Original Article

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TANAFFOS

Non Invasive Ventilation's Effectiveness (NIV) in Patients with Interstitial Lung Disease and Hypercapnic Respiratory Failure

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Background: The therapeutic options for patients with interstitial lung disease (ILD) are limited. On the other hand, the role of noninvasive ventilation (NIV) in ILD management is not clear. This study investigated the effect of nighttime NIV in hypercapnic ILD patients.

Materials and Methods: In this unblinded randomized clinical trial, we included a total of 20 ILD patients admitted in a specialized center with hypoxia, $PaCO_2$>45, and HCO_3>27. Participants were randomly allocated into two groups; intervention (nighttime NIV plus standard treatment) and control (standard treatment). The severity of dyspnea and the quality of life (QoL) was evaluated at beginning of the trial and after 30 days through Modified medical research council (mMRC) dyspnea scale and the SF-36 health survey questionnaire. Paired or Wilcoxon Signed rank tests and independent samples t-test or Mann-Whiney U test were used for between and within groups analyses, respectively.

Results: The mean age of 20 patients enrolled was 62.57±6.67 and 40% were male. Although, a clinical significant improvement of dyspnea was detected in NIV group (P=0.046) after intervention, it was not statistically different from control group. Significant improvement was observed in physical functioning (P<0.001), social functioning (P=0.004) and pain (P=0.003) detected after 30 days in NIV group and the observed improvement in QoL was significantly higher than control group for physical functioning (P=0.042) and general health (0.049).

Conclusion: Our results suggest NIV treatment in patients with ILD and hypercapnic respiratory failure could be advised in order to improve physical functioning.

Key words: Noninvasive ventilation; Interstitial lung disease; Respiratory insufficiency; Hypercapnia; Surveys and questionnaires

INTRODUCTION

Interstitial lung disease (ILD) is a heterogenous group of devastating and progressive lung disease with similarities in pathogenesis and imaging characteristics (1, 2). Respiratory failure occurs commonly in ILD as the terminal event after prolonged course of the disease, but may be rarely the initial presentation of the disease. The treatment of acute respiratory failure in ILD may be challenging (3). Invasive mechanical ventilation is a conventional treatment for these patients. Despite the poor prognosis of the patients admitted with acute respiratory failure due to ILD, Non Invasive Ventilation (NIV) has

been considered as an alternative for selected patients with ILD. NIV could improve the short term prognosis in this group of patients (4, 5). In the retrospective study of small group of patients with ILD and chronic hypercapnic respiratory failure, Koschel and coworkers reported the beneficial effect of NIV on arterial blood gas parameters (5). Also, NIV has been used in several patients with end stage Chronic Obstructive Pulmonary Disease(COPD), lung fibrosis, and lung malignancy as a palliative treatment(6). The authors reported its beneficial effect on relieving dyspnea(6). However, the effect of NIV as outpatient treatment in ILD is unclear.

The adequate and reliable assessment of physical functioning is critical for evaluating the positive effects of a therapeutic modality. On the other hand, dyspnea is the most common and important symptom in ILD and affects the quality of life (QoL) significantly. Therefore, we decided to assess the effect of NIV on the severity of dyspnea and quality of life in patients with ILD.

MATERIALS AND METHODS

Study design and participants

In this unblinded randomized clinical trial, we enrolled a total of 20 patients with confirmed ILD who were admitted due to exacerbation of dyspnea and hypoxia. The sample size was estimated in the current study considering statistical power 0.80 for detecting the effect size of 5% based on mMrc scale, 20 patients (Figure 1).

Inclusion criteria were documented ILD according to HRCT and restrictive pattern in spirometry, $PaCO_2$>45 and HCO_3>27. We excluded patients with Congestive Heart Failure (Ejection Fraction less than 30% in echocardiography) (7), pneumonia, and pulmonary thromboembolism. Patients were randomly assigned in 1:1 ratio to receive NIV or standard treatment. Randomization was done through permuted block randomization with block size 2.

