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Effects of high-flow nasal cannula oxygen therapy on oral intake of do-not-intubate patients with respiratory diseases

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ABSTRACT

High-flow nasal cannula (HFNC) oxygen therapy is used widely for hypoxemic respiratory failure. However, it is unknown whether the use of HFNC is compatible with retaining the ability to eat and drink of patients with end-stage respiratory diseases as a part of palliative care. A retrospective study was conducted on subjects with hypoxic respiratory failure due to end-stage respiratory diseases, including interstitial pneumonia and malignant respiratory diseases, who were treated with HFNC or reservoir mask oxygen therapy and died with do-not-resuscitate (DNR) and do-not-intubate (DNI) status. We compared the duration of eating solids and drinking liquids and clinical variables in the HFNC group with those in the reservoir mask group. The data from a total 43 subjects including 20 with HFNC and 23 with a reservoir mask were analyzed. Fitting HFNC to subjects temporarily improved oxygenation. Durations of survival, eating solids, and drinking liquids in the HFNC group were significantly longer than those in the reservoir mask group. No significant adverse effects were observed in either group. In conclusion, the use of HFNC led to prolonged survival while preserving the ability of oral intake in patients with DNR and DNI status.

Keywords: high-flow nasal cannula, palliative care, oxygen therapy, lung cancer, interstitial pneumonia

Abbreviations:
DNR: do not resuscitate
DNI: do not intubate
HFNC: high-flow nasal cannula
NIV: non-invasive ventilation
QOL: quality of life
SpO$_2$: oxygen saturation of a peripheral artery

INTRODUCTION

The high-flow nasal cannula (HFNC) is a device that can administer a high flow rate (30 to 60 L/min) and high concentration of oxygen by heating and humidifying it.[1-4] HFNC can provide

adequate oxygen support for acute hypoxemic respiratory failure in various diseases such as interstitial lung diseases, pneumonia, sepsis, multiple traumas, cardiac diseases, and malignant diseases.[5-10] Moreover, the use of HFNC for patients with end-stage respiratory diseases is also useful as a palliative treatment to manage dyspnea and hypoxemia.[5,11-13] Peters et al reported that this technique improved oxygenation and reduced breathing frequency in patients in respiratory failure with do-not-resuscitate (DNR) or do-not-intubate (DNI) status.[14]

The ability to eat and drink is one of the most important factors for maintaining quality of life (QOL) in both healthy subjects and patients with end-stage diseases. It is expected that patients with HFNC are able to eat and drink orally without disturbing oxygenation.[5] The high-concentration reservoir mask is another device for oxygen delivery which is conveniently able to supply a high fraction of inspired oxygen (F_IO_2).[9,12,15] In contrast to HFNC, a mask has to be taken off and changed to a simple nasal cannula while a patient is eating or drinking. Reduced oxygenation and dyspnea associated with removing the reservoir mask may disturb oral intake by such patients. However, the advantages of the use of HFNC for oral intake by patients with hypoxic respiratory failure due to end-stage respiratory diseases have not been fully elucidated.

The purpose of the present study was to examine the usefulness of HFNC as palliative oxygen therapy in patients with respiratory failure due to end-stage respiratory diseases, specifically interstitial pneumonia and malignancies, with DNR and DNI status. We focused on the ability to eat and drink while using HFNC and compared the duration of oral intake during the use of HFNC with that during the use of a reservoir mask.

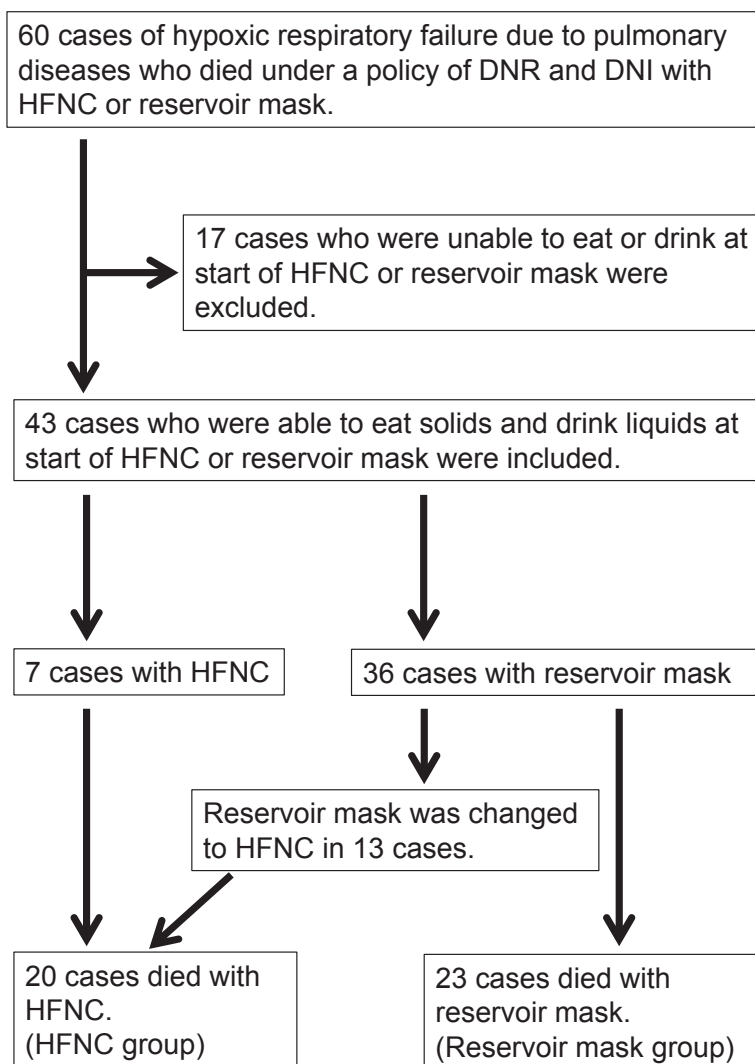## METHODS

Study design and subjects

A retrospective and observational study was conducted at Kariya Toyota General Hospital, a 672-bed regional medical center. Electronic medical records of consecutive subjects who underwent oxygen therapy using either HFNC or a reservoir mask for progressive respiratory diseases and who died with DNR and DNI status at the Department of Respiratory Medicine and Allergology, Kariya Toyota General Hospital from August 2013 to December 2016 were reviewed. During the observation period, patients underwent oxygen therapy using HFNC both in the intensive care unit and medical wards.

