Efficacy and Safety of Two Different Flow Rates of Nasal High-Flow Therapy in Preterm Neonates ≥28 Weeks of Gestation: A Randomized Controlled Trial

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Abstract

Objective The study aimed to compare the efficacy and safety of two different nasal high-flow rates for primary respiratory support in preterm neonates

Study Design In this single-center, double-blinded randomized controlled trial, preterm neonates ≥28 weeks of gestation with respiratory distress from birth were randomized to treatment with either increased nasal flow therapy (8–10 L/min) or standard nasal flow therapy (5–7 L/min). The primary outcome of nasal high-flow therapy failure was a composite outcome defined as the need for higher respiratory support (continuous positive airway pressure [CPAP] or mechanical ventilation) or surfactant therapy.

Results A total of 212 neonates were enrolled. Nasal high-flow failure rate in the increased flow group was similar to the standard flow group (22 vs. 29%, relative risk = 0.81 [95% confidence interval: 0.57–1.15]). However, nasal flow rate escalation was significantly more common in the standard flow group (64 vs. 43%, $p = 0.004$). None of the infants in the increased flow group developed air leak syndromes.

Conclusion Higher nasal flow rate (8–10 L/min) when compared with lower nasal flow rate of 5 to 7 L/min did not reduce the need for higher respiratory support (CPAP/mechanical ventilation) or surfactant therapy in moderately and late preterm neonates. However, initial flow rates of 5 L/min were not optimal for most preterm infants receiving primary nasal flow therapy.

Keywords
- nasal high flow
- continuous positive airway pressure
- respiratory distress
- neonate

Key Points

- Use of high nasal flows (8–10 L/min) did not reduce the need for higher respiratory support in moderately and late preterm infants.
- Nasal flow rate of 5 L/min was not optimal for most preterms with respiratory distress from birth.
- Careful patient selection and optimized flow settings could enhance nasal flow success in neonates.

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Continuous positive airway pressure (CPAP) has become the mainstay for noninvasive respiratory support in preterm neonates. Over the past decade, surveys of neonatal networks have reported an increased use of nasal high flow (nHF) for noninvasive respiratory support in preterm neonates.[1–3] The increased use of nHF has been attributed to its ease of application, lower incidence of nasal injuries, and better patient and nursing comfort in comparison to nasal CPAP.[4–7] Recent studies have shown that nHF therapy resulted in higher rates of treatment failure as compared with CPAP when used as the primary respiratory support mode in preterm neonates >28 weeks of gestation.[8,9] However, 75% of the neonates in these studies were successfully managed with nHF. Furthermore, the need for mechanical ventilation did not increase following primary nHF therapy if CPAP was available as backup. Considering that nHF therapy could be effective for primary respiratory support in a substantial proportion of preterm neonates, it is essential to identify criteria and mechanisms that would facilitate applying this intervention to select preterm populations in a manner that reduces treatment failures.[10]

Increasing the nHF rates in neonates has shown to result in favorable physiological effects such as generation of higher nasopharyngeal pressures, improved oxygenation, enhanced CO2 elimination, and reduction in apneic episodes.[11–13] It is still unclear if these effects could translate into improved clinical outcomes in preterm neonates. Recent studies have also reported large variability in the distending pressures achieved with higher flow rates.[14,15] There are only few data available directly comparing different flow ranges in the neonatal population. There is no consensus on optimal nasal flow rates for preterm infants.[16] We conducted this randomized controlled trial to assess the effect of increased (8–10 L/min) versus standard nasal flow (5–7 L/min) in reducing the need for higher respiratory support and surfactant when applied as a primary respiratory support modality for preterm neonates ≥28 weeks of gestation.

Materials and Methods

Trial Design and Settings

This single-center, parallel group, double-blinded randomized controlled trial was conducted in the neonatal intensive care unit (NICU) of Surya Hospital, Mumbai between October 15, 2017 and January 14, 2020. The study was approved by the institutional ethics committee, and the trial was prospectively registered with the clinical trial registry of India (CTRI/2017/10/010001). Written consent was obtained from one of the parents prior to enrolment in the trial.

