




The starting temperature of high-flow nasal cannula and perceived comfort in critically ill patients: A pragmatic randomized controlled trial

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Abstract

Background: High-flow nasal cannula (HFNC) therapy is a non-invasive respiratory treatment characterized by high tolerability, which largely derives from the patient's comfort.

Aims: The primary aim of this study was to explore whether the patient's perceived comfort was the same regardless of different approaches used to reach the target humidification temperature. The secondary aim was to assess the patient's perceived nasal dryness and humidity.

Study Design: This single-centre, pragmatic, randomized trial was registered at clinicaltrials.gov (NCT05688189). Patients in the intensive care unit (ICU) in need of HFNC therapy were randomly assigned to one of three study arms: a two-step increase (31 to 34 to 37°C), a one-step increase in temperature (34–37°C) or no temperature increase (started and remained at 37°C). The patients were asked to rate their perceived comfort, as well as their perceived nasal dryness and humidity on a scale from 1 (lowest value) to 5 (highest value).

Results: We enrolled 21 patients, aged 34–85 years. The mean (± 1 standard deviation) comfort level was 3.3 (1.3) for patients who received a one-step increase, 3.1 (1.3) for those who received no increase and 2.7 (1.7) for those who received a two-step increase ($p = .714$). There was also no difference in nasal dryness ($p = .05$) or humidity ($p = .612$) across the study arms. Greater comfort was fairly correlated with less nasal humidity ($p = -0.34$, 95% confidence interval -0.68 to 0.07) but not with nasal dryness ($p = 0.01$, $p = .94$).

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Conclusions: After 30 min of HFNC therapy at a target temperature of 37°C, overall comfort was rated similarly in the three study arms. Additional studies are needed to accumulate evidence corroborating the findings of this study.

Relevance to Clinical Practice: The temperature of the mixture of air and oxygen is a fundamental component of HFNC therapy. A pragmatic approach irrespective of the initial temperature setting seems to yield a similar comfort score in hospitalized patients with mild respiratory failure because of extrapulmonary causes.

KEYWORDS

high-flow nasal cannula, oxygen inhalation therapy, patient comfort, temperature

1 | BACKGROUND

There is increasing use of oxygen therapy via high-flow nasal cannula (HFNC) in patients with acute respiratory failure, even outside the intensive care unit (ICU).¹ An HFNC system delivers 30–60 L/min of a humidified air and oxygen mixture at a fixed oxygen concentration (21%–100%) and temperature (31–37°C) through a nasal interface.² Evidence has shown the advantages of HFNC compared with conventional oxygen therapy.³ Specifically, it allows better matching between the delivered gas flow and the patient's peak inspiratory flow, creates a variable positive end-expiratory pressure effect and generates a wash out of carbon dioxide from the upper airways.⁴ Furthermore, the humidified air and oxygen mixture promotes mucociliary function and reduces upper airway resistance.⁵ Working in synergy, these mechanisms improve oxygenation and reduce the neuroventilatory drive and work of breathing.⁶

An important issue concerning HFNC therapy is the tolerability of the device and the treatment itself, which has been documented to influence greatly the patient's perceived comfort.^{7,8} Despite the documented physiological benefits relating to the respiratory rate and breathing work reduction including the possibility to speak, drink and eat,⁹ during HFNC therapy, the patient's comfort could be compromised if the flow and temperature are not initiated and set appropriately,¹⁰ and if the size of the nasal cannula does not match to the size of the nostrils.¹¹ As many of the effects of HFNC therapy are flow-dependent, the maximum tolerated flow needs to be delivered to maximize respiratory support, while the fraction of inspired oxygen should be adjusted to the target of peripheral oxygen saturation.¹² Episodes of discomfort lead to negative outcomes, such as a lower tolerance to continue the treatment, resulting in attempts to remove the device and worsening the respiratory condition.¹³ Therefore, promoting comfort by ensuring optimal HFNC management is recommended, especially because HFNC therapy is administered for a longer period of time than non-invasive ventilation as it is applied mainly in cycles lasting for hours.¹⁴

To date, there is limited evidence regarding the best setting of the humidification temperature.¹⁵ Furthermore, there are no pragmatic studies about the real-life use of HFNC therapy at different starting humidification temperatures in the ICU. Comfort has been

What is known about the topic

- High-flow nasal cannula (HFNC) is an increasingly widespread respiratory therapy.
- HFNC ensures high levels of comfort for patients.
- The comfort of patients receiving HFNC therapy mainly depends on the temperature and flow that are set.

