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Original Research Article

A Comparative Analysis of the Efficacy of Nasal Continuous Positive Airway Pressure and Heated Humidified High-Flow Nasal Cannula in the Treatment of Neonatal Respiratory Distress: A Randomised Controlled Trial

Pavithra Shree B. E.[1]

[1]Department of Paediatrics, Adichunchanagiri Institute of Medical Sciences, B. G. Nagara, Mandya District, Karnataka, India

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Corresponding Author: Dr. Pavithra Shree B E
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Abstract

Background: Nasal continuous positive airway pressure (nCPAP) is the established first-line non-invasive respiratory support for neonatal respiratory distress, but it is associated with nasal trauma, abdominal distension and demanding nursing care. Heated humidified high-flow nasal cannula (HFNC) is simpler to apply and better tolerated, although evidence on its efficacy as primary support remains conflicting. This trial compared the two modalities as primary respiratory support in neonates with respiratory distress.

Methods: One hundred and twenty neonates of gestational age 28 weeks or above and birth weight 1000 g or above, presenting within 24 hours of birth with respiratory distress and a Silverman-Anderson score of 4 or more, were randomised in a 1:1 ratio to bubble nCPAP or HFNC. The primary outcome was treatment failure within 72 hours, defined by predefined oxygenation, clinical, blood gas and apnoea criteria. Secondary outcomes included the need for mechanical ventilation, duration of support, feeding milestones, nasal trauma and other complications.

Results: Treatment failure occurred in 15 of 60 neonates (25.0 percent) on HFNC and 11 of 60 (18.3 percent) on nCPAP, a difference that was not statistically significant (risk difference 6.7 percentage points, 95 percent CI −8.2 to 21.6, $p = 0.375$). The need for mechanical ventilation within 72 hours was comparable (13.3 versus 11.7 percent, $p = 0.783$). Nasal trauma was markedly less frequent with HFNC (10.0 versus 35.0 percent, $p = 0.001$), as was abdominal distension (8.3 versus 23.3 percent, $p = 0.024$), and full enteral feeds were achieved earlier (5.2 versus 6.8 days, $p < 0.001$).

Conclusion: HFNC and nCPAP produced comparable rates of treatment failure and of escalation to mechanical ventilation, although the trial was not powered to establish equivalence. HFNC was associated with significantly less nasal trauma and abdominal distension and with earlier attainment of full enteral feeds, and represents a reasonable primary support option in neonates with mild to moderate respiratory distress where nCPAP can be instituted promptly on failure.

Keywords: Continuous Positive Airway Pressure; Cannula; Respiratory Distress Syndrome, Newborn; Noninvasive Ventilation; Infant, Premature; Oxygen Inhalation Therapy.

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Introduction

Respiratory distress is the commonest indication for admission to a neonatal intensive care unit and remains a leading contributor to neonatal morbidity and mortality in India. It arises from a heterogeneous group of conditions, of which respiratory distress syndrome due to surfactant deficiency, transient tachypnoea of the newborn, meconium aspiration syndrome and congenital pneumonia account for the overwhelming majority. The pathophysiological common denominator across most of these conditions is a reduction in functional residual capacity with consequent alveolar collapse, ventilation-perfusion mismatch and increased work of breathing, and the therapeutic principle that follows is the application of positive distending pressure to recruit and stabilise the alveolus. Nasal continuous positive airway pressure has occupied the position of first-line non-invasive support for five decades on the strength of exactly this rationale. Cochrane synthesis of continuous distending pressure in preterm infants established a reduction in respiratory failure and in mortality relative to supportive care alone.[1] The COIN trial

demonstrated that nCPAP initiated at birth in very preterm infants reduced the need for intubation and surfactant relative to immediate intubation, at the cost of an increased incidence of pneumothorax.[2] Contemporary practice, reflected in international consensus guidance, therefore favours early nCPAP with selective surfactant administration over prophylactic intubation. Nasal CPAP is not, however, without cost. Nasal trauma ranging from erythema to columellar necrosis is common, gastric distension from swallowed gas interferes with the establishment of enteral feeding, the interface requires meticulous and continuous nursing attention to maintain seal and position, and the equipment and its consumables carry a recurring expense that is not trivial in a resource-constrained unit.

Heated humidified high-flow nasal cannula therapy emerged as an alternative that addresses several of these drawbacks. Gas delivered at flows exceeding the inspiratory demand of the neonate, fully conditioned to body temperature and saturation, generates a variable distending pressure while washing out the nasopharyngeal dead space, reducing the inspiratory resistive work imposed by the upper airway and preserving mucociliary function. Physiological work has demonstrated that the pressure generated is real but unmeasured and unregulated, varying with flow rate, cannula to nares ratio and the degree of mouth opening, and this uncontrolled nature of the delivered pressure constitutes the principal theoretical objection to the technique.[3,4] Against this, the loose-fitting interface causes far less nasal injury, permits easier access to the face for feeding and parental contact, and is substantially simpler for nursing staff to apply and maintain.

The evidence comparing the two modalities is extensive but not concordant, and the discordance follows a clear pattern according to the clinical context in which they are compared. In the post-extubation setting the two are broadly equivalent, as demonstrated by Manley and colleagues in very preterm infants and by Collins and colleagues in a comparable population.[5,6] As primary support the picture is less settled.