All subjects were provided with appropriate palliative care, which included oxygen therapy, rehabilitation, pain relievers, and sedation if needed. For sedation and pain relief, opioids including morphine, oxycodone, and fentanyl were intravenously, subcutaneously, or orally administered. Midazolam, a sedative, was intravenously injected.

A flow chart illustrating the inclusion process is shown in Figure 1. HFNC or a reservoir mask was in use at death in 60 cases. Of the 60 patients, 17 subjects who were unable to ingest orally at the start of oxygen therapy with HFNC or a reservoir mask were excluded. The data from 43 subjects were analyzed (Figure 1). The reservoir mask and HFNC were applied to 36 and 7 subjects, respectively. In 13 subjects, the reservoir mask was changed to HFNC. Finally, the reservoir mask and HFNC were applied to 23 and 20 subjects, respectively, until death (Figure 1).

Oxygen therapy and device

The HFNC device (Optiflow, Fisher & Paykel, Auckland, NZ) consists of an air-oxygen blender with adjustable F_IO_2 (up to 100%) that delivers a modifiable gas flow (up to 60 L/min) through a heated humidifier (MR850, Fisher & Paykel). If needed, the reservoir mask (Oxygen Mask Type Three-In-One, Japan Medicalnext Co., Osaka, Japan) was changed to a nasal cannula

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┌─────────────────────────────────────────────────────────────┐
│ 60 cases of hypoxic respiratory failure due to pulmonary     │
│ diseases who died under a policy of DNR and DNI with         │
│ HFNC or reservoir mask.                                       │
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                    │          ┌─────────────────────────────────────┐
                    │─────────▶│ 17 cases who were unable to eat or   │
                    │          │ drink at start of HFNC or reservoir  │
                    │          │ mask were excluded.                  │
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│ 43 cases who were able to eat solids and drink liquids at     │
│ start of HFNC or reservoir mask were included.                │
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┌───────────────────┐   ┌──────────────────────────────┐
│ 7 cases with HFNC │   │ 36 cases with reservoir mask │
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        │                       │
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        │          │ Reservoir mask was changed     │
        │◀─────────│ to HFNC in 13 cases.           │
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┌───────────────────┐          ┌──────────────────────────┐
│ 20 cases died with│          │ 23 cases died with       │
│ HFNC.             │          │ reservoir mask.          │
│ (HFNC group)      │          │ (Reservoir mask group)   │
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Fig. 1 Flow diagram of participants

Flow of participants.
DNR: do-not-resuscitate
DNI: do-not-intubate
HFNC: high-flow nasal cannula

(Oxygen Cannula Type Finefit, Japan Medicalnext Co.) with a 10 L/min flow of oxygen or less while subjects were eating or drinking. Oxygen saturation of a peripheral artery (SpO_2) was measured using a pulse oximeter (Pulsox-Me300; Teijin Pharma Co., Tokyo, Japan). Selection and change of the oxygen device were performed by experienced chest physicians in order to maintain oxygenation and subject comfort.

Assessments

We examined the duration of the time in which subjects were able to eat solids and drink.

Jellied food was included in solids. The period from the start of oxygen therapy with HFNC or a reservoir mask to death was assessed. Characteristics of subjects including age, sex, primary diseases, laboratory test results, prior oxygen therapy device, SpO_2, sedation use, length of hospital stay, and oral intake were assessed from electronic medical records.

Statistical analysis

Data were expressed as means ± SD, median [interquartile range], or number (n) of subjects. A paired or unpaired *t*-test, chi-square test, or Fisher's exact test was used to evaluate statistical significance. When data failed a normality test by the Shapiro-Wilk test, the Mann-Whitney U test or Wilcoxon signed-ranks test was performed. Kaplan-Meier plots were used to compare the probability of survival or capability of oral intake. A Cox regression analysis was used to evaluate the effects of oxygen devices and duration of oral intake on survival. Statistical analyses were conducted using SPSS ver. 24 (SPSS Inc., Chicago, IL). *P* <0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the 43 subjects included in this study are shown in Table 1. The HFNC group (70.4 ± 11.6 years old, n=20) was significantly younger than the reservoir mask group (79.0 ± 8.1 years old, n=23). In both groups, subjects were predominantly male. Primary diseases of the HFNC group were lung cancer (n=10, 50%), interstitial lung disease (n=9, 45%), and malignant lymphoma (n=1, 5%). Primary diseases of the reservoir mask group included lung cancer (n=13, 56.5%), interstitial lung disease (n=9, 39.1%), and malignant pleural mesothelioma (n=1, 4.4%). There was no significant difference in white blood cell counts, serum C-reactive protein, or serum creatinine measured within 24 hours prior to fitting the oxygen device between the groups.

