Research Article

Role of Domiciliary Noninvasive Ventilation in Chronic Obstructive Pulmonary Disease Patients Requiring Repeated Admissions with Acute Type II Respiratory Failure: A Prospective Cohort Study

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Abstract

Background: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with acute hypercapnic respiratory failure (AHRF) is associated with high mortality and increased risk for further exacerbations and hospitalization. While there is ample evidence regarding the benefit of noninvasive ventilation (NIV) during AECOPD, evidence supporting long-term noninvasive ventilation (LTNIV) for more stable COPD patients is limited. **Objective:** The aim of this study is to assess the effectiveness of LTNIV in COPD patients requiring frequent hospital admissions and NIV support for AHRF. **Materials and Methods:** A prospective cohort study including 120 patients having survived an admission requiring NIV support for AHRF due to COPD, with a history of ≥3 similar episodes in the past year. Patients were advised LTNIV (30) with standard treatment, or (90) standard treatment alone. Both groups were followed up for 1 year. Among non-NIV group 10 died, and 8 lost follow-up, whereas two died in NIV group. The primary endpoint was death. Data of remaining 100 patients were analyzed for other objectives-number of readmissions, AHRF, Intensive Care Unit (ICU)/ventilator requirement, dyspnea, quality of life, exercise tolerance, lung function, and arterial blood gases. **Results:** LTNIV group had 40% reduction in mortality (6.6% vs. 11.1%). There was significant reduction in number of hospital admissions (28.6% vs. 84.7%: P <0.05), ICU admissions (7.1% vs. 56.9%: P = 0.01), ventilator requirement (3.6% vs. 30.6%: P = 0.003), AHRF (7.1% vs. 48.6%: P = 0.000) and improvement in partial arterial CO_2 pressure (39.8 ± 2.1 vs. 57.03 ± 3.7 mmHg) and severe respiratory insufficiency score (P < 0.05) among LTNIV group, but no significant change in lung function and exercise tolerance. **Conclusion:** Patients tolerated LTNIV well and had a better outcome compared to those without NIV. LTNIV may be considered in patients with recurrent AHRF.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, home mechanical ventilation, hypercapnic respiratory failure, long-term noninvasive ventilation, noninvasive ventilation

Introduction

Chronic obstructive pulmonary disease (COPD) is the 4th leading cause of death in the world and is projected to be the 3rd leading cause of death by 2020 as per GOLD 2017. Globally, the prevalence of COPD is alarmingly rising in countries of all levels of development. Hence in the arena of management, more importance is being given to modify the disease process, to provide better medical care and thus reduce the burden on patients, caregivers, and society. Main factors that determine the prognosis include frequency of exacerbations and respiratory failure, which may or may not require ventilator assistance.[1] Advances in technology have revolutionized mechanical ventilation. Over the past three decades, the application of noninvasive ventilation (NIV) has emerged as a core therapy in the management of patients with acute and chronic respiratory failure.[2] It has become an integral tool in the management of respiratory failure, in both home setting and the critical care units.[3]

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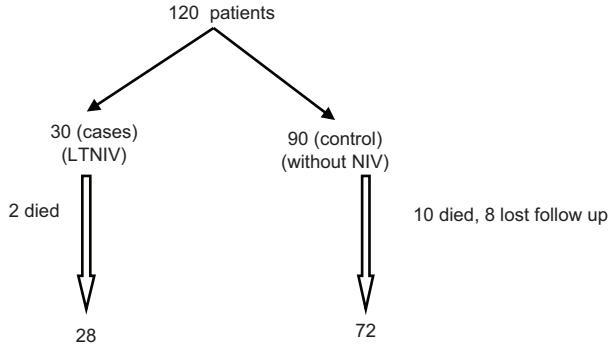
Despite the success of NIV in the management of acute hypercapnic respiratory failure (AHRF) in COPD patients, survivors in this group have a high risk of further life-threatening events. Previous studies on the benefits of home NIV in patients with COPD are conflicting. While there is ample evidence regarding the benefit of NIV during an acute exacerbation of COPD, evidence supporting long-term noninvasive ventilation (LTNIV) for more stable COPD patients is limited. This study is aimed to assess the effectiveness of LTNIV in COPD patients requiring frequent hospital admissions and NIV support for AHRF.

