Comparative Evaluation of High-Flow Nasal Cannula and Non-Invasive Ventilation in Patients with Type II Respiratory Failure: A Randomized Controlled Study

Dr Sagar Solanki [1*], Dr Sumit Redhu [2], Dr mohd Anash [3], Dr Sanjay Sahay [4], Dr Rajinder Saini [5]
[1-5] Rama Medical College Hospital, Hapur, Uttar Pradesh, India

* Corresponding Author: **Dr Sagar Solanki**

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Abstract

Background: Type II respiratory failure remains a significant cause of morbidity and mortality in critically ill patients. While non-invasive ventilation (NIV) is the established standard of care, high-flow nasal cannula (HFNC) has emerged as a promising alternative respiratory support modality.

Objective: To compare the clinical efficacy, safety, and patient tolerance of HFNC versus NIV in patients with acute type II respiratory failure.

Methods: This prospective randomized controlled trial was conducted over 18 months in a tertiary care respiratory intensive care unit. Eighty patients with acute type II respiratory failure were randomly allocated to receive either HFNC (n=40) or NIV (n=40). Primary outcome measures included improvement in arterial blood gas parameters (pH, $PaCO_2$, PaO_2), respiratory rate, heart rate, and treatment failure rates. Secondary outcomes included patient comfort scores, complications, duration of respiratory support, intensive care unit length of stay, and in-hospital mortality.

Results: Both groups demonstrated significant improvement in arterial blood gas parameters at 1, 6, 12, and 24 hours. The NIV group showed faster correction of hypercapnia and respiratory acidosis at 1 hour (mean $PaCO_2$: 52.3±6.8 vs 58.7±7.2 mmHg, $p<0.001$). However, by 24 hours, differences in pH and $PaCO_2$ were not statistically significant between groups. HFNC demonstrated superior patient comfort scores (8.2±1.1 vs 5.6±1.4, $p<0.001$) and significantly lower rates of skin breakdown (2.5% vs 22.5%, $p=0.006$). Treatment failure rates were comparable (HFNC: 12.5% vs NIV: 15.0%, $p=0.74$). No significant differences were observed in ICU length of stay or mortality rates.

Conclusion: HFNC represents an effective and well-tolerated alternative to NIV in managing acute type II respiratory failure, particularly in patients who may not tolerate NIV. While NIV provides faster initial correction of hypercapnia, HFNC offers comparable efficacy with superior comfort and fewer interface-related complications.

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Introduction

Type II respiratory failure, characterized by hypercapnia ($PaCO_2$ >45 mmHg) with or without hypoxemia, represents a critical clinical condition requiring prompt intervention [1, 2]. The underlying pathophysiology involves inadequate alveolar ventilation relative to carbon dioxide production, commonly occurring in patients with chronic obstructive pulmonary disease exacerbations, obesity hypoventilation syndrome, neuromuscular disorders, and chest wall deformities [3, 4]. Without appropriate respiratory support, progressive hypercapnic respiratory failure leads to respiratory acidosis, altered mental status, cardiovascular complications, and potentially fatal outcomes [5].

Non-invasive ventilation has been established as the first-line treatment for acute hypercapnic respiratory failure over the past three decades [6, 7]. Multiple randomized controlled trials and meta-analyses have demonstrated that NIV reduces the need for endotracheal intubation, decreases mortality, shortens hospital length of stay, and improves patient outcomes compared to

conventional oxygen therapy [8–10]. Current international guidelines strongly recommend NIV as standard care for acute exacerbations of chronic obstructive pulmonary disease with respiratory acidosis [11, 12]. Despite these benefits, NIV is associated with several limitations including poor patient tolerance, interface-related complications, claustrophobia, difficulty with secretion clearance, and contraindications in certain patient populations [13, 14].

High-flow nasal cannula therapy has emerged as an innovative respiratory support modality that delivers heated and humidified oxygen at flow rates up to 60 liters per minute through nasal prongs [15, 16]. The physiological mechanisms underlying HFNC efficacy include washout of nasopharyngeal dead space, provision of positive end-expiratory pressure, reduction in inspiratory resistance, improved mucociliary clearance, and delivery of consistent FiO_2 [17, 18]. Initially utilized primarily for hypoxemic respiratory failure, recent evidence suggests potential benefits in hypercapnic conditions [19, 20].

Several observational studies have reported promising results with HFNC in patients with chronic obstructive pulmonary disease and hypercapnia [21, 22]. The proposed mechanisms for carbon dioxide elimination include reduction in anatomical dead space ventilation, decreased work of breathing, and improved ventilation-perfusion matching [23]. However, comparative data directly evaluating HFNC against the established standard of NIV in type II respiratory failure remain limited. Most existing studies have focused on hypoxemic respiratory failure or post-extubation settings [24, 25].

The decision regarding optimal respiratory support modality in type II respiratory failure has significant clinical implications. While NIV provides proven efficacy, implementation challenges and patient intolerance may limit its effectiveness in routine practice [26]. If HFNC demonstrates comparable efficacy with improved tolerance, it could represent a valuable alternative or complementary strategy, particularly in patients unable to tolerate NIV [27]. Furthermore, the relative simplicity of HFNC application may facilitate earlier initiation of respiratory support and broader applicability across various healthcare settings [28].

Given the paucity of high-quality randomized controlled trials directly comparing these modalities in type II respiratory failure, there exists a critical knowledge gap regarding their relative efficacy, safety profiles, and optimal patient selection criteria [29, 30]. Understanding the comparative benefits and limitations of HFNC versus NIV will inform evidence-based clinical decision-making and potentially improve outcomes for patients with acute hypercapnic respiratory failure.