Results of oxygen therapy are shown in Table 2. In both groups, oxygen therapy had been started before HFNC or reservoir mask was applied. SpO_2 measured before fitting HFNC (87.0 ± 5.7%) was not significantly different from that before fitting reservoir mask (85.1 ± 7.7%) (*P* = 0.37). In the HFNC group, the reservoir mask had been used in 13 subjects for 0 to 5 days (median, 1 day) before HFNC was applied. In contrast, once applied, HFNC was not changed to the reservoir mask. The continuation rate of HFNC (100%, 20/20) was significantly higher than that of the reservoir mask (63.9%, 23/36) (*P* = 0.002). Non-invasive ventilation (NIV) was used prior to HFNC application by one subject. In the HFNC group, the SpO_2 measured within 30 minutes after fitting HFNC was significantly higher than that before fitting HFNC (92.8 ± 3.3% vs. 87.0 ± 5.7%). Both flow and F_IO_2 of patients receiving HFNC oxygen therapy were significantly higher at death than the initial values.

Outcomes after administration of HFNC and reservoir mask, including hospital stays, sedation use, and status of drinking and eating, are compared in Table 3. The overall length of hospital stays was not different between the groups. Midazolam was used as a sedative because of severe dyspnea for less than 24 hours before death only in the reservoir mask group. When administration of midazolam was started, subjects were already unable to eat solids or drink liquids. The duration from starting HFNC oxygen therapy until death (8.9 [3.8–17.0] days) was significantly longer than that from starting reservoir mask oxygen therapy until death (3.1 [2.2–4.7] days). The period in which subjects in the HFNC group were able to eat solids (7.8 [2.6–14.3] days) was significantly longer than that in the reservoir mask group (0.3 [0.1–1.6] days). The period in which subjects in the HFNC group were able to drink (7.8 [2.6–14.3] days)

Table 1 Clinical characteristics of patients in HFNC and reservoir mask groups

	HFNC (n=20)	Reservoir mask (n=23)	*P* value
Age, years	70.4 ± 11.6 (51–90)	79.0 ± 8.1 (63–93)	0.008*
Male/female	19/1	18/5	0.191
Cause of respiratory failure			0.533
Lung cancer	10 (50%)	13 (56.5%)	
Interstitial lung disease	9 (45%)	9 (39.1%)	
Malignant lymphoma	1 (5%)	0	
Malignant pleural mesothelioma	0	1 (4.4%)	
White blood cell, ×10^3/μL†	11.8 ± 4.1 (7.1–20.3) (n=15)	10.3 ± 3.8 (3.4–15.4) (n=11)	0.362
Serum C-reactive protein, mg/dL†	6.0 ± 6.1 (0.2–16.7) (n=15)	10.9 ± 7.5 (0.8–22.6) (n=11)	0.100
Serum creatinine, mg/dL†	1.2 ± 1.4 (0.5–5.9) (n=15)	0.7 ± 0.3 (0.3–1.1) (n=11)	0.171
Admission, year 2013/2014/2015/2016	4/7/6/3	0/11/8/4	0.162

Data are given as mean ± SD (range) or number (%).

*Significantly different (*P* <0.05) between the groups.

Chi-square test, Fisher's exact test, or unpaired *t*-test was used.

HFNC: high-flow nasal cannula

†Data were collected within 24 hours prior to fitting HFNC or reservoir mask.

Table 2 Data on oxygen therapy with HFNC and reservoir mask groups

	HFNC (n=20)	Reservoir mask (n=23)
Prior oxygen therapy device		
Non-invasive ventilation	1 (5%)	0
Nasal cannula or simple mask	6 (30%)	23 (100%)
Reservoir mask	13 (65%)	
Duration of reservoir mask use before HFNC, day (n=13)	0.5 [0.2–1.5]	
SpO₂ before fitting reservoir mask, %		85.1 ± 7.7 (70–100)
SpO₂ soon after fitting reservoir mask, %		**92.4 ± 5.2 (76–99)
SpO₂ before fitting HFNC, %	87.0 ± 5.7 (75–95)	
SpO₂ soon after fitting HFNC, %	*92.8 ± 3.3 (87–99)	
Initial flow of HFNC oxygen therapy, L/min	40 [36.25–50]	
Flow of HFNC oxygen therapy at death, L/min	†50 [50–60]	
Initial F_IO_2 of HFNC oxygen therapy, %	72.5 [50–90]	
F_IO_2 of HFNC oxygen therapy at death, %	‡100 [100–100]	

Data are given as mean ± SD (range), median [interquartile range], or number (%).

*Significantly different vs. before fitting HFNC (*P* <0.001).

†Significantly different vs. initial flow of HFNC (*P* <0.001).

‡Significantly different vs. initial F_IO_2 of HFNC (*P* <0.001).

**Significantly different vs. before fitting reservoir mask (*P* <0.001).

Paired *t*-test or Wilcoxon signed-ranks test was used.

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was also significantly longer than that in the reservoir mask group (0.3 [0.1–3.0] days). There was no statistically significant difference in the periods in which subjects were not able to eat or drink until death between the HFNC and reservoir mask groups (Table 3). HFNC was well tolerated with no drop-out or remarkable adverse event.

