A phase II study of High-Flow Nasal Cannula for relieving dyspnea in advanced cancer patients.

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Abstract

**Background:** The efficacy and tolerability of high-flow nasal cannula (HFNC) for relieving dyspnea in advanced cancer patients with limited prognosis requires elucidation.

**Methods:** Patients with advanced cancer who had dyspnea at rest (numeric rating scale, NRS≥3) and respiratory failure were enrolled. They were treated with HFNC for five days. Primary endpoint was change of mean modified Borg scale at 24 hours. Key secondary endpoints consisted of change in modified Borg scale during the study period and feasibility (Trial Identifier, UMIN000035738).

**Results:** Between February 2019 and February 2022, 25 patients were enrolled and 21 were analyzed. Twenty patients used inspired oxygen and the mean fraction of inspired oxygen (FiO2) was 0.34 (range, 0.21–1.0). At baseline, mean NRS (dyspnea) was 5.9 (range, 3–10). Median survival time was 19 days (range, 3–657).

The change of mean modified Borg scale was 1.4 (80% confidence interval [CI]: 0.8–1.9) at 24 hours, 11 patients showed 1.5 points improvement of modified Borg scale. Within 1 hour, nine patients showed 1.5 points improvement of modified Borg scale and such early responders were likely to maintain dyspnea improvement for 24 hours. Nineteen patients could continue HFNC for 24 hours and 11 patients completed five days of HFNC.

**Conclusion:** To our knowledge, this trial is the first prospective study to show the efficacy and tolerability of HFNC regarding dyspnea for five days in patients under palliative care. HFNC can be a palliative treatment option in advanced cancer patients with dyspnea.

Introduction

Approximately 10–70% of patients with advanced cancer and receiving palliative care present with dyspnea.1 Opioids and/or sedation are generally administered to relieve symptoms, but their efficacy is sometimes unsatisfactory. Moreover, patients’ quality of life is sometimes disturbed by detrimental effects of these medications, such as sleepiness or affected conversation.2,3 Development of effective
Non-pharmacological therapy is therefore critical for those who have dyspnea. Conventional oxygen therapy is frequently used for patients who are experiencing dyspnea with hypoxemia, but usually provides only moderate relief. Non-invasive ventilation may be an alternative method only when patients have intolerable discomfort or complications.

High-flow nasal cannula (HFNC) is an innovative device that can deliver gases at flow rates from 30 to 60 L/min for patients with a constant fraction of inspired oxygen (FiO₂) at 0.21 to 1.0, and it can be used to flush out the anatomical dead space with the assistance of a positive airway pressure effect. HFNC also minimizes inspiratory resistance by providing a gas flow that matches or exceeds the patients’ peak inspiratory flow, and delivers humidified gas warmed to 37°C which helps to promote expectoration. HFNC therefore lessens patients’ workload and consequently leads to an improvement of dyspnea. In the context of quality of life, patients are able to eat and speak during HFNC. Growing knowledge demonstrates huge benefits of HFNC over conventional oxygen therapy in patients with acute respiratory failure and stable hypercapnic chronic obstructive pulmonary disease. In the palliative settings, several retrospective studies have reported the efficacy and tolerability of HFNC for dyspnea. Although a few prospective studies have been conducted, the utility of HFNC was tested only for a short duration (2 hours at the longest). The primary aim of this trial was to assess the efficacy and tolerability of HFNC regarding dyspnea including severe as well as moderate for longer durations in patients under palliative care.

Materials And Methods

1. Patients

Patients with advanced cancer with Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4 were eligible for inclusion in this study if they met the following criteria: adults aged 20 years or older, having dyspnea at rest (numeric rating scale, NRS ≥ 3), with respiratory failure (partial pressure of arterial oxygen [PaO₂] ≤ 60 mmHg or an oxygen saturation [SpO₂] ≤ 90%), and known do-not-intubate status. We excluded patients who had already received HFNC. Other exclusion criteria include disturbed consciousness (Glasgow Coma Scale ≤ 12) and cognitive dysfunction. Patients who received opioids were allowed, but those who took frequent opioid rescue (≥ 8 times/day) and those receiving continuous sedation at registration were excluded.