Objectives

Primary Objective: To compare the efficacy of high-flow nasal cannula therapy versus non-invasive ventilation in improving arterial blood gas parameters (pH, $PaCO_2$, PaO_2) in patients with acute type II respiratory failure.

Secondary Objectives:

1. To compare the effect of HFNC and NIV on respiratory rate and heart rate at various time intervals
2. To evaluate and compare treatment failure rates between the two modalities
3. To assess patient comfort and tolerance with HFNC versus NIV
4. To compare the incidence of complications associated with each respiratory support modality
5. To compare duration of respiratory support, intensive care unit length of stay, and in-hospital mortality between groups

Materials and Methods

Study Design

This prospective, randomized controlled trial was conducted to compare the clinical efficacy and safety of HFNC versus NIV in patients with acute type II respiratory failure. The study employed a parallel-group design with 1:1 allocation ratio.

Study Setting and Population

The study was conducted in the respiratory intensive care unit of a tertiary care teaching hospital over an 18-month period from January 2022 to June 2023. The facility is a 20-bed specialized respiratory ICU equipped with comprehensive monitoring capabilities and staffed by respiratory medicine specialists, intensivists, and trained respiratory therapists available around the clock.

All patients admitted to the respiratory ICU during the study period were screened for eligibility. Consecutive patients meeting inclusion criteria were approached for participation. The study protocol received approval from the institutional ethics committee, and written informed consent was obtained from all participants or their legally authorized representatives prior to enrollment.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Age ≥18 years
2. Acute type II respiratory failure defined as:
   - $PaCO_2$ >45 mmHg
   - pH <7.35
   - Clinical signs of respiratory distress (dyspnea, use of accessory muscles, tachypnea)
3. Hemodynamic stability (systolic blood pressure >90 mmHg without vasopressor support)
4. Ability to protect airway and clear secretions
5. Glasgow Coma Scale score ≥13

Exclusion Criteria:

1. Immediate need for endotracheal intubation (pH <7.25, respiratory arrest, severe hemodynamic instability)
2. Contraindications to NIV (facial trauma, recent upper airway or gastrointestinal surgery, active gastrointestinal bleeding, fixed upper airway obstruction)
3. Pneumothorax without chest tube drainage
4. Severe encephalopathy or agitation precluding cooperation
5. Pregnancy
6. Do-not-intubate status
7. Refusal to participate in the study

Randomization and Intervention Protocol

Following eligibility confirmation and informed consent, patients were randomly allocated to either HFNC or NIV group using computer-generated random number sequences in sealed opaque envelopes. Block randomization with block sizes of 10 was employed to ensure balanced allocation throughout the study period. Allocation concealment was

maintained until intervention initiation.

Baseline assessments were performed immediately before intervention commencement, including demographic data, clinical examination, arterial blood gas analysis, vital signs, and comfort assessment. All patients received standard medical therapy according to underlying etiology, including bronchodilators, corticosteroids, antibiotics when indicated, and appropriate fluid management.

HFNC Application Protocol

Patients randomized to HFNC received therapy via a dedicated high-flow nasal cannula system (Airvo 2, Fisher & Paykel Healthcare). The following protocol was implemented:

1. **Initial Settings:**
   - Flow rate: 50-60 L/min (adjusted based on patient comfort and clinical response)
   - FiO_2: Titrated to maintain SpO_2 88-92% in COPD patients or 92-96% in other etiologies
   - Temperature: 37°C
2. **Monitoring and Adjustment:**
   - Continuous pulse oximetry monitoring
   - Arterial blood gas analysis at 1, 6, 12, and 24 hours
   - Flow rate optimization based on patient comfort and respiratory effort
   - FiO_2 adjustment to maintain target oxygen saturation
3. **Weaning Criteria:**
   - Sustained improvement in clinical parameters and arterial blood gases
   - Reduction in respiratory rate to <25 breaths/minute
   - Gradual reduction in FiO_2 and flow rate
   - Transition to conventional oxygen therapy when FiO_2 <0.35 and flow <30 L/min

NIV Application Protocol

Patients randomized to NIV received therapy via BiPAP mode using ICU ventilators (Servo-i, Maquet or V60, Philips Respironics) with oronasal masks. The following protocol was implemented:

1. **Initial Settings:**
   - Inspiratory Positive Airway Pressure (IPAP): 12-14 cmH_2O
   - Expiratory Positive Airway Pressure (EPAP): 4-5 cmH_2O
   - FiO_2: Titrated to maintain target SpO_2
   - Backup respiratory rate: 12-15 breaths/minute
2. **Titration Protocol:**
   - IPAP increased by 2 cmH_2O increments every 15-30 minutes as tolerated up to maximum 20-22 cmH_2O
   - EPAP increased to 6-8 cmH_2O if required for oxygenation
   - Target tidal volume: 6-8 mL/kg ideal body weight
   - Adjustment based on patient-ventilator synchrony and gas exchange
3. **Application Schedule:**
   - Continuous application for first 6-12 hours
   - Subsequent application: minimum 16-18 hours daily with breaks for meals and oral care
   - Monitoring during breaks with arterial blood gas analysis if clinical deterioration
4. **Weaning Criteria:**
   - Sustained clinical improvement and resolution of respiratory acidosis
   - Gradual reduction in pressure support and daily NIV duration
   - Transition to conventional oxygen therapy when IPAP ≤10 cmH_2O and application <6 hours daily

Outcome Measures

Primary Outcome Measures:

1. Change in arterial blood gas parameters (pH, $PaCO_2$, PaO_2) from baseline at 1, 6, 12, and 24 hours
2. Treatment failure rate (defined as need for endotracheal intubation or switch to alternative respiratory support modality)

Secondary Outcome Measures:

1. Respiratory rate and heart rate at baseline, 1, 6, 12, and 24 hours
2. Oxygen saturation (SpO_2) trends
3. Patient comfort score (assessed using visual analog scale 0-10, where 0=extremely uncomfortable and 10=extremely comfortable)
4. Interface-related complications (skin breakdown, nasal trauma, gastric distension, aspiration)
5. Duration of respiratory support (hours)
6. ICU length of stay (days)
7. In-hospital mortality

Statistical Analysis

Sample size calculation was performed based on previous literature reporting mean $PaCO_2$ reduction of 8±5 mmHg with NIV. To detect a difference of 3 mmHg between groups with 80% power and 5% significance level, 36 patients per group were required. Accounting for potential 10% dropout, 40 patients per group were enrolled.

All statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY). Continuous variables were expressed as mean ± standard deviation or median with interquartile range depending on distribution. Categorical variables were expressed as frequencies and percentages.

Normality of distribution was assessed using Shapiro-Wilk test and visual inspection of histograms. For normally distributed continuous variables, independent samples t-test was used for between-group comparisons and paired t-test for within-group comparisons. For non-normally distributed variables, Mann-Whitney U test and Wilcoxon signed-rank test were employed. Chi-square test or Fisher's exact test was used for categorical variables.

Repeated measures ANOVA was performed to assess trends in physiological parameters over time. A two-tailed p-value <0.05 was considered statistically significant. Intention-to-treat analysis was performed for all outcomes.

Results

Baseline Characteristics

A total of 112 patients with acute type II respiratory failure were screened during the study period. After applying inclusion and exclusion criteria, 80 patients were enrolled and randomized (40 to HFNC group and 40 to NIV group). All randomized patients completed the study protocol and were included in the final analysis (Figure 1).

Table 1: Demographic and Baseline Clinical Characteristics of Study Participants

Variable	HFNC Group (n=40)	NIV Group (n=40)	p-value
Age (years), mean ± SD	61.3 ± 11.8	62.7 ± 10.5	0.58
Male gender, n (%)	26 (65.0)	27 (67.5)	0.81
Body Mass Index (kg/m²), mean ± SD	26.8 ± 4.6	27.3 ± 5.2	0.65
Primary Diagnosis, n (%)			
COPD exacerbation	21 (52.5)	20 (50.0)	0.82
Obesity hypoventilation syndrome	8 (20.0)	9 (22.5)	0.78
Pneumonia with Type II RF	7 (17.5)	6 (15.0)	0.76
Bronchiectasis exacerbation	4 (10.0)	5 (12.5)	0.72
Comorbidities, n (%)			
Hypertension	18 (45.0)	20 (50.0)	0.65
Diabetes mellitus	12 (30.0)	14 (35.0)	0.63
Ischemic heart disease	8 (20.0)	7 (17.5)	0.77
Baseline Physiological Parameters			
pH, mean ± SD	7.28 ± 0.05	7.27 ± 0.06	0.42
$PaCO_2$ (mmHg), mean ± SD	64.8 ± 8.3	65.2 ± 7.9	0.82
PaO_2 (mmHg), mean ± SD	54.6 ± 7.8	53.8 ± 8.2	0.66
Respiratory rate (breaths/min), mean ± SD	32.4 ± 4.6	31.8 ± 4.3	0.55
Heart rate (beats/min), mean ± SD	108.6 ± 12.4	106.8 ± 13.2	0.52
SpO_2 (%), mean ± SD	84.2 ± 5.6	83.8 ± 6.1	0.76

COPD = Chronic Obstructive Pulmonary Disease; RF = Respiratory Failure; SD = Standard Deviation

