

Noninvasive Positive-Pressure Ventilation in Patients With Milder Chronic Obstructive Pulmonary Disease Exacerbations: A Randomized Controlled Trial

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OBJECTIVES: To determine the effect of the addition of noninvasive positive-pressure ventilation (NPPV) to standard medical therapy on length of hospital stay among patients presenting with mild exacerbations of chronic obstructive pulmonary disease (COPD) requiring hospitalization. **DESIGN:** Randomized controlled unblinded study with concealed allocation. **SETTING:** Respiratory ward of a single-center, academic, tertiary-care hospital. **PARTICIPANTS:** Patients with a prior history of COPD who presented with a recent onset of shortness of breath and a pH of > 7.30 were eligible for inclusion in the study. **INTERVENTIONS:** NPPV daily for 3 days for intervals of 8, 6, and 4 hours, respectively, plus standard therapy, versus standard therapy alone. **MEASUREMENTS:** Borg dyspnea index at baseline, 1 hour, and daily. Length of hospital stay, endotracheal intubation, hospital survival. **RESULTS:** We found that NPPV was generally poorly tolerated, with only 12 of 25 patients wearing it for the prescribed 3 days. With the exception of a decrease in dyspnea at 1 hour and 2 days, significant between-group differences were not seen for any measured variable. **CONCLUSIONS:** The effectiveness and cost-effectiveness of the addition of NPPV to standard therapy in milder COPD exacerbations remains unclear. *Key words:* bi-level positive airway pressure, BiPAP, length of stay, chronic obstructive pulmonary disease, noninvasive ventilation, dyspnea. [Respir Care 2005;50(5):610–616. © 2005 Daedalus Enterprises]

Introduction

The use of noninvasive positive-pressure ventilation (NPPV) to avoid endotracheal intubation in exacerbations

of chronic obstructive pulmonary disease (COPD) was first described by Meduri et al in 1989.¹ This case series was followed by many others suggesting benefit^{2–7} and a study by Brochard et al using historical controls documenting a large reduction in the need for intubation.⁸ Since that time, a number of randomized controlled trials have been published,^{9–18} most of which have documented benefit from

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the addition of NPPV, including a reduction in the need for intubation,^{10,11,14,15,16} a decrease in the total duration of mechanical ventilation (invasive and noninvasive),¹⁰ and a decreased hospital length of stay.^{10,14,17} Some trials have also reported a reduction in mortality^{10,16} and pneumonia.¹⁰ The one trial that reported a lack of benefit¹⁸ in-

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cluded 24 patients treated on a general ward, none of whom required intubation or died. This latter study differed from other studies as it included patients with milder exacerbations of COPD. An economic evaluation that attempted to determine the financial impact of using NPPV in COPD exacerbations by retrospective modeling suggested that NPPV was not only effective but also saved money in patients with severe COPD exacerbations.¹⁹ However, when the base case was explored using sensitivity analyses, this cost savings disappeared as the need for intubation in the control arm decreased, suggesting that there is an added cost in patients with milder exacerbations of COPD.¹⁹

NPPV has been demonstrated to decrease the work of breathing (WOB) in exacerbations of COPD,⁸ and this is believed to be the mechanism through which NPPV achieves benefit. Some patients with severe exacerbations of COPD clearly develop respiratory muscle fatigue, evidenced by a gradual reduction in minute ventilation and rise in P_{aCO_2} related to this increased WOB that requires intervention with some form of assisted ventilation. All patients developing an exacerbation of COPD that requires hospitalization have an increased WOB and, we hypothesize, potentially develop some degree of associated respiratory muscle fatigue. We further hypothesize that adding intermittent NPPV during the initial days of hospital stay would afford respiratory muscle rest for patients with milder COPD exacerbations and that this rest would allow these patients to recover more quickly and to be discharged home earlier. The objective of this trial was to determine whether the addition of NPPV to standard therapy during the first 3 days of admission in milder COPD exacerbations could decrease length of hospital stay.

Methods

Patients

During the period July 1, 1997, to September 30, 2000, we screened all patients diagnosed as having COPD who presented with an exacerbation to the emergency room and were admitted to London Health Sciences Centre, Victoria Campus, London, Ontario, Canada, an academic, tertiary-care, teaching hospital. The diagnosis of COPD was documented in a prior admission to hospital, or the patient had received such a diagnosis from their family physician and was being treated with appropriate medication. Those patients who presented with a recent onset of shortness of breath and a pH of > 7.30 were eligible for inclusion in the study.