2. Intervention

Patients received HFNC for five days by an Optiflow nasal cannula using an AIRVO 2 humidified high-flow system (Fisher & Paykel Healthcare, Auckland, New Zealand). Gas flow rate and heat were initially set at 40 L/min and 37°C. During HFNC treatment, they were adjusted to maintain participants’ comfort (≥ 30 L/min and 31°C to 37°C). A FiO₂ was subsequently adjusted to keep a SpO₂ of 90% or more. After 5 days of study treatment, all patients were switched to conventional oxygen therapy.
3. End Points and Assessments

Patient-reported dyspnea was assessed using modified Borg scale and NRS. Primary endpoint was the change of mean modified Borg scale (from 0 “no shortness of breath”, to 10 “worst possible shortness of breath”) at 24 hours. The health care provider presents the modified Borg scale to the patient at rest for 5 minutes and asks them to verbalize their score. Secondary endpoints consisted of changes of mean modified Borg scale; mean comfort level by NRS (from 0 “most uncomfortable”, to 10 “most comfortable”); vital signs (i.e., respiratory rate, \(\text{SpO}_2\), Glasgow Coma Scale) and the retention rate of HFNC and opioid use. These were collected at 1, 2 and 24 hours and then on days 3, 4, and 5, respectively.

4. Statistical Analyses

A previous clinical trial that showed HFNC was noninferior to non-invasive ventilation in decreasing dyspnea in patients receiving palliative care.\(^4\),\(^12\) We therefore assumed that HFNC will improve the change of modified Borg scale from 1.5 to 2.5 at 24 hours. As a result, 21 patients were required to achieve 80% of statistical power with one-sided \(\alpha\) of 0.10. Accounting for a dropout rate of 20%, we planned to enroll 26 patients.

Responders were defined as the patients that showed \(\geq 1.5\) points of improvement of modified Borg scale at 24 hours. Similarly, early responders were defined as the patients that showed \(\geq 1.5\) points of improvement of modified Borg scale at 1 hour or 2 hours. Between responders and non-responders, baseline characteristics and the treatment outcome were compared by unpaired t-test.

5. Ethics

Two institutions (Wakayama Medical University and Naga Municipal Hospital) participated in this study. Open label, single-arm study was conducted in accordance with the Declaration of Helsinki and all appropriate regulations and laws in Japan. The participants provided written informed consent. The study was approved by the institutional review board at each participating center and registered with the UMIN Clinical Trials Registry (UMIN000035738).

Results

1. Patients

Between February 2019 and February 2022, 25 patients were enrolled. One patient was excluded because they did not meet criteria (ECOG performance status of 2), so 24 patients received HFNC as protocol treatment (safety analysis set). Regarding the efficacy analysis, three patients were excluded because they withdrew within 24 hours so their modified Borg scale at 24 hours could not be collected (Fig. 1).

2. Characteristics at inclusion
Baseline characteristics of the participants are shown in Table 1. Mean age was 72 years (range, 48–92); male/female 17/4; ECOG performance status 3/4 17/4. The most common underlying disease was lung cancer, and opioids were administered to 10 patients for cancer-related pain or dyspnea. Their intravenous morphine-equivalent dose was 21 mg/day (range, 5–70 mg/day). Twenty patients used inspired oxygen and their mean FiO2 was 0.34 (range, 0.21–1.0). At baseline, mean modified Borg scale (dyspnea) was 5.2 (range, 2–10), mean NRS (dyspnea) was 5.9 (range, 3–10), and mean respiratory rate was 19 breaths/min (range, 12–25 breaths/min), respectively. Median survival time of all participants was 19 days (range, 3–657 days) (Fig. 2).
| **Table 1**  |  |
| **Patient characteristics** | **n = 21** |
| Age |  |
| mean (range) | 72 (48–92) |
| Sex-no. |  |
| Male / Female | 17 / 4 |
| Smoking status-no. |  |
| Never / (ex-) smoker | 3 / 18 |
| ECOG performance status-no. |  |
| 3 / 4 | 17 / 4 |
| Underlying malignancies-no. |  |
| Lung cancer / Malignant pleural mesothelioma | 20 / 1 |
| Opioid use for dyspnea relief at enrollment-no. |  |
| Yes / No | 7 / 14 |
| Intravenous morphine-equivalent dose (for dyspnea relief) |  |
| mean (range), mg / day | 21 (5–70) |
| Opioid use for cancer-related pain or dyspnea at enrollment-no. |  |
| Yes / No | 10 / 11 |
| Intravenous morphine-equivalent dose (for cancer-related pain or dyspnea) |  |
| mean (range), mg / day | 21 (5–70) |
| Type of oxygen therapy at enrollment-no. |  |
| Cannula / Mask / Room air | 13 / 7 / 1 |
| Fraction of inspired oxygen |  |
| mean (range) | 0.34 (0.21–1.0) |
| Respiratory rate |  |
| mean (range), / min | 19 (12–25) |
| Numeric rating scale score at enrollment (dyspnea) |  |

**Abbreviations:** ECOG; Eastern Cooperative Oncology Group, PS; Performance Status.
<table>
<thead>
<tr>
<th></th>
<th>n = 21</th>
</tr>
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<tbody>
<tr>
<td>mean (range)</td>
<td>5.9 (3–10)</td>
</tr>
<tr>
<td>Modified Borg scale score at enrollment (dyspnea)</td>
<td>5.2 (2–10)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG; Eastern Cooperative Oncology Group, PS; Performance Status.