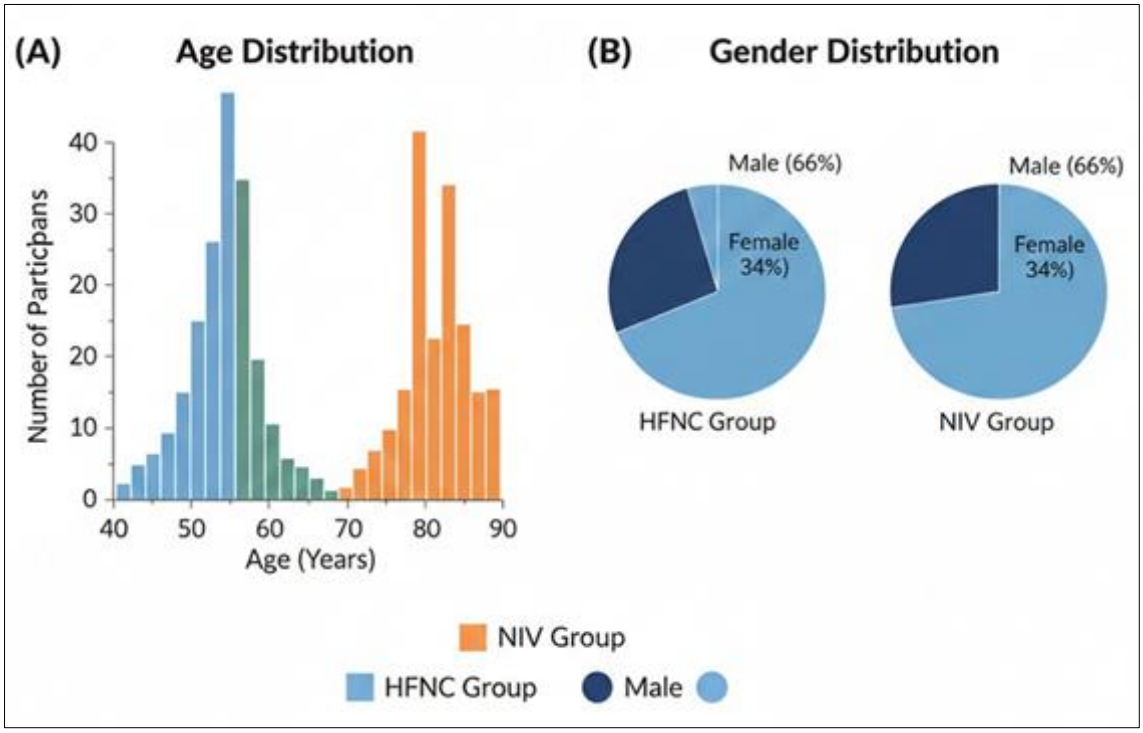

Fig 1: Age and Gender Distribution of Study Participants

Baseline demographic and clinical characteristics were comparable between the two groups (Table 1). The mean age was 61.3±11.8 years in the HFNC group and 62.7±10.5 years in the NIV group (p=0.58). Male predominance was observed in both groups (HFNC: 65%, NIV: 67.5%, p=0.81). Chronic obstructive pulmonary disease was the most common underlying etiology (HFNC: 52.5%, NIV: 50.0%), followed by obesity hypoventilation syndrome, pneumonia with type II respiratory failure, and bronchiectasis with acute exacerbation.

Baseline physiological parameters and arterial blood gas values demonstrated similar severity of respiratory failure in both groups. Mean pH was 7.28±0.05 in HFNC group versus 7.27±0.06 in NIV group (p=0.42). Mean baseline $PaCO_2$ was 64.8±8.3 mmHg in HFNC group and 65.2±7.9 mmHg in NIV group (p=0.82). Baseline PaO_2, respiratory rate, heart rate, and oxygen saturation showed no significant differences between groups (all p>0.05).

Arterial Blood Gas Parameters

Both treatment modalities resulted in significant improvement in arterial blood gas parameters over time (Table 2). Analysis of pH trends revealed progressive normalization in both groups. At 1 hour, the NIV group demonstrated faster correction of respiratory acidosis with mean pH of 7.32±0.04 compared to 7.29±0.05 in HFNC group (p=0.003). This early advantage persisted at 6 hours (NIV: 7.35±0.03 vs HFNC: 7.33±0.04, p=0.01). However, by 12 hours, the difference narrowed (NIV: 7.37±0.03 vs HFNC: 7.36±0.03, p=0.08), and at 24 hours, both groups achieved comparable pH normalization (NIV: 7.39±0.02 vs HFNC: 7.38±0.03, p=0.21).

Table 2: Comparison of Physiological and Arterial Blood Gas Parameters Between HFNC and NIV at Different Time Intervals

Parameter	Time Point	HFNC Group (n=40)	NIV Group (n=40)	p-value
pH	Baseline	7.28 ± 0.05	7.27 ± 0.06	0.42
	1 hour	7.29 ± 0.05	7.32 ± 0.04	0.003
	6 hours	7.33 ± 0.04	7.35 ± 0.03	0.01
	12 hours	7.36 ± 0.03	7.37 ± 0.03	0.08
	24 hours	7.38 ± 0.03	7.39 ± 0.02	0.21
$PaCO_2$ (mmHg)	Baseline	64.8 ± 8.3	65.2 ± 7.9	0.82
	1 hour	58.7 ± 7.2	52.3 ± 6.8	<0.001
	6 hours	51.4 ± 6.3	47.8 ± 5.6	0.008
	12 hours	46.8 ± 5.4	44.6 ± 4.8	0.052
	24 hours	43.7 ± 4.9	42.1 ± 4.2	0.12
PaO_2 (mmHg)	Baseline	54.6 ± 7.8	53.8 ± 8.2	0.66
	1 hour	72.4 ± 8.6	70.8 ± 9.2	0.42
	6 hours	78.6 ± 7.4	77.2 ± 8.6	0.43
	12 hours	81.5 ± 7.6	80.4 ± 8.1	0.53
	24 hours	84.3 ± 7.8	83.6 ± 8.4	0.69
Respiratory Rate (breaths/min)	Baseline	32.4 ± 4.6	31.8 ± 4.3	0.55
	1 hour	27.8 ± 3.8	24.6 ± 3.2	<0.001
	6 hours	24.2 ± 3.1	22.8 ± 2.8	0.04
	12 hours	22.4 ± 2.8	21.6 ± 2.6	0.18
	24 hours	20.8 ± 2.6	20.2 ± 2.4	0.29

