ORIGINAL ARTICLE

The Effect of High Flow Nasal Oxygen Cannula Versus Conventional Oxygen Therapy in COPD Patients with Indication for Long-term Oxygen Therapy: A Pilot Randomized Crossover Study

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Background: Long-term oxygen therapy (LTOT) is recommended to be used in stable chronic obstructive pulmonary disease (COPD) patients with severe resting hypoxemia. High-flow nasal oxygen cannula (HFNC) demonstrated benefits in acute hypoxemic respiratory failure. The mechanisms of HFNC by washing out dead space and decreasing work of breathing may be also beneficial in COPD patient who has an indication for LTOT.

Objective: To compare the effect of HFNC versus conventional oxygen therapy (COT) in terms of respiratory rate, gas exchange, and health-related quality of life.

Materials and Methods: A pilot randomized crossover study was conducted in eleven stable COPD patients. Subjects were randomly assigned to HFNC at a flow rate of 30 L/minute or simple nasal cannula at 2 to 4 L/minute for two weeks in a cross-over fashion. The primary outcome was respiratory rate. The secondary outcomes included blood pressure, heart rate, oxygen saturation (SpO_2), transcutaneous carbon dioxide pressure ($PtcCO_2$), and St.George's Respiratory Questionnaire (SGRQ) score.

Results: The duration of HFNC and COT use was 8 (IQR 3 to 13) and 14 (IQR 10 to 20) hours/day, respectively (p=0.039). Respiratory rate was significantly lower with HFNC compared to COT at 18 breaths/minute (IQR 16 to 20) versus 22 breaths/minute (IQR 20 to 25) , respectively (p=0.018). SpO_2 was significantly higher with HFNC compared to COT (p=0.046). No differences in blood pressure, heart rate, $PtcCO_2$, and SGRQ score were observed between the two groups. No serious adverse event from HFNC was observed.

Conclusion: The present pilot study demonstrated that HFNC was tolerable in patients with stable COPD who had an indication for LTOT. Respiratory rate was significantly lower and SpO_2 was significantly higher with HFNC compared to COT. Another study with larger sample size is needed to further clarify the efficacy of HFNC in stable COPD patients.

Keywords: Chronic obstructive pulmonary disease; Dyspnea; High-flow nasal cannula; Oxygen therapy; Respiratory rate

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Chronic obstructive pulmonary disease (COPD) is a common non-communicable disease in clinical practice. It is one of the top three causes of death worldwide and most of them occur in low- to middle-income countries[1]. A recent study demonstrated the prevalence of COPD was 12.2% in the general population[2]. In Thailand, the estimated prevalence of COPD varied between 5% and 8%, which was lower than the previous study. However, it is difficult to evaluate because of underdiagnosis and low awareness of the disease[3,4]. Data from COPD clinic at Siriraj Hospital indicates that 217 patients with stable COPD were reported and 26 of them were patients with severe COPD who had an indication for long term oxygen therapy (LTOT).

Previous studies demonstrated that COPD patients with severe resting hypoxemia who received LTOT for at least 15 hours per day had better clinical outcomes by increasing survival, decreasing hospitalization[5,6], and improving exercise tolerance[7,8]. The Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD) 2020 report recommends to use LTOT for patients with stable COPD who have

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already received appropriate treatment and have one of the following criteria including 1) arterial partial pressure of oxygen (PaO_2) of 55 mmHg or less or arterial oxygen saturation (SaO_2) of 88% or less with or without hypercapnia confirmed twice over a three-week period, or 2) PaO_2 between 55 to 60 mmHg or SaO_2 of 88%, if there was evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia with an hematocrit of more than 55%[1].