3. Primary and secondary outcomes

Figure 3 shows the change of mean modified Borg scale during study period. The change of mean modified Borg scale at 24 hours, the primary endpoint, was 1.4 (80% CI, 0.8–1.9). At other timepoints, they were 1.3 (1 hour), 1.5 (2 hours), 0.82 (day 3), 1.8 (day 4), and 2.3 (day 5). Throughout the study treatment, no significant treatment effects were observed for mean level of comfort by NRS, respiratory rate, SpO₂, Glasgow coma scale, and intravenous morphine-equivalent dose of opioid use (Supplementary Table 1).

4. Subgroup analysis

Eleven patients (52%: 95% CI, 32–71) showed ≥ 1.5 points improvement of modified Borg scale at 24 hours and were thus considered to be responders. Between responders and non-responders, there were no differences in baseline characteristics (Supplementary Table 2). Ten patients had ≥ 1.5 points improvement of modified Borg scale within 2 hours and were considered to be early responders. As shown in Fig. 4a and b, these early responders were likely to maintain dyspnea improvement for 24 hours.

5. Feasibility

Mean HFNC time in overall participants was 88 hours (range, 2–120 hours). The retention rate of HFNC was 100% at 1 hour, 100% at 2 hours, 79% at 24 hours, 71% on day 3, 54% on day 4, and 46% on day 5 (Fig. 5). At the end of treatment, mean gas flow rate was 35 L/min (range, 30–45 L/min), mean FiO₂ was 0.36 (range, 0.21–0.8), and mean temperature was 35°C (range, 31–37°C). Adverse events (AEs) related to HFNC occurred in 16 patients, the most common being discomfort caused by heat in five patients, discomfort in the nose in four patients, disturbance of noise in two patients and dry mouth in two patients. Four patients felt respiratory asynchrony and two patients were distressed by restriction of body movement. Epistaxis was presented in one patient. None had severe AEs. Twelve patients discontinued treatment due to adverse events (i.e., uncomfortableness) and one due to delirium.

None of the patients had initiation of opioids after enrollment. Mean intravenous morphine-equivalent dose for cancer-related pain or dyspnea were 21 mg on day 1, 19 mg on day 2, 23 mg on day 3, 23 mg on day 4, and 27 mg on day 5 (n = 10). None of the patients received sedative drugs such as midazolam.
Discussion

Effective and feasible means of managing dyspnea are limited in clinical practice. Nonpharmacologic interventions such as airflow interventions of directing a fan at the cheek, standard supplemental oxygen for patients with hypoxemia, and other psychoeducational, self-management, or complementary approaches are usually offered as means of relieving dyspnea. For those without adequate relief from nonpharmacologic intervention, systemic opioids should be offered. Other pharmacologic interventions, such as corticosteroids and benzodiazepines, have also been discussed.\(^1\) In a recently reported randomized trial, high-dose dexamethasone did not improve dyspnea in patients with cancer more effectively than a placebo, but was associated with a higher frequency of adverse events.\(^{14}\) Given these circumstances, construction of evidence of the ways to relieve dyspnea, especially those under palliative care, is urgent.

Regarding oxygen therapy, several retrospective studies have reported the efficacy and tolerability of HFNC for dyspnea.\(^{10,11}\) Their clinical relevance was questionable, however, because they included patients in early stage and because they did not assess patient-reported outcomes. A few prospective studies with shorter duration of HFNC (2 hours at the longest) have been reported.\(^{12,13}\) A randomized trial compared HFNC with non-invasive ventilation and HFNC improved the change of modified Borg scale 2.1 at 2 hours, although further detail was not reported.\(^{12}\) Another trial, conducted in the emergency department, assessed the utility of HFNC compared with conventional oxygen therapy, but only for 60 minutes.\(^{13}\) A recent trial compared HFNC with conventional oxygen therapy.\(^{15}\) In the trial, only patients with severe dyspnea (VAS score ≥ 8 and a respiratory rate ≥ 30) were included and suggested a benefit of HFNC in relieving dyspnea at 72 hours. In short, the clinical utility of HFNC with longer duration for patients with moderate to severe dyspnea under palliative care has not been investigated.