Table 3 Outcomes after administration of HFNC and reservoir mask

	HFNC (n=20)	Reservoir mask (n=23)	*P* value
In-hospital mortality	100%	100%	1.000
Overall hospital stay, days	24.0 ± 12.1 (1.9–45.2)	21.6 ± 14.0 (3.3–55.0)	0.560
Sedation	17 (85.0%)	16 (69.6%)	0.294
Opioid use	17 (85.0%)	12 (54.2%)	0.049*
Midazolam use	0	6 (25.0%)	0.023*
Duration from admission until application of HFNC or reservoir mask, days	7.2 [2.9–19.0]	16.1 [5.1–26.9]	0.201
Survival from starting oxygen therapy with HFNC or reservoir mask until death, days	8.9 [3.8–17.0]	3.1 [2.2–4.7]	0.005*
Able to eat solids, days	7.8 [2.6–14.3]	0.3 [0.1–1.6]	0.002*
Unable to eat solids, days	1.4 [0.6–2.5]	2.2 [1.4–3.1]	0.468
Able to drink, days	7.8 [2.6–14.3]	0.3 [0.1–3.0]	0.002*
Unable to drink, days	0.9 [0.6–2.0]	2.0 [1.2–3.0]	0.370

Data are given as mean ± SD (range), median [interquartile range], or number (%).
*P <0.05.
Chi-square test, Fisher's exact test, unpaired t-test, or Mann-Whitney U test was used.

Kaplan-Meier plots of the probability of survival from starting HFNC or reservoir mask therapy to death are shown in Figure 2A. Kaplan-Meier plots of the probability of survival of subjects who were able to eat solids and drink liquids from starting HFNC or reservoir mask therapy to the points when eating solids and drinking liquids stopped are shown in Figure 2B and C. There were significant differences in all plots between the groups.

Next, to assess the association of oxygen devices with durations of oral intake in survival, a Cox regression analysis was performed. When a Cox model with two variables, oxygen device and duration of eating solids, was examined, the survival was significantly associated with length of eating solids (hazard ratio: 0.53, 95%CI [0.42–0.69], P <0.001). The use of HFNC was not significantly associated with survival (hazard ratio: 0.79, 95%CI [0.33–1.90], P = 0.600). Similarly, a Cox model with oxygen device and duration of drinking as variables showed that the survival was significantly associated with length of drinking (hazard ratio: 0.51, 95%CI [0.40–0.66], P <0.001) but not with the use of HFNC (hazard ratio: 0.67, 95%CI [0.27–1.65], P = 0.380).

The reservoir mask was changed to HFNC in 13 of 36 patients (Figure 1, Table 2). For subgroup analysis, clinical characteristics and outcomes of patients to whom the reservoir mask was changed to HFNC (change-to-HFNC group, n=13) and continued until death (reservoir mask group, n=23) were compared. The change-to-HFNC group (70.4 ± 10.0 years old) was
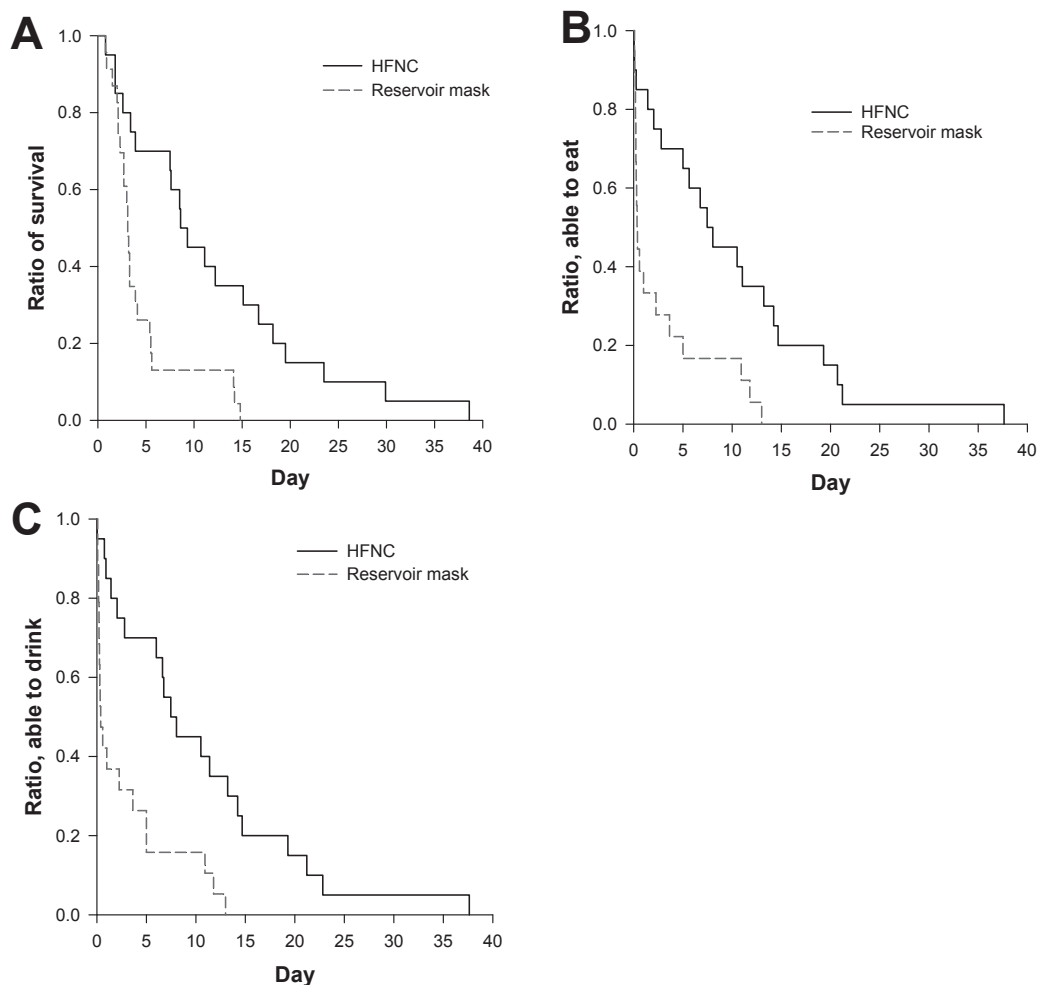
Fig. 2 Kaplan-Meier survival curves in HFNC group (n=20) and reservoir mask group (n=23)
Fig. 2A: Kaplan-Meier plots of the probability of survival from starting HFNC (HFNC group) or reservoir mask therapy (reservoir mask group) to death. There was a significant difference in survival (*P* <0.001).
Fig. 2B/2C: Kaplan-Meier plots of the probability of survival from starting HFNC or reservoir mask therapy to the point when eating solids (Fig. 2B) or drinking liquids (Fig. 2C) stopped. There were significant differences in durations of eating (*P* = 0.001) (Fig. 2B) and drinking (*P* <0.001) (Fig. 2C) between the groups.

