.27±2.45 vs. 3.00±1.90 *p*-value=0.774, respectively). However, these difference did not reach statistical significance. The patient satisfaction based on an overall comfort scale increased more in BiPAP S/T with AVAPS group then the BiPAP S/T group (1.64±2.77 vs. 1.09±3.02, *p*-value=0.663), but this was not statistically significant (Table 3).

Vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiratory rate (RR), decreased in both treatment groups after an hour of treatment. There was a trend for larger decreases in SBP, DBP, and RR at an hour after treatment (T_1-T_0) in BiPAP S/T with AVAPS group than in the BiPAP S/T group (31.45±26.25 vs. 18.18±21.15, *p*-value=0.206; 12.09±18.96 vs.7.36±15.00, *p*-value=0.524; and 7.09±7.14 vs. 7.00±6.16, *p*-value=0.975, respectively), but these differences were not statistically significant (Table 4). There were statistically significant decreases in both respiratory rate and systolic blood pressure in individuals in both groups based on paired t tests (Table 2).

Table 1. Patient baseline characteristics

Parameters	BiPAP S/T with AVAPS N=11	BiPAP S/T without AVAPS N=11
Age (years)*	77 (64,84)	69 (49,77)
Sex		
Male	10 (90.9%)	10 (90.9%)
Female	1 (9.1%)	1 (9.1%)
Underlying disease		
Asthma	1 (9.1%)	0 (0%)
Diabetes	0 (0%)	1 (9.1%)
Hypertension	6 (54.5%)	5 (45.5%)
Dyslipidemia	2 (18.2%)	0 (0%)
Chronic kidney disease	1 (9.1%)	2 (18.2%)
Coronary artery disease	2 (18.2%)	4 (36.4%)
Initial vital signs†		
SBP**	166.00±38.24	138.36±22.61
DBP**	95.36±18.58	80.55±19.16
Pulse rate**	116.09±18.93	113.55±16.63
RR**	32.55±6.46	32.64±6.27
Initial ABG		
Arterial pH**	7.34±0.07	7.39±0.06
Arterial PCO_2**	47.90±23.12	45.36±7.22
O_2 saturation**	94.09±7.36	96.82±4.98

SBP-systolic blood pressure; DBP-diastolic blood pressure; RR-respiratory rate

*Median (interquartile range); †From initial assessment (T_0); **Mean ±Standard deviation

The duration of NIV use and length of stay in the emergency department were similar in both group (Table 4). The majority of patients were admitted by a medicine team: 7 (63.6%) in BiPAP S/T with AVAPS group and 6 (54.5%) in BiPAP S/T without AVAPS group.

During our pilot study period, there was only one minor complication with discomfort with the facemask in the BiPAP S/T with AVAPS group. No complications or events that led to aspiration, intubation, and death occurred in our study.

Discussion

This study demonstrated that both BiPAP S/T and BiPAP S/T with AVAPS decreased dyspnea and decreased respiratory rates and systolic blood pressures in patients with COPD with acute exacerbations. The patients' comfort and satisfaction score and dyspnea levels showed a non-significant trend favoring AVAPS at 1 hour after application of the device in patients with AECOPD.

The major theoretical advantage of BiPAP S/T with AVAPS is the auto-adjusting IPAP level to maintain targeted tidal volumes. This allows the ventilator to maintain a given tidal volume in an environment of deteriorating respiratory compliance. Its application was thought to be more tolerable and effective in these patients than with the BiPAP S/T mode because the fixed IPAP might deliver tidal volumes less than the patient needs during treatment of AECOPD as the result of dynamic changes in airway resistance and lungs mechanics.[25] Consequently, auto-adjusting

Table 2. Comparison of baseline with post treatment ABGs, vital signs, and symptoms

