ORIGINAL RESEARCH

Prospective cross-sectional multicenter study on domiciliary noninvasive ventilation in stable hypercapnic COPD patients

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Background: Domiciliary noninvasive ventilation (NIV) use in stable hypercarbic COPD is becoming increasingly widespread. However, treatment compliance criteria and factors related to compliance remain to be defined.

Methods: This research was designed as a prospective, cross-sectional, multicenter real-life study. Chronic hypercapnic COPD patients who were using domiciliary NIV for at least 1 year and being followed up in 19 centers across Turkey were included in the study. The patients who used NIV regularly, night or daytime and ≥ 5 hours/d, were classified as "high-compliance group," and patients who used NIV irregularly and <5 hours/d as "low-compliance group."

Results: Two hundred and sixty-six patients with a mean age of 64.5±10.3 years were enrolled, of whom 75.2% were males. They were using domiciliary NIV for 2.8±2 years. Spontaneous time mode ($p<0.001$) and night use ($p<0.001$) were more frequent in the high-compliance group (n=163). Also, mean inspiratory positive airway pressure values of the high-compliance group were significantly higher than the low-compliance group (n=103; $p<0.001$). Cardiac failure ($p=0.049$) and obesity ($p=0.01$) were significantly more frequent in the high-compliance group. There were no difference between 2 groups regarding hospitalization, emergency department and intensive care unit admissions within the last year, as well as modified Medical Research Council dyspnea and COPD Assessment Test scores. With regard to NIV-related side effects, only conjunctivitis was observed more frequently in the high-compliance group ($p=0.002$).

Conclusion: Determination of the patients who have better compliance to domiciliary NIV in COPD may increase the success and effectiveness of treatment. This highly comprehensive study on this topic possesses importance as it suggests that patient and ventilator characteristics may be related to treatment compliance.

Keywords: COPD, noninvasive ventilation, compliance

Introduction

Chronic obstructive pulmonary disease (COPD) is an increasing and important cause of morbidity and mortality worldwide. Among the diseases leading to death, COPD was ranked as 4th in 2015 and is expected to rise to the 3rd rank by 2020.[1] In particular, chronic hypercapnic respiratory failure is conversely associated with overall prognosis in COPD, and also, if a patient developed hypercapnia once, 2-year mortality rate increases to approximately 30%–40%.[2] In chronic hypercarbic COPD patients, long-term noninvasive ventilation (NIV) use is becoming increasingly widespread. However, the meta-analysis and clinical guidelines do not recommend domiciliary NIV except in selected patients.[3,4]

In stable COPD, long-term NIV use has been demonstrated to provide clinical and functional benefit via several mechanisms. During sleep, it may improve nocturnal hypoventilation and reduce daytime hypercapnia, thus leading to restoration of chemosensitivity and changes in ventilatory pattern. It has been demonstrated to reduce chronic muscle weakness, improve inspiratory muscle functions, and thereby, reduce hyperinflation. Also, it has been reported to improve duration and effectiveness of sleep.[5,6]

In terms of domiciliary NIV rates in COPD, our country is in the 2nd rank among European Respiratory Society (ERS)-member European countries after Germany.[7] In our country, due to population density and high COPD prevalence, hospitals in large cities cannot meet the increasing need of hospitalization of these patients. Therefore, domiciliary NIV is more frequently prescribed in COPD patients who were hospitalized due to acute hypercarbic respiratory failure to shorten the hospitalization period or to reduce the rates of readmission. Ventilator devices for the patients are provided by our government according to the consensus criteria.[8]

When we searched the literature, we could not find a comprehensive study investigating compliance to domiciliary NIV. In this study, we aimed to explore treatment compliance rates and conditions possibly related to compliance to domiciliary NIV in chronic hypercapnic COPD patients. Also, we evaluated the relationship between domiciliary NIV compliance and symptom scores, hospitalization, and emergency department and intensive care unit (ICU) admissions within the last year.

Our hypothesis was that the symptom scoring and emergency department and hospital admission would be better in the high-compliance group when compared with the low-compliance group.