All patients had to be admitted to the respiratory ward, whose nursing staff had been briefed on the fundamentals of NPPV. Patients were excluded from the study for the following reasons: respiratory arrest; decreased level of

consciousness; hemodynamic instability; excess secretions; inability to communicate with the patient, either due to a language barrier, the patient being mentally challenged, or the patient having a substantial psychiatric disorder; use of continuous positive airway pressure at home; associated pneumonia demonstrated on chest radiograph; or patient judged to be in respiratory extremis by the admitting physician. During the study period, those patients with COPD exacerbations who did not require immediate intubation and who either had $pH < 7.30$ or were judged to be in respiratory extremis were routinely treated with NPPV.

The study protocol was approved by the Review Board for Health Sciences Research Involving Human Subjects at the University of Western Ontario. Informed consent was obtained from all patients. Patients who consented to participate were randomized to group using a random-number computer generator program, in permuted blocks of 2, 4, or 6, and sealed, opaque, sequentially numbered envelopes prepared by an individual not associated with clinical patient care.

Standard Therapy

Patients assigned to standard therapy received supplemental oxygen to maintain oxygen saturation $\geq 90\%$ (the goal being to use the minimum amount of supplemental oxygen to achieve an oxygen saturation at or just above 90%). In addition, they received pharmacotherapy with inhaled β agonists and inhaled ipratropium bromide, as clinically indicated, systemic steroids, and antibiotics for infectious exacerbations not due to pneumonia. Decisions regarding the use of these interventions were made by the attending staff.

NPPV Treatment

NPPV was administered using the Vision BiPAP (bi-level positive airway pressure) ventilator (Respironics, Murrysville, Pennsylvania). This device is capable of providing independently adjustable inspiratory and expiratory positive airway pressure. The respiratory therapist staff received extensive briefing prior to the study, as well as informal briefing throughout the trial. BiPAP was initiated within 24 hours of arrival to the emergency room on a respiratory medicine ward, in an unmonitored room. As the goal was to provide respiratory muscle rest, the protocol was to have the patient wear the BiPAP for 8 hours the first day, 6 hours the second day, and 4 hours the third day, and then stop. BiPAP was initiated at a level of 4 cm H_2O of expiratory positive airway pressure and 9 cm H_2O of inspiratory positive airway pressure, in a spontaneous mode, and titrated as necessary for patient comfort. The objectives were to have the patient breathing comfortably, as evidenced by a drop in respiratory rate and heart rate,

with oxygen saturations $> 90\%$ and a normal pH on arterial blood gases. While nursing staff on the respiratory ward were taught enough to be familiar with NPPV, the respiratory therapists assumed the responsibility of explaining the equipment to the patients and applying it. They were also called to deal with any difficulties encountered during therapy. Patients received NPPV in a regular ward room, with no monitoring, and a nurse:patient ratio varying from 1:6 during the day to 1:11 at night. NPPV was initiated using a full-face mask but was changed to a nasal mask for those finding the full-face mask to be uncomfortable. While we did not measure the effect of the addition of NPPV on respiratory muscle work directly, the approach used was similar to that previously demonstrated to achieve respiratory muscle rest and avoid the need for endotracheal intubation.^{11,13,15}

Follow-up

At baseline, demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) II score, arterial blood gases, and Borg scale (measure of breathlessness) were recorded for all patients. At the time of randomization, respiratory rate, heart rate, blood pressure, arterial blood gases, and fraction of inspired oxygen (F_{IO_2}) were recorded. For those patients randomized to NPPV, the initial settings used for inspiratory and expiratory positive airway pressure and whether the patient tolerated NPPV were recorded. Patients were followed throughout their intensive care unit (ICU) and hospital stay. Subjective dyspnea was assessed using the Borg index,²⁰ measured at the time of randomization, one hour after randomization (during NPPV therapy for those randomized to this treatment and compliant with it), and then daily for the remainder of the hospital stay. Endotracheal intubation was performed if the patient consented to intubation *and* any of the following criteria were met: cardiac arrest *or* respiratory arrest *or* apnea with or without loss of consciousness *or* inability to protect airway *or* marked respiratory distress/in extremis *or* psychomotor agitation making nursing care impossible and requiring sedation *or* heart rate < 50 beats/min with loss of alertness *or* hemodynamic instability (systolic arterial pressure below 70 mm Hg). The need for re-intubation was recorded, as were the duration of further mechanical ventilation (if necessary), the length of ICU and hospital stay, and vital status on discharge from ICU and hospital. Most recent results of patients' spirometry were obtained, if possible, from the pulmonary function laboratory.