Data presented as mean ± standard deviation

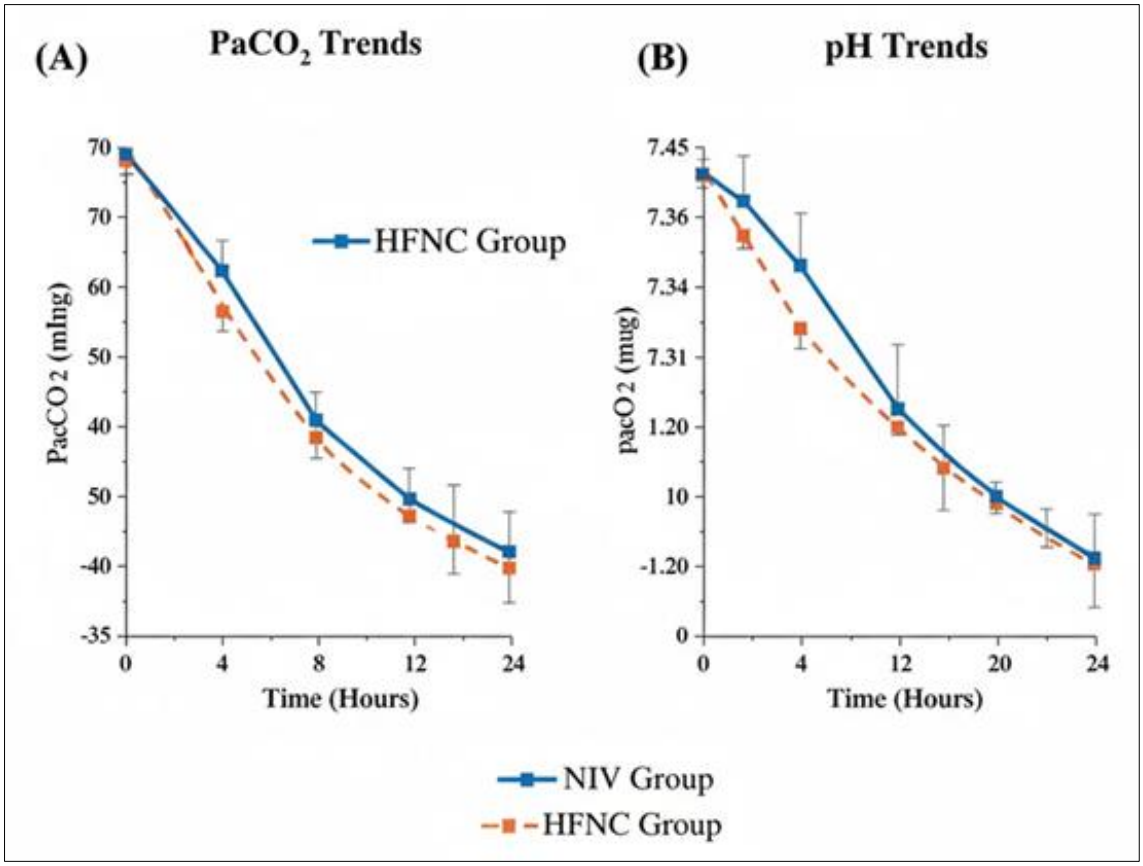

Fig 2: Trend of $PaCO_2$ and pH Changes Over Time in HFNC and NIV Groups

$PaCO_2$ reduction followed similar temporal patterns (Figure 2). The NIV group showed more rapid hypercapnia correction at 1 hour (mean $PaCO_2$: 52.3±6.8 mmHg vs 58.7±7.2 mmHg in HFNC, $p<0.001$) and 6 hours (47.8±5.6 mmHg vs 51.4±6.3 mmHg, $p=0.008$). By 12 hours, $PaCO_2$ levels were 44.6±4.8 mmHg in NIV group versus 46.8±5.4 mmHg in HFNC group ($p=0.052$). At 24 hours, both groups demonstrated effective carbon dioxide elimination with no statistically significant difference (NIV: 42.1±4.2 mmHg vs HFNC: 43.7±4.9 mmHg, $p=0.12$).