Nowadays, high-flow oxygen therapy has been increasingly used in current clinical practice. High-flow nasal oxygen cannula (HFNC) provides high flow rate of gas and constant fraction of inspired oxygen (FiO_2). It has shown benefits in terms of physiologic and clinical outcomes in patients with acute hypoxemic respiratory failure and it is recommended to use as a first-line treatment in acute hypoxemic respiratory failure[9]. The mechanisms of HFNC include 1) washing out nasopharyngeal dead space, 2) generating positive end-expiratory airway pressure (PEEP) from 1 to 7 cmH_2O, 3) altering nasopharyngeal resistance, and 4) increasing heat and humidification to protect airway mucosa and dryness symptom[10]. In normal subjects and patients with COPD, dry and cool air can trigger muscarinic receptor at nasal mucosa and results in bronchoconstriction[11,12]. HFNC provides warmed and humidified gas that may help to reduce bronchoconstriction. Few studies have evaluated the role of HFNC in patients with stable COPD[13,14]. Furthermore, the duration of HFNC use in these studies was very short. In addition, dyspnea symptoms and health-related quality of life were not evaluated in these studies. The aim of the present study was to evaluate the physiologic effects of longer duration of HFNC compared to COT in stable COPD patients who had an indication for LTOT.

Materials and Methods

Study design and subjects

A pilot randomized crossover study was conducted in COPD clinic of the Division of Respiratory Diseases and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand between June 2019 and March 2021. The protocol for the present study was approved by the Siriraj Institutional Review Board (COA No. Si 260/2019), and it was registered in the Thai Clinical Trial Registration (registration No. TCTR20190502002). Written informed consent to participate was obtained from each subject or their relatives. The present research project was supported by the Faculty of Medicine Siriraj Hospital, Mahidol University (grant number [IO] R016231037 (Fund3)).

The researchers enrolled patients 40 years or older who had known diagnosis of COPD based on post-bronchodilator forced expiratory volume at 1 second (FEV_1) over forced vital capacity (FVC) of less than 70% and had an indication for LTOT according to GOLD guideline[1]. Patients with history of lung resection, history of COPD exacerbation within the past three months, history of myocardial infarction, or heart failure within the past three months were excluded.

Study protocol and data collection

A crossover design was chosen for the present study because the researchers primarily focused on the physiologic variables that the within-patient variation was less than the traditional randomized parallel-group study, and it required fewer subjects. Subjects who met all eligibility criteria and none of the exclusion criteria were randomly assigned to receive HFNC (AIRVO-2™, Fisher & Paykel Healthcare, Auckland, New Zealand) or COT via a simple nasal cannula for at least 15 hours per day. The sequence of the therapy was allocated using sealed opaque envelope into 1) sequence A: subjects received HFNC at flow rate of 30 L/minute, temperature of 34°C, and FiO_2 was adjusted to achieve oxygen saturation by pulse oximetry (SpO_2) of at least 92%, then COT at flow rate of 2 to 4 L/minute, and 2) sequence B: subjects received COT at flow rate of 2 to 4 L/minute and then HFNC at flow rate of 30 L/minute, temperature of 34°C, and FiO_2 was adjusted to achieve SpO_2 of at least 92%. Each intervention was applied for two weeks in a cross-over fashion (Figure 1) without a washout period between the two interventions because it was a physiologic study to test two oxygen devices that was quite different from the study to test the effect of medication that may have the remaining effect of the intervention or medication, so we did not expect to see a carryover effect from such treatment.

Baseline demographic and clinical data including age, gender, body mass index, co-morbidity, smoking history, current COPD medication, history of exacerbation of COPD, baseline pulmonary function test, and arterial blood gas were collected. At each visit, vital signs, SpO_2, transcutaneous carbon