Participants

Moderately preterm (28–$33^{6/7}$ weeks) and late preterm infants (34–$36^{6/7}$ weeks) with respiratory distress (Silverman Andersen score ≥ 3) and/or FiO_2 requirement ≥30% within the first 6 hours of birth were enrolled. Besides inborn neonates, we also included eligible neonates born in maternity centers located within a 3-km radius of our hospital. High-risk infant deliveries at these centers were conducted only after arrival of our neonatal team. This facilitated early transfer of outborn infants to our neonatal unit. Infants with birth weight <1,000 grams, hemodynamic and/or neurological instability, air leak syndromes, prenatally diagnosed serious congenital malformations, and those who received mechanical ventilation and/or surfactant prior to NICU admission were excluded. Infants meeting the criteria for mechanical ventilation at the time of study eligibility assessment were also excluded. Eligible infants were transported by using mask CPAP or oxygen by nasal cannula.

Randomization

Eligible infants were randomized to either an initial nasal flow rate of 8 L/min (increased nasal flow [INF]) or 5 L/min (standard nasal flow [SNF]). Randomization was stratified for the gestational age (28–$30^{6/7}$, 31–$33^{6/7}$, and 34–$36^{6/7}$ weeks), and random sequences were generated in permuted variable blocks with sizes 2, 4, and 6. The sequence was generated by a statistician who was not involved in the study enrolment process. Allocation concealment was done by using serially numbered, opaque, and sealed envelopes.

Blinding

Upon enrolment in the study, the intensivist from the pediatric intensive care unit was called to open the sealed envelopes and assign the infants to the allocated intervention. The pediatric intensivist would set the initial flow and also conceal the flow rate display by using paper strips (►**Supplementary Fig. 1** [available in the online version]). Treating clinicians made subsequent flow rate adjustments, as indicated. Thus, the treating clinicians, nurses, parents, and outcome assessors were blinded to the initial flow rates and subsequent flow adjustments. The starting flow rate was denoted as "F" liters/min in the medical charts and flow increment or decrement by 1 L/min was recorded as "F ± 1" L/min along with the timing of flow change. When the neonate was weaned off the nHF support or upgraded to CPAP/ventilator support, the flow generator was switched off prior to discarding the paper strips. This ensured blinding of the flow rates even after nHF support was ceased. Since the flow rate display was concealed, it was important to ensure that the intended flow rates were correctly dialed by the clinicians and that there were no discrepancies between the prescribed and the set flow rate. Prior to the trial, all neonatal clinicians anticipated to be involved in flow rate adjustments demonstrated competency in performing blinded flow rate adjustments (►**Video 1**). This run in period was also utilized to ensure that adequate clinical judgement was demonstrated, and patient safety was not compromised through the blinding process.

Video 1

Setting up the airvo nasal high flow system and the blinding process. Online content including video sequences viewable at: https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0041-1726122.

Trial Protocol and Procedures

Enrolled infants were assessed every 15 to 30 minutes for the optimization of respiratory support. FiO_2 in both groups was titrated to maintain oxygen saturation between 92 and 95%. For infants needing respiratory support escalation in either group, nasal flow rates were increased to a predefined maximum level (7 L/min in SNF group and 10 L/min in INF group) before considering CPAP support or surfactant administration. The sequence of respiratory support and criteria for escalation and weaning of respiratory support in this study are shown in ►Fig. 1.

AIRVO 2 high-flow system (Fisher & Paykel healthcare, New Zealand) in the junior mode (flow limits ranging from 2–25 L/min) was used to provide nasal flow therapy and Optiflow Junior nasal cannula was used as the nasal interface. The interface was applied such that the nasal prong diameter was less than 50% of the nostril of the neonate, thus allowing egress of air as per manufacturer recommendations. The Fisher and Paykel bubble CPAP system was used to provide rescue CPAP for the study infants. Caffeine (10 mg/kg of base followed by a daily maintenance dose of 5–8 mg/kg/day) was administered to all preterm neonates born before 32 weeks, starting on day 1 and continued until 34 weeks of postmenstrual age or discontinuation of respiratory support, whichever was later.

Further details of trial protocol and procedures are provided in the ►Supplementary Material (available in the online version).

Outcomes and Sample Size

Our primary outcome was nHF failure within 120 hours of birth; a composite outcome defined by the need for surfactant therapy or higher respiratory support (CPAP/mechanical