What this paper adds

- The patient's perceived comfort does not significantly differ across the three starting temperature approaches (31, 34 or 37°C) to achieve the target humidification temperature (37°C) of HFNC therapy.
- The patient's perceived comfort of HFNC therapy may be affected by low nasal humidity.
- Future studies are needed to accumulate evidence corroborating the findings of this study.

defined as a core concept of nursing discipline: It is a fundamental outcome of nursing care and the underlined intent of all therapeutic nursing actions.¹⁶ Moreover, comfort has been recognized as one of the outcomes of a good patient experience of health care services.¹⁷ Therefore, investigating the factors that promote comfort is imperative to advance the evidence available in the context of HFNC therapy and in the nursing science as a whole.

2 | AIMS

The primary aim of this study was to explore whether the patient's perceived comfort is the same regardless of different approaches used to reach the target humidification temperature for HFNC therapy. The secondary aim was to assess the patient's perceived nasal dryness and humidity. Specifically, we hypothesized that there is a difference in the patient's perceived comfort when the initial HFNC temperature is gradually raised to the target with a one-step (34–37°C) or a

two-step (31 to 34 to 37°C) increase compared with a starting temperature of 37°C.

3 | METHODS

3.1 | Design and setting

This single-centre, parallel-arm interventional, non-pharmacological, pragmatic, randomized trial was performed at the general and post-surgery ICUs of the Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, a tertiary-level hospital in Milan, Italy. The study was designed by following the nine domains of the Pragmatic Explanatory Continuum Indicator Summary second version (PRECIS-2) regarding the eligibility criteria, the recruitment, the setting and the organization of the study; the flexibility of the intervention delivery and adherence; the follow-up, the primary outcome and analysis.¹⁸ The study was preliminarily registered at clinicaltrials.gov (registration number NCT05688189) and is reported here following the Consolidated Standards of Reporting Trials (CONSORT) statement—extension for pragmatic trials (Table S1).¹⁹

3.2 | Participant recruitment

The inclusion criteria were age ≥ 18 years, receiving HFNC therapy as per clinical indication, without delirium as screened with the Confusion Assessment Method for ICU (CAM-ICU)²⁰ and willing to participate. The exclusion criterion was an inability to provide informed consent. The patient enrolment period lasted from 18 January to 6 February 2023.

3.3 | Sample size

Based on a previous study, the effect size (Cohen's d) for an HFNC therapy temperature of 31 and 37°C, while holding the flow rate constant at 30 and 60 L/min, was 1.4 and 0.9, respectively.¹⁰ Given the absence of similar trials in the field, and our pragmatic approach to HFNC therapy in ICU as using a flow rate of 40–50 L/min to reach the target temperature of 37°C, the expected effect size was 1.1 (Cohen's effect size f), which is a compromise between the effect sizes for 31 and 37°C. To explore whether patients perceived a difference in comfort between at least two HFNC settings, the total sample size was calculated with one-way analysis of variance, with a 15% non-parametric correction. Therefore, with $\alpha = 0.01$ and power = 0.90, a sample size of 21 patients was required.

3.4 | Randomization

The randomization sequence was generated with the *blockrand* function in the R open source software²¹ to achieve an equal number of

subjects in each study arm. Blocks of different size were permuted to ensure that assignment to a study arm could not be predicted. Specifically, the allocation sequence was generated with a password-protected hardware device and kept in the research office of one researcher (see authors). Sequentially numbered, opaque, sealed envelopes marked with a patient identification code were prepared by the administrative staff who were not involved in the study; then, these envelopes were made available to the ICU. Thus, the first assessment of the patient's eligibility according to the inclusion/exclusion criteria was performed by the nursing staff at the ICU level, and subsequently by a research nurse (see authors). When a patient was deemed eligible for participation in the study, the envelopes were opened by the research nurse. Each envelope included an allocation sheet wrapped in carbon paper, which had been folded and placed in aluminium foil. The research nurse and the whole research team were blinded to the block size and number.