Materials and Methods

This prospective cohort study was conducted at a tertiary care center in North Kerala and patients were recruited from September 2015 to November 2016. We screened COPD patients admitted in our department with severe exacerbation and persistent respiratory acidosis (indicated by an arterial pH <7.35 and partial arterial CO_2 pressure ($PaCO_2$) >45 mmHg) despite initial treatment with bronchodilators, corticosteroids ± antibiotics, *z* requiring NIV/ventilatory support with history of ≥3 similar episodes (including present episode) in the past 1 year, who were under optimal medical treatment (tiotropium 9 μg + fomoterol 6 μg metered-dose inhaler (MDI) 2 puffs morning and budesonide 200 μg + formoterol 6 μg MDI 2 puffs at night, theophylline, vaccinated with pneumococcal and influenza vaccine). The study population included those who survived the present episode of AHRF and $PaCO_2$ remained >45 mmHg at the time of discharge. Arterial blood gas (ABG) analysis for inclusion purpose was done 6 h after stopping NIV support. Those with coexisting obstructive sleep apnea/obesity hypoventilation syndrome, chest wall or neuromuscular disease, significant systemic illness, and moribund patients were excluded from the study.

A total of 120 patients admitted with AHRF met the inclusion criteria. All the patients were advised long-term NIV on discharge. Patients and a close relative were counseled in detail about benefits and problems of LTNIV use. Only 30 patients were willing for home NIV for financial and social reasons. The remaining 90 patients receiving only standard treatment were taken as controls [Flow chart 1]. All the patients were followed up for 1 year.

Patients were instructed to use NIV while in bed and intermittently for 2 h while awake (1 h during forenoon and 1 h during the afternoon) during 1st month using an oronasal mask. After that, patients were instructed to use NIV for a minimum of 6 h every night. Pressure setting advised was 1 cm of H_2O less than the pressure with which the patient was managed at the time of discharge. Adequate instructions regarding how to use NIV machine, service center contacts for any emergency were given to the patient. These patients were assessed 1 month, 6 months and 1 year on follow-up. Baseline 6 min walk test (6MWT) and spirometry were done during the



Flowchart 1: Flow chart showing patient recruitment, allocation into NIV and non NIV group and patients available for follow-up analysis

1st month visit as patients were not fit to perform these tests at the time of discharge. ABG and 6MWT were repeated in the follow-up visits. Spirometry was repeated during the final visit. Compliance was assessed during review visits using questionnaire and details collected over the phone, at the 4th, 8th, and 10th months. Instructions regarding the use of saline nasal drops as needed and adequate hydration to relieve drying of the nose, pressure relieving dressings on the bridge of the nose to prevent ulceration and effective mouth care, were also given.

Death was the primary endpoint of the study. Secondary endpoints included some readmissions, AHRF, Intensive Care Unit (ICU)/ventilator requirement, quality of life, exercise tolerance, lung function, and ABGs. Quality of life was assessed using severe respiratory insufficiency (SRI) questionnaire.

Written informed consent was obtained from all patients, and the study protocol was approved by the Institutional Research and Ethical Committee. Statistical analysis was performed using SPSS version 18 software. Differences were measured using Chi-square test and *t*-test. Results are presented as mean with standard deviation. A value of $P < 0.05$ was considered as statistically significant.

Observations

Males constituted majority of the study population - 71.4% (NIV group), 59.7% (non-NIV group). Mean age of the NIV group was 56.8 ± 4.1 and control group was 59.8 ± 3.2 years. The mean inspiratory positive airway pressure prescribed was 15.4 cm of H_2O (range 12–18 cm of H_2O) and mean expiratory positive airway pressure (EPAP) was 7.4 cm of H_2O (range 5–9 cm of H_2O). Baseline values are depicted in Table 1.

Mortality among the NIV group was 6.6% (2 out of 30) and non-NIV group was 11.1% (10 out of 90) (relative risk - 0.6) revealing a 40% reduction in mortality among those using home NIV. NIV group revealed lesser number of hospital admissions (28.6% vs. 84.7%), ICU admissions (7.1% vs. 56.9%), ventilator requirement (3.6% vs. 30.6%), and AHRF (7.1% vs. 48.6%) [Table 2].