Methods

This study was designed as a prospective, cross-sectional multicenter real-life trial between April 2015 and June 2016. Nineteen centers from our country participated in this study. Inclusion criteria were as follows: stable hypercarbic COPD patients using domiciliary NIV for at least 1 year, age ≥40 years, and ≥10 pack-year smoking history. Patients who did not have definitive diagnosis of COPD, had COPD exacerbation within the past 6 weeks prior to enrollment, were using NIV for non-COPD conditions, and did not meet aforementioned criteria were excluded from the study. Demographic and clinical characteristics were obtained by face-to-face interviews with the patients and their relatives. All diseases included in the Charlson Comorbidity Index

were questioned and recorded for each patient.[9] The number of hospitalizations and emergency department and ICU admissions within the last year were recorded retrospectively based on patients' self-report and hospital records. Dyspnea was assessed based on the modified Medical Research Council's (mMRC) dyspnea scale[10] and the disease control status was measured by the COPD Assessment Test (CAT) for each patient.[11] Pulmonary function test (PFT) and arterial blood gas (ABG) were measured if the patients' tests were not performed within the last 6 months and the results were recorded. During the interview, detailed information was obtained from each patient regarding the side effects of NIV therapy and ventilator usage features. Daily period of use in some of the patients was recorded by a readout of the ventilator's built-in software. For these patients (n=115), statistically high correlation between the card readout and self-report was detected. Therefore, for the patients without available ventilator's built-in software data, periods of NIV use were recorded based on the common statement of the patients and their relatives. Patients who use NIV everyday regularly, night or daytime and ≥5 hours/d, were classified as "high-compliance group," and patients who used NIV irregularly and <5 hours/d were the "low-compliance group." The groups were compared in terms of demographic, clinical, and laboratory characteristics, NIV-related side effects, ventilator type and setting, and also rates of hospitalization and emergency department and ICU admissions within the last year. The study was approved by the ethics committee of Karadeniz Technical University, School of Medicine, with the ethics committee number 24237859-242. A written informed consent was taken from each patient before the study.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 23 software (IBM Corporation, Armonk, NY, USA). Descriptive data were expressed as count and percentage for categorical variables and as mean and SD for continuous variables. Independent t-test was used to analyze the significant differences between the categorical variables having 2 groups. The χ^2 test was used to analyze the correlation between the 2 categorical variables, while the Pearson correlation coefficients were used to analyze the correlation between the 2 numerical variables. p-value of <0.05 was considered statistically significant.

Results

Two hundred and sixty-six stable chronic hypercapnic COPD patients with a mean age of 64.5±10.3 years were enrolled,

of whom 75.2% (n=200) were males. Patients were being followed up for COPD for a mean of 8.5±5 years and were using domiciliary NIV for 2.8±2 years. All patients had a history of smoking of at least 10 pack/yr, and 20.7% were current smokers. About 59.8% of the patients had comorbidities, and the most common accompanying 3 comorbidities were cardiac failure, diabetes mellitus, and cerebrovascular diseases, respectively. Obstructive sleep apnea (OSA) previously diagnosed by polysomnography was an accompanying comorbidity in 12.4% of the patients, and obesity (body mass index [BMI] over 30 kg/m^2) was seen in 20.7% of the patients. About 89.4% of the patients were using domiciliary long-term oxygen therapy (LTOT). Patients' mean forced expiratory volume in 1 second (FEV$_1$) was 0.96±0.5 L, 34.5% of the expected value, and forced vital capacity (FVC) was 1.62±1 L, 47.2% of the expected value; the FEV$_1$/FVC ratio had a mean of 54%. Clinical and laboratory characteristics of the patients are given in Table 1. Ventilator type and setting: Of the patients, 50.4% were using the device in spontaneous time (ST) mode, 49.6% in spontaneous (S) mode. 92.5% of the patients were using noninvasive positive pressure ventilation (NPPV) via oronasal mask and 7.5% via nasal mask. Mean inspiratory positive airway pressure (IPAP) used by patients was 18±5.5 cmH$_2$O, and mean expiratory positive airway pressure was 5.8±1.3 cmH$_2$O. Of the patients, 40.2% were using the ventilator at daytime and 59.8% at night; 67.7% of the ventilators had a humidification system. About 88.7% of the patients were informed about the ventilator

Table 1 Clinical and laboratory characteristics of the patients

The number of patients: 266	Mean	SD
Age (years)	64.5	10.3
BMI (kg/m^2)	28.5	7.7
Smoking (pack/yr)	45.5	25.7
FEV$_1$ (%)	34.5	14.3
FEV$_1$/FVC (%)	53.9	10.1
pH	7.41	0.04
PaCO$_2$ (mmHg)	50.97	7.3
PaO$_2$ (mmHg)	73.8	25.2
SaO$_2$ (%)	92.2	5.2
Compliance of NIV (hours/d)	6.3	3
IPAP (cmH$_2$O)	18.1	5.5
EPAP (cmH$_2$O)	5.8	1.3
CAT score	24.3	8
mMRC score	3.9	1.1

Abbreviations: BMI, body mass index; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PaO$_2$, partial arterial oxygen pressure; PaCO$_2$, partial arterial carbon dioxide pressure; SaO$_2$, oxygen saturation; NIV, noninvasive ventilation; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; CAT, COPD Assessment Test; mMRC, modified Medical Research Council.