significantly younger than the reservoir mask group (79.0 ± 8.1 years old) (Table 4). SpO$_2$ values before and soon after fitting reservoir mask were not significantly different between the groups (Table 5). The SpO$_2$ after fitting the reservoir mask was significantly higher than that before fitting it in the reservoir mask group but not in the change-to-HFNC group (Table 5). Duration from starting the reservoir mask oxygen therapy until death in the change-to-HFNC group (10.8 [4.4–16.7] days) was significantly longer than that in the reservoir mask group (3.1 [2.2–4.7] days). The period in which subjects in the change-to-HFNC group were able to eat solids after starting reservoir mask oxygen therapy (7.3 [3.8–14.3] days) was significantly longer than that

in the reservoir mask group (0.3 [0.1–1.6] days) (Table 6). The period in which subjects in the HFNC group were able to drink (7.5 [3.8–14.3] days) was also significantly longer than that in the reservoir mask group (0.3 [0.1–3.0] days) (Table 6). There was no statistically significant difference in the periods in which subjects were not able to eat or drink until death between the change-to-HFNC and reservoir mask groups (Table 6).

Table 4 Clinical characteristics of patients of change-to-HFNC and reservoir mask groups

	Change-to-HFNC (n=13)	Reservoir mask (n=23)	P value
Age, years	70.4 ± 10.0 (49–90)	79.0 ± 8.1 (63–93)	0.015*
Male/female	12/1	18/5	0.385
Cause of respiratory failure			0.504
Lung cancer	7 (53.8%)	13 (56.5%)	
Interstitial lung disease	5 (38.5%)	9 (39.1%)	
Malignant lymphoma	1 (7.7%)	0	
Malignant pleural mesothelioma	0	1 (4.4%)	
Admission, year 2013/2014/2015/2016	2/4/6/1	0/11/8/4	0.175

Data are given as mean ± SD (range) or number (%).
*Significantly different ($P < 0.05$) between the groups.
Chi-square test, Fisher's exact test, or unpaired t-test was used. HFNC, high-flow nasal cannula.
Reservoir mask was changed to HFNC in 13 of 36 cases (change-to-HFNC group).

Table 5 Data on oxygen therapy with change-to-HFNC and reservoir mask groups

	Change-to-HFNC (n=13)	Reservoir mask (n=23)	P value
SpO_2 before fitting reservoir mask, %	87 [82.5–92]	87 [80–90]	0.478
SpO_2 soon after fitting reservoir mask, %	91 [89–92.5]	**93 [90–95]	0.116
SpO_2 before fitting HFNC, %	87.8 ± 5.1 (78–95)		
SpO_2 soon after fitting HFNC, %	*92.4 ± 3.0 (87–98)		
Initial flow of HFNC oxygen therapy, L/min	40 [37.5–55]		
Flow of HFNC oxygen therapy at death, L/min	†60 [50–60]		
Initial F_1O_2 of HFNC oxygen therapy, %	79.6 ± 17.4 (40–100)		
F_1O_2 of HFNC oxygen therapy at death, %	‡97.7 ± 8.3 (70–100)		

Data are given as mean ± SD (range) or median [interquartile range].
*Significantly different vs. before fitting HFNC ($P = 0.004$).
†Significantly different vs. initial flow of HFNC ($P = 0.016$).
‡Significantly different vs. initial F_1O_2 of HFNC ($P = 0.003$).
**Significantly different vs. before fitting reservoir mask ($P < 0.001$).
Paired or unpaired t-test or Wilcoxon signed-ranks test was used.

Table 6 Outcomes after administration of reservoir mask therapy in change-to-HFNC and reservoir mask groups

|	Change-to-HFNC (n=13)	Reservoir mask (n=23)	P value
Overall hospital stay, days	23.3 ± 10.5 (5.6–45.2)	21.6 ± 14.0 (3.3–55.0)	0.689
Sedation	12 (92.3%)	16 (69.6%)	0.213
Opioid use	12 (92.3%)	12 (54.2%)	0.025*
Midazolam use	0	6 (25.0%)	0.068
Duration from admission until application of reservoir mask, days	6.1 [5.0–18.6]	16.1 [5.1–27.0]	0.182
Survival from starting oxygen therapy with reservoir mask until death, days	10.8 [4.4–16.7]	3.1 [2.2–4.7]	0.015*
Able to eat solids from starting oxygen therapy with reservoir mask, days	7.3 [3.8–14.3]	0.3 [0.1–1.6]	0.004*
Unable to eat solids, days	1.7 [0.6–2.5]	2.2 [1.4–3.1]	0.738
Able to drink from starting oxygen therapy with reservoir mask, days	7.5 [3.8–14.3]	0.3 [0.1–3.0]	0.004*
Unable to drink, days	0.8 [0.6–1.8]	2.0 [1.2–3.0]	0.601

Data are given as mean ± SD (range), median [interquartile range], or number (%).
*P <0.05.
Chi-square test, Fisher's exact test, unpaired *t*-test, or Mann-Whitney U test was used.