ABG among the two groups at the end of the study showed statistically significant improvement in NIV group

[Figures 1and 2]. Patients using home NIV revealed the better quality of life compared to non-NIV group [Table 3].

However, we could not reveal significant improvement in lung function and exercise tolerance [Table 4].

Compliance with NIV use was good in the study group. The average nocturnal use of NIV was >5 h per night. Regarding the adverse effects, 10 out of 28 patients with NIV reported minor adverse effects-abdominal distension (5), nasal drying (2), and nasal bridge ulceration (3). Pressure area assessment, skin care, and oral hygiene were assessed at each review. None of the patients had significant adverse effects requiring discontinuation of NIV.

Discussion

Owing to its significant burden both on the individual and society, COPD is an area of intensive epidemiologic and clinical research. Measures are being widely implemented to improve management and provide a better quality of life for the patients. Advanced COPD is characterised by irreversible severe airflow obstruction and chronic hypercapnia. Globally, home mechanical ventilation (HMV), mainly noninvasive is increasingly employed to treat patients suffering from chronic hypercapnic respiratory failure.[4] The rapid growth of HMV has been attributed to increased awareness of and experience with the indication and technology; the availability of affordable NIV machines; pressure to reduce hospital stay; and improved life expectancy in treated patients. Compared with older reports, COPD patients constitute an increasingly high proportion of the population on HMV, and a growing number of them are maintained on home NIV. Even though it has been shown to reduce intubation and in-hospital mortality in patients with AHRF, little information exists on the outcomes following discharge. Respiratory muscle fatigue significantly contributes to gas exchange abnormalities in COPD. NIV may help overcome the fatigue by resting the respiratory muscles and thus help improve gas exchange. Patients with COPD are more likely to have nocturnal hypoventilation, especially during rapid eye movement (REM) sleep. This is due to atonia of intercostal muscles and results in decreased chest wall

Table 1: Baseline values

	NIV group	Non NIV group
Males	71.4% (21)	59.7% (56)
Females	28.6% (9)	40.3% (34)
Age (yrs)	56.8±4.1	59.8±3.2
$PaCO_2$ (mmHg)	49.2±1.9	49.1±2.1
PaO_2 (mmHg)	59.3±3.1	58.9±2.8

Table 2: Comparison of outcome between patients on noninvasive ventilation and controls

	NIV group	Non NIV group	
Mortality	6.6% (2)	11.1% (10)	RR=0.6
Hospital admissions	28.6% (8)	84.7% (61)	*P*=0.002
ICU admissions	7.1% (2)	56.9% (41)	*P*=0.003
Ventilator requirement	3.6% (1)	30.6% (22)	*P*=0.002
AHRF	7.1% (2)	48.6%(35)	*P*=0.000

Table 3: Comparison of arterial blood gas and SRI score between noninvasive ventilation group and control group

	Baseline	End of study	*P*
$PaCO_2$ - NIV group (mmHg)	49.2±1.9	39.8±2.1	0.001
$PaCO_2$ - Non NIV group (mmHg)	49.1±2.1	56.1±3.7	
PaO_2 - NIV group (mm Hg)	59.3±3.1	67.8±3.3	0.004
PaO_2 - Non NIV (mm Hg)	58.9±2.8	56.4±3.8	
SRI - NIV group	51.7±5.3	67.6±7	0.000
SRI - Non NIV	50.9±3.2	55.4±3.2	

Table 4: Comparison of FEV1 and exercise tolerance between noninvasive ventilation and control groups

	Baseline	End of study	*P*
FEV1 - NIV (%)	42.1±1.9 (1st month)	40.5±1.1	0.12
FEV1 - Non NIV	41.2±2.1 (1st month)	36.8±1.3	
6MWT (metres) - NIV	308.2±30.1 (1st month)	304±26.0	0.20
6MWT - Non NIV	307.4±25.4 (1st month)	291.3±18.2	