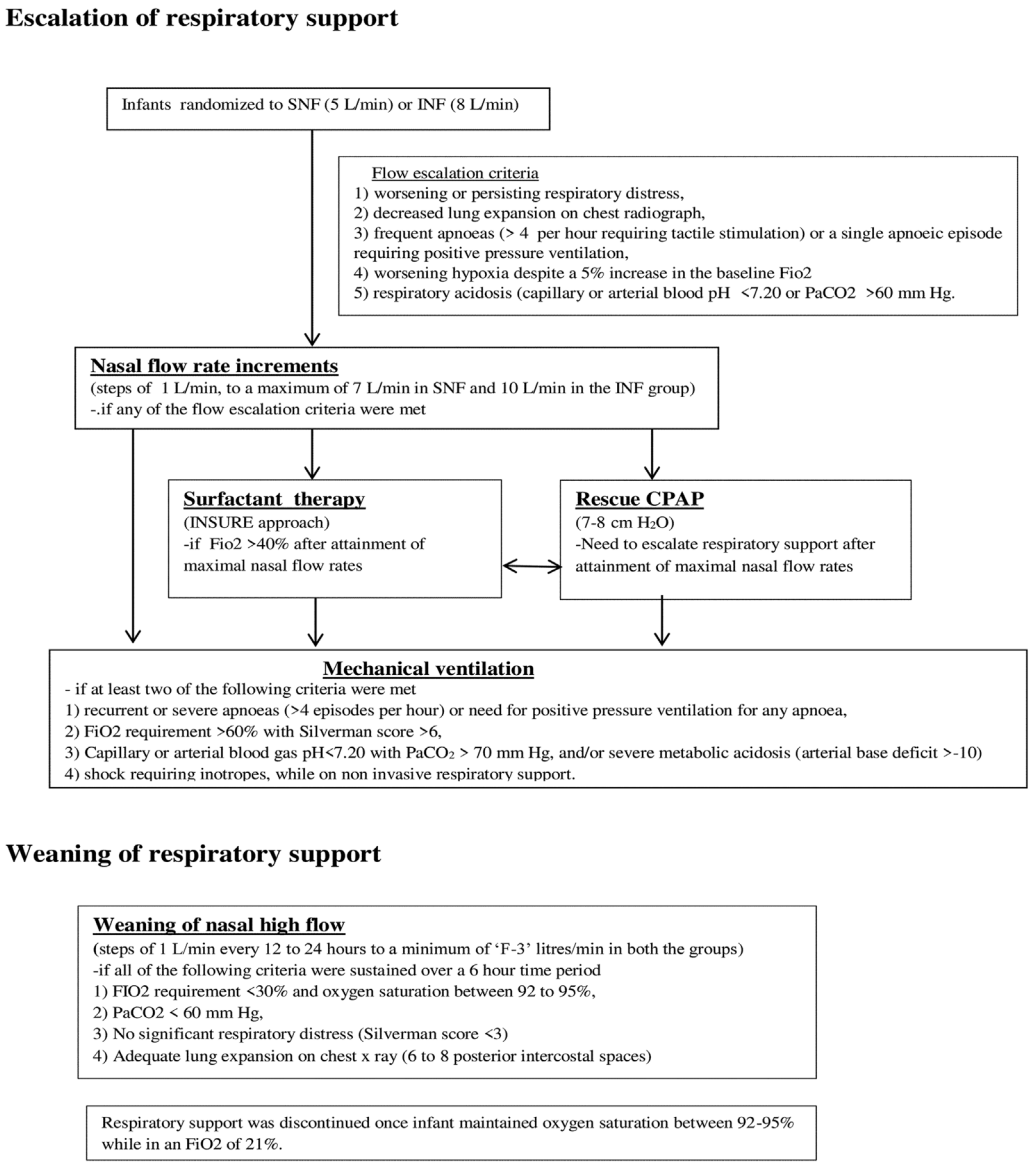

Fig. 1 Sequence of respiratory support escalation and weaning. INF, increased nasal flow; INSURE, intubate–surfactant–extubate; SNF, standard nasal flow.

ventilation). Success with nHF was defined in those neonates that were exclusively managed on nHF support from the time of randomization until 5 days of postnatal age. Prespecified secondary outcomes were all-cause mortality, incidence of air leaks and nasal injuries, and duration of respiratory support.

We have previously reported that 26% of preterm neonates on primary nHF therapy needed higher respiratory support (CPAP/mechanical ventilation) within 72 hours of postnatal age, and an additional 18% were rescued with surfactant by INSURE approach while on nHF therapy.[17] Hence, in this study, we anticipated the baseline nHF failure rate to be 35%. Assuming an absolute reduction in the failure rate from 35 to 17% by using high-nasal flow, a sample of 100 patients in each group was required for a study power of 80% and two tailed α error of 0.05.

The data and safety monitoring board reviewed the data after recruitment of 120 patients. Interim analysis by an independent statistician blinded to the treatment allocation, showed no clear evidence of harm or inferior efficacy in either group and recommended that patient enrolment could continue.