Kaplan-Meier plots of the probability of survival from starting reservoir mask therapy to death are shown in Figure 3A. Kaplan-Meier plots of the probability of survival of subjects who were able to eat solids and drink liquids from starting reservoir mask therapy to the points when eating solids and drinking liquids stopped are shown in Figure 3B and C. There were significant differences in all plots between the groups.

Next, the effects of the change of oxygen device and durations of oral intake in survival were assessed by a Cox regression analysis with two variables. A Cox model with oxygen device and duration of eating solids showed that the survival was significantly associated with length of eating solids (hazard ratio: 0.81, 95%CI [0.74–0.90], P <0.001) but not with the change to HFNC (hazard ratio: 2.22, 95%CI [0.94–5.23], P = 0.070). Similarly, a Cox model with oxygen device and duration of drinking as variables showed that the survival was significantly associated with length of drinking (hazard ratio: 0.81, 95%CI [0.73–0.90], P <0.001) but not with the change to HFNC (hazard ratio: 2.28, 95%CI [0.97–5.36], P = 0.059).

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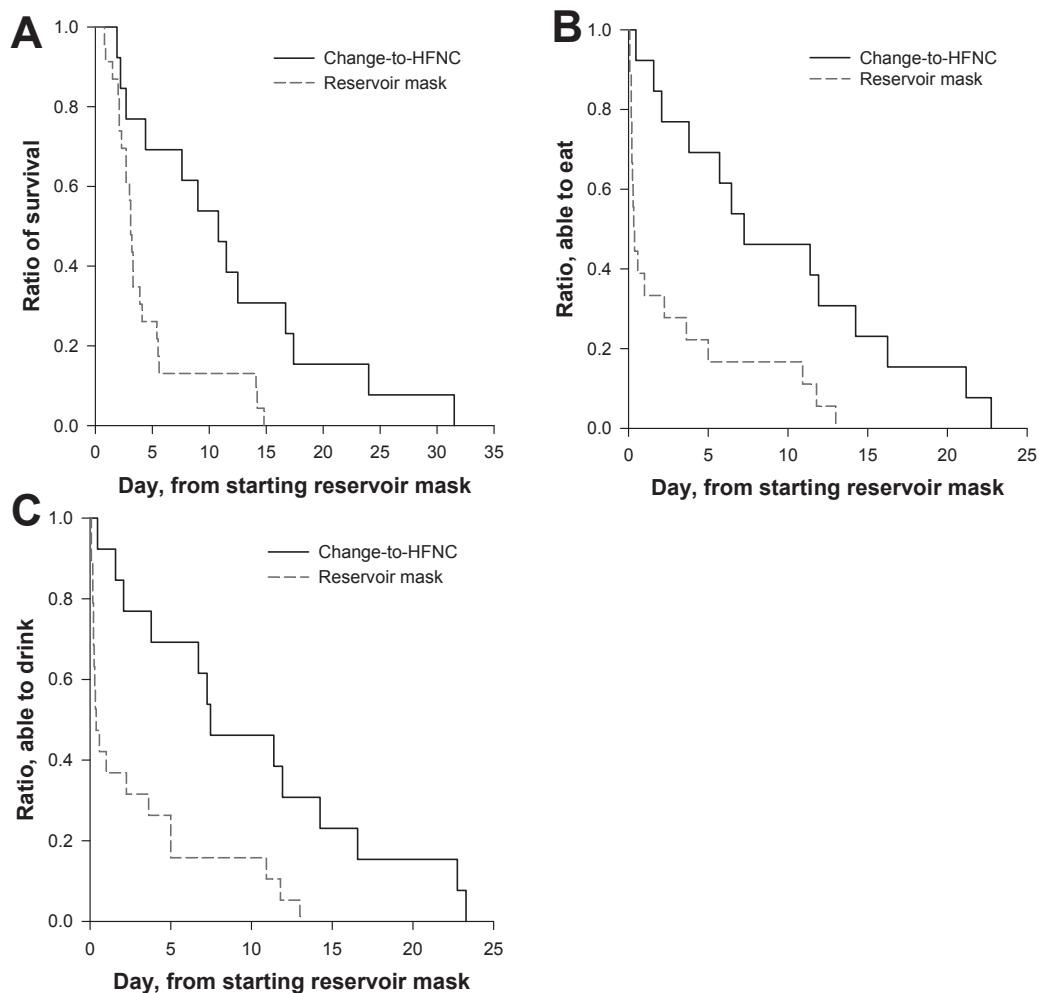
Fig. 3 Kaplan-Meier survival curves in change-to-HFNC group (n=13) and reservoir mask group (n=23)

Fig. 3A: Kaplan-Meier plots of the probability of survival from starting reservoir mask therapy to death. The reservoir mask was applied to 36 subjects. In 13 subjects, the reservoir mask was changed to HFNC (change-to-HFNC group). In the other 23 subjects, the reservoir mask therapy was continued until death (reservoir mask group). There was a significant difference in survival ($P = 0.005$).

Fig. 3B/3C: Kaplan-Meier plots of the probability of survival from starting reservoir mask therapy to the point when eating solids (Fig. 3B) or drinking liquids (Fig. 3C) stopped. There were significant differences in durations of eating ($P = 0.002$) (Fig. 3B) and drinking ($P = 0.002$) (Fig. 3C) between the groups.