The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.457). Iranian registry for clinical trial code is IRCT20190312043032N1. (2020.01.30)

Interventions and outcomes evaluation

Intervention group was treated with NIV during sleep in addition to usual medical treatment, while control group received only medical treatment (anti-reflux and antitussive). Before intervention and after one month of trial, mMRC and SF-36 questionnaires were completed for all patients again. Questionnaires were completed by a person that was not informed about the intervention and control group. During the trial period, the compliance of patients for NIV and medical treatment was followed by telephone call. All patients in intervention group used NIV at least 4 hours during sleep, compatible with good compliance.

Dyspnea and quality of life were assessed by modified Medical Research Council (mMRC) (8) dyspnea scale and the SF-36 health survey questionnaire (9), respectively before discharge. The mMRC scale is a five-rating tool for assessment of experienced dyspnea by patients (8). It was shown that the mMRC dyspnea scale is a concise and practical tool for evaluating the quality of life in patients with COPD (8). The SF-36 questionnaire is a multi-item tool that evaluates the quality of health in different eight domains; Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health (9). We applied validated Iranian version of SF-36 questionnaire (10).

Statistical analysis

Between groups and within groups differences of variables before and after intervention were compared. Numerical variables were reported as mean and standard deviation and categorical variables as frequency (percentage). Normality of continuous data was evaluated by using Shapiro-Wilk test and Q-Q plot. Non-normality distributed continuous data were subjected to logarithmic transformation and those with normal distribution were

compared between groups by using independent samples t-test and non-normal one with non-parametric Mann-Whitney U test. Chi-squared test also was used for between groups comparisons in terms of categorical data. Within group comparisons for continuous data and categorical variables were conducted by using paired samples t-test (or non-parametric Wilcoxon signed rank test) and Mc-Nemar tests, respectively. Statistical analysis was performed by SPSS version 16 (Armonk, NY, USA: IBM Corp).

RESULTS

The mean age of 20 patients enrolled was 62.57±6.67 and 40% were male, and the two groups were comparable in terms of age, gender and severity of dyspnea at the beginning of study (P>0.05) (Table 1).

Dyspnea grading through mMRC questionnaire were reported grade 3 and 4 at the beginning and end of the study. The severity of dyspnea was higher in the NIV group and all of them were in grade four. Although, a significant clinical improvement of dyspnea was detected in NIV group (P=0.046) after intervention, however it was not statistically different from control group (Table 2).

Significant improvement was observed in physical functioning (P<0.001), social functioning (P=0.004) and pain (P=0.003) detected after 30 days in NIV group and the observed improvement in QoL was significantly higher than control group for physical functioning (P=0.042) and general health (P=0.049)(Table 3).

Table 1. Demographic characteristics of study participants in two groups

Variable	NIV γ group (N=10)	Control group (N=10)	P value*
Age, year	63.3±7.13	61.2±6.33	0.731
Male, n(%)	4 (40%)	4 (40%)	1

*Resulted from independent samples t-test and chi-squared test for continuous and categorical data.

γ Noninvasive ventilation

Table 2. Modified medical research council (mMRC) before and after intervention in NIV and control groups

	Before		After		P[1]
	3	4	3	4	
Control group	2 (20%)	8 (80%)	3 (30%)	7 (70%)	0.31
NIV γ group	0 (0%)	10 (100%)	4 (40%)	6 (60%)	0.049
P[2]	0.21		0.5		

P[1]: within group analysis, resulted from Mc-Nemar Test

P[2]: Between group analysis, resulted from Chi-squared or Fisher exact tests

γ Noninvasive ventilation

Table 3. The mean SF-36 questionnaire domains before and after intervention in NIV and control groups

	NIV γ group			Control group			P value2
	Before Mean±SD	After Mean±SD	P value[1]	Before Mean±SD	After Mean±SD	P value[1]	
Physical functioning	5±2.3	15±4.3	<0.001*	10±5.7	14±7.7	0.037*	0.042*
Role functioning/physical	7.5±12	13.8±18.1	0.34	12.5±17.6	17.5±16.8	0.34	0.87
Role functioning/emotional	10±16.1	14.8±17.5	0.34	36.6±29.1	23.3±27.4	0.10	0.35
Energy/fatigue	74±16.1	76.5±5.2	0.62	77.6±6.5	72.5±6.3	0.023*	0.09φ
Emotional well-being	53.6±7.1	50.8±2.6	0.20	48.7±6.7	48.8±6.1	0.97	0.36
Social functioning	24±8.7	35±5.2	0.004*	34±6.5	36.5±7.9	0.16	0.44
Pain	10±9.8	23.7±7	0.003*	25±5.8	28.7±6	0.081	0.72
General health	2.5±3.5	4.5±5.5	0.16	11±5.6	7±5.3	0.003	0.049*