Table 2 Distribution of the side effects related to NIV

Side effects	Number (n)	%
Headache	98	36.8
Sleep disruption	81	30.5
Feeling of suffocation	54	20.3
Nasal skin lesion	41	15.4
Conjunctivitis	38	14.3
Extremely high air pressure	37	13.9
Overall side effects	159	59.8

Abbreviation: NIV, noninvasive ventilation.

use and only 38.7% returned for follow-up visit by the ventilator prescribing physician. The most common 3 side effects related to NPPV were headache, sleep disruption, and feeling of suffocation. All side effects and their frequencies are given in Table 2.

Comparison of the groups

BMI was significantly higher (29.5±8 vs 27±7 kg/m^2; p=0.01) and the proportion of female gender was higher (29% vs 18%; p=0.056) but not statistically significant in the high-compliance group (n=163) compared to the low-compliance group (n=103). There was no difference between the groups in terms of other demographic characteristics (age, educational level, smoking status, and having a roommate). There was no difference with regard to patients' PFTs (FVC, FEV$_1$, FEV$_1$/FVC) and ABG values (partial arterial oxygen pressure, partial arterial carbon dioxide pressure [PaCO$_2$], oxygen saturation, pH) either.

With regard to comorbidities, heart failure was more in the high-compliance group (p=0.049), and while the number of patients with dementia (n=4) was less all of them were in the low-compliance group (p=0.02). In the high-compliance group, obesity was more frequent (p=0.01) and OSA was proportionally more frequent (15.3% vs 7.8%), but the difference was not statistically significant (p=0.07).

When the groups were compared in terms of NIV type and setting, ST mode (p<0.001) and night use (p<0.001) was more frequent in the high-compliance group. Also, mean IPAP values of the high-compliance group were significantly higher than the low-compliance group (p<0.001). There was no difference between the 2 groups in terms of other ventilator usage features (Table 3). With regard to NIV-related side effects, only conjunctivitis was observed more frequently in the high-compliance group (p=0.002), and there was no difference in terms of other side effects.

There was no difference between the high- and low-compliance groups in terms of hospitalization and emergency department and ICU admissions within the last year and also

Table 3 Comparison of the groups with respect to NIV use, type, and setting

The NIV use, type and setting			High-compliance group	Low-compliance group	Total	χ^2	*p*-value
Predominant period of use	Daytime	N	44	62	106		
		%	27.0	61.4	40.2	30.695	**0.000[a]**
	Night	N	119	39	158		
		%	73.0	38.6	59.8		
Mode	ST mode	N	99	35	134		
		%	60.7	34.0	50.4	18.074	**0.000[a]**
	S mode	N	64	68	132		
		%	39.3	66.0	49.6		
Humidification system	Yes	N	114	66	180		
		%	69.9	64.1	67.7	0.991	0.319
	No	N	49	37	86		
		%	30.1	35.9	32.3		
Type of mask	Nasal	N	10	10	20		
		%	6.1	9.7	7.5	1.159	0.282
	Oronasal	N	153	93	246		
		%	93.9	90.3	92.5		
IPAP (cmH$_2$O)	High-comp group		163	18.97	5.79	3.531	**0.000[a]**
	Low-comp group		103	16.70	4.63		
EPAP (cmH$_2$O)	High-comp group		163	5.8	1.39	0.421	0.674
	Low-comp group		102	5.74	1.1		
Daytime headache	Yes	N	85	47	132		
		%	52.1	45.6	49.6	1.072	0.300
	No	N	78	56	134		
		%	47.9	54.4	50.4		
Somnolence	Yes	N	51	32	83		
		%	31.3	31.1	31.2	0.001	0.970
	No	N	112	71	183		
		%	68.7	68.9	68.8		

Notes: Two patients had missing data regarding the use of time (daytime/night). Bold is significant. [a]$p < 0.001$.
Abbreviations: NIV, noninvasive ventilation; ST, spontaneous time; S, spontaneous; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; comp, compliance.