3.5 | Interventions

HFNC therapy was carried out as per usual clinical practice: an ICU physician assessed the oxygen need and set the oxygen concentration (21%–100%) and the flow (30–60 L/min, generally 40–50 L/min). The humidification temperature was set by the ICU nurse based on the assigned study arm (31 to 34 to 37°C, 34–37°C or 37°C). Subjects in the first arm (31 to 34 to 37°C) initially received HFNC therapy at 31°C, which was then raised in two steps every 15 min to 34°C and then to 37°C. Subjects in the second arm (34–37°C) received therapy starting at 34°C, which was raised in one step after 15 min to 37°C. Subjects in the third arm (37°C) received therapy starting at 37°C. HFNC treatment was provided on an AIRVO 2™ system (Fisher & Paykel Healthcare, New Zealand).

3.6 | Data collection and outcome measures

After receiving HFNC therapy at 37°C (the target temperature) for 30 min, the patients were asked to rate their comfort (primary outcome) regarding the HFNC treatment received on a 5-point visual numerical scale from 1 (lowest comfort) to 5 (highest comfort). At the same time, patients were also asked to rate their nasal dryness and humidity (secondary outcomes) on a 5-point visual numerical scale from 1 (lowest) to 5 (highest). The measures were chosen based on the literature in the field.^{10,22}

At the baseline, general data were collected such as age, gender, ethnicity, status of current smoking, body mass index (BMI) and pre-hospital oxygen dependence. Moreover, clinical data such as the American Society of Anesthesiologists (ASA) score, the Respiratory rate–Oxygenation (ROX) Index, the Sequential Organ Failure Assessment (SOFA) evaluation and the Charlson Comorbidity Index were collected at the beginning of the intervention delivery. At the end of the intervention, after 30 min, when the target temperature was reached, dyspnoea was assessed according to the

Borg Category-Ratio (Borg CR10) scale from 1 (no dyspnoea) to 10 (extreme dyspnoea)¹⁰; data regarding the vital signs were also collected and the primary and secondary outcomes were measured.

Data were collected by a research nurse at the bedside (e.g., Borg CR10) or by accessing the clinical records (e.g., BMI). No follow-up was required whereas the ICU length of stay, as the number of days spent from ICU admission to discharge, was recorded at the end of the study.

3.7 | Statistical analysis

The data are expressed as counts and percentages (%) and means with ± 1 standard deviation (SD). Differences in the mean comfort, nasal humidity and nasal dryness scores as well as the Borg CR10 scores across the HFNC temperature settings were analysed with the Kruskal-Wallis test. Correlations between selected variables were explored using Spearman's rank correlation ($\rho \leq 0.2$, none/poor; 0.3–0.5, fair; 0.6–0.7, moderate; ≥ 0.8 , strong/perfect), using bootstrap 95% confidence intervals (CIs). For primary and secondary outcomes, we reported Cohen's effect-size measure f , computed as a square root of the ratio between the between-group variance and the within-group variance. The statistician responsible for data analysis was provided an anonymized dataset and thus was blinded to the treatment each patient received. All analyses were performed using the *Hmisc* and *confintr* packages in R version 4.3.0.¹⁷

3.8 | Ethical approval

The study was approved by the Ethics Committee of Milano Area 2 (approval number 1050_2022). Each patient provided written informed consent to participate in the study.

4 | RESULTS

4.1 | Study population

From 18 January to 6 February 2023, 23 patients were potentially eligible and 21 were enrolled—approximately one patient per day. Figure 1 shows the study flow diagram. There were no issues during enrolment, and the randomization procedures were performed as planned. Moreover, the study protocol was applied as planned and there were no violations. Most patients were male (15/21, 71.4%) and aged 34–85 years. Most patients (18/21, 85.7%) received HFNC therapy for post-surgical mild extrapulmonary respiratory failure; no patients were dependent on oxygen prior to hospital admission. ICU length of stay was 4.8 (7.7) days; no patient died during this period. The patient characteristics are summarized in Table 1.

4.2 | Comfort and nasal dryness and humidity

The highest average comfort score was 3.3 (1.3) out of 5 (best), as reported by patients who received a one-step increase (34–37°C), followed by a score of 3.1 (1.3) reported by those who started the treatment at the target temperature of 37°C and 2.7 (1.7) by those who received a two-step increase (31 to 34 to 37°C); however, the differences were not statistically different ($p = .714$). The between-group and within-group variance were 0.619 and 2.095, respectively, thus yielding an effect-size measure f of 0.54.

Nasal dryness was rated on average 3.4 (1.7) out of 5 (highest) by patients who started therapy at the target temperature, 3.3 (1.7) by those who received a one-step increase and 1.6 (1) by those who received a two-step increase. Nasal humidity was scored on average 3.4 (1.3) out of 5 (highest) by those who received a two-step increase, 3.1 (1.3) by those who started at the target temperature and 2.9 (1.1) by patients who received a one-step increase. There was no difference in nasal dryness ($f = 1.81$, $p = .05$) or humidity ($f = 0.61$, $p = .612$) across the study arms. The perceived comfort, nasal dryness and humidity scores are presented in Table 2.

Greater comfort was fairly correlated with lower nasal humidity ($\rho = -0.34$, 95% CI -0.68 to 0.07) but not with nasal dryness ($\rho = 0.01$, $p = .94$). Nasal dryness and nasal humidity were negatively correlated ($\rho = -0.43$, 95% CI -0.74 to 0.03). When we investigated the overall duration of exposure to HFNC therapy—from treatment initiation to comfort assessment—the only significant correlation was between nasal dryness and the duration of exposure ($\rho = -0.49$, 95% CI -0.78 to -0.05). Comfort ($\rho = -0.16$, $p = .58$) and nasal humidity ($\rho = 0.12$, $p = .67$) were poorly correlated with the duration of the exposure.

The Borg CR10 score varied from an average of 1.4 (1.8)—very weak to 3.9 (2.5)—moderate across the groups ($p = .081$). There were no statistically significant changes in the vital signs observed after the comfort assessment (Table 2).

5 | DISCUSSION

The findings show that regardless of differences in the initial temperature settings and assuming a large effect, patients receiving HFNC therapy for post-surgical mild extrapulmonary respiratory failure rated comfort similarly. Moreover, perceived nasal dryness and humidity were similar in the three study arms, albeit somewhat lower (dryness) and higher (humidity) when the temperature setting was raised in a two-step increase from 31 to 37°C. However, the magnitude of differences found in primary and secondary outcomes among groups remains large.

HFNC therapy represents a simple system with clinical effects that depend largely on flow, the oxygen concentration and the temperature setting.¹¹ Previous studies found that flow exerts a greater effect than temperature because flow is a key contributor to carbon dioxide washout from the anatomic dead space and to improvement in oxygenation.^{23,24} HFNC is known to be better tolerated and to

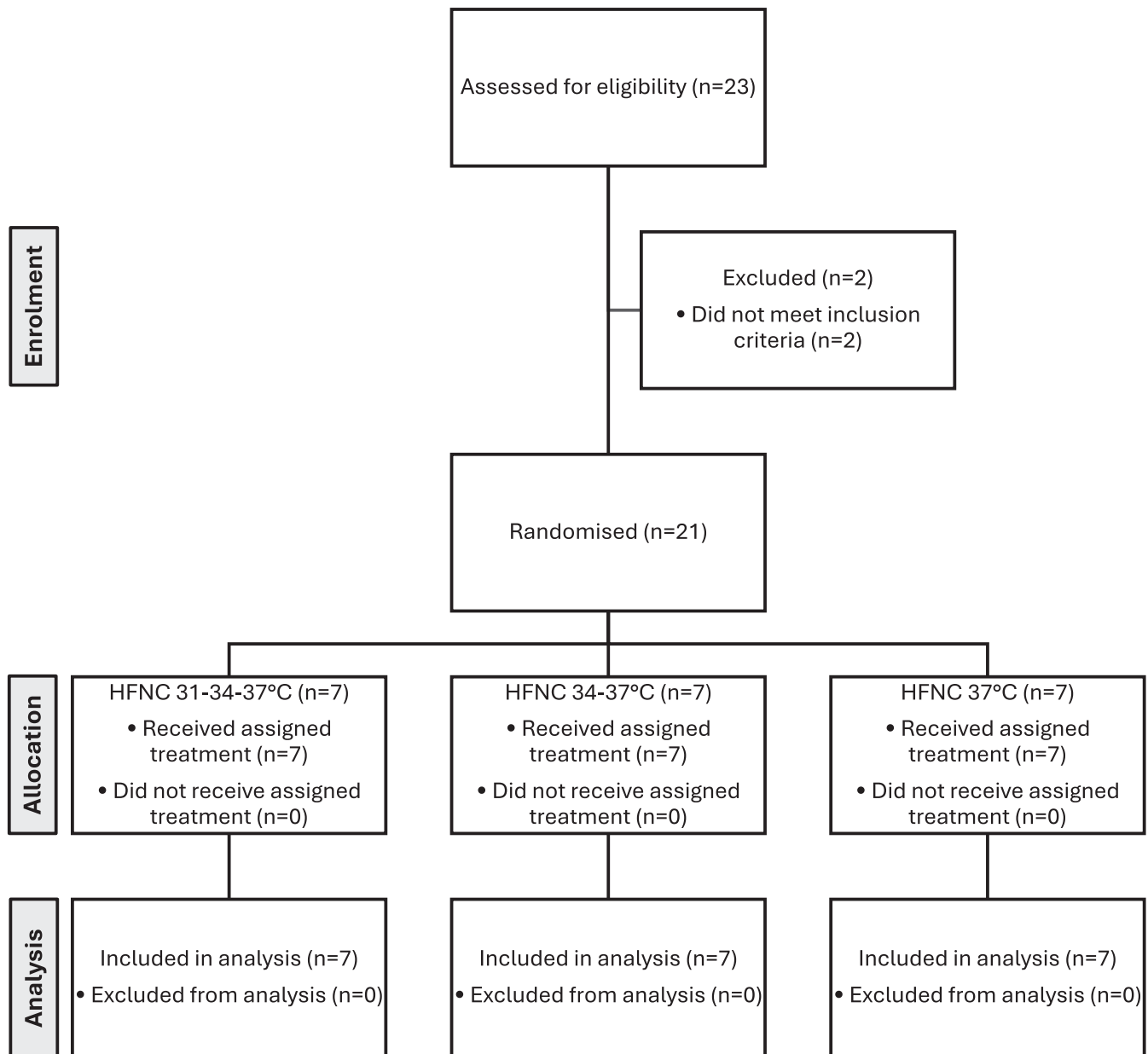


FIGURE 1 Flow diagram of the participants through each trial stage.

afford greater comfort than non-invasive ventilation.^{25–27} Higher comfort may ameliorate the tolerance of the treatment; for example, there is evidence of a link between discomfort and a poor outcome, such as the need for reintubation.²⁸

We assessed comfort at 37°C—the most effective temperature and closest to normal human body temperature—30 min after this target temperature was reached. However, the total duration of exposure to HFNC therapy differed across the arms: 30 min in the arm that started at 37°C, 45 min in the arm with a one-step increase (34–37°C) and 60 min in the arm with a two-step increase (31 to 34 to 37°C). Previous studies on perceived comfort of patients treated with diverse respiratory devices, including HFNC, have focused mainly on the correlation between oxygen flow rate and comfort.^{29–31} Maggiore et al.³² reported that HFNC produced better oxygenation and

enhanced comfort compared with non-invasive ventilation at the same fraction of inspired oxygen. The flow setting also has an important influence on comfort. Basile et al.³³ reported diminishing comfort at flow rates >60 L/min, despite better physiological outcomes (i.e., PaO₂/FiO₂ and respiratory rate). Butt et al.³⁴ documented that HFNC flow settings were associated with high mean comfort scores: there was maximum comfort at an HFNC flow rate of 30–40 L/min, with a clear and gradual decrease in comfort at a rate of 50–60 L/min. According to the pragmatic trial nature of our study, we did not stratify the patients based on the flow rate.

High-flow oxygen therapy can dry out the nasal mucosa unless it is properly humidified. For this reason, fully conditioned gas (37°C containing 44 mg H₂O/L, 100% relative humidity) delivered via HFNC prevents mucosal drying and has a protective effect on mucociliary

TABLE 1 Characteristics of the study population at the baseline.

Characteristics	Group 31-34-37°C (N = 7)	Group 34-37°C (N = 7)	Group 37°C (N = 7)	Overall (N = 21)
Age, years	63.6 (15.3)	54.2 (16.1)	72.3 (10.9)	63.3 (15.5)
Sex, female	2 (28.6%)	1 (14.3%)	3 (42.9%)	6 (28.6%)
BMI categories				
Underweight	0 (0%)	0 (0%)	1 (14.3%)	1 (4.8%)
Healthy weight	2 (28.6%)	5 (71.4%)	0 (0%)	7 (33.3%)
Overweight	4 (57.1%)	0 (0%)	3 (42.9%)	7 (33.3%)
Obesity	1 (14.3%)	2 (28.6%)	3 (42.9%)	6 (28.6%)
Ethnicity				
Caucasian	6 (85.7%)	5 (71.4%)	7 (100%)	18 (85.7%)
Hispanic	0 (0%)	2 (28.6%)	0 (0%)	2 (9.5%)
African	1 (14.3%)	0 (0%)	0 (0%)	1 (4.8%)
Current smoker	4 (57.1%)	0 (0%)	1 (14.3%)	5 (23.8%)
ROX index	17.9 (4.8)	16.8 (7.1)	17.1 (8)	17.3 (6.5)
ASA score	2 (0.6)	2.4 (0.5)	2.4 (0.5)	2.3 (0.6)
Charlson Comorbidity Index	3.1 (2.7)	3.1 (1.4)	4.9 (1.9)	3.7 (2.1)
SOFA score	2.4 (0.5)	1.9 (0.7)	3 (1.8)	2.4 (1.2)

Note: Data are presented as mean \pm 1 SD or counts and %.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; ROX, Respiratory rate–Oxygenation; SOFA, Sequential Organ Failure Assessment.

TABLE 2 High-flow nasal cannula settings and measures after 30 min at the target temperature.

Variables	Parameters	Study arms (temperature settings)			p-Value
		31-34-37°C	34-37°C	37°C	
HFNC settings	FiO ₂ , %	34.3 (7.9)	36.4 (4.8)	40.7 (14.3)	.59
	Flow, L/min	45 (8.2)	42.9 (5.7)	44.3 (8.9)	.93
Vital signs	Body temperature, °C	36.2 (0.3)	36.1 (0.8)	36.9 (0.8)	.151
	Heart rate, beats/min	80.7 (17.8)	75.3 (17.9)	85.4 (10.9)	.336
	Systolic blood pressure, mmHg	119.1 (24.8)	123.3 (15.0)	136.4 (26.1)	.379
	Diastolic blood pressure, mmHg	67.9 (10.7)	65.7 (5.6)	59.0 (7.5)	.148
	Mean blood pressure, mmHg	83.7 (14.7)	87.1 (9.2)	85.4 (14.2)	.697
	Respiratory rate, breaths/min	16.9 (3.8)	17.6 (4.5)	16.7 (5.4)	.926
	Oxygen saturation, %	96.9 (2.1)	96.9 (2.7)	97.4 (2.4)	.151
Dyspnoea	Borg CR10, 1-10	1.4 (1.8)	3.6 (2.6)	3.9 (2.5)	.081
Outcome measures	Comfort, 1-5	2.7 (1.7)	3.3 (1.3)	3.1 (1.3)	.714
	Dryness, 1-5	1.6 (1.0)	3.3 (1.7)	3.4 (1.7)	.05
	Humidity, 1-5	3.4 (1.3)	2.9 (1.1)	3.1 (1.3)	.612

Note: Data are presented as mean \pm 1 SD. Metrics: Borg CR10 from 1 (no dyspnoea) to 10 (extreme dyspnoea); Comfort from 1 (lowest) to 5 (highest); Dryness from 1 (lowest) to 5 (highest); Humidity from 1 (lowest) to 5 (highest).

Abbreviations: Borg CR10, Borg Category-Ratio anchored at the number 10; FiO₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula.

function, with clearance of secretions and airway defence.³⁵ In addition, optimal gas humidification can reduce inflammation of the tracheal mucosa after intubation and accelerate weaning in tracheostomized patients.^{36,37}

A potential drawback of HFNC therapy delivered at 37°C is excessive humidity felt at the nose and an uncomfortably high

temperature, which is why patients do not always tolerate HFNC treatment well.³⁸ The optimal temperature for HFNC is controversial: A temperature setting of 37°C can achieve optimal humidification efficiency, but there is no conclusive evidence that 37°C is the best temperature for HFNC because of the retained humidification function of the upper respiratory tract.³⁸ While authors have reported that

HFNC reduces the dryness sensation (based on subjective evaluations) in patients during and after extubation,³² Sato et al.³⁹ did not find a statistically significant difference in the prevalence of upper airways dryness (based on an objective evaluation using an oral moisture measuring device) in the HFNC group compared with the conventional oxygen therapy group. One possible explanation is that the added humidity is not sufficient to moisturize the oral cavity in patients on HFNC therapy who often open their mouths, especially when the flow rate is high. In addition, heated and humidified high-flow oxygen primarily reduces nasal dryness but not dryness of the mouth and throat.

In our study, nasal dryness and humidity perceived by patients were negatively correlated. This finding reflects the importance of setting the humidification temperature optimally so that there is a balance between dryness and humidity. Although there were no statistically significant differences across the arms, the large effect sizes for dryness and humidity indicate a notable difference. Indeed, only patients who started HFNC therapy at 37°C reported the highest nasal dryness (3.4 out of 5). This could be because of the immediate sensation of heat perceived by the patients. On the contrary, patients who received a two-step increase (31 to 34 to 37°C) reported the highest level of nasal humidity (3.4 out of 5), likely because they could feel the rise in humidity as the temperature increased. The improvement in nasal dryness with time suggests that gradual adaptation with a one- or two-step increase might optimize overall comfort and reduce nasal warming, while benefitting from maximum humidity.¹⁰ However, because the warming and moisturizing function of the upper airway is normally preserved during HFNC therapy, starting oxygen support while gradually raising the temperature may be explored further, leading to better clinical outcomes such as better tolerance, longer duration of HFNC therapy and greater comfort.⁴⁰ Given the importance of comfort, the initial HFNC settings need to be weighed against the patient management goals to achieve physiological improvement and tolerability. The HFNC settings are mainly decided by physicians, nurses or respiratory therapists, depending on local clinical practice. In any case, nurses are always present at the bedside and can customize the settings according to the patient's needs to ensure better comfort at the beginning and during the treatment.

5.1 | Limitations

This study has several limitations. First, the population was recruited at a single centre and included many post-surgical patients without severe respiratory failure. Second, we used a general mono-dimensional tool. The concept of comfort is complex⁴¹ and its measurement requires validated tools in the context of HFNC as recently reported by a review.⁴² Third, none of the enrolled patients had prior experience with oxygen therapy, so their perception of HFNC therapy as a life-saving treatment may have affected the findings. Other types of patients in whom humidification is more relevant should be involved in future studies, for example, those with chronic obstructive

pulmonary disease, where the chronicity of the disease and the oxygen dependence may affect the patient's perception. Fourth, we did not differentiate the temperature effect from the exposure time effect: because comfort may be influenced by a process of adaptation, it is possible that differences in the duration of the exposure may have affected the underlined adaptive mechanisms. Moreover, the effect size used to determine the sample size of this study proved to be overly large in comparison with the one uncovered in our analysis. Nonetheless, the substantial effect size observed for the primary and secondary outcomes suggests an interesting area of research to confirm the effect.

6 | CONCLUSIONS

Comfort is an important nursing outcome and in the context of HFNC therapy, it may be affected by the temperature setting at the treatment initiation. In this study, after 30 min of HFNC therapy at a target temperature of 37°C, patients rated substantially different levels of perceived comfort across groups, regardless of the initial therapy temperature (31, 34 or 37°C). However, these differences were not statistically significant. Moreover, there was no significant difference in nasal dryness or humidity across the study arms, suggesting that HFNC therapy can be initiated even at 37°C. Nonetheless, given the large effect size found for these secondary outcomes, it is recommended to customize the therapy rather than apply a standard approach, also considering any complication involving the airway mucosa and mucociliary clearance at lower temperatures. Furthermore, continuing to accumulate evidence in the field through a fully powered trial is recommended.

AUTHOR CONTRIBUTIONS

Alessandro Galazzi, Filippo Binda and Simone Gambazza designed the study and wrote the original draft. Alessandro Galazzi and Filippo Binda also coordinated data collection and data curation. Simone Gambazza performed formal analysis of data. Chiara Dossena, Andrea Cislighi and Ileana Adamini made the data collection. Alvisa Palese, Giacomo Grasselli and Dario Laquintana gave expert comment and reviewed the manuscript. Giacomo Grasselli and Dario Laquintana also contributed to study supervision. All authors critically revised the content of the manuscript, read and approved the final version.

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DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Milano Area 2 (ethic approval number 1050_2022). Patients gave their written informed consent to participate in the study. This pragmatic trial was registered at clinicaltrials.gov (registration number NCT05688189).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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