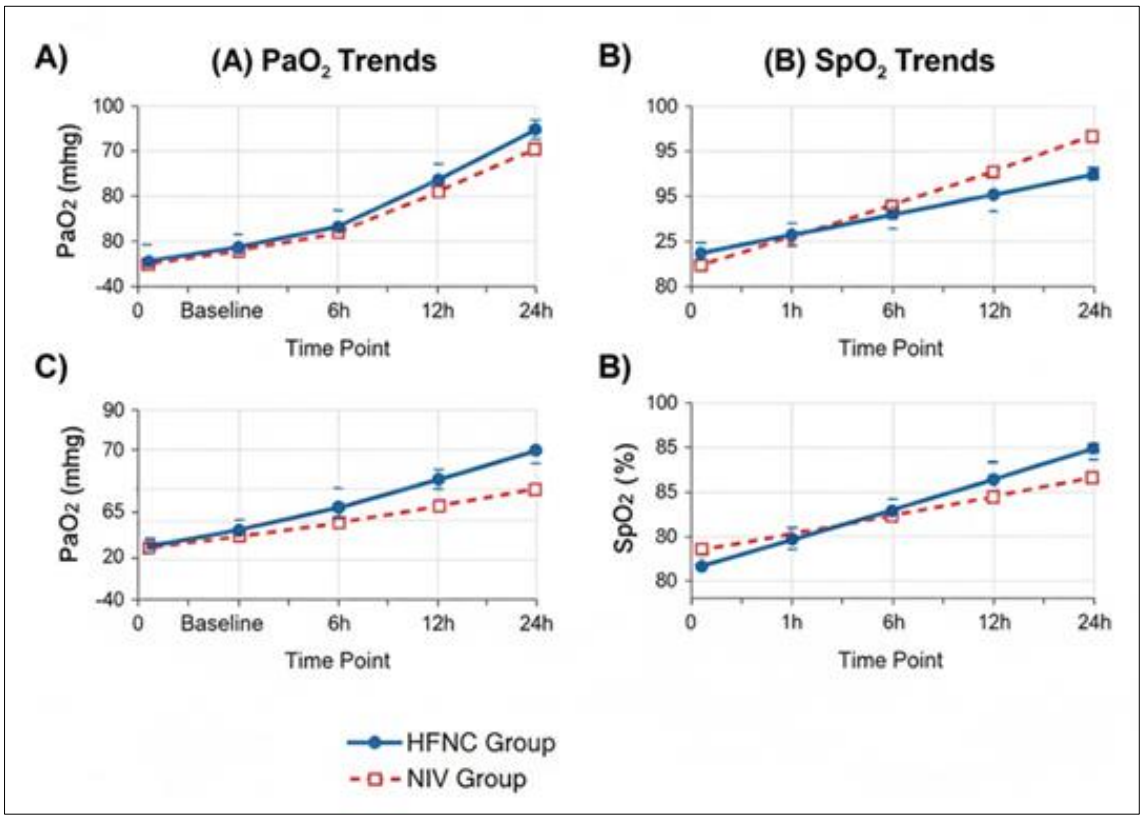

Fig 3: Comparison of Oxygenation Parameters (SpO_2 / PaO_2) Between Groups

Oxygenation parameters improved significantly in both groups (Figure 3). Mean PaO_2 at 1 hour increased to 72.4±8.6 mmHg in HFNC group and 70.8±9.2 mmHg in NIV group ($p=0.42$). Progressive improvement continued with comparable oxygenation achieved at 24 hours (HFNC: 84.3±7.8 mmHg vs NIV: 83.6±8.4 mmHg, $p=0.69$). SpO_2 trends paralleled PaO_2 changes with no significant differences between groups at any time point.

Respiratory Rate and Heart Rate

Respiratory rate decreased significantly from baseline in both groups. Mean baseline respiratory rate was 32.4±4.6 breaths/minute in HFNC group and 31.8±4.3 breaths/minute in NIV group ($p=0.55$). At 1 hour, NIV group showed greater reduction (24.6±3.2 breaths/minute vs 27.8±3.8 breaths/minute, $p<0.001$). By 24 hours, respiratory rates were comparable (HFNC: 20.8±2.6 vs NIV: 20.2±2.4 breaths/minute, $p=0.29$).

Heart rate reductions were similar between groups. Baseline heart rates were 108.6±12.4 beats/minute in HFNC group and 106.8±13.2 beats/minute in NIV group ($p=0.52$). Both groups demonstrated progressive heart rate reduction with no significant differences at 1, 6, 12, or 24 hours (all $p>0.05$).

Patient Comfort and Tolerance

Patient comfort scores differed significantly between modalities (Table 3). The HFNC group reported substantially higher comfort scores compared to NIV group (mean score: 8.2±1.1 vs 5.6±1.4, $p<0.001$). Patients in the HFNC group specifically reported better tolerance, less claustrophobia, easier communication, and ability to eat and drink while receiving therapy. In the NIV group, 18 patients (45%) reported significant discomfort related to mask interface, with 12 patients (30%) experiencing claustrophobia requiring temporary interruption of therapy.

Table 3: Clinical Outcomes, Complications, ICU Stay, and Treatment Failure Rates

Outcome Variable	HFNC Group (n=40)	NIV Group (n=40)	p-value
Treatment Failure, n (%)	5 (12.5)	6 (15.0)	0.74
Escalation to NIV	3 (7.5)	-	-
Escalation to intubation	2 (5.0)	4 (10.0)	0.40
Switch to HFNC	-	2 (5.0)	-
Patient Comfort Score (0-10), mean ± SD	8.2 ± 1.1	5.6 ± 1.4	<0.001
Complications, n (%)			
Skin breakdown/pressure ulcers	1 (2.5)	9 (22.5)	0.006
Nasal discomfort	8 (20.0)	2 (5.0)	0.04
Gastric distension	0 (0)	5 (12.5)	0.02
Aspiration	0 (0)	1 (2.5)	0.31
Claustrophobia	0 (0)	18 (45.0)	<0.001
Duration of respiratory support (hours), mean ± SD	72.4 ± 28.6	68.8 ± 32.4	0.59
ICU length of stay (days), mean ± SD	5.8 ± 2.4	6.2 ± 2.8	0.49
Hospital length of stay (days), mean ± SD	9.6 ± 3.8	10.2 ± 4.2	0.51
In-hospital mortality, n (%)	2 (5.0)	2 (5.0)	1.00

SD = Standard Deviation; ICU = Intensive Care Unit

Treatment Failure and Clinical Outcomes

Treatment failure, defined as need for endotracheal intubation or switch to alternative respiratory support, occurred in 5 patients (12.5%) in HFNC group and 6 patients (15.0%) in NIV group (p=0.74). Among HFNC failures, 3 patients required escalation to NIV and subsequently improved, while 2 required intubation. In the NIV group, 4 patients required intubation due to worsening hypercapnia and altered mental status despite optimal NIV settings, and 2 patients could not tolerate NIV and were switched to HFNC with subsequent improvement.

The causes of treatment failure in HFNC group included progressive hypercapnia despite maximal settings (n=3), severe patient-ventilator asynchrony (n=1), and hemodynamic instability (n=1). In NIV group, treatment failures resulted from mask intolerance precluding adequate therapy delivery (n=2), worsening respiratory acidosis (n=3), and aspiration event (n=1).