CAT and mMRC scores (*p*>0.05). The comparison of the groups in terms of these results is given in Table 4.

In the Pearson's correlation analysis, a statistically significant, positive but weak relationship was detected between the compliance of NIV and CAT score and IPAP level. Additionally, a statistically positive and strong (83%) correlation was detected between the card readout and self-report in the patients (n=105). The results of the correlation analysis are given in Table 5.

Discussion

Despite the lack of clear scientific evidence supporting the use of long-term NIV for stable hypercapnic COPD patients, domiciliary NIV is becoming increasingly widespread.[3] However, to date, standard criteria concerning the time of NIV therapy initiation and treatment compliance in stable COPD remain to be defined. This situation causes deficits for informing and follow-up of the patients by NIV prescribing physicians.[7] In this study, we detected that 86.7% of the patients to whom domiciliary NIV was initiated were informed about the ventilator use, and only 38.7% of the patients returned for follow-up visit by NIV prescribing physicians. Similarly, in a web-survey study performed in ERS-member European countries, only 46% of the COPD patients to whom domiciliary NIV was initiated are being followed up regularly.[7] However, careful follow-up in these patients may prevent early deterioration.[12]

Patients must be made to understand that good tolerance and compliance to the ventilator should be ensured to obtain optimal benefit from domiciliary NIV therapy. Our search results revealed no previous "compliance criteria to long-term NIV therapy for COPD patients" in the literature. Therefore, we considered at least 5 hours/d use, which was suggested in many publications in terms of efficacy and compliance, as the cut off value.[3,13,14] In this setting, compliance rate for NIV therapy was 61% in our study. In a recent prospective observational study, distribution of the preferred mask types in COPD patients who use domiciliary NIV was explored,

Table 4 Comparison of the groups in terms of hospitalization and emergency department and ICU admissions within the last year and symptom scoring

Groups	The number of patients	Mean	SD	t	p-value
The number of emergency department admission					
High compliance	144	4.4	5.3	−0.207	0.836
Low compliance	75	4.5	4.1		
The number of hospitalization					
High compliance	135	3.3	3.5	1.488	0.138
Low compliance	85	2.7	2.0		
The number of ICU admission					
High compliance	76	1.9	1.6	0.755	0.452
Low compliance	40	1.7	1.6		
CAT score					
High compliance	163	25	7.6	1.771	0.078
Low compliance	103	23	8.5		
mMRC score					
High compliance	163	3.9	1.1	0.428	0.669
Low compliance	103	3.9	1.1		

Notes: High-compliance group (n=163); low-compliance group (n=103).
Abbreviations: ICU, intensive care unit; CAT, COPD Assessment Test; mMRC, modified Medical Research Council.

and compliance of ≥5 hours was achieved by 70% of the cohort.[15] For many patients, domiciliary NIV is a difficult-to-tolerate treatment method, and they feel uncomfortable.[16] The most important components determining the compliance of the patient to NIV include patient's comfort, mask fit and leak, the presence of side effects (ie, nasal congestion, conjunctivitis, sleep interruption), symptoms (dyspnea, morning headache, hypersomnolence), comorbidities, and change in ABG values.[17] In this study, we detected significantly higher rate of cardiac failure in the high-compliance group than the low-compliance group. To date, the effects of domiciliary NIV on the heart in COPD patients have been rarely investigated. A recent review indicated that use of long-term NIV in chronic hypercapnic respiratory failure contributes to the reduction in the work of breathing and improvement in gas exchange, which in turn may have beneficial effects on the heart.[18] Additionally, peripheral blood samples were taken from 20 stable hypercarbic COPD patients before and

3 months after the initiation of NIV, and it was detected that reductions in $PaCO_2$ during NIV were associated with decreases in proBNP levels in a recent study.[19] While the number of dementia patients was very low in our study, the fact that all of these patients were in the low-compliance group may indicate the importance of cognitive function for treatment compliance. We observed higher rate of obesity in the high-compliance group. A recent study included 213 COPD patients (48% obese) and 47.7 months follow-up. The results showed that survival was better in obese COPD than nonobese COPD, and also compliance to NIV was associated with better prognosis only in obese COPD.[20] This might be due to the fact that improvements obtained from NIV therapy are more in case of coexistence of obesity and COPD. With regard to side effects, we detected that only conjunctivitis was more frequently seen in the high-compliance group. This may be attributed to longer duration of ventilator exposure and higher IPAP levels in the high-compliance group. We did