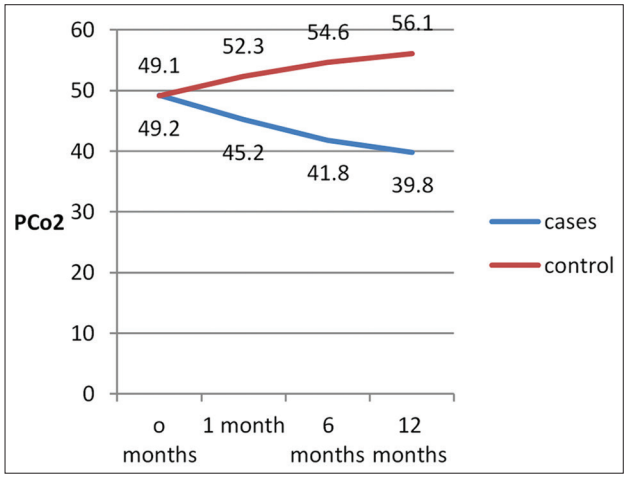


Figure 1: $PaCO_2$ trend over the study period

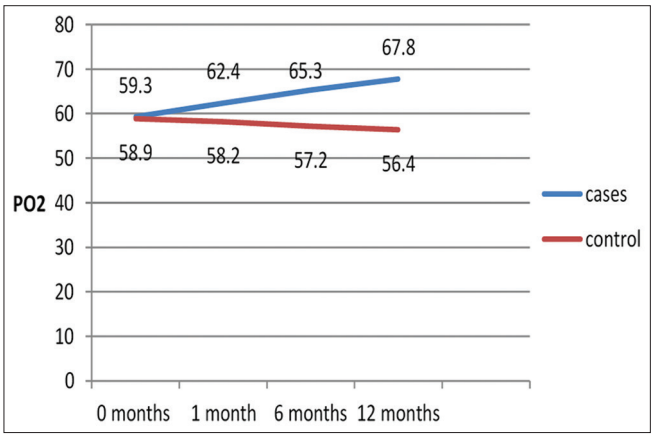


Figure 2: Changes in PaO_2 over the study period

compliance. This atonia results in diaphragm being the only muscle of respiration. Moreover, the hypercapnic ventilatory response is reduced during sleep, especially during REM sleep.

Over the past decade, more and more patients are using home NIV in India along with home oxygen. The demand for home NIV is increasing because of the rising cost of in-patient care in hospitals, availability of compact NIV machines and comfortable masks. However, there are no data from India to support LTNIV use.

In this study, death was taken as the primary endpoint, and secondary endpoints included other patient-centered outcomes. We found that there was a significant reduction in mortality, hospital re-admissions, ICU admissions, AHRF, ventilator requirement and improvement in $PaCO_2$, PaO_2 and SRI score in domiciliary NIV group. By previous studies, we found nosignificant changes in lung function following initiation of LTNIV.

Previous studies reveal conflicting results on home NIV in COPD patients. Earlier small studies showed benefit from home NIV, but the later randomized control trials yielded conflicting results in chronic hypercapnic COPD patients. The discrepancies in the results are due to the difference in criteria in patient selection, use of NIV settings incapable of achieving adequate ventilation, and poor adherence to NIV.

Several outcome measures have been investigated for the use of home NIV in COPD patients. Uncontrolled data have suggested that home NIV might reduce both hospital admission and clinic visits in severe COPD with hypercapnic respiratory failure. Jones *et al.* administered home NIV to 11 stable COPD patients with chronic hypercapnia who did not respond to conventional treatment.[5] Hospital admissions and clinic visits were halved in the subsequent year, together with a sustained improvement in ABGs. A cost saving was revealed with home NIV in severe COPD in another similar uncontrolled observational study.[6]

Conversely, results from randomized controlled trials (RCTs) have been conflicting. There are studies suggesting that home NIV was not superior to standard treatment instable severe COPD. RCT of domiciliary noninvasive positive pressure ventilation in severe COPD by Garrod *et al.* revealed no significant changes in lung function.[7] Nocturnal NIV in COPD patients with prolonged hypercapnia for acute respiratory failure: randomized, controlled, parallel group study conducted by Struik *et al*. concluded that there is an improvement in arterial gases, but no effect on survival/admissions.[8]

A more recent study by Cheung *et al.* tested the hypothesis that continuation of home NIV after an episode of AHRF treated by NIV in COPD patients would reduce the likelihood of recurrent AHRF leading to death or requiring NIV/intubation.[9] The proportion of patients developing recurrent AHRF in the NIV group was 38.5% versu. 60.2% at 1 year ($P = 0.039$).