The HIPSTER trial, a multicentre non-inferiority study of 564 preterm infants of gestational age 28 weeks or above with early respiratory distress, was stopped early because high-flow therapy proved inferior to nCPAP for the primary outcome of treatment failure, although the rate of intubation did not differ significantly between the groups.[7]

Murki and colleagues, in an Indian randomised trial of preterm infants with respiratory distress, reached the same conclusion, again with a significantly higher rate of treatment failure on high flow but no difference in the rate of mechanical ventilation at three or seven days.[8] By contrast, the HUNTER trial in Australian non-tertiary special care nurseries and the earlier study of Yoder and colleagues found high flow to be an acceptable alternative in the populations studied.[9,10]

The consistent thread running through these apparently contradictory results is that treatment failure on high flow is frequently rescued successfully by nCPAP without recourse to intubation, so that the higher failure rate does not translate into a higher rate of mechanical ventilation. Cochrane and subsequent meta-analytic synthesis has confirmed this pattern, together with a consistent and substantial advantage for high flow in respect of nasal trauma, air leak and abdominal distension.[11,12] The practical question for a unit is therefore not which modality is superior in the abstract but whether high flow can be used as initial support in appropriately selected neonates, with nCPAP held in reserve, without increasing the rate of intubation or of adverse outcome. Indian data addressing this question in a mixed population of preterm and near-term neonates with respiratory distress of varied aetiology, as encountered in a medical college neonatal unit serving a rural catchment, remain limited. The present randomised controlled trial was therefore undertaken to compare the efficacy and the tolerability of nCPAP and HFNC as primary respiratory support in neonates with respiratory distress.

Aims and Objectives: The trial aimed to determine whether heated humidified high-flow nasal cannula therapy constituted an acceptable alternative to nasal continuous positive airway pressure as the initial mode of non-invasive respiratory support in neonates presenting with respiratory distress. The primary objective was to compare the incidence of treatment failure within the first 72 hours of support, defined by predefined criteria of oxygenation, clinical severity, blood gas derangement and apnoea, between neonates randomised to nasal continuous positive airway pressure and those randomised to high-flow nasal cannula.

The secondary objectives were to compare the proportion of neonates requiring escalation to invasive mechanical ventilation within 72 hours and within seven days, the proportion requiring surfactant replacement, the serial evolution of the Silverman-Anderson retraction score and of the fraction of inspired oxygen over the first 48 hours, and the arterial blood gas parameters at six hours. Further secondary objectives were to compare the total duration of non-invasive respiratory support, the total duration of supplemental oxygen, the time to attainment of full enteral feeding, the time to regain birth weight and the duration of hospitalisation, and to compare the tolerability of the two modalities in terms of the incidence and

severity of nasal trauma, abdominal distension and feed intolerance, and the comfort score recorded at 24 hours. The final objective was to compare the incidence of complications including air leak syndrome, pulmonary haemorrhage, necrotising enterocolitis, culture-positive sepsis, intraventricular haemorrhage, bronchopulmonary dysplasia and death before discharge.

Materials and Methods

Study Design and Setting: This prospective, randomised, controlled, open-label trial with blinded outcome assessment was conducted in the neonatal intensive care unit of the Department of Paediatrics, Adichunchanagiri Institute of Medical Sciences, B. G. Nagara, Mandya District, Karnataka, over an eighteen-month period from January 2024 to June 2025. The unit provides intramural and extramural neonatal care to a predominantly rural and semi-urban catchment and is equipped for bubble continuous positive airway pressure, heated humidified high-flow therapy, conventional mechanical ventilation, surfactant administration and blood gas analysis.

Approval of the Institutional Ethics Committee was obtained before the commencement of enrolment and the trial was registered prospectively with the Clinical Trials Registry of India. Written informed consent was obtained from a parent or legal guardian of every neonate before randomisation. The trial was conducted in accordance with the principles of the Declaration of Helsinki and with the National Ethical Guidelines for Biomedical and Health Research Involving Children issued by the Indian Council of Medical Research, and is reported in accordance with the CONSORT statement.

Participants: Neonates were eligible if the gestational age was 28 completed weeks or above, the birth weight was 1000 g or above, the postnatal age at the time of screening was less than 24 hours, and there was clinical respiratory distress with a Silverman-Anderson retraction score of 4 or above requiring supplemental oxygen to maintain peripheral oxygen saturation between 90 and 94 percent. Written informed consent from a parent or legal guardian was mandatory. Neonates were excluded if they had already received surfactant or invasive mechanical ventilation before screening, if intubation was judged to be immediately necessary at the time of screening, or if there was a major congenital malformation, congenital cyanotic heart disease, congenital diaphragmatic hernia, choanal atresia, cleft palate, tracheo-oesophageal fistula or any anomaly of the upper airway precluding the use of a nasal interface. Further exclusions comprised neonates with an Apgar score below 4 at five minutes, those with severe birth asphyxia or hypoxic ischaemic encephalopathy of stage II or above, those with pneumothorax or other air leak identified at screening, those with shock requiring inotropic support at the time of screening, those with a non-respiratory cause of tachypnoea such as metabolic acidosis or severe anaemia, and those whose parent or guardian declined consent.

Sample Size Calculation: The sample size was calculated for the primary outcome, the incidence of treatment failure within 72 hours. On the basis of previously published data in comparable neonatal populations, the incidence of treatment failure was anticipated to be 10 percent with nasal continuous positive airway pressure and 30 percent with high-flow nasal cannula. The standard formula for the comparison of two independent proportions was applied:

$$n \text{ per group} = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times [p_1(1 - p_1) + p_2(1 - p_2)] / (p_1 - p_2)^2$$

Substituting $Z_{1-\alpha/2} = 1.96$ for a two-sided alpha of 0.05, $Z_{1-\beta} = 0.84$ for 80 percent power, $p_1 = 0.10$ and $p_2 = 0.30$:

$$n = (2.80)^2 \times [0.0900 + 0.2100] / (0.20)^2$$

$$n = 7.84 \times 0.3000 / 0.0400$$

$$n = 2.352 / 0.0400 = 58.8$$

Fifty-nine neonates per group were therefore required, and this was rounded to 60 per group, giving a total sample of 120. It is acknowledged that this calculation was framed to detect a difference of 20 percentage points and that the trial consequently possessed limited power to detect smaller differences or to establish equivalence between the two modalities, a limitation addressed in the discussion.

Randomisation and Blinding: Eligible neonates were allocated in a 1:1 ratio to nasal continuous positive airway pressure or to high-flow nasal cannula using a computer-generated block randomisation sequence with variable block sizes, stratified by gestational age above and below 32 weeks. Allocation was concealed in sequentially numbered, sealed, opaque envelopes prepared by a person not otherwise involved in the trial and opened at the cot side only after consent had been obtained and eligibility confirmed. Blinding of the treating team and of the bedside nurse to the allocated device was not feasible, since the two interfaces are visibly different. Outcome assessment was, however, blinded. Serial Silverman-Anderson scores, nasal trauma grading and comfort scores were recorded by a trained observer who was not part of the treating team, and blood gas and radiographic interpretation was performed by personnel unaware of the allocation. The decision to declare treatment failure was made against written predefined criteria rather than by

clinical judgement, in order to limit the influence of unblinding on the primary outcome.

Interventions: Neonates allocated to nasal continuous positive airway pressure received bubble continuous positive airway pressure delivered through short binasal prongs of a size appropriate to the nares, with an initial positive end-expiratory pressure of 5 cm of water, adjusted in increments of 1 cm to a maximum of 7 cm according to the clinical response and the oxygen requirement.

Prong position and nasal integrity were checked and documented every four hours, and a hydrocolloid barrier dressing was applied to the columella and the nasal bridge as a routine preventive measure. Neonates allocated to high-flow nasal cannula received heated humidified gas through binasal cannulae occluding no more than half of the diameter of the nares, at an initial flow of 5 litres per minute, adjusted within a permitted range of 4 to 6 litres per minute according to clinical response. Gas in both arms was blended, heated to 37 degrees Celsius and fully humidified, and the fraction of inspired oxygen in both arms was titrated to maintain a peripheral oxygen saturation of 90 to 94 percent.

All neonates in both arms received care according to standard unit protocol, comprising thermoneutral environment, continuous cardiorespiratory and saturation monitoring, intravenous fluids with early trophic feeds where tolerated, antibiotics where sepsis was suspected, and caffeine citrate where gestational age was below 34 weeks. Surfactant was administered by the less invasive technique or after brief intubation, according to the prevailing unit protocol, where the fraction of inspired oxygen requirement exceeded 0.40 in a neonate with radiological features of respiratory distress syndrome.

Outcome Definitions: The primary outcome was treatment failure within 72 hours of the initiation of the allocated support, defined by the occurrence of any one of the following predefined criteria: a requirement for a fraction of inspired oxygen exceeding 0.40 for more than one hour to maintain a peripheral oxygen saturation of 90 to 94 percent; a Silverman-Anderson score exceeding 6 persisting for more than one hour; an arterial or capillary pH below 7.20 with a partial pressure of carbon dioxide exceeding 60 mmHg on two consecutive samples; or more than two episodes of apnoea requiring stimulation within one hour, or any single episode of apnoea requiring positive pressure ventilation. Neonates in the high-flow arm who met failure criteria were rescued with nasal continuous positive airway pressure where the failure criterion was not itself an indication for immediate intubation, and neonates in the continuous positive airway pressure arm who met failure criteria proceeded to intubation and mechanical ventilation. Secondary outcomes comprised the need for invasive mechanical ventilation within 72 hours and within seven days, the requirement for surfactant, the serial Silverman-Anderson score and fraction of inspired oxygen at baseline and at 1, 6, 12, 24 and 48 hours, blood gas parameters at six hours, the total duration of non-invasive support and of supplemental oxygen, the time to full enteral feeding defined as 150 mL per kilogram per day tolerated without gastric residuals, the time to regain birth weight, the duration of hospital stay, and the comfort score recorded at 24 hours using the COMFORTneo scale.

Nasal trauma was graded by the blinded observer every 12 hours on a three-point scale as stage 1 denoting non-blanching erythema, stage 2 superficial ulceration and stage 3 necrosis, and stages 2 and 3 were grouped as moderate to severe injury. Abdominal distension was recorded where the abdominal girth increased by more than 2 cm from the baseline measurement in association with gastric residuals leading to interruption of feeds. Complications recorded comprised air leak syndrome confirmed radiologically, pulmonary haemorrhage, necrotising enterocolitis of modified Bell stage II or above, culture-positive sepsis, intraventricular haemorrhage of grade III or above on cranial ultrasonography, bronchopulmonary dysplasia defined as an oxygen requirement at 28 days of life, and death before discharge.

Statistical Analysis: Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics version 26.0. Analysis followed the intention-to-treat principle, with every randomised neonate analysed in the group to which allocation had been made. The normality of continuous variables was assessed by the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean with standard deviation and compared by the independent samples Student t test, and non-normally distributed variables were expressed as median with interquartile range and compared by the Mann-Whitney U test.

Categorical variables were expressed as frequencies with percentages and compared by the Pearson chi-square test, with the Fisher exact test substituted where any expected cell frequency was below five. The risk difference for the primary outcome was reported with its 95 percent confidence interval. Serial Silverman-Anderson scores and fractions of inspired oxygen were analysed by repeated-measures analysis of variance with time as the within-subject factor and group as the between-subject factor, with the Greenhouse-Geisser correction applied where the assumption of sphericity was violated. A two-tailed p value below 0.05 was considered statistically significant.

Results

Table 1: Baseline demographic and perinatal characteristics of the two groups (N = 120)

Variable	HFNC (n = 60)	nCPAP (n = 60)	Test statistic	p value
Gestational age, weeks (mean ± SD)	32.8 ± 2.4	33.1 ± 2.3	t = 0.70	0.486
Gestational age <32 weeks, n (%)	22 (36.7)	19 (31.7)	$\chi^2 = 0.34$	0.560
Birth weight, g (mean ± SD)	1784 ± 412	1826 ± 438	t = 0.54	0.590
Birth weight <1500 g, n (%)	17 (28.3)	15 (25.0)	$\chi^2 = 0.17$	0.680
Small for gestational age, n (%)	13 (21.7)	11 (18.3)	$\chi^2 = 0.21$	0.646
Male sex, n (%)	34 (56.7)	32 (53.3)	$\chi^2 = 0.13$	0.713
Caesarean delivery, n (%)	38 (63.3)	36 (60.0)	$\chi^2 = 0.14$	0.706
Complete antenatal corticosteroids, n (%)	41 (68.3)	39 (65.0)	$\chi^2 = 0.15$	0.699
Prolonged rupture of membranes >18 h, n (%)	11 (18.3)	13 (21.7)	$\chi^2 = 0.21$	0.646
Maternal hypertensive disorder, n (%)	14 (23.3)	12 (20.0)	$\chi^2 = 0.19$	0.661
Apgar score <7 at 5 minutes, n (%)	8 (13.3)	9 (15.0)	$\chi^2 = 0.07$	0.795
Delivery room CPAP given, n (%)	26 (43.3)	24 (40.0)	$\chi^2 = 0.14$	0.711
Postnatal age at enrolment, h (mean ± SD)	3.8 ± 2.6	4.1 ± 2.8	t = 0.61	0.543
Outborn, n (%)	15 (25.0)	17 (28.3)	$\chi^2 = 0.17$	0.681

HFNC, heated humidified high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure; SD, standard deviation; CPAP, continuous positive airway pressure.

Table 2: Primary respiratory diagnosis and baseline respiratory parameters (N = 120)

Variable	HFNC (n = 60)	nCPAP (n = 60)	Test statistic	p value
Primary diagnosis, n (%)			$\chi^2 = 0.34$	0.952
Respiratory distress syndrome	34 (56.7)	33 (55.0)		
Transient tachypnoea of the newborn	18 (30.0)	19 (31.7)		
Meconium aspiration syndrome	5 (8.3)	4 (6.7)		
Pneumonia or sepsis-related distress	3 (5.0)	4 (6.7)		
Silverman-Anderson score (mean ± SD)	5.4 ± 1.2	5.6 ± 1.3	t = 0.88	0.381
Silverman-Anderson score >6, n (%)	16 (26.7)	18 (30.0)	$\chi^2 = 0.17$	0.685
Fraction of inspired oxygen (mean ± SD)	0.34 ± 0.08	0.35 ± 0.08	t = 0.69	0.492
Respiratory rate, /min (mean ± SD)	68.4 ± 9.6	69.8 ± 10.2	t = 0.77	0.442
Heart rate, /min (mean ± SD)	148.6 ± 14.2	150.2 ± 15.1	t = 0.60	0.552
Peripheral oxygen saturation, % (mean ± SD)	91.2 ± 3.4	90.8 ± 3.6	t = 0.63	0.532
Baseline pH (mean ± SD)	7.28 ± 0.06	7.27 ± 0.06	t = 0.91	0.363
Baseline pCO_2, mmHg (mean ± SD)	49.6 ± 7.4	50.8 ± 7.8	t = 0.86	0.390
Radiological grade III or IV RDS, n (%)	9 (15.0)	10 (16.7)	$\chi^2 = 0.06$	0.804

HFNC, heated humidified high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure; SD, standard deviation; RDS, respiratory distress syndrome; pCO_2, partial pressure of carbon dioxide.

Table 3: Serial Silverman-Anderson score, oxygen requirement and blood gas parameters (N = 120)

Parameter and time point	HFNC (n = 60)	nCPAP (n = 60)	Test statistic	p value
Silverman-Anderson score				
Baseline	5.4 ± 1.2	5.6 ± 1.3	t = 0.88	0.381
1 hour	4.2 ± 1.3	4.0 ± 1.4	t = 0.81	0.416
6 hours	3.1 ± 1.4	2.9 ± 1.5	t = 0.76	0.452
12 hours	2.4 ± 1.3	2.2 ± 1.4	t = 0.81	0.416
24 hours	1.8 ± 1.2	1.6 ± 1.2	t = 0.91	0.362
48 hours	1.2 ± 1.0	1.1 ± 1.0	t = 0.55	0.583
Fraction of inspired oxygen				
Baseline	0.34 ± 0.08	0.35 ± 0.08	t = 0.69	0.492
6 hours	0.28 ± 0.06	0.27 ± 0.06	t = 0.91	0.363
24 hours	0.24 ± 0.04	0.23 ± 0.04	t = 1.37	0.172
48 hours	0.22 ± 0.03	0.22 ± 0.03	t = 0.00	1.000
Blood gas at 6 hours				
pH	7.32 ± 0.05	7.33 ± 0.05	t = 1.10	0.273
pCO_2, mmHg	45.2 ± 6.8	43.8 ± 6.4	t = 1.16	0.247
Base excess, mmol/L	−3.2 ± 2.4	−2.9 ± 2.3	t = 0.70	0.486
SpO_2 to FiO_2 ratio	342 ± 48	351 ± 52	t = 0.99	0.325

Values are mean ± standard deviation. HFNC, heated humidified high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure; pCO_2, partial pressure of carbon dioxide; SpO_2, peripheral oxygen saturation; FiO_2, fraction of inspired oxygen. Repeated-measures analysis of variance for Silverman-Anderson score: effect of time $F = 186.42$, $p < 0.001$; group by time interaction $F = 0.62$, $p = 0.648$.

Table 4: Primary outcome, treatment failure within 72 hours, and escalation of support (N = 120)

Outcome	HFNC (n = 60)	nCPAP (n = 60)	Test statistic	p value
Treatment failure within 72 h, n (%)	**15 (25.0)**	**11 (18.3)**	**$\chi^2 = 0.79$**	**0.375**
Risk difference (95% CI), percentage points	6.7 (−8.2 to 21.6)	—	—	—
Criterion precipitating failure, n				
FiO_2 requirement >0.40	8	6		
Silverman-Anderson score >6	4	3		
Respiratory acidosis	2	1		
Recurrent apnoea	1	1		
Time to failure, h, median (IQR)	14 (8–26)	12 (7–22)	U = 76.5	0.612
Rescued with alternate mode, n (% of failures)	9 (60.0)	—	—	—
Mechanical ventilation within 72 h, n (%)	8 (13.3)	7 (11.7)	$\chi^2 = 0.08$	0.783
Mechanical ventilation within 7 days, n (%)	9 (15.0)	8 (13.3)	$\chi^2 = 0.07$	0.795
Surfactant administered, n (%)	14 (23.3)	13 (21.7)	$\chi^2 = 0.05$	0.832
More than one surfactant dose, n (%)	3 (5.0)	4 (6.7)	Fisher exact	1.000

HFNC, heated humidified high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure; CI, confidence interval; FiO_2, fraction of inspired oxygen; IQR, interquartile range. Neonates failing HFNC were rescued with nCPAP where the failure criterion was not itself an indication for immediate intubation.

Table 5: Secondary outcomes relating to duration of support, feeding and hospitalisation (N = 120)

Outcome	HFNC (n = 60)	nCPAP (n = 60)	Test statistic	p value
Duration of non-invasive support, h (mean ± SD)	62.4 ± 28.6	68.2 ± 31.4	t = 1.06	0.293
Duration of supplemental oxygen, h (mean ± SD)	84.6 ± 36.2	89.4 ± 38.7	t = 0.70	0.485
Time to full enteral feeds, days (mean ± SD)	5.2 ± 2.1	6.8 ± 2.6	t = 3.70	<0.001
Time to regain birth weight, days (mean ± SD)	9.4 ± 3.2	10.8 ± 3.6	t = 2.25	0.026
Duration of parenteral fluids, days (mean ± SD)	4.6 ± 2.0	5.9 ± 2.4	t = 3.22	0.002
Duration of hospital stay, days (mean ± SD)	12.4 ± 5.8	13.6 ± 6.2	t = 1.10	0.275
COMFORTneo score at 24 h (mean ± SD)	11.2 ± 2.4	13.8 ± 2.8	t = 5.46	<0.001
Device application time, min (mean ± SD)	3.4 ± 1.1	6.8 ± 2.2	t = 10.72	<0.001
Interface repositioning episodes per 24 h, median (IQR)	2 (1–3)	5 (4–7)	U = 512.0	<0.001
Sedation or analgesia required, n (%)	4 (6.7)	11 (18.3)	$\chi^2 = 3.73$	0.053

HFNC, heated humidified high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure; SD, standard deviation; IQR, interquartile range. A lower COMFORTneo score denotes greater comfort.

Table 6: Complications and adverse events (N = 120)

Complication	HFNC (n = 60)	nCPAP (n = 60)	Test statistic	p value
Nasal trauma, any grade, n (%)	6 (10.0)	21 (35.0)	$\chi^2 = 10.75$	0.001
Stage 1, non-blanching erythema	5 (8.3)	12 (20.0)		
Stage 2, superficial ulceration	1 (1.7)	7 (11.7)		
Stage 3, necrosis	0 (0.0)	2 (3.3)		
Moderate to severe nasal trauma, n (%)	1 (1.7)	9 (15.0)	Fisher exact	0.008
Abdominal distension with feed intolerance, n (%)	5 (8.3)	14 (23.3)	$\chi^2 = 5.06$	0.024
Pneumothorax, n (%)	2 (3.3)	3 (5.0)	Fisher exact	1.000
Pulmonary interstitial emphysema, n (%)	1 (1.7)	2 (3.3)	Fisher exact	1.000

Pulmonary haemorrhage, n (%)	1 (1.7)	2 (3.3)	Fisher exact	1.000
Necrotising enterocolitis stage II or above, n (%)	2 (3.3)	3 (5.0)	Fisher exact	1.000
Culture-positive sepsis, n (%)	7 (11.7)	9 (15.0)	$\chi^2 = 0.29$	0.593
Intraventricular haemorrhage grade III or above, n (%)	2 (3.3)	2 (3.3)	Fisher exact	1.000
Bronchopulmonary dysplasia at 28 days, n (%)	4 (6.7)	5 (8.3)	Fisher exact	1.000
Death before discharge, n (%)	3 (5.0)	4 (6.7)	Fisher exact	1.000

HFNC, heated humidified high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure. Nasal trauma stages 2 and 3 were grouped as moderate to severe injury. Bronchopulmonary dysplasia was defined as a requirement for supplemental oxygen at 28 days of life. All deaths occurred in neonates who had progressed to invasive mechanical ventilation.

Participant Flow and Baseline Characteristics: One hundred and forty-two neonates with respiratory distress were screened during the study period. Twenty-two were excluded, nine because immediate intubation was judged necessary at screening, six because of a major congenital malformation, four because consent was declined and three because a non-respiratory cause of tachypnoea was identified. One hundred and twenty neonates were randomised, 60 to high-flow nasal cannula and 60 to nasal continuous positive airway pressure, and all completed follow-up to discharge or death without protocol violation or crossover other than the protocol-specified rescue.

The two groups were closely comparable at baseline. The mean gestational age was 32.8 ± 2.4 weeks in the high-flow group and 33.1 ± 2.3 weeks in the continuous positive airway pressure group (t = 0.70, p = 0.486), and 22 neonates (36.7 percent) and 19 neonates (31.7 percent) respectively were born before 32 weeks ($\chi^2 = 0.34$, p = 0.560).

Mean birth weight was 1784 ± 412 g and 1826 ± 438 g (t = 0.54, p = 0.590). Thirty-four neonates (56.7 percent) in the high-flow group and 32 (53.3 percent) in the continuous positive airway pressure group were male ($\chi^2 = 0.13$, p = 0.713). A complete course of antenatal corticosteroids had been received by 41 mothers (68.3 percent) and 39 mothers (65.0 percent) respectively ($\chi^2 = 0.15$, p = 0.699). The mean postnatal age at enrolment was 3.8 ± 2.6 hours and 4.1 ± 2.8 hours (t = 0.61, p = 0.543). Baseline characteristics are presented in Table 1.

Primary Diagnosis and Baseline Respiratory Status: Respiratory distress syndrome was the commonest diagnosis, present in 34 neonates (56.7 percent) in the high-flow group and 33 (55.0 percent) in the continuous positive airway pressure group, followed by transient tachypnoea of the newborn in 18 (30.0 percent) and 19 (31.7 percent), meconium aspiration syndrome in 5 (8.3 percent) and 4 (6.7 percent), and pneumonia or sepsis-associated respiratory distress in 3 (5.0 percent) and 4 (6.7 percent). The distribution of diagnoses did not differ significantly between the groups (χ^2 = 0.34, p = 0.952). The mean baseline Silverman-Anderson score was 5.4 ± 1.2 in the high-flow group and 5.6 ± 1.3 in the continuous positive airway pressure group (t = 0.88, p = 0.381), and severe distress with a score above 6 was present in 16 neonates (26.7 percent) and 18 neonates (30.0 percent) respectively ($\chi^2 = 0.17$, p = 0.685). The mean baseline fraction of inspired oxygen was 0.34 ± 0.08 and 0.35 ± 0.08 (t = 0.69, p = 0.492). Diagnostic and baseline respiratory data are set out in Table 2.

Evolution of Respiratory Status: Repeated-measures analysis of variance demonstrated a highly significant effect of time on the Silverman-Anderson score (F = 186.42, p < 0.001), confirming improvement in both groups, but no significant group by time interaction (F = 0.62, p = 0.648), indicating that the trajectory of improvement did not differ between the modalities. The mean score fell from 5.4 ± 1.2 to 4.2 ± 1.3 at one hour, 3.1 ± 1.4 at six hours, 1.8 ± 1.2 at 24 hours and 1.2 ± 1.0 at 48 hours in the high-flow group, and from 5.6 ± 1.3 to 4.0 ± 1.4, 2.9 ± 1.5, 1.6 ± 1.2 and 1.1 ± 1.0 respectively in the continuous positive airway pressure group, with no significant between-group difference at any individual time point. The fraction of inspired oxygen likewise declined comparably, being 0.28 ± 0.06 and 0.27 ± 0.06 at six hours (t = 0.91, p = 0.363) and 0.24 ± 0.04 and 0.23 ± 0.04 at 24 hours (t = 1.37, p = 0.172). Blood gas parameters at six hours were similar, with a mean pH of 7.32 ± 0.05 and 7.33 ± 0.05 (t = 1.10, p = 0.273) and a mean partial pressure of carbon dioxide of 45.2 ± 6.8 mmHg and 43.8 ± 6.4 mmHg (t = 1.16, p = 0.247). These data appear in Table 3.

Primary Outcome: Treatment failure within 72 hours occurred in 15 of 60 neonates (25.0 percent) allocated to high-flow nasal cannula and in 11 of 60 neonates (18.3 percent) allocated to nasal continuous positive airway pressure. The risk difference was 6.7 percentage points with a 95 percent confidence interval extending from −8.2 to 21.6 percentage points, and the difference was not statistically significant ($\chi^2 = 0.79$, p = 0.375). The criterion precipitating failure was an oxygen

requirement exceeding 0.40 in 8 and 6 neonates, a Silverman-Anderson score exceeding 6 in 4 and 3 neonates, respiratory acidosis in 2 and 1 neonate, and recurrent apnoea in 1 neonate in each group. The median time to treatment failure was 14 hours with an interquartile range of 8 to 26 hours in the high-flow group and 12 hours with an interquartile range of 7 to 22 hours in the continuous positive airway pressure group (U = 76.5, p = 0.612).

Of the 15 neonates who failed high-flow therapy, 9 (60.0 percent) were successfully rescued with nasal continuous positive airway pressure and avoided intubation, while 6 proceeded directly to mechanical ventilation. Consequently the need for invasive mechanical ventilation within 72 hours did not differ between the groups, occurring in 8 neonates (13.3 percent) in the high-flow group and 7 neonates (11.7 percent) in the continuous positive airway pressure group (χ^2 = 0.08, p = 0.783), and the need for mechanical ventilation within seven days was likewise comparable at 9 neonates (15.0 percent) and 8 neonates (13.3 percent) (χ^2 = 0.07, p = 0.795). Surfactant was administered to 14 neonates (23.3 percent) and 13 neonates (21.7 percent) respectively (χ^2 = 0.05, p = 0.832). Primary outcome data are detailed in Table 4.

Secondary Outcomes: The total duration of non-invasive respiratory support was 62.4 ± 28.6 hours in the high-flow group and 68.2 ± 31.4 hours in the continuous positive airway pressure group (t = 1.06, p = 0.293), and the total duration of supplemental oxygen was 84.6 ± 36.2 hours and 89.4 ± 38.7 hours respectively (t = 0.70, p = 0.485). Neither difference reached statistical significance.

Feeding outcomes favoured high-flow therapy. Full enteral feeds were attained at 5.2 ± 2.1 days in the high-flow group compared with 6.8 ± 2.6 days in the continuous positive airway pressure group (t = 3.70, p < 0.001), and birth weight was regained at 9.4 ± 3.2 days and 10.8 ± 3.6 days respectively (t = 2.25, p = 0.026). The duration of hospital stay was 12.4 ± 5.8 days and 13.6 ± 6.2 days, a difference that was not significant (t = 1.10, p = 0.275). The COMFORTneo score at 24 hours, on which a lower value denotes greater comfort, was 11.2 ± 2.4 in the high-flow group and 13.8 ± 2.8 in the continuous positive airway pressure group (t = 5.46, p < 0.001), and the mean time required to apply and stabilise the device was 3.4 ± 1.1 minutes and 6.8 ± 2.2 minutes respectively (t = 10.72, p < 0.001). Secondary outcomes are presented in Table 5.

Complications and Adverse Events: n Nasal trauma of any grade was substantially less frequent with high-flow therapy, occurring in 6 of 60 neonates (10.0 percent) compared with 21 of 60 neonates (35.0 percent) on continuous positive airway pressure (χ^2 = 10.75, p = 0.001). The difference was more pronounced for injury of moderate or severe grade, which was recorded in 1 neonate (1.7 percent) and 9 neonates (15.0 percent) respectively (Fisher exact test, p = 0.008). Abdominal distension with feed intolerance occurred in 5 neonates (8.3 percent) and 14 neonates (23.3 percent) respectively (χ^2 = 5.06, p = 0.024).

Serious complications were infrequent and did not differ significantly between the groups. Pneumothorax occurred in 2 neonates (3.3 percent) in the high-flow group and 3 neonates (5.0 percent) in the continuous positive airway pressure group (Fisher exact test, p = 1.000), pulmonary haemorrhage in 1 neonate (1.7 percent) and 2 neonates (3.3 percent), necrotising enterocolitis of stage II or above in 2 neonates (3.3 percent) and 3 neonates (5.0 percent), culture-positive sepsis in 7 neonates (11.7 percent) and 9 neonates (15.0 percent) (χ^2 = 0.29, p = 0.593), and intraventricular haemorrhage of grade III or above in 2 neonates (3.3 percent) in each group. Bronchopulmonary dysplasia, defined as an oxygen requirement at 28 days of life, developed in 4 neonates (6.7 percent) and 5 neonates (8.3 percent) respectively. Three neonates (5.0 percent) in the high-flow group and 4 neonates (6.7 percent) in the continuous positive airway pressure group died before discharge (Fisher exact test, p = 1.000), all deaths occurring in neonates who had progressed to mechanical ventilation. Complication data appear in Table 6.

Discussion

This randomised controlled trial in 120 neonates with respiratory distress found no statistically significant difference between heated humidified high-flow nasal cannula and nasal continuous positive airway pressure in the incidence of treatment failure within 72 hours, in the requirement for invasive mechanical ventilation, in the requirement for surfactant, or in the rate of improvement of the Silverman-Anderson score and the oxygen requirement. High-flow therapy was, however, associated with significantly less nasal trauma, significantly less abdominal distension with feed intolerance, earlier attainment of full enteral feeds, an earlier return to birth weight, better comfort scores and a substantially shorter time to device application. The numerically higher rate of treatment failure with high-flow therapy, 25.0 percent against 18.3 percent, is directionally consistent with the two largest and most rigorous trials addressing this question as primary support. The HIPSTER trial was stopped early on interim analysis because treatment failure was significantly commoner with high flow than with continuous positive airway pressure in preterm infants of gestational age 28 weeks or above, and Murki and colleagues, in an Indian population closely comparable to the present one, reported an almost identical pattern with treatment failure in 26.3

percent on high flow against 7.9 percent on continuous positive airway pressure.[7,8] The failure rate on high flow observed here, at 25.0 percent, is remarkably close to both of those figures. The difference lies entirely in the comparator arm, where the present failure rate of 18.3 percent substantially exceeds the 7.9 percent reported by Murki and colleagues, and it is this that accounts for the loss of statistical significance. Several factors plausibly contribute, including a population that was on average less preterm and included a substantial proportion of neonates with transient tachypnoea and meconium aspiration rather than respiratory distress syndrome alone, and a permitted maximum positive end-expiratory pressure of 7 cm of water. The honest interpretation is therefore not that the present trial contradicts HIPSTER and Murki but that it was underpowered to detect a difference of the magnitude those trials observed, having been designed to detect a 20 percentage point difference. This point is developed further among the limitations.

What the present data do establish, and what is entirely concordant with the published evidence, is that the higher failure rate on high-flow therapy did not translate into a higher rate of intubation. Nine of the 15 high-flow failures were rescued successfully with continuous positive airway pressure, and the rate of mechanical ventilation at 72 hours and at seven days was accordingly indistinguishable between the groups. Precisely this pattern was reported in HIPSTER, where the intubation rate did not differ significantly despite the significant difference in the primary outcome, and by Murki and colleagues, who noted that 32 of their 35 high-flow failures were rescued with continuous positive airway pressure.[7,8] Meta-analytic synthesis has confirmed the pattern at scale, with no significant difference in the application of mechanical ventilation between the two modalities across pooled trials.[11,12] The clinical corollary is important and practical: a strategy of initial high-flow therapy is defensible provided that continuous positive airway pressure is immediately available at the cot side and that predefined failure criteria trigger its prompt application. Such a strategy is not defensible in a unit where the only escalation available is intubation. The tolerability findings were the most clear-cut in this trial and are among the most consistent findings in the entire literature. The reduction in nasal trauma from 35.0 percent to 10.0 percent, and in moderate to severe injury from 15.0 percent to 1.7 percent, is of the same order as the pooled estimates and reflects the fundamental difference between an interface that must seal against the nares to generate pressure and one that must deliberately not.[11,12] The reduction in abdominal distension from 23.3 percent to 8.3 percent, and the associated attainment of full enteral feeds 1.6 days earlier, follows from the lower and less consistently transmitted pharyngeal pressure and consequently reduced aerophagia. Yoder and colleagues similarly reported comparable efficacy with better nasal tolerance in a large neonatal population, and the HUNTER trial, conducted in non-tertiary special care nurseries where nursing familiarity and ease of application carry particular weight, likewise supported high flow as a practical alternative in a population of gestational age 31 weeks and above.[9,10] In a unit with high nurse to patient ratios, the finding that a high-flow device could be applied and stabilised in half the time required for continuous positive airway pressure is not a trivial consideration. It should be emphasised, in fairness to the counter-argument, that the very features responsible for the superior tolerability of high-flow therapy are also the source of the principal objection to it. The distending pressure generated is neither measured nor controlled, varying with flow rate, with the ratio of cannula to nares diameter and with the degree of mouth opening, as physiological studies have documented.[3,4] A neonate whose respiratory failure is driven by atelectasis requiring a defined and reliable distending pressure is therefore theoretically better served by continuous positive airway pressure, and the observation in HIPSTER and in the Murki trial that the disadvantage of high flow was most evident in infants with more severe respiratory distress is consistent with this reasoning.[7,8]

The present trial enrolled a population with predominantly mild to moderate distress, with a mean Silverman-Anderson score of approximately 5.5 and severe distress in fewer than a third, and its findings should not be extrapolated to neonates presenting with severe distress or to those below 28 weeks of gestation, who were excluded. The absence of any difference in mortality, bronchopulmonary dysplasia, air leak, necrotising enterocolitis, sepsis or intraventricular haemorrhage is consistent with the published literature but must be interpreted with the caution appropriate to the small number of events in each category. The trial was powered for treatment failure and possessed negligible power to detect a difference in any of these outcomes, and the equality observed should be read as an absence of evidence of harm rather than as evidence of the absence of harm. Isolated reports of serious air leak complicating high-flow therapy exist and should temper any assumption that the loose interface renders barotrauma impossible.[13]

Limitations

Several limitations qualify these findings. Most importantly, the trial was powered to detect a 20 percentage point difference in treatment failure and therefore lacked the power to detect the smaller

difference that the larger published trials have demonstrated, so the absence of a statistically significant difference in the primary outcome must not be construed as evidence of equivalence. A formally designed non-inferiority trial with an appropriate margin and a correspondingly larger sample would be required to support such a claim.

The trial was conducted at a single centre, and both the case mix and the availability of immediate rescue with continuous positive airway pressure limit generalisability to units with different populations or resources. Blinding of the treating team was not feasible because the two interfaces are visibly different, and although outcome assessment was blinded and failure was declared against written predefined criteria, the possibility of performance bias in the intensity of ancillary care cannot be excluded. Neonates below 28 weeks of gestation, those below 1000 g and those requiring immediate intubation were excluded, so the findings do not apply to the most immature and most severely affected infants, in whom the choice of modality matters most. The distending pressure actually delivered in the high-flow arm was not measured, so the physiological basis of the observed effects could not be examined directly. Follow-up extended only to discharge, so neurodevelopmental outcome and the longer-term respiratory consequences were not assessed. Finally, the number of events for serious complications was small in both arms, and the trial should not be regarded as having addressed the comparative safety of the two modalities with any precision.

Conclusion

In neonates of gestational age 28 weeks or above with mild to moderate respiratory distress, heated humidified high-flow nasal cannula and nasal continuous positive airway pressure produced comparable rates of treatment failure within 72 hours, 25.0 percent and 18.3 percent respectively, and identical rates of escalation to invasive mechanical ventilation, surfactant requirement and improvement in the Silverman-Anderson score. High-flow therapy was significantly better tolerated, with nasal trauma reduced from 35.0 percent to 10.0 percent, abdominal distension from 23.3 percent to 8.3 percent, full enteral feeds attained 1.6 days earlier, better comfort scores and a device application time half that of continuous positive airway pressure. The practical conclusion is that high-flow nasal cannula constitutes a reasonable first-line option in neonates with mild to moderate respiratory distress, but only within a strategy that pairs it with predefined failure criteria and with immediate availability of nasal continuous positive airway pressure as rescue. Sixty percent of the high-flow failures in this trial were salvaged by continuous positive airway pressure without recourse to intubation, and it was this rescue pathway rather than any intrinsic equivalence of the two modalities that preserved the parity in mechanical ventilation rates. Where such rescue is not immediately available, or where the neonate presents with severe distress, continuous positive airway pressure remains the safer initial choice. Because the present trial was powered to detect a 20 percentage point difference and cannot exclude a smaller but clinically meaningful disadvantage of high-flow therapy, and because the largest published trials have demonstrated exactly such a disadvantage, an adequately powered non-inferiority trial in an Indian population with a prespecified margin remains necessary before high-flow therapy can be recommended as a routine replacement for continuous positive airway pressure.

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