Complications

Interface-related complications occurred significantly more frequently in NIV group. Skin breakdown and pressure ulcers developed in 9 patients (22.5%) receiving NIV compared to only 1 patient (2.5%) in HFNC group (p=0.006). Nasal bridge erythema and discomfort were the most common sites. Gastric distension occurred in 5 NIV patients (12.5%) versus none in HFNC group (p=0.02). One patient in NIV group experienced aspiration requiring intubation. Nasal discomfort was reported by 8 patients (20%) in HFNC group but did not necessitate therapy discontinuation. No pneumothorax or other serious adverse events occurred in either group.

Duration of Respiratory Support and Hospital Outcomes

Mean duration of respiratory support was 72.4±28.6 hours in HFNC group and 68.8±32.4 hours in NIV group (p=0.59). ICU length of stay was comparable between groups (HFNC: 5.8±2.4 days vs NIV: 6.2±2.8 days, p=0.49). Total hospital length of stay did not differ significantly (HFNC: 9.6±3.8 days vs NIV: 10.2±4.2 days, p=0.51).

In-hospital mortality occurred in 2 patients (5%) in each group (p=1.00). In HFNC group, deaths resulted from refractory respiratory failure with multiorgan dysfunction despite intubation and mechanical ventilation. In NIV group, mortality was attributed to progressive respiratory failure and septic shock. All deaths occurred in patients who had treatment failure requiring intubation.

Discussion

This randomized controlled trial provides important comparative evidence regarding HFNC versus NIV in acute type II respiratory failure. The principal finding is that while NIV demonstrates faster initial correction of hypercapnia and respiratory acidosis, HFNC achieves comparable efficacy by 24 hours with superior patient comfort and fewer complications.

The pathophysiological mechanisms underlying HFNC efficacy in type II respiratory failure deserve consideration. HFNC generates positive airway pressure through high flow delivery, with estimated PEEP levels of 3-5 cmH_2O depending on flow rates and mouth closure [31]. This positive pressure may improve alveolar ventilation and reduce work of breathing. Additionally, nasopharyngeal dead space washout by high flows reduces rebreathing of carbon dioxide, effectively improving alveolar ventilation efficiency [32]. The provision of heated and humidified gas optimizes mucociliary function and may facilitate secretion clearance, particularly relevant in patients with chronic obstructive pulmonary disease [33].

Our findings regarding faster initial pH and $PaCO_2$ correction with NIV align with established understanding of NIV mechanisms. Positive pressure ventilation directly augments alveolar ventilation, providing immediate support for carbon dioxide elimination [34]. The pressure gradient between IPAP and EPAP generates tidal volumes that supplement patient effort, explaining the more rapid physiological response [35]. However, the convergence of outcomes by 24 hours suggests that HFNC, though slower in onset, ultimately achieves adequate ventilatory support through its distinct mechanisms.

Several recent studies have evaluated HFNC in hypercapnic populations, though methodological differences complicate direct comparisons. A multicenter randomized trial by Doshi *et al.* [36] reported similar intubation rates between HFNC and NIV in patients with acute exacerbations of COPD, consistent with our failure rate findings. However, their study included less severe hypercapnia at baseline (mean pH 7.32), potentially limiting generalizability to patients with more pronounced acidosis. Conversely, a study by Cortegiani *et al.* [37] found higher failure rates with HFNC compared to NIV in severe hypercapnic respiratory failure, possibly reflecting differences in patient selection and institutional expertise.

The superior comfort scores observed with HFNC represent a clinically meaningful advantage with potential implications for therapy adherence and effectiveness. Patient comfort

encompasses multiple dimensions including physical interface pressure, breathing ease, communication ability, and psychological factors such as claustrophobia [38]. Our observation of 45% of NIV patients reporting significant mask discomfort is consistent with literature reporting NIV intolerance rates of 30-50% [39]. This discomfort may lead to therapy interruptions, reducing cumulative ventilatory support and potentially compromising efficacy. The open interface of HFNC eliminates mask-related issues while permitting eating, drinking, and communication, enhancing patient acceptance [40].

Interface-related complications occurred substantially more frequently with NIV in our study. Facial skin breakdown affects 20-30% of NIV patients in various series and represents a significant morbidity [41]. These pressure injuries cause pain, may necessitate therapy interruption, and occasionally progress to serious soft tissue infections. Strategies to minimize complications include careful mask fitting, protective dressings, and regular interface changes, yet complete prevention remains challenging [42]. The minimal interface contact with HFNC largely eliminates this complication, though nasal discomfort may occur at very high flow rates [43].

Gastric distension and aspiration risk constitute important NIV-related concerns. Positive pressure ventilation may force air into the stomach, particularly at higher pressures or with poor patient synchrony [44]. While generally manageable, severe gastric distension can compromise diaphragmatic excursion and increase aspiration risk. The aspiration event in our NIV group, though uncommon, highlights this potential complication. HFNC eliminates this risk due to its lower delivered pressures and open system [45].

Treatment failure rates in our study (12.5% HFNC, 15.0% NIV) compare favorably with historical data. Meta-analyses report NIV failure rates of 10-40% in hypercapnic respiratory failure, varying with underlying etiology and severity [46]. The comparable failure rates between modalities, combined with superior tolerance, suggest HFNC may be appropriate first-line therapy in selected patients. Importantly, three HFNC failures responded to subsequent NIV, suggesting sequential therapy approaches merit consideration [47].

Our mortality rates (5% each group) were lower than some published series, potentially reflecting careful patient selection excluding severe acidosis (pH <7.25) likely requiring intubation. This pragmatic approach parallels real-world clinical practice where extremely severe cases proceed directly to invasive ventilation [48]. The comparable mortality between groups provides reassurance regarding HFNC safety in appropriately selected patients.