BiPAP S/T with AVAPS				
Parameters	**T_0**	**T_1**	**Difference# (mean ± SD)**	**p-value***
Δ pH	7.34±0.07	7.36±0.09	+ 0.01±0.03	0.297
Δ $PaCO_2$	47.90±23.12	45.45±24.70	– 1.5±4.67	0.337
Δ SpO_2	94.09±7.36	98.55±1.64	+ 4.45±7.05	0.62
Δ **MBS**	8.27±1.95	4.18±1.78	– 4.09±1.81	**<0.001**
Δ **NRS**	8.55±1.69	4.46±1.81	– 4.09±1.76	**<0.001**
Δ **Dyspnea**	7.36±2.20	4.09±1.87	– 3.27±2.45	**0.001**
Δ Satisfaction	6.82±2.40	8.46±1.92	+ 1.64±2.77	0.078
Δ HR	116.09±18.93	109.91±19.66	– 6.18±13.21	0.152
Δ **RR**	32.55±6.46,	25.45±6.33	– 7.09±7.14	**0.008**
Δ **SBP**	166.00±38.24	134.55±19.70	– 31.45±26.25	**0.003**
Δ DBP	95.36±18.58	83.27±12.08	– 12.09±18.96	0.061
BiPAP S/T without AVAPS				
Parameters	**T_0**	**T_1**	**Difference# (mean ± SD)**	**p-value***
Δ pH	7.39±0.06	7.38±0.09	– 0.01±0.06	0.618
Δ **$PaCO_2$**	45.36±7.22	41.00±5.23	– 2.70±3.16	**0.024**
Δ SpO_2	96.82±4.98	99.36±1.12	+ 2.55±4.2	0.071
Δ **MBS**	7.09±1.97	4.18±1.66	– 2.91±1.64	**<0.001**
Δ **NRS**	7.00±1.84	4.09±1.87	– 2.91±1.92	**0.001**
Δ **Dyspnea**	6.27±1.90	3.27±1.68	– 3.00±1.90	**< 0.001**
Δ Satisfaction	6.09±2.17	7.18±1.72	+ 1.09±3.02	0.258
Δ **HR**	113.55±16.63	104.36±14.96	– 9.18±11.36	**0.023**
Δ **RR**	32.64±6.27	25.64±5.73	– 7.00±6.16	**0.004**
Δ **SBP**	138.36±22.61	120.18±13.57	– 18.18±21.15	**0.017**
Δ DBP	80.55±19.16	73.18±13.73	– 7.36±15.00	0.134

T_0-baseline; T_1-60 minutes after intervention; *p value; #Different score between T_0 minus T_1; MBS-modified Borg scale, NRS-numerical rating scale.

Paired t tests for individual subjects in each group, Bold numbers are significant at a p-value < 0.05.

IPAP with BiPAP S/T with AVAPS might improve the patient's comfort level and reduce dyspnea measured by MBS, NRS, and dyspnea and comfort scales better than BiPAP S/T. Our study did not show a statistically significant difference, but this may due to the small sample size of our study. A larger scale study is needed to better evaluate the effect of AVAPs in these patient.

In addition, this study found a decrease in BP and heart rate in both study groups after NIV application, but the trend toward greater decreases in SBP and DBP with BiPAP S/T with the AVAPS group compared with the BiPAP S/T group did not reach statistical significance. The physiologic changes during AECOPD include increases in heart rate, blood pressure, and sympathic nervous activity.[26] Decreases in sympathetic

Table 3. Primary Outcomes

Parameters	BiPAP S/T with AVAPS N=11 (mean ± SD)	BiPAP S/T without AVAPS N=11 (mean ± SD)	*p*-value
MBS			
Score at T_0	8.27±1.95	7.09±1.97	
Score at T_1	4.18±1.78	4.18±1.66	0.125
T_0-T_1*	4.09±1.81	2.91±1.64	
NRS			
Score at T_0	8.55±1.69	7.00±1.84	
Score at T_1	4.46±1.81	4.09±1.87	0.148
T_0-T_1*	4.09±1.76	2.91±1.92	
Dyspnea/comfort scale			
Score at T_0	7.36±2.20	6.27±1.90	
Score at T_1	4.09±1.87	3.27±1.68	0.774
T_0-T_1*	3.27±2.45	3.00±1.90	
Patient satisfaction with overall comfort			
Score at T_0	6.82±2.40	6.09±2.17	
Score at T_1	8.46±1.92	7.18±1.72	0.663
T_0-T_1**	1.64±2.77	1.09±3.02	

T_0-baseline; T_1-60 minutes after intervention; MBS-modified Borg scale, NRS-numerical rating scale; *Different score between T_0 minus T_1 (T_0-T_1); **Different score between T_1 minus T_0 (T_1-T_0).

tone should happen when patients feel more comfortable, and this decreases the BP and heart rate.