[1] resulted from paired samples t-test or non-parametric Wilcoxon signed rank test, 2 resulted from independent samples t-test or non-parametric Mann-Whitney U test for comparing the changes from baseline between two group

* show significant difference

φ show marginally significant difference

γ Noninvasive ventilation

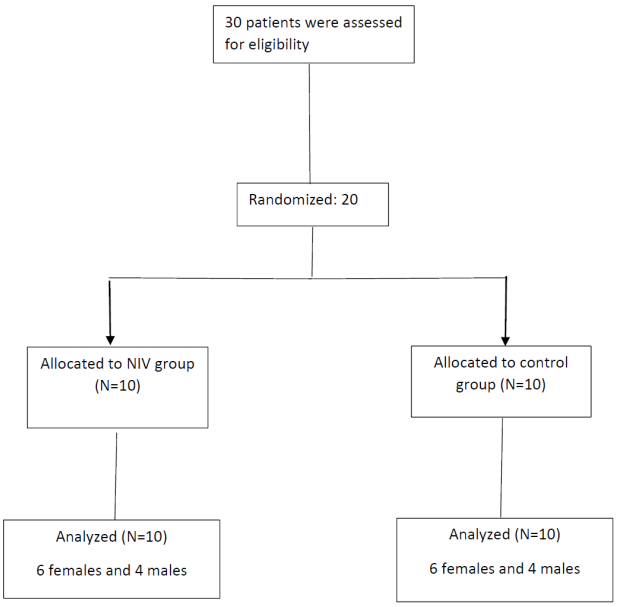

Figure 1. Consort flow diagram of patients

DISCUSSION

In this randomized clinical trial, night NIV in 10 patients admitted with acute hypercapnic respiratory failure for 30 days resulted in improvement of dyspnea, physical and social functioning and also pain. NIV is recommended for management of acute or acute on chronic hypercapnic respiratory failure in exacerbation of chronic obstructive pulmonary disease (11, 12). Also, the beneficial effect of NIV in decrease of mortality in patients with respiratory failure after lung resection was reported (13). A number of studies evaluated the effect of NIV in the management of patients with ILD and acute hypercapnic respiratory failure in avoiding tracheal intubation and its complication (5, 14-17). Studies of NIV as a long-term therapeutic modality in these patients are limited (4, 18, 19).

In the study of ten patients with IPF in Brazil, proportional assisted ventilation during submaximal exercise test increased exercise capacity and decreased the severity of dyspnea based on the Borg scale (19). We cannot compare their results with ours precisely, because of their different method in short term ventilatory support only during exercise. Nonetheless, it could be supportive study for the beneficial effects of ventilatory support in ILD.

In study of Dreher et al., pulmonary rehabilitation plus nighttime NIV significantly improved exercise capacity and quality of life in patients with ILD and chronic hypercapnic respiratory failure (20). Their inclusion criteria were similar to ours and the evaluation method for assessing dyspnea was Borg scale, but exercise capacity was measured by 6-minute walk test (6MWT). Their results are compatible with our results and suggest the therapeutic effect of NIV in hypercapnic ILD.

To our best knowledge, this research is one of the few studies on the therapeutic role of NIV as a long term treatment in ILD. Based on results of our study, NIV could decrease the severity of breathlessness in physical and social function, and so improves quality of life noticeably. Mentioned changes in this group of incurable diseases are valuable.

Our study has several limitations. First, the limited number of cases makes it difficult to generalize the results. Second, the period of intervention and follow up was not long. The longer course of treatment could be more informative. Finally, we did not have objective methods such as 6MWT and cardiopulmonary exercise test for evaluation of the effect of NIV.

In conclusion, our results suggest that NIV treatment could be advised in patients with ILD and hypercapnic respiratory failure to improve physical and general health. For confirmation, larger controlled trials are needed.

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