Table 5 Assessment of the relationship between the compliance of NIV and IPAP levels, BMI, symptom scores and card readout

		BMI (kg/m²)	mMRC score	CAT score	IPAP (cmH₂O)	Compliance of NIV (card readout) (hours/d)
Compliance of NIV (all patients [N=266]; card readout or self-report; hours/d)	r	0.046	0.092	0.163	0.267	0.832
	p-value	0.460	0.134	0.008**	0.000***	0.000***
	N	266	266	266	266	115

Note: **p<0.01, ***p<0.001.
Abbreviations: NIV, noninvasive ventilation; IPAP, inspiratory positive airway pressure; BMI, body mass index; mMRC, modified Medical Research Council; CAT, COPD Assessment Test.

not detect any difference in terms of hypercarbia findings (headache and hypersomnolence) between 2 groups. Some studies exploring the relationship of different types of NIV with treatment compliance in COPD have been published.[21,22] High IPAP use is proposed as one of the most common reasons for treatment incompatibility.[23] However, in later randomized controlled trials, high-intensity NPPV has been demonstrated to increase tolerance and compliance compared to the low-intensity NPPV.[3,21] Similarly, we detected higher IPAP use in the high-compliance group. Furthermore, we also showed a weak but positive correlation between compliance of NIV (hours/d) and IPAP level. The rate of use in ST mode was higher than S mode in the high-compliance group compared to the low-compliance group in our study. This may be explained by the fact that in ST mode the patient can use higher IPAP, and also ventilation support continues in case of apnea. Sixty-eight percent of the patients had some kind of humidification system; however, we did not detect any difference between the groups in terms of humidifier use. Similarly, in patients with sleep apnea and for whom continuous positive airway pressure treatment was initiated, addition of heat humidification did not make any difference in terms of compliance.[24] Exacerbation is the most important factor for increased morbidity and mortality in COPD patients. Approximately 10%–25% of the patients who were admitted to the hospital with hypercapnic respiratory failure due to COPD die in hospital.[25] However, the effects of domiciliary NIV on clinical outcomes of chronic hypercapnic COPD patients have been contradictory in studies and meta-analyses.[26–28] While in one study, domiciliary NIV significantly decreased hospital admissions,[29] in another it demonstrated a borderline decrease,[30] and conversely in another study, it has been demonstrated that hospital admissions are less in patients receiving standard care compared to the patients using NIV.[31] In a multicenter Italian study, low-intensity NPPV with LTOT and LTOT alone were compared, and no difference was detected in terms of hospital admissions at the end of 2-year follow-up.[32] On the other hand, in a recent observational study, it has been suggested that decrease may be observed in hospitalization rates and ICU admissions in patients who received high-intensity NPPV.[33] We did not detect any difference between the high- and the low-compliance groups in terms of hospitalization and emergency department and ICU admissions within the last year. Furthermore, there was no difference between the 2 groups in terms of mMRC and CAT scores in our study. Similarly, in a recent multicenter randomized controlled trial, while a significant improvement in PaCO$_2$ was obtained after 3-month NPPV therapy in stable

hypercarbic COPD patients compared to the control group, no difference was detected between the groups in terms of CAT and dyspnea score.[14] This study has several limitations. First, while the patients were recruited prospectively in a certain period of time, but many patients' ABG and PFTs were recorded retrospectively, if present, in their previous follow-ups. Second, we could only get card readout data in 115 patients, but also we detected a statistically high concordance between these patients' own statement and card readout data. Third, the number of hospital admissions within the last year were recorded retrospectively. Finally, this study was designed as a real-life trial and we included COPD patients with accompanying OSA or obesity. However, we thought that this was not a substantial limitation, and also we had the opportunity to investigate the effect of coexistence of these situations with COPD on the domiciliary NIV compliance.

Conclusion

We believe that the patient and ventilator factors which may be related to domiciliary NIV treatment compliance were comprehensively evaluated in our study, which has revealed very substantial results. Accurate determination of the patients who may have better compliance to NIV therapy will enable better patient selection and also help in defining optimal ventilator type and settings suitable for the patient so as to improve their treatment compliance. New studies on this topic are needed to increase long-term treatment compliance and response.

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Disclosure

The authors report no conflicts of interest in this work.

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