Home NIV was found to reduce mortality in COPD patients with persistent hypercapnia in a study in Germany by Köhnlein *et al*. This study was conducted in stable COPD patients (no exacerbation in a 4 weeks run in period). 1-year mortality was 12% in NIV group and 33% in control group, revealing a clear advantage for home NIV compared to control. This trial had to be terminated early because of significant mortality reduction observed in the NIV group.[10]

In contrast, the RESCUE trial from the Netherlands failed to show a survival benefit in patients with home NIV. In this trial, the patients were recruited following an acute exacerbation of COPD with respiratory acidosis requiring NIV support. On discharge from hospital, the patients were randomized to receive either domiciliary NIV or standard care. Even though this study reduced mean noctutnal $PaCO_2$ in the NIV group compared to standard care, there was no effect on survival.[8] This study has a recruitment protocol similar to our study, i.e., patients were recruited following an acute hypercapneic exacerbation of COPD. However, previous history of hypercapnic respiratory failure was not considered as an inclusion criteria. Hence, the recruited patients may not have had significant chronic type II respiratory failure that may have benefited from home NIV.

In another recently published trial by Murphy *et al*. it was found that adding home NIV to home oxygen therapy prolonged the time to readmission and death. The eligibility criteria for this study were very stringent. Patients were assessed 2 weeks after an episode of resolution of decompensated respiratory acidosis. Persistent hypercapnia ($PaCO_2$ >53 mmHg) with pH >7.3, was required to be eligible for the study. This study also adopted a mean inspiratory pressure of 24 cm H_2O and EPAP of 4 cm H_2O.[11]

In this study, even though there is mortality benefit as well as improvement in $PaCO_2$, there was no improvement in forced expiratory volume in 1 s or 6MWD at the end of 1 year study. As all the patients had severe-to-very severe COPD with chronic type II respiratory failure, an improvement in these parameters could not be demonstrated.

The benefits of domiciliary NIV are well documented mainly in patients with neuromuscular disorders. In several studies, participants reported experiencing benefits such as improved breathing, a sense of immediate relief, good sleep, increased alertness, and reduced dyspnea on exertion after LTNIV use. In a study by Ando *et al*. Regarding acceptance of NIV in patients with motor neurone disease; eventhough, it was found to be effective in respiratory support, many of the patients were not tolerating NIV due to psychological reasons. The threat to the self, the sense of loss of control, and negative views of NIV resulting from anxiety were more important to those patients than prolonging life in its current form.[12] Acceptance was not a problem in our patients; eventhough, the psychological aspects were not analyzed based on structured questionnaire.

One of the limitations of our study is the small sample size. Even though there was active and control group, it was not a RCT. We could not design an RCT as the acceptability of LTNIV is low in our clinical experience due for financial and social reasons.

Conclusion

Over the past two decades, noninvasive ventilation has emerged as an indispensable respiratory modality in the management of hypercapnic respiratory failure. In our study, patients tolerated LTNIV well and had better outcome compared to those without NIV. There was significant reduction in mortality, hospital admissions, ICU admissions, AHRF, ventilator requirement, and improvement in $PaCO_2$, PaO_2, and SRI score in domiciliary NIV group. Hence, long-term domiciliary NIV can be considered as a treatment option in those admitted with recurrent type II respiratory failure.

The benefits of LTNIV should be confirmed with multicenter RCT. Since there are no definite guidelines for LTNIV, various trials have adopted various cut-off values for $PaCO_2$ to be eligible for LTNIV. Like the LTOT guidelines, definite protocol should be formulated for initiation, maintenance, and cessation of LTNIV use in patients with recurrent hypercapnic respiratory failure.

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Conflicts of interest

There are no conflicts of interest.

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