Statistical Analysis

Descriptive statistics were used to summarize the data in both groups. Categorical variables were compared with the Chi-square test, while continuous variables were analyzed by using Student's *t*-test for normal distributions or the Wilcoxon rank-sum test for skewed distributions. Relative risk and median differences (Hodges–Lehmann estimates) were computed along with 95% confidence intervals. Analysis was done by intention to treat principle. No adjustments were done for multiple comparisons.

Considering the potential impact of nasal flow rate increments on nHF success- failure rates, we performed post hoc sensitivity analysis to compare flow rate increments in our study groups. Kaplan–Meier curves were plotted to compare the rates of nHF success and flow increments in both groups. We constructed violin plots to depict the distributional ranges and densities of nasal flow rates in the first 48 hours in both groups. We also conducted ancillary analyses to investigate the association of nHF failure with patient characteristics at study entry. A two tailed *p*-value of <0.05 was considered to be statistically significant. Stata Version 13.1 (Statacorp, 4905 Lakeway Drive, College station, TX) was used for all the analyses and graphical displays.

Results

A total of 212 neonates were enrolled in the study. In all, 128 neonates (60%) were between 31 and 34 weeks of gestation, 52 (25%) were <31 weeks, and 32 (15%) were >34 weeks. The primary outcome was analyzed in 209 infants. The details of the study enrolment process are shown in ►Fig. 2. The final diagnosis was respiratory distress syndrome in all except five infants in the late preterm subgroup (two in the SNF group and three in the INF group); these infants were diagnosed to have transient tachypnea of newborn. The maternal and infant baseline characteristics were similar in both groups (►Table 1).

The nHF failure rate was 22% ($n=22$) in the INF group and 29% ($n=31$) in the SNF group ($p=0.22$; $p=0.26$ by log rank test, ►Supplementary Fig. 2 [available in the online version]). The need for mechanical ventilation was not significantly different between the groups. (3.7 vs. 3.9%, $p=0.94$). Of the two deaths, one occurred at 48 hours of age due to refractory pulmonary hypertension. The other infant developed necrotizing enterocolitis stage III on day 30 of postnatal age and expired four days later. None of the infants in the increased flow group developed pneumothorax. Other neonatal morbidities were similar in both the study groups (►Table 2).

We observed a bimodal distribution of the flow rates in the SNF group (►Fig. 3) suggesting that flow rate increments were more frequent in the group initiated on nHF rate of 5 L/min. (64 vs. 43%, $p=0.003$, $p=0.006$ by log-rank test, ►Supplementary Fig. 2 [available in the online version]). The median maximal nasal flow rates were 7 L/min in the SNF group and 8 L/min in the INF group. Only 36% of patients ($n=39$) in the SNF group were successfully supported with flow rates of 5 L/min. The flow rates were either 7 or 8 L/min in more than half of the study infants (53%). Flow rates greater than 8 L/min were required in 21% infants ($n=44$). Among infants that were exclusively managed on nHF support (nHF success, $n=156$), nasal flow rates had to be increased in 49% (n/N = 37/76) of the patients in the SNF group as compared with 27% (n/N = 22/80) in the INF group ($p=0.008$).

Infants that failed nHF had significantly lower gestational age, higher baseline SA scores and oxygen requirements. The overall duration of respiratory support was also significantly longer in the nHF failure cohort. (►Supplementary Table 1 [available in the online version])

Discussion

Our study shows that higher nasal flow rate (8–10 L/min) did not reduce the combined need for higher respiratory support or surfactant therapy among preterm infants ≥28 weeks of gestation with respiratory distress since birth. However, the frequency of nasal flow rate escalation was significantly higher in the group initiated on flow rates of 5 L/min, suggesting that starting flow rates of 5 L/min may not be optimal for preterm neonates on primary nasal flow support. Most of the study infants that were stabilized with nasal flow support required flow rates of 7 to 8 L/min.

Recent studies have demonstrated that increasing nasal flows could significantly increase nasopharyngeal and oesophageal PEEP, potentially simulating a CPAP effect.[18,19] In our RCT, the overall nHF failure rate remained the same in both groups. Our findings add to the existing evidence that suggests 20 to 25% failure rates with primary nHF therapy in preterm neonates. The rate of mechanical ventilation in our study cohort (<5%) was lower than that reported in recent studies involving primary nHF therapy.[8,20] While the