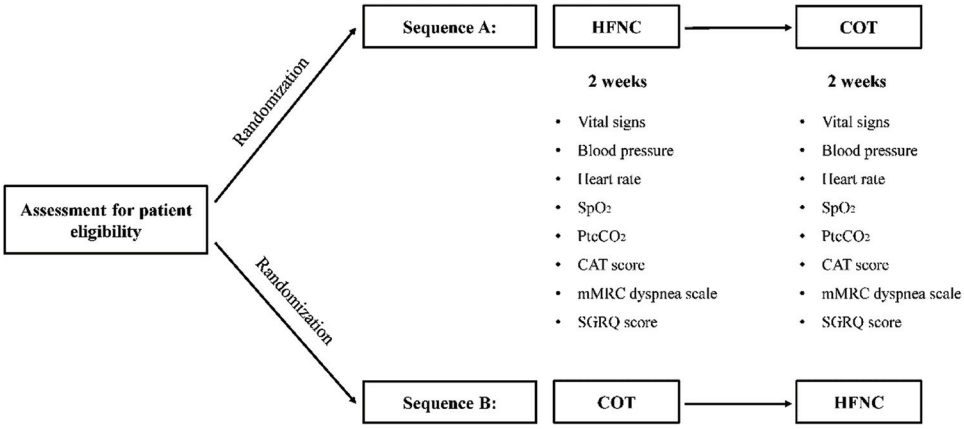

Figure 1. Study protocol.

CAT=COPD assessment test; COT=conventional oxygen therapy; HFNC=high-flow nasal oxygen cannula; mMRC=modified Medical Research Council; $PtcCO_2$=transcutaneous carbon dioxide pressure; SGRQ=St. George Respiratory Questionnaire; SpO_2=oxygen saturation by pulse oximetry

dioxide pressure ($PtcCO_2$) using a Sentec Digital Monitoring System (SenTec, Therwil, Switzerland), COPD assessment test (CAT) score, and St. George Respiratory Questionnaires (SGRQ) were evaluated and recorded after patient receiving each intervention for 30 minutes in a silent room.

Outcomes

The primary outcome was the effect of HFNC on respiratory rate compared to COT. The secondary outcomes were mean arterial pressure, heart rate, SpO_2, $PtcCO_2$, CAT score, and health-related quality of life between the two interventions.

Statistical analysis

Based on a previous study comparing HFNC and COT in patients with stable COPD[14], the researchers estimated that the decrease in respiratory rate after applying HFNC at flow rate of 30 L/minute for two weeks was approximately 20%. Using a two-sided α value of 0.05 and a power of 80% to detect the difference between the two groups, a sample size of 15 subjects in each group was calculated. To compensate for patients who would withdraw from the study, the researchers increased the sample size by 10% to 17 patients. Continuous variables were expressed as median (interquartile range, IQR). Categorical variables were expressed as frequency or percentage. Wilcoxon sign rank sum was used to compare continuous variables and chi-square test was used to compare categorical variables. A two-sided p-value of less than 0.05 was considered statistically significant. Data was analyzed using PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The present study was stopped early due to COVID-19 pandemic situation in Bangkok, Thailand. During the study period, 26 patients with stable COPD using home oxygen therapy in COPD clinic were screened and 15 of them were excluded as shown in the CONSORT diagram (Figure 2). Finally, 11 subjects were enrolled. Median age was 68 years (IQR 65 to 76) and 90.9% of them were males. Post-bronchodilator FEV_1/FVC and FEV_1 were 35.2 (IQR 31.0 to 53.9) % and 28.8 (IQR 22.1 to 34.9) % of predicted, respectively. Baseline respiratory rate, SpO_2, and $PtcCO_2$ were 23 breaths/minute (IQR 20 to 25), 90% (IQR 89 to 92) , and 49.2 mmHg (IQR 46.0 to 60.6), respectively. Other baseline demographics and clinical characteristics of enrolled subjects are shown in Table 1 and 2. Six subjects were randomized into sequence A, and five subjects were randomized into sequence B. Two subjects in each group were withdrawn. Four subjects were withdrawn with two subjects in sequence A due to active heart failure and unfamiliar to use HFNC and two subjects in sequence B due to active heart failure and refusing to participate after enrollment, as shown in Figure 2.