Sample Size and Statistical Analysis

After reviewing current length of stay at our institution for patients with milder exacerbations of COPD over the

preceding year, we estimated that the expected length of stay in the control arm would be 6 days. Using a type 1 error of 5%, we estimated that we would need 35 patients in each group to have a power of 80% to detect a reduction in length of stay in the NPPV group to 4 days (a reduction in length of stay of 2 d). The latter was considered a clinically important difference in length of stay. Unfortunately, due to a reduction in beds throughout the hospital that occurred after initiation of the study, accessibility to the respiratory ward became more restricted, and a total of 52 patients were randomized prior to closing the study due to insufficient funds. This led to a decrease in our power to detect a statistically significant difference of 2 days to 63%.

Baseline comparisons of the 2 study groups were conducted using the chi-square statistic or Fisher's exact test, where appropriate, for categorical variables and the Student's *t* test for continuous variables. The primary outcome of median length of hospital stay was tested using the nonparametric Mann Whitney U test. Mean length of stay was also compared between groups using the 2-sample Student's *t* test. Survival analysis was used to compare the time to discharge. We used both Student's *t* tests and General Linear Model repeated measures of analyses to assess dyspnea levels measured by the Borg scale between the 2 groups.

Results

During the 3 years and 2 months of the study there were 355 hospital admissions due to exacerbations of COPD (this included repeat admissions for the same patient). Patients excluded are outlined in Figure 1. The remaining 52 consented to participate and were randomized, 25 to NPPV plus standard therapy, and 27 to standard therapy alone. The 2 groups were similar in age, proportion of males, most recent percent of predicted forced expiratory volume in the first second, body-mass index, baseline pH, P_{aCO_2} , and Borg score for dyspnea (Table 1). The control group appeared to have a higher APACHE II score, but this did not reach statistical significance ($p = 0.125$). There were no differences in pharmacologic co-interventions, including the use of furosemide, prednisone, albuterol, or ipratropium bromide, between study groups (see Table 1).

For those patients randomized to NPPV, the mean initial settings were an inspiratory positive airway pressure of 9.8 ± 0.6 cm H₂O and expiratory positive airway pressure of 4.7 ± 0.6 cm H₂O. Of these 25 patients, 3 refused NPPV after its initial application, leaving 22 who used it for a minimum of 1 hour. Seventeen patients were compliant with NPPV for 2 days and 12 patients for the full 3 days prescribed. For those patients compliant with therapy (> 1 h on the respective day), the mean duration of NPPV use for day 1 was 6.2 ± 3.1 hours, ranging from 1 to 9

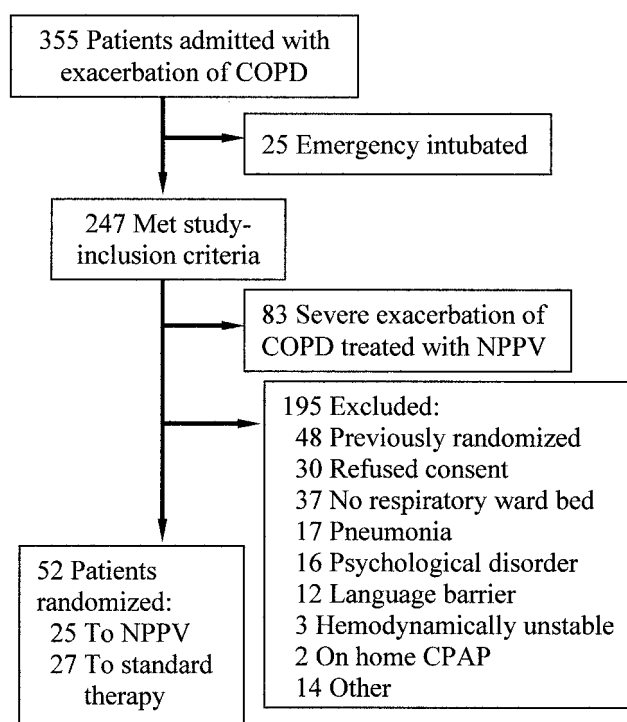


Fig. 1. Flow diagram of patients presenting with exacerbations of chronic obstructive pulmonary disease (COPD) during the study period, identifying those included and excluded. NPPV = noninvasive positive-pressure ventilation. CPAP = continuous positive airway pressure.

hours (22 patients); for day 2 it was 5.7 ± 1.1 hours, ranging from 3 to 7 hours (17 patients); and for day 3 a total of 4.2 ± 0.3 hours, ranging from 4 to 5 hours (12 patients).