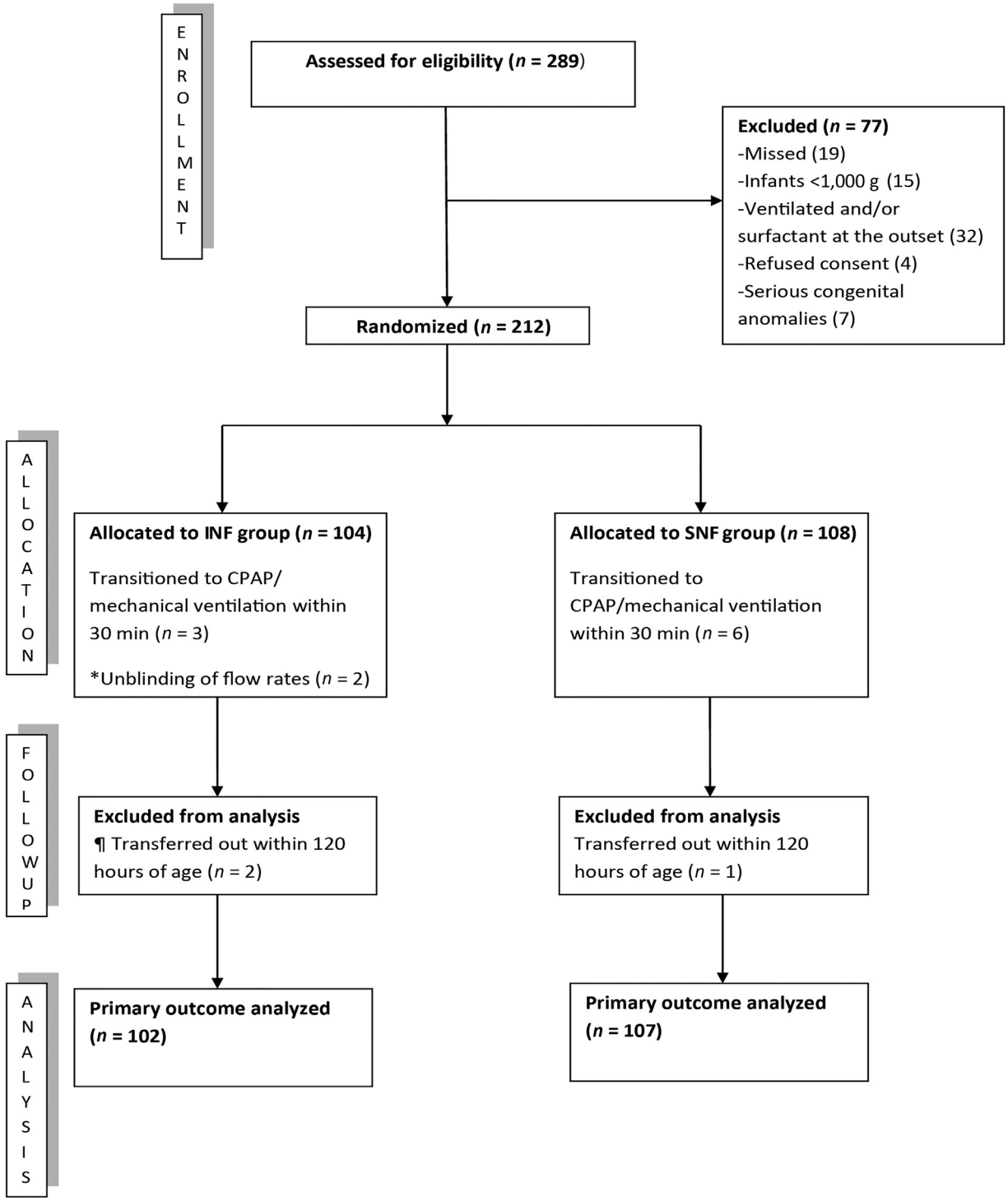

Fig. 2 Flow diagram of patient enrolment process. *High-flow system had to be reset or replaced due to malfunction during the study period resulting in unblinding of the flow rates.

mean gestational ages were similar across the studies, the use of INSURE and rescue CPAP could have contributed to a lower rate of mechanical ventilation in our study.

The current trial was pragmatic in allowing flow rate increments in both groups before switching over to higher respiratory support. As a result, although nHF failure occurred only in a quarter of the patients, an escalation in the flow rate was required in approximately 54% ($n = 114$) of our study patients. A significantly higher proportion of infants in the SNF group needed early increments in flow rate to avert treatment failure. The fact that a flow rate of less than 6 L/min was optimal only for 36% of the infants in the SNF group also suggests the need for optimized flow settings in neonates. At least one prior study has found that a nasal flow rate of 3 to 5 L/min was similarly efficacious to CPAP in preterm infants >28 weeks of gestation[21]; therefore, the effectiveness of lower flow rates (5 L/min) in certain preterm infants cannot be ruled out.