DISCUSSION

The main findings of the present study are that in subjects with hypoxic respiratory failure due to end-stage interstitial pneumonia or malignant respiratory diseases with DNR and DNI status, 1) HFNC oxygen therapy temporarily improved oxygenation with no obvious adverse effects, 2) the use of HFNC resulted in longer survival than the use of a reservoir mask, and 3) durations of eating solids and drinking liquids by the HFNC group were significantly longer than those in the reservoir mask group. The results of a Cox regression model showed that durations of eating

solids and drinking liquids are significantly associated with survival. To our knowledge, this is the first study to demonstrate that the use of HFNC allows patients with hypoxic respiratory failure to eat and drink in a palliative care setting.

In the present study, approximately 60% and 40% of the subjects had malignant diseases and interstitial lung disease, respectively (Table 1). Oxygen therapy plays an important role in palliative care for end-stage respiratory diseases such as lung cancer and interstitial lung disease.[12,16,17] It has been established that HFNC oxygen therapy has physiological benefits for patients with hypoxic respiratory failure compared with simple mask and nasal cannula oxygen therapy.[2,7,18] Recently, Koyauchi et al reported that HFNC has a survival rate equivalent to that of NIV with better tolerability in patients with end-stage interstitial lung disease with DNI status.[11] Consistent with findings in the previous reports, changing the oxygen device to HFNC significantly increased SpO_2 within a short period (Tables 2 and 5). Hui et al reported that the use of HFNC improved oxygenation and dyspnea without disturbing eating and drinking in patients with advanced cancer, including lung cancer.[6] Moreover, our results show that the use of HFNC was related to the longer survival and duration of oral intake than the use of a reservoir mask. In the present subgroup analysis, the change of oxygen device from a reservoir mask to HFNC also led to the longer survival and duration of oral intake after starting reservoir mask oxygen therapy (Table 6, Figure 3). In contrast, durations of periods in which patients were unable to eat solids or drink liquids until death were not significantly different between the groups (Tables 3 and 6). These results strongly suggest that maintenance of the ability to eat and drink by the use of HFNC is mostly due to improved oxygenation. Midazolam, a strong sedative, was given to six subjects in the reservoir mask group before death (Tables 3 and 6). However, these subjects could not eat or drink when the administration of midazolam was started. Thus, the effects of midazolam use on the length of oral intake can be ruled out in the present cohort. Recently, Sanuki et al reported that HFNC may improve swallowing in healthy volunteers.[19] However, it is unknown whether the HFNC oxygen therapy helps patients with hypoxemic respiratory failure to swallow food and drink. Future studies are necessary to confirm this hypothesis.

The oxygen administration device was changed from the reservoir mask to HFNC in 13 of 36 (36.1%) cases (Figure 1, Table 2). The most common reason for this change was to improve oxygenation and support respiration in patients with severe dyspnea. We note that one patient exhibited hemoptysis. Indeed, the SpO_2 significantly increased after fitting the reservoir mask in the reservoir mask group but not in the change-to-HFNC group (Table 5). Notably, the device was changed on the same day that reservoir mask oxygen therapy was started in almost half (6 of 13) of the subjects (Table 2). HFNC was well tolerated and the continuation rate was 100% until death. It is known that the oxygen mask tends to be uncomfortable.[9,12] Maggiore et al reported that the HFNC reduced patient discomfort related to the interface and dryness compared with Venturi mask oxygen therapy.[9] Although a reservoir mask is able to supply high concentrations of oxygen, face masks have to be changed to a nasal cannula while patients are eating or drinking. Moreover, the sedative midazolam was applied with the reservoir mask only in order to relieve dyspnea (Table 3). Taken together, HFNC could be beneficial for patients who feel uncomfortable with an oxygen mask.

Because the number of HFNC devices was limited during the observation period at Kariya-Toyota General Hospital, HFNC was applied to patients with hypoxemia and severe dyspnea if it was available. Although the patients underwent oxygen therapy using HFNC in both medical wards and the intensive care unit during the present study period, HFNC has been used only in the intensive care unit since 2017. Another important issue is that the longer use of HFNC is expensive.[5] In the present cases, flow rate (50.8 L/min on average) and F_IO_2 (96.0% on average) were extremely high at death (Table 2). However, which levels of flow rate and F_IO_2

are appropriate for end-stage respiratory diseases are unknown. Thus, the utility and protocol of HFNC in populations with end-stage respiratory diseases should be studied.

It is well known that NIV is also a useful method to support ventilation and oxygenation in patients with hypoxemic respiratory failure receiving palliative care.[20,21] In the present study, NIV was used prior to HFNC application by one subject with interstitial lung disease (Table 2). During the same observation period, a total of 13 patients including 11 with interstitial lung disease, one with lung cancer, and one with malignant pleural mesothelioma died with DNR and DNI status using NIV. In 10 of the 13 cases, NIV was started at the intensive care unit. At Kariya Toyota General Hospital where the present study was conducted, NIV had been recommended to few patients with advanced thoracic malignancy with DNR and DNI status in the general ward since the HFNC became available. Koyauchi et al compared the efficacy and tolerability of HFNC with those of NIV. They found that periods in which patients with HFNC were unable to eat food before death were significantly shorter than those with NIV.[11] However, the present study did not aim to examine whether HFNC is superior to non-invasive positive pressure ventilation in palliative care or not. Further studies will be important.