Borg scores describing patient dyspnea were available for 80–90% of patients at each designated time point; however, the number of patients having data for consecutive measurements dropped off over time, with only 60% having data out to day 3. Repeated-measures analysis was therefore only done out to day 3. While there was no difference in the baseline Borg index as a measure of dyspnea, the mean Borg index at 1 hour into the study was significantly better in those patients randomized to and receiving NPPV, compared to controls ($p = 0.004$, Fig. 2). The Borg index on day 2 was also significantly lower in the NPPV group, compared to controls ($p = 0.031$, see Fig. 2). Overall, from Figure 2 it appears that patients randomized to NPPV had a more rapid and sustained improvement in their breathlessness than the control group, and this was found to be statistically significant, using repeated measures of analysis over the first 3 days ($p = 0.014$).

The rate of intubation was similar in the 2 study groups: 2 of 25 patients in the NPPV group, and 2 of 29 in the control group. However, 4 patients in the standard-therapy

group received NPPV as rescue therapy as an alternative to endotracheal intubation after developing increasing respiratory distress. Of these 4 patients, 1 required intubation and the other 3 recovered with NPPV alone. Therefore, a total of 5 of 27 patients (19%) in the standard-therapy group developed worsening respiratory distress requiring urgent ventilatory support (either NPPV or immediate endotracheal intubation), compared to 2 of 25 in the NPPV group (8%). This difference was not statistically significant ($p = 0.422$). No patients in the NPPV group developed nosocomial infections, while 2 patients in the standard-therapy group did. One patient, who required endotracheal intubation, developed a ventilator-associated pneumonia, and a second patient, who did not require intubation, developed both a urinary tract infection and a hospital-acquired pneumonia.

The median hospital length of stay was 2 days less for those patients in the NPPV arm of the study, compared to controls (Table 2); however, this did not reach statistical significance. One patient, in the NPPV group, was considered an important outlier, with a length of stay of 374 days in the NPPV arm, the next longest length of stay in either group being 36 days. The median length of stay for patients treated with NPPV after excluding this patient remained 2 days less than controls, and there appeared to be a trend toward this difference being significant ($p = 0.073$). Time to hospital discharge also had a trend toward a lower time for patients in the NPPV arm, as seen in Figure 3, (log rank test $p = 0.063$ after excluding the NPPV outlier; including the outlier $p = 0.253$).

Discussion

From this trial of patients presenting with milder exacerbations of COPD we can draw the following conclusions. First, NPPV is not well tolerated in this patient group, with only 12 of 25 completing the 3-day course. This level of intolerance is greater than that reported in studies of patients with more severe exacerbation, such as a 10% intolerance rate in a study by Avdeev et al¹⁴ and the day-2 NPPV utilization rate of patients in the Plant et al study of 76% (of the 24% of patients not using NPPV on day 2, 9% had been intubated).¹⁶ Second, despite this poor tolerance, the group of patients treated with NPPV appeared to have a more rapid reduction in their dyspnea levels, as measured by the Borg index. Third, while length of stay was less in the NPPV group, this did not reach statistical difference.

It is important to place this trial in context with those previously published on the use of NPPV in patients with COPD exacerbations.^{9–14,16–18} The majority of the literature is composed of trials designed to look at patients presenting with more severe exacerbations of COPD, reflected by lower baseline pH, higher baseline P_{CO_2} , and higher intu-

Table 1. Baseline Characteristics and Co-interventions

Characteristic	NPPV (n = 25)	Control (n = 27)	P
Age (mean \pm SD)	69 \pm 9	71 \pm 8	0.447
Sex (male/female)	10/15	14/13	0.392
FEV ₁ (% of predicted)*	36 \pm 12	31 \pm 15	0.187
BMI (kg/m ²)	24 \pm 7	23 \pm 6	0.611
APACHE II	17 \pm 4	19 \pm 5	0.125
P _a CO ₂ (mm Hg)	50 \pm 15	51 \pm 17	0.924
pH	7.40 \pm 0.04	7.40 \pm 0.05	0.961
Borg score	5.7 \pm 2.4	6.1 \pm 2.5	0.566
History of prior endotracheal intubation	2/25	3/27	0.704
Co-intervention			
Ipratropium bromide	25/25	27/27	
Short-acting beta-agonist	25/25	27/27	
Long-acting beta-agonist	3/25	2/27	
Theophylline	2/25	3/27	
Inhaled steroids	16/25	14/27	
Systemic steroids	22/25	25/27	
Antibiotics	21/25	26/27	
Furosemide	8/25	11/27	

NPPV = noninvasive positive-pressure ventilation

*Forced expiratory volume in the first second (FEV₁) was available for only 23/25 of the NPPV group and 25/27 of the control group.

BMI = body-mass index

APACHE = Acute Physiology and Chronic Health Evaluation

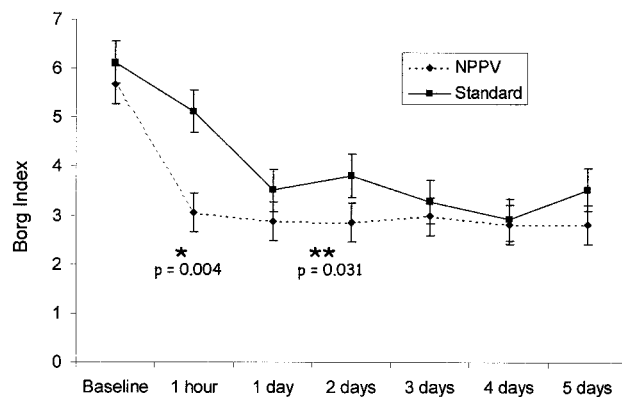


Fig. 2. This figure illustrates relative dyspnea levels, using the Borg dyspnea scale, of each group over time. While those patients randomized to noninvasive positive-pressure ventilation (NPPV) appear to be less dyspneic over the first 2 days, the difference only achieved statistical significance at one hour after randomization and on day 2.

bation rates and mortality in the control groups.^{9–14,16,17} These trials consistently report either a reduction in intubation rate,^{11,13,17} mortality rate,^{9,14} or both^{10,16} for patients receiving NPPV. One of these trials did perform a subgroup analysis on a less severe group who presented with a baseline pH > 7.30.¹⁶ However, the failure rate (20%) and hospital mortality (14%) of the standard-treatment group were much higher than those in our study, suggest-

ing that even their “milder” patients were sicker than the population we studied.¹⁶

The trial population that appears to be most similar to our own is that of a Spanish study, by Barbe et al,¹⁸ who studied a total of 24 patients admitted to a respiratory ward with exacerbations of COPD, none of whom required intubation or died. Of these patients, 14 were randomized to 2 daily sessions of NPPV for 3 hours each, and 10 patients to standard therapy. Interestingly, while trials on patients with more severe exacerbations either do not clearly report tolerance of NPPV or report relatively low levels of intolerance,^{14,16} Barbe et al found that 4 of 14 (29%) of patients randomized to NPPV did not tolerate it because of claustrophobia or anxiety on day 1. In the current study, while only 48% (12 of 25) completed all 3 days, a similar number to the Spanish study, 17 of 25 (68%) used it for at least 2 days. The regimens varied in their approach, the current study attempting to have patients use NPPV for 8 hours the first day, then 6 and 4 hours in subsequent days, in contrast to 3 hours twice a day for 3 days. The longer duration of therapy may be harder for patients to tolerate who do not feel as dyspneic. It is not clear why tolerance rates vary among trials, but a reasonable assumption would be that sicker, more dyspneic patients receive subjectively greater benefit from NPPV than those with milder exacerbations.

Contrary to our study, Barbe et al¹⁸ reported no difference between study groups in level of dyspnea. Perhaps

Table 2. Hospital Outcomes for Study Groups

	NPPV (n = 25)	Standard Therapy (n = 27)	
Intubated (number and %)	2/25 (8)	2/27 (7)	
Failed treatment (number and %)*	2/25 (8)	5/27 (19)	
Nosocomial infection (number)	0/25	2/27	
Survived hospitalization (number and %)	24/25 (96)	25/27 (93)	
Length of Hospital Stay			
All Patients			
Mean \pm SD	21.2 \pm 73.7	9.1 \pm 7.3	p = 0.397
Median (range)	5 (2–374)	7 (2–36)	p = 0.136
Excluding 1 outlier in NPPV group with 374-day stay			
Mean \pm SD	6.5 \pm 5.6	9.1 \pm 7.3	p = 0.175
Median (range)	5 (2–31)	7 (2–36)	p = 0.073

NPPV = noninvasive positive-pressure ventilation

*Failed treatment means patient reached criteria for intubation but was either intubated or received noninvasive ventilation if they were in the control arm.

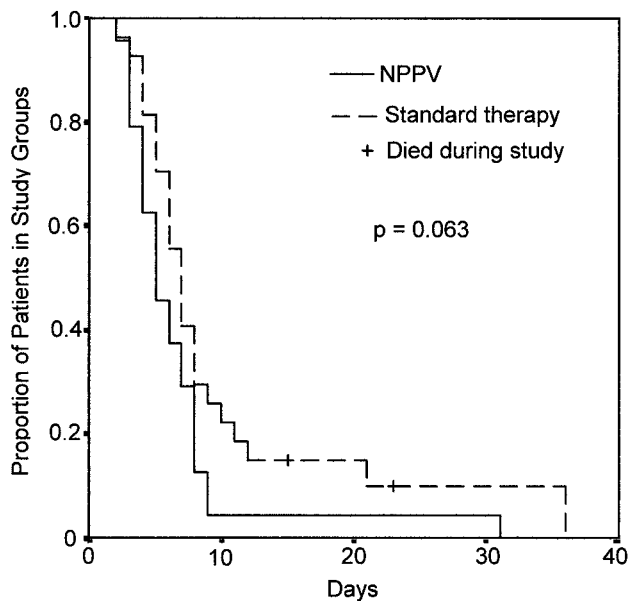


Fig. 3. This figure illustrates the time to discharge for the 2 study groups. Those patients randomized to noninvasive positive-pressure ventilation (NPPV) demonstrated a strong trend toward a reduction in length of hospital stay.

greater benefit is received by an initial more prolonged period of support, such as our goal of 8 hours continuously versus 2 periods of 3 hours on day 1. A second reason for the lack of effect on dyspnea found in the Spanish study that may also apply to other outcomes is the lack of power in a study of 20 patients. Finally, the differences may reflect the greater degree of dyspnea in our study; baseline Borg scores were higher (6.2 and 5.8 for control and NPPV groups, respectively) than those of Barbe et al (both < 5 at baseline).

We had hypothesized that the addition of NPPV would decrease hospital length of stay by 2 days, and indeed, we

found this to be true in our study population, the median length of stay in the NPPV group being 5 days, compared to 7 days in the control group. However, this did not reach statistical significance and may have occurred by chance alone. In addition, APACHE II score was higher and forced expiratory volume in the first second was lower in the control group, biasing them toward a longer length of stay.²¹ Prior to adopting a new therapeutic technology, one has to consider not only the effectiveness of the technology but also its associated costs and potential harms. An economic evaluation of the addition of NPPV to standard treatment for patients presenting with exacerbations of COPD concluded that NPPV for the base case analysis was not only more effective but also costs less.¹⁹ However, the base case analysis used a population of patients found in randomized controlled trials that, on average, were presenting with quite severe exacerbations of COPD. Among the sensitivity analyses performed was an analysis examining the effect of the severity of the COPD exacerbation by varying the rate of intubation in the control arm. This analysis found that for patients with milder exacerbations of COPD, such as those represented in this trial, there were added costs.

This study has some limitations. First, we were unable to enroll our goal number of patients to achieve adequate power to determine whether the difference in length of stay found of 2 days was truly significant or due to chance alone. Second, we did not measure respiratory-muscle WOB to determine whether our hypothesis that NPPV decreases WOB in this setting is correct. While it would have been ideal to have this information, the approach used was similar to that found in the literature in studies that have reported both clinical benefit^{11,13,15} and a reduction in the WOB.⁸ We believe that the current body of literature would support the assumption that if patients

tolerate NPPV and experience an improvement in dyspnea (as our patients did), they experience a reduction in the WOB. We also wished to make our study results as generalizable as possible and therefore kept the study design simple, applying NPPV without any extra monitoring on a respiratory ward. Finally, our primary outcome, length of hospital stay, can be influenced by other variables in a study that is not blinded and relatively small in size.

Conclusions

In summary, the addition of NPPV to standard therapy for patients with milder exacerbations of COPD is not well tolerated, greater than 50% of patients not wearing it as recommended. Despite this, patients appear to demonstrate a more rapid improvement in their level of dyspnea. While hospital length of stay was less in the NPPV group, it did not reach statistical significance, and bias appeared to be present favoring the NPPV arm. This, coupled with the associated increased costs, precludes us from recommending this therapy for patients with milder COPD exacerbations. We have not ruled out the fact that NPPV is effective or even cost-effective in this patient population and we would recommend further research to clarify the answer to this question.

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