ICU and hospital length of stay did not differ between groups, consistent with several comparative studies [49, 50]. Both modalities facilitate earlier mobilization compared to invasive ventilation, potentially explaining similar discharge timelines despite different mechanisms of action. The duration of respiratory support was also similar, suggesting that once initiated, therapy requirements follow comparable trajectories regardless of modality.

Several limitations warrant consideration in interpreting our findings. First, the single-center design may limit generalizability, as institutional expertise, protocols, and patient populations vary. Multicenter trials would strengthen external validity. Second, we excluded patients with severe acidosis (pH <7.25), a group where NIV evidence is strongest. Our results apply to moderate hypercapnic respiratory failure and extrapolation to severe cases requires caution. Third, attending clinicians were not blinded to interventions due to the nature of respiratory support devices, potentially introducing bias in subjective assessments and decisions regarding treatment failure. However, objective physiological outcomes were measured systematically, minimizing this concern.

Fourth, we did not evaluate long-term outcomes beyond hospital discharge. Some studies suggest NIV may provide benefits for selected patients as chronic domiciliary therapy [51]. Whether acute HFNC success predicts long-term respiratory support needs remains unexplored. Fifth, cost-effectiveness analysis was not performed. While HFNC equipment may have lower acquisition costs than ICU ventilators, consumable costs and staffing requirements differ. Comprehensive economic evaluation would inform resource allocation decisions.

The optimal patient selection criteria for HFNC versus NIV requires further definition. Our inclusion criteria identified patients likely to benefit from either modality, but predictive factors for differential response deserve investigation. Candidate variables include baseline pH severity, body mass index, secretion burden, prior NIV experience, and psychological factors. Predictive models could guide personalized therapy selection, maximizing efficacy while optimizing resource utilization [52].

Our findings have practical clinical implications. HFNC represents a reasonable first-line option for acute type II respiratory failure in patients who may tolerate it poorly or have relative contraindications. The superior comfort and lower complication rates support its use when patient acceptance is prioritized. However, patients with severe acidosis or rapidly progressive deterioration likely benefit from NIV's faster physiological correction. A pragmatic approach involves HFNC initiation with close monitoring and low threshold for NIV escalation if inadequate response occurs within 1-2 hours [53].

The success of HFNC escalation to NIV in three patients suggests sequential strategies merit further study. Starting with better-tolerated HFNC and reserving NIV for inadequate responders may optimize the benefit-to-burden ratio. Conversely, early NIV for rapid stabilization followed by transition to HFNC for continued support represents another potential approach. Comparative effectiveness research evaluating these algorithms would enhance clinical decision-making [54].

Future research directions include investigation of HFNC in specific subpopulations such as obesity hypoventilation syndrome, neuromuscular diseases, and chest wall disorders where NIV evidence is robust but tolerance challenges exist. Studies evaluating HFNC as bridge therapy to long-term NIV or as alternative for NIV-intolerant patients requiring chronic support would address important clinical questions. Additionally, physiological studies using esophageal pressure monitoring and electrical impedance tomography could elucidate mechanisms of HFNC effectiveness in hypercapnic conditions [55].

Conclusion

This randomized controlled trial demonstrates that high-flow nasal cannula therapy represents an effective alternative to non-invasive ventilation for managing acute type II respiratory failure. While NIV provides faster initial correction of hypercapnia and respiratory acidosis, HFNC

achieves comparable physiological outcomes by 24 hours with significantly superior patient comfort and fewer interface-related complications. Treatment failure rates and mortality are similar between modalities. These findings support HFNC as a viable first-line respiratory support option in appropriately selected patients with moderate hypercapnic respiratory failure, particularly those likely to experience NIV intolerance. Close monitoring with readiness to escalate to NIV or invasive ventilation remains essential. The choice between HFNC and NIV should be individualized based on severity of acidosis, patient factors, and institutional resources.

Recommendations

Based on the findings of this study, the following recommendations are proposed:

1. **Clinical Application:** HFNC should be considered as a first-line respiratory support modality in patients with acute type II respiratory failure who have moderate hypercapnia (pH 7.25-7.35) and are hemodynamically stable.
2. **Patient Selection:** Patients with severe acidosis (pH <7.25), rapidly deteriorating clinical status, or altered mental status should receive NIV as initial therapy due to its faster physiological correction.
3. **Monitoring Protocol:** Regardless of modality chosen, arterial blood gas analysis should be performed at 1-2 hours after initiation to assess treatment response, with low threshold for escalation if inadequate improvement.
4. **Sequential Therapy:** In cases of HFNC failure without urgent indication for intubation, escalation to NIV should be attempted before proceeding to invasive mechanical ventilation.
5. **Patient Comfort Optimization:** For patients experiencing NIV intolerance despite appropriate interface adjustments, HFNC represents a suitable alternative that may provide adequate respiratory support with better tolerance.
6. **Complication Prevention:** Regular assessment for interface-related complications should be performed with NIV, including skin inspection and evaluation for gastric distension.
7. **Training Requirements:** Healthcare personnel should receive comprehensive training in both HFNC and NIV application, monitoring, and troubleshooting to optimize therapy delivery.
8. **Protocol Development:** Institutions should develop standardized protocols for HFNC and NIV application in type II respiratory failure, including clear escalation and de-escalation criteria.
9. **Further Research:** Large multicenter randomized controlled trials are needed to validate these findings across diverse populations and settings, with focus on patient-centered outcomes and cost-effectiveness.
10. **Personalized Approach:** The selection of respiratory support modality should be individualized considering disease severity, patient factors, previous experience with therapies, and institutional expertise.

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