There were no significant differences in complications related to use of BiPAP S/T with AVAPS compare with BiPAP S/T without AVAPS in our study, including intubation rates, facial ulcers, mental status changes, and mortality in the emergency department. Previous randomized trials had a 26% intubation rate in the NIV groups but no patient required intubation during our study period.[9] This might be explained by differences in inclusion criteria; our patients were less severely ill based on physiologic parameters.

Since this is a pilot study with a small sample size, we could not prove differences in MBS, NRS, dyspnea and comfort scale and in patient satisfaction based on an overall comfort scale. However, our results suggest that a larger study might demonstrate a significant difference in these parameters with the use of AVAPS, and a power analysis based on the differences observed in the changes in MBS indicates that a follow-up study would need 35 patients in each arm to identify a statistical difference in outcomes. Another limitation is the short time of follow up after starting NIV, but ED and hospital outcomes were not different between study groups in our trial.

We think a large randomized trial and longer follow up period should be done to test our hypothesis since this could change current practice to utilize BiPAP S/T with AVAPS in patients with AECOPD. In particular, a larger study could identify patient with AECOPD who benefit the most from the addition of AVAPS.

Conclusion

BiPAP S/T with AVAPS can be considered another management strategy for patients with AECOPD. BiPAP S/T with AVAPS may alleviate symptoms better than BiPAP S/T in patients with AECOPD by

Table 4. Secondary outcomes

Parameters	BiPAP S/T with AVAPS (mean ± SD)	BiPAP S/T without AVAPS (mean ± SD)	*p*-value
SBP			
Score at T_0	166.00±38.24	138.36±22.61	
Score at T_1	134.55±19.70	120.18±13.57	0.21
T_0-T_1*	31.45±26.25	18.18±21.15	
DBP			
Score at T_0	95.36±18.58	80.55±19.16	
Score at T_1	83.27±12.08	73.18±13.73	0.52
T_0-T_1*	12.09±18.96	7.36±15.00	
Heart rate			
Score at T_0	116.09±18.93	113.55±16.63	
Score at T_1	109.91±19.66	104.36±14.96	0.57
T_0-T_1*	6.18±13.21	9.18±11.36	
Respiratory rate			
Score at T_0	32.55±6.46	32.64±6.27	
Score at T_1	25.45±6.33	25.64±5.73	0.98
T_0-T_1*	7.09±7.14	7.00±6.16	
GCS			
Score at T_0	14.91±3.02	15.00±0.00	
Score at T_1	15.00±0.00	15.00±0.00	0.33
T_0-T_1*	0.09±0.30	0.00±0.00	
Arterial pH			
Score at T_0	7.34±0.07	7.39±0.06	
Score at T_1	7.36±0.09	7.38±0.09	0.33
T_0-T_1*	0.01±0.03	0.01±0.06	
Arterial PCO_2			
Score at T_0	47.90±23.12	45.36±7.22	
Score at T_1	45.45±24.70	41.00±5.23	0.51
T_0-T_1*	1.5±4.67	2.70±3.16	
O_2 saturation			
Score at T_0	94.09±7.36	96.82±4.98	
Score at T_1	98.55±1.64	99.36±1.12	0.449
T_0-T_1*	4.45±7.05	2.55±4.18	
Duration of NIV (hours)	4.36±3.15	5.23±4.40	0.602
Length of stay in ED (hours)	9.18±7.38	12.68±10.72	0.383
Disposition			
Discharge to home	1 (9.1%)	0 (0%)	
Admission	7 (63.6%)	6 (54.5%)	
Transfer to another facility	1 (9.1%)	1 (9.1%)	
Observation unit	2 (18.2%)	4 (36.4%)	

SBP-systolic blood pressure; DBP-diastolic blood pressure; NIV-non-invasive ventilation; ED-emergency department; *Different score between T_0 minus T_1 (T_0-T_1) **Different score between T_1 minus T_0 (T_1-T_0)

decreasing dyspnea and increasing patient comfort, but a larger study is needed to confirm this hypothesis.

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