This study has several limitations. The data were collected retrospectively from small numbers of patients with various lung diseases in a single institution. The baseline characteristics, specifically age and use of sedating drugs, were not matched between the groups. Overall lengths of hospital stays were not different between the groups. Due to the nature of palliative care, several important data such as F_IO_2, baseline arterial blood gases, changes in respiratory frequency, respiratory patterns such as a use of accessory muscles, and statuses of health-related QOL and dyspnea were not examined. Changes in SpO_2 and dyspnea while eating or drinking were not assessed. Nevertheless, our results show that HFNC is useful for supplying oxygen and helping patients continue their oral intake with few disadvantages. Moreover, HFNC was better tolerated than the reservoir mask in our cohort. Future studies with a larger cohort in multiple centers are necessary.

CONCLUSIONS

HFNC oxygen therapy helps patients eat and drink during end-stage respiratory diseases with DNI or DNR status. HFNC may be a beneficial tool as palliative oxygen therapy for patients with progressive respiratory failure due to lung cancer and interstitial pneumonia.

AUTHORS' CONTRIBUTIONS

HS, NT, and YS were responsible for the present study's concept and design, as well as for data acquisition and drafting of the manuscript. TK, NY, YH, EY, and NH supervised the research work. SI was responsible for data acquisition, analysis, interpretation, and drafting of the manuscript. All authors have approved the submission of the manuscript.

AVAILABILITY OF DATA AND MATERIALS

The datasets analyzed during this study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

FUNDING

CONSENT FOR PUBLICATIONS

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The retrospective study was approved by the Institutional Review Board of Kariya Toyota General Hospital (approval No. 434). No patient identifiers were included. Informed consent to participate and publish was not required for this retrospective analysis.

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REFERENCES

1   Chikata Y, Onodera M, Oto J, Nishimura M. F_IO_2 in an adult model simulating high-flow nasal cannula therapy. *Respir Care*. 2017;62(2):193–198. doi:10.4187/respcare.04963.

2   Ward JJ. High-flow oxygen administration by nasal cannula for adult and perinatal patients. *Respir Care*. 2013;58(1):98–122. doi:10.4187/respcare.01941.

3   Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. *Respir Care*. 2010;55(4):408–413.

4   Frat JP, Coudroy R, Marjanovic N, Thille AW. High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. *Ann Transl Med*. 2017;5(14):297. doi:10.21037/atm.2017.06.52.

5   Epstein AS, Hartridge-Lambert SK, Ramaker JS, Voigt LP, Portlock CS. Humidified high-flow nasal oxygen utilization in patients with cancer at Memorial Sloan-Kettering Cancer Center. *J Palliat Med*. 2011;14(7):835–839. doi:10.1089/jpm.2011.0005.

6   Hui D, Morgado M, Chisholm G, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. *J Pain Symptom Manage*. 2013;46(4):463–473. doi:10.1016/j.jpainsymman.2012.10.284.

7   Nishimura M. High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. *Respir Care*. 2016;61(4):529–541. doi:10.4187/respcare.04577.

8   Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23):2185–2196. doi:10.1056/NEJMoa1503326.

9   Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med*. 2014;190(3):282–288. doi:10.1164/rccm.201402-0364OC.

10 Mokart D, Geay C, Chow-Chine L, et al. High-flow oxygen therapy in cancer patients with acute respiratory failure. *Intensive Care Med*. 2015;41(11):2008–2010. doi:10.1007/s00134-015-3994-8.

11 Koyauchi T, Hasegawa H, Kanata K, et al. Efficacy and tolerability of high-flow nasal cannula oxygen

therapy for hypoxemic respiratory failure in patients with interstitial lung disease with do-not-intubate orders: a retrospective single-center study. *Respiration*. 2018;96(4):323–329. doi:10.1159/000489890.

12 Tiep B, Carter R, Zachariah F, et al. Oxygen for end-of-life lung cancer care: managing dyspnea and hypoxemia. *Expert Rev Respir Med*. 2013;7(5):479–490. doi:10.1586/17476348.2013.816565.

13 Shah N, Mehta Z, Mehta Y. High-flow nasal cannula oxygen therapy in palliative care #330. *J Palliat Med*. 2017;20(6):679–680. doi:10.1089/jpm.2017.0108.

14 Peters SG, Holets SR, Gay PC. High-flow nasal cannula therapy in do-not-intubate patients with hypoxemic respiratory distress. *Respir Care*. 2013;58(4):597–600. doi:10.4187/respcare.01887.

15 Sim MA, Dean P, Kinsella J, Black R, Carter R, Hughes M. Performance of oxygen delivery devices when the breathing pattern of respiratory failure is simulated. *Anaesthesia*. 2008;63(9):938–940. doi:10.1111/j.1365-2044.2008.05536.x.

16 Ahmadi Z, Wysham NG, Lundstrom S, Janson C, Currow DC, Ekstrom M. End-of-life care in oxygen-dependent ILD compared with lung cancer: a national population-based study. *Thorax*. 2016;71(6):510–516. doi:10.1136/thoraxjnl-2015-207439.

17 Kreuter M, Bendstrup E, Russell AM, et al. Palliative care in interstitial lung disease: living well. *Lancet Respir Med*. 2017;5(12):968–980. doi:10.1016/S2213-2600(17)30383-1.

18 Mauri T, Turrini C, Eronia N, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med*. 2017;195(9):1207–1215. doi:10.1164/rccm.201605-0916OC.

19 Sanuki T, Mishima G, Kiriishi K, et al. Effect of nasal high-flow oxygen therapy on the swallowing reflex: an in vivo volunteer study. *Clin Oral Investig*. 2017;21(3):915–920. doi:10.1007/s00784-016-1822-3.

20 Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J*. 2017;50(2):1602426. doi:10.1183/13993003.02426-2016.

21 Nava S, Ferrer M, Esquinas A, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. *Lancet Oncol*. 2013;14(3):219–227. doi:10.1016/S1470-2045(13)70009-3.