Table 1 Baseline characteristics

Baseline characteristics	Standard nasal flow ($n = 108$)	High-nasal flow ($n = 104$)	p-Value
Maternal characteristics			
Maternal age (y)	33 (30–36)	32 (29–36)	0.27
Multiple pregnancy	49 (45%)	40 (38%)	0.31
Pregnancy-induced hypertension	35 (32%)	28 (27%)	0.38
Antepartum hemorrhage	12 (11%)	6 (5.8%)	0.16
Gestational diabetes	19 (18%)	25 (24%)	0.25
PPROM > 24 h	16 (15%)	21 (20%)	0.30
Cesarean delivery	99 (92%)	97 (93%)	0.83
Any prenatal steroid exposure	107 (99%)	99 (95%)	0.5
Complete course of prenatal steroids	87 (81%)	75 (72%)	0.15
Infant characteristics			
Gestational age (wk)	32.4 ± 1.6	32.4 ± 1.9	0.73
Gestation (wk)			
$28–30^{6/7}$	24 (22%)	28 (27%)	
$31–33^{6/7}$	67 (62%)	61 (59%)	
$34–36^{6/7}$	17 (16%)	15 (14%)	
Birth weight (g)	1,634 ± 415	1,657 ± 470	0.71
Outborn	49 (45%)	48 (46%)	0.9
Male sex	64 (59%)	58 (56%)	0.6
Small for gestational age	15 (14%)	14 (13%)	0.7
Need for positive pressure ventilation at birth	24 (22%)	34 (33%)	0.9
Apgar's score at 5 min	7 (7–8)	7 (7–8)	0.18
SNAPPE score	5 (5–11)	5 (5–9)	0.83
Capillary or arterial pH before randomization	7.25 ± 0.06	7.25 ± 0.05	0.83
$PaCO_2$ before randomization (mm Hg)	54.3 ± 10	54.3 ± 9.5	0.98
Baseline FiO_2 at randomization	0.35 (0.3–0.4)	0.35 (0.3–0.4)	0.95
Time of admission (min)	20 (15–60)	22 (15–60)	0.3
Time of initiation of nHF (min)	30 (15–60)	30 (15–60)	0.86
CPAP prior to randomization	47 (44%)	42 (40%)	0.66
Prerandomization CPAP duration (min)	30 (15–45)	30 (15–50)	0.80

Abbreviations: PPROM, preterm premature rupture of membranes; SA Silverman Andersen score; SNAPPE II, Score for Neonatal Acute Physiology-Perinatal Extension II.
Note: Data expressed as n (%), mean ± standard deviation or median (25th–75th percentile).

We also found that approximately 50% of the infants with gestational age <31 weeks, failed nHF and were stabilized with higher respiratory support, highlighting the need for cautious use of nasal flow therapy. Observed associations of nHF failure with higher levels of oxygen and lower gestational age in our study, similar to previous reports,[22,23] provide additional clinical insights to identify a selected population for application of nHF. Preterm infants with gestational age of 34 to $36^{6/7}$ weeks and those with a prerandomization FiO_2 of ≤30% could be considered ideal candidates for primary nHF application.

A major strength of the study was the blinding of flow rates, ruling out performance bias in the interpretation of the primary outcome and the flow increments. High-prenatal steroid exposure rates make this cohort generalizable to populations with similar access to high quality maternal and neonatal care.

Our study had certain limitations. Intentionally, the effect of INF rates was not compared with CPAP, the current standard of noninvasive respiratory support in preterm neonates. Rather, we aimed to study the clinical effects of different nasal flow ranges that could have important implications for centers that continue to employ nHF for primary respiratory support in preterm neonates. Although the starting flow rates in both groups were distinctly different, the difference in the maximally achieved flow rates between the groups was small and could have led to similar failure rates in the two groups. Our findings are not generalizable to