To our knowledge, this trial is the first prospective study to assess the efficacy and tolerability of HFNC regarding dyspnea for five days in patients under palliative care. Unlike previous reports, we included patients with moderate dyspnea, making the study more relevant to daily clinical practice. This is thought to be valuable because we specifically sought relief of dyspnea for patients with cancer whose prognoses were less than a month. In participants overall, the change of mean modified Borg scale in this study was 1.4 at 24 hours. Although this did not reach the prespecified endpoint, it should be noted that almost all participants (95%) had already received conventional oxygen therapy before enrollment. Nonetheless, it is noteworthy that 11 patients (52%) showed 1.5-points improvement, the threshold in this study, and 12 patients (57%) showed 1.0-point improvement, a minimally clinically important difference (MCID) in the chronic lung disease.\(^{16}\) Regarding tolerability, about half of the patients could continue HFNC for five days despite their survival times being quite limited.

For patients with limited prognosis, exploration of early signals of durable efficacy with HFNC is critical. Although no baseline characteristics to predict responders could be elucidated, early change of modified Borg scale (at 1 or 2 hours) can be a surrogate marker of durable benefit of HFNC. Surrogacy of this early response should be explored in larger clinical trials.
This study has some limitations that require consideration. First, as this was a single-arm study, and HFNC was not compared with other options such as conventional oxygen therapy, non-invasive ventilation, and opioid use. Also, the placebo-like effect in assessing efficacy could not be fully eliminated. However, limited existing knowledge allowed conduction of this phase trial to explore the efficacy of HFNC. A second limitation is that opioid use could have caused an additive effect. To eliminate the limitation, we excluded participants who took frequent opioid rescue, and opioid usage was not significantly changed during study period. Finally, this was a small study conducted by the thoracic cancer department. Whether this result can be incorporated in non-thoracic cancer patients is still unknown. Further studies on HFNC compared with conventional oxygen therapy for relief of dyspnea are required to solve these limitations and remaining questions.

In conclusion, this trial is the first prospective study to show five-day efficacy and tolerability of HFNC for dyspnea in patients under palliative care. HFNC can be a palliative treatment option for patients with advanced cancer with dyspnea.

Declarations

Presentation of this study

The contents of this study were presented at the European Society for Medical Oncology (ESMO) congress (September 2022) in Paris, France.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki, was approved by the relevant institutional review boards, and was registered with the UMIN Clinical Trials Registry (UMIN000035738).

Competing interests

All authors have no conflict of interest to declare.

Authors' contributions

Eri Takase, the principal investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Takase, Akamatsu, Yamamoto.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Takase, Akamatsu, Yamamoto.

Critical revision of the manuscript for important intellectual content: Takase, Akamatsu.

Statistical analysis: Takase, Akamatsu, Shimokawa.
Administrative, technical, or material support: Takase, Teraoka, Akamatsu.

Supervision: Kanai, Yamamoto.

**Funding**

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**Availability of data and materials**

All data can be available on https://center6.umin.ac.jp/cgi-open-bin/ctr/index.cgi.

**Consent to participate**

All participants provided written informed consent.

**Consent for publication**

Consent for publication was obtained from all individual participants included in the study.

**References**


Figures
Figure 1. CONSORT diagram.

- 25 patients enrolled from Feb 2019 to Feb 2022
- 24 patients received protocol treatment (= Safety analysis set)
- 1 patient did not meet inclusion criteria (ECOG PS 2)
- 21 patients included in analysis (= Efficacy analysis set)
- 3 patients not evaluated for primary analysis (withdrew in ≤24 hours)

Figure 1

See image above for figure legend

Figure 2. Kaplan-Meier curve of overall survival.

![Kaplan-Meier curve](image_url)
Figure 2
See image above for figure legend

Figure 3. Change of mean modified Borg scale during the study period.

Figure 3
See image above for figure legend
Figure 4 a) Change in mean modified Borg scale with early responders and non-responders at 1 hour and b) at 2 hours.

Figure 4
See image above for figure legend

Figure 5. Retention rate of HFNC among safety analysis set (n = 24).
Figure 5

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Abbreviations: HFNC; High-Flow Nasal Cannula.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementary.docx