Seven subjects were analyzed for the physiological outcomes. Respiratory rate was significantly lower with HFNC compared to COT at 18 breaths/minute (IQR 16 to 20) versus 22 breaths/minute (IQR 20 to 25) , respectively (p=0.018). SpO_2 was significantly higher with HFNC compared to COT at 95% (IQR 93 to 98) versus 93% (IQR 90 to 96), respectively (p=0.046). There was a trend towards lower $PtcCO_2$ and SGRQ score in HFNC group compared to COT at 47.2 mmHg (IQR 37.7

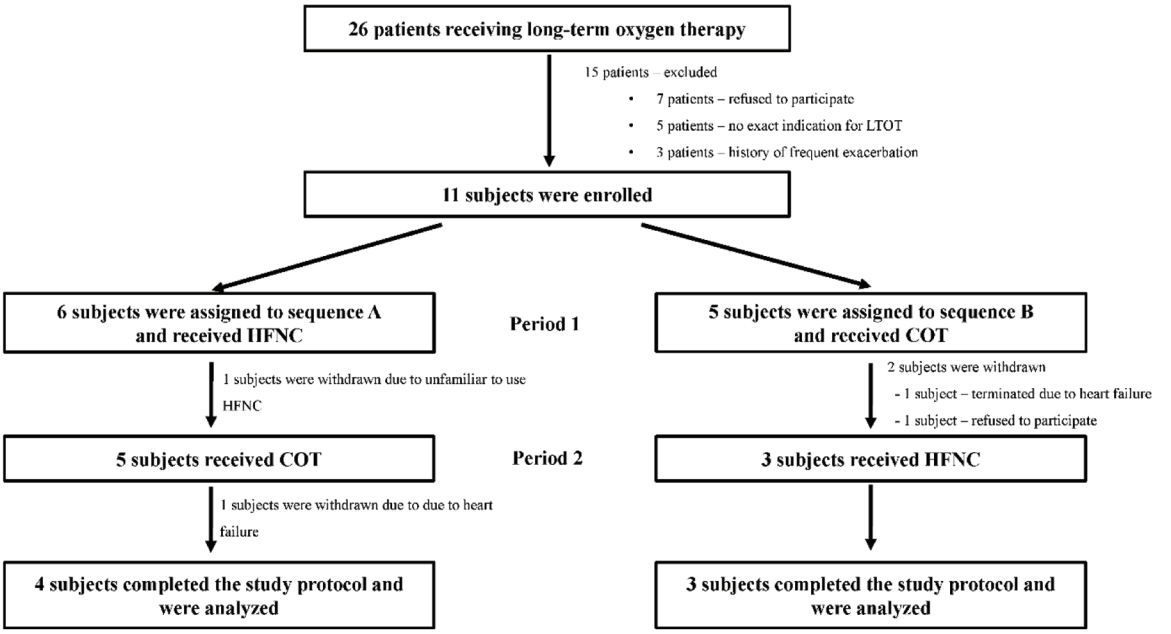

Figure 2. CONSORT diagram.

HFNC=high-flow nasal oxygen cannula; LTOT=long-term oxygen therapy

Table 1. Baseline demographics and patient characteristics

Variables	n=11
Age (years); median (IQR)	68 (65 to 76)
Male; n (%)	10 (90.9)
Body mass index (kg/m^2); median (IQR)	20.1 (17.6 to 29.5)
Tobacco smoking (pack years); median (IQR)	40 (27.5 to 60.0)
Comorbidity; n (%)	
Hypertension	7 (63.6)
Cardiovascular disease	3 (27.3)
Pulmonary hypertension	4 (36.4)
Malignancy	1 (9.1)
Others	5 (45.5)
Current COPD medication; n (%)	
Long-acting β_2-agonist	11 (100)
Long-acting antimuscarinic	11 (100)
Inhaled corticosteroids	10 (90.9)
Theophylline	10 (90.9)
mMRC dyspnea scale; median (IQR)	3 (2 to 3)
CAT score; median (IQR)	19 (15 to 21)
SGRQ score; median (IQR)	49 (33 to 70)

CAT=COPD assessment test; COPD=chronic obstructive pulmonary disease; mMRC=modified Medical Research Council; SGRQ=St. George Respiratory Questionnaires; IQR=interquartile range

Table 2. Baseline vital signs, gas exchange, and pulmonary function test

Variables	n=11; median (IQR)
Respiratory rate (breaths/minute)	23 (20 to 25)
Mean arterial pressure (mmHg)	84 (76 to 93)
Heart rate (beats/minute)	91 (84 to 100)
SpO_2 (%)	90 (89 to 92)
Arterial blood gas	
pH	7.42 (7.38 to 7.44)
$PaCO_2$ (mmHg)	50.6 (42.0 to 55.5)
PaO_2 (mmHg)	53.5 (49.7 to 60.6)
$PtcCO_2$ (mmHg)	49.2 (46.0 to 56.1)
Pulmonary function test	
Post-bronchodilator FEV_1/FVC (%)	35.2 (31.0 to 53.9)
Post-bronchodilator FEV_1 (L)	0.70 (0.56 to 0.90)
Post-bronchodilator FEV_1 (% predicted)	28.8 (22.1 to 34.9)
Post-bronchodilator FVC (L)	1.84 (1.72 to 2.33)
Post-bronchodilator FVC (% predicted)	59.7 (54.1 to 74.1)

CO_2=carbon dioxide; FEV_1=force expiratory volume at 1 second; FVC=force vital capacity; $PaCO_2$=arterial partial pressure of carbon dioxide; PaO_2=arterial partial pressure of oxygen; $PtcCO_2$=transcutaneous carbon dioxide pressure; SpO_2=oxygen saturation by pulse oximetry; IQR=interquartile range

to 55.6) versus 48.8 mmHg (IQR 40.1 to 63.0) and 43.5 (IQR 37.6 to 71.5) versus 51.6 (IQR 34.2 to 69.9), respectively, but no statistical significance was found. No differences in mean arterial pressure, heart rate, and CAT score were observed between the two groups (Table 3).

All enrolled subjects tolerated HFNC until the end of the study. Treatment duration for HFNC and

Table 3. Comparing physiologic variables between high flow nasal cannula (HFNC) and conventional oxygen therapy (COT)

Variables	HFNC (n=7); median (IQR)	COT (n=7); median (IQR)	p-value
Respiratory rate (breaths/minute)	18 (16 to 20)	22 (20 to 25)	0.018
Mean arterial pressure (mmHg)	86 (73 to 88)	83 (79 to 95)	0.105
Heart rate (beats/minute)	89 (82 to 95)	95 (75 to 100)	0.752
SpO_2 (%)	95 (93 to 98)	93 (90 to 96)	0.046
$PtcCO_2$ (mmHg)	47.2 (37.7 to 55.6)	48.8 (40.1 to 63.0)	0.310
CAT score	14 (8 to 22)	13 (11 to 21)	0.932
SGRQ score	43.5 (37.6 to 71.5)	51.6 (34.2 to 69.9)	0.866
Treatment duration (hours/day)	8 (3 to 13)	14 (10 to 20)	0.039

CAT=COPD assessment test; $PtcCO_2$=transcutaneous carbon dioxide pressure; SGRQ=St. George Respiratory Questionnaires; SpO_2=oxygen saturation by pulse oximetry; IQR=interquartile range

COT were 8 (IQR 3 to 13) and 14 (IQR10 to 20) hours/day, respectively (p=0.039). Four subjects (57.1%) preferred HFNC over COT because of improved sensation of dyspnea and facilitating secretion clearance. There was no serious adverse event from HFNC. Only one minor adverse event was reported that one patient developed uncomfortable and erythema at the nose during HFNC use. No COPD exacerbation occurred during the study period.

Discussion

The present study demonstrated that HFNC significantly reduced respiratory rate and improved oxygenation in patients with stable COPD who had an indication of LTOT. However, no significant differences in $PtcCO_2$, hemodynamic variables, dyspnea score, and health-related quality of life when compared to COT. Most subjects preferred HFNC over COT because it improved sensation of dyspnea and facilitated secretion clearance. However, the duration of HFNC use was significantly lower than COT.

The result of the present study was consistent with the previous studies in terms of reducing respiratory rate with HFNC. The short-term physiological studies demonstrated that implementing HFNC for 20 to 60 minutes significantly reduced respiratory rate varying between 2 to 5 breaths/minute compared to COT[13-16]. The major mechanism of HFNC for reducing respiratory rate can be explained by reducing dead space ventilation and improving alveolar ventilation[17,18]. In addition, HFNC alters nasopharyngeal resistance by decreasing inspiratory resistance and increasing expiratory resistance that leads to increase expiratory time and reduce respiratory rate[19,20]. Furthermore, the effect of PEEP generated by HFNC helps to reduce respiratory rate by reducing expiratory flow limitation, dynamic hyperinflation, and work of breathing[21-23].

Washing out airway dead space by HFNC may enhance CO_2 clearance. However, the present study did not demonstrate significant difference in $PtcCO_2$ between HFNC and COT although there was a trend towards decrease in $PtcCO_2$ with HFNC. This result was different from a previous study by Fraser et al.[13] comparing HFNC at flow rate of 35 L/minute and COT for 20 minutes in 30 patients with stable COPD. It demonstrated that $PtcCO_2$ was significantly lower with HFNC compared to COT at 43.3 mmHg versus 46.7 mmHg ($p<0.001$). Lower flow rate of HFNC in our study compared to the study by Fraser et al. might explain why there was no significant decrease in $PtcCO_2$. In addition, a study by McKinstry et al.[14] evaluated change in $PtcCO_2$ with HFNC at flow rate of 15, 30, and 45 L/minute. They demonstrated that elimination of CO_2 with HFNC had a flow-dependent effect. Furthermore, a study by Braunlich et al.[24] in stable hypercapnic COPD patients demonstrated that combining higher flow rate of HFNC and more leaks further reduced capillary PCO_2. Thus, the lack of significant change in $PtcCO_2$ in the present study might be explained by a small sample size.

In the present study, the researchers did not observe the improvement in dyspnea score and health-related quality of life with HFNC that might be explained by shorter duration of HFNC use. A randomized crossover study by Nagata et al.[25] compared HFNC with COT in 32 patients with stable hypercapnic COPD. They found no significant difference in dyspnea score. However, health-related quality of life assessed by SGRQ significantly improved after six weeks of HFNC use compared to COT. Furthermore, a randomized study by Storgaard et al. comparing long-term use of HFNC and COT in 200 COPD patients with chronic hypoxemic respiratory failure found that HFNC significantly

improved dyspnea score and health-related quality of life at three months and one year compared to COT[26].

Limitation

The present study has limitations. First, the present study was a preliminary study and had a small number of enrolled subjects due to the situation of COVID-19 outbreak in Thailand. This might limit the generalizability of the trial findings. However, physiological benefits of HFNC were still observed in the present study. Second, the average duration of HFNC use per day was less than our expectation because the HFNC device was complex, and patients were unfamiliar to use compared to COT. Nonetheless, it was longer than other previous physiological studies. Third, the present study was a short-term study, and it might not be enough to detect the difference in important clinical outcomes such as health-related quality of life or rate of COPD exacerbation.

Conclusion

The present study preliminary results showed that HFNC was tolerable in patients with stable COPD who had an indication for LTOT. It demonstrated physiological benefit by significantly reducing respiratory rate and improving oxygenation compared to COT. Further study and larger sample size are needed to evaluate the effect of HFNC on clinical outcomes.

What is already known on this topic?

HFNC demonstrated benefits in hypoxemic respiratory failure. It has also been evaluated in patients with stable COPD and acute hypercapnic COPD that showed physiologic benefits in terms of improving alveolar ventilation and alleviating inspiratory effort. However, the evidence of using longer duration of HFNC in COPD patients who have an indication for LTOT is limited.

What this study adds?

HFNC is feasible and tolerable in patients with stable COPD who had an indication for LTOT. The mechanisms of HFNC by washing out dead space, the effect of heat and humidification, and decreasing work of breathing leads to physiological benefit by significantly reducing respiratory rate and improving oxygenation compared to conventional oxygen therapy.

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Authors' contributions

All authors conceived and designed the study. NR and AN collected the data. NR, AN, BC, and KK analyzed and interpreted the data. NR and AN prepared the first draft of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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