Table 2 Neonatal outcomes

Outcomes	Standard nasal flow group ($n = 107$)	Increased nasal flow group ($n = 102$)	Relative risk/ median difference (95% CI)	*p*-Value
Treatment failure				
nHF Failure[a]	31 (29%)	22 (22%)	0.81 (0.57–1.15)	0.22
28–$30^{6/7}$ wk	12/23 (52%)	11/26 (42%)	0.83 (0.48–1.42)	0.34
31–$33^{6/7}$ wk	14/67 (21%)	11/61 (18%)	0.91 (0.56–1.48)	0.71
34–$36^{6/7}$ wk	5/17 (29%)	0/15	0	0.03
CPAP	24 (22%)	21 (20%)	0.94 (0.67–1.34)	0.75
CPAP days (in nHF failure)	9 (6–15)	8 (5–17)	−1 (−4 to 4)	0.63
Surfactant	29 (27%)	18 (18%)	0.74 (0.50–1.09)	0.10
Mechanical ventilation	4 (3.7%)	4 (3.9%)	1.02 (0.50–2.08)	0.94
Reasons for nHF failure				
Increased oxygen need and respiratory distress	16 (52%)	11 (50%)	0.96 (0.51–1.82)	1.00
Apnea and respiratory acidosis	2 (6.4%)	2 (9%)	1.22 (0.43–3.45)	1.00
Increased oxygen need and respiratory acidosis	2 (6.4%)	2 (9%)	1.22 (0.43–3.45)	1.00
Increased respiratory distress and decreased lung expansion on chest radiograph	4 (13%)	3 (14%)	1.04 (0.41–2.6)	1.00
Increased oxygen need	5 (16%)	2 (9%)	0.65 (0.19–2.2)	0.68
Increased respiratory distress	2 (6.4%)	2 (9%)	1.22 (0.43–3.45)	1.00
Time to nHF failure (hours)	3 (1.5–4.5)	3 (2–4.5)	−0.25 (−1 to 1)	0.72
Duration of primary nHF therapy	5 (2–7)	4 (2–7)	0 (−1 to 1)	0.71
Restarting of respiratory support after week 1	4 (3.7%)	5 (4.8%)	1.14 (0.63–2.09)	0.70
Nasal flow rates				
Median nasal flow rate (L/min)	6 (5–7)	7 (7–8)	2 (1–3)	0.008
Maximum nasal flow rate (L/min)	7 (5–7)	8 (8–10)	3 (3–3)	0.001
Nasal flow rate increments (%)	68 (64%)	44 (43%)	0.66 (0.49–0.87)	0.004
Proportion of infants at specified flow rates				
("F" L/min)[b]	39 (36%)	58 (57%)		
("F + 1" L/min)	15 (14%)	13 (13%)		
("F + 2" L/min)	53 (49%)	31 (30%)		
Reasons for flow increments				
Increased respiratory distress	25/68 (37%)	19/44 (43%)	1.17 (0.74–1.86)	0.47
Increased oxygen need	18/68 (26%)	11/44 (25%)	0.95 (0.56–1.63)	0.84
Decreased lung expansion	12/68 (17%)	6/44 (14%)	0.82 (0.41–1.65)	0.56
Respiratory acidosis	6/68 (8.8%)	4/44 (9%)	1.02 (0.46–2.26)	0.97
Apnea or other causes	7/68 (10%)	4/44 (9%)	0.92 (0.40–2.08)	0.82
Nasal flow increments in nHF success	49% (37/76)	27% (22/80)	0.62 (0.43–0.88)	0.008
Proportion of infants at specified flow rates				
("F" L/min)[b]	39 (51%)	58 (73%)		
("F + 1" L/min)	15 (20%)	12 (15%)		
("F + 2" L/min)	22 (29%)	10 (12%)		
Caffeine	95 (89%)	87 (86%)	0.86 (0.59–1.24)	0.45
Days on caffeine	14 (8–21)	12 (7–20)	−1 (−2 to 4)	0.58
Duration of respiratory support (overall cohort) (d)	6 (4–9)	5 (4–8)	0 (−1 to 1)	0.36
Bronchopulmonary dysplasia	4 (3.7%)	4 (3.9%)	1.02 (0.50–2.08)	0.94

(*Continued*)

Table 2 (*Continued*)

Outcomes	Standard nasal flow group ($n = 107$)	Increased nasal flow group ($n = 102$)	Relative risk/ median difference (95% CI)	*p*-Value
Other outcomes				
All-cause mortality	1 (0.9%)	1 (0.9%)	1.02 (0.25–4.12)	0.97
Intraventricular hemorrhage (grade III or higher)	1 (0.9%)	1 (0.9%)	1.04 (0.06–16.4)	0.97
Air leak syndromes	1 (0.9%)	0		1.00
Culture positive sepsis	7 (6.5%)	6 (5.9%)	0.94 (0.51–1.72)	0.94
Patent ductus arteriosus (needing medical treatment)	8 (7.5%)	4 (3.9%)	0.67 (0.30–1.51)	0.26
Necrotizing enterocolitis (stage 2 or higher)	3 (2.8%)	3 (2.9%)	1.02 (0.45–2.31)	0.95
Retinopathy of prematurity (requiring treatment)	5 (4.7%)	3 (2.9%)	0.62 (0.15–2.54)	0.51
Time to reach full feeds (d)	4 (2–6)	4 (2–6)	0 (−1 to 0)	0.48
Time to full oral feeds (d)	15 (7–21)	12 (6–24)	0 (−3 to 3)	0.91
Duration of hospital stay (d)	23 (12–32)	22 (10–36)	1 (−1 to 2)	0.78
Nasal injury	9 (8.4%)	6 (5.9%)	0.80 (0.43–1.53)	0.80

Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; nHF, nasal high flow.
Note: Data expressed as *n* (%), (n/N) % or median (25th–75th percentile). The *p*-values are based on Chi-square test and two sample *t*-test/Wilcoxon rank sum test for categorical and continuous variables.
[a]nHF failure defined as need for CPAP or mechanical ventilation or surfactant.
[b]"F" liters/min denotes the starting flow rate in each group (5 L/min in the standard group and 7 L/min in the increased flow group).
[c]Dilation of nares, columella indentation or excoriation, notching on the bridge of the nose, redness/bleeding/excoriation of any area of nose.

extremely preterm neonates or those with severe respiratory distress that requires mechanical ventilation at the outset. Some of the criteria used for escalation of flow rates, such as respiratory distress and lung expansion, were subjective. Although blinding reduces the risk of bias, the subjective element in the primary outcome is another limitation.

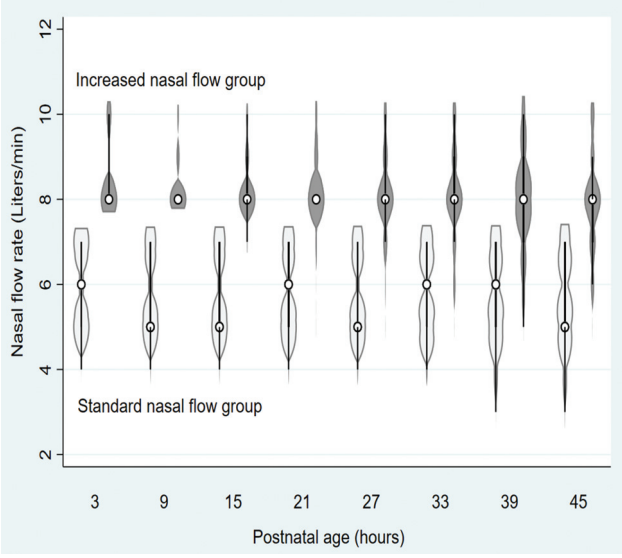

Fig. 3 Nasal flow rate distribution plots. Violin plots showing nasal flow rate distribution at 3 hourly time intervals in the first 48 hours of life in the standard nasal flow group (light shaded violins) and increased nasal flow group (dark-shaded violins).Two flow peaks (at 5 and 7 L/min) noted in the standard flow group at every time point, indicating the increased frequency of flow escalation in that group.

Prerandomization CPAP use (in the delivery room and briefly during transport) in this study could also have impacted the primary outcome.

A proportion of infants (21%) in our study were exposed to nasal flow rates greater than 8 L/min that are not licensed for use in neonates outside of research settings. Although there were no air leaks noted in the higher flow group in this study, the safety of higher nasal flows (>8 L/min) in neonates remains an important issue. A recent multicenter study comparing higher nasal flow therapy (3 L/kg/min) versus standard flows (2 L/kg/min) in older infants with bronchiolitis reported greater discomfort and prolonged ICU length of stay in the high flow group.[24] Flow rates greater than 8 L/min are currently not approved in premature infants. The nasal injury reported in the study occurred in the infants that failed nHF, typically in the 28 to 31 weeks of subgroup and were CPAP related.

In summary, higher initial nasal flows, despite being safe, did not reduce the need for higher respiratory support among moderately preterm neonates presenting with respiratory distress since birth. Nasal flow rates of 5 L/min were not optimal for most preterm infants receiving primary nasal flow therapy. Careful patient selection and optimization of flow settings are important considerations in the use of primary nasal flow therapy in preterm neonates.

Authors' Contributions

H.B. conceptualized the study and drafted the initial manuscript. S.S. and S.M. collected the data and performed the initial analysis. L.S. and N.K. conducted literature search,

supervised the study conduct, and critically reviewed the manuscript. B.G. and J.A. were involved in patient screening and enrollment and contributed to data analysis. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

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Conflict